Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

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eTable 1. Guidelines reviewed, by developer

	Guideline	Year
	American Academy of Family Physicians (AAFP)	
1	Guideline for the Detection and Management of Post–Myocardial Infarction Depression	2009
2	Summary of Recommendations for Clinical Preventive Services	2016
	American Association for Thoracic Surgery (AATS)	
3	The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups	2012
	American Cancer Society (ACS)	
4	American Cancer Society Colorectal Cancer Survivorship Care Guidelines	2015
5	Breast Cancer Screening for Women at Average Risk: 2015 Guideline Update From the American Cancer Society	2015
6	American Cancer Society Prostate Cancer Survivorship Care Guidelines	2014
7	American Cancer Society Guideline for the Early Detection of Prostate Cancer	2010
8	American Cancer Society Lung Cancer Screening Guidelines	2013
9	American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline	2015
	American College of Cardiologists/American Health Association (ACC/AHA)	
10	2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease	2016
11	Management of Patients With Peripheral Artery Disease (Compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations)	2013
12	2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease	2014
13	AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease	2011
14	2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease	2012
15	Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women - A Guideline from the American Heart Association	2011
16	2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults	2013

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17	2013 ACCF/AHA Guideline for the Management of Heart Failure	2013
18	2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk	2013
19	2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation	2014
20	2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease	2011
21	2015 ACC/AHA/HRS Guideline for the Management of Adult Patients With Supraventricular Tachycardia	2015
	American College of Chest Physicians	
22	Screening for lung cancer: Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines	2013
23	Evaluation of Individuals With Pulmonary Nodules: When Is It Lung Cancer? Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines	2013
	American College of Physicians (ACP)	
24	Screening for Prostate Cancer: A Guidance Statement From the Clinical Guidelines Committee of the American College of Physicians	2013
25	Screening for Colorectal Cancer: A Guidance Statement From the American College of Physicians	2012
26	Screening for Cancer: Advice for High-Value Care From the American College of Physicians	2015
27	Cardiac Screening With Electrocardiography, Stress Echocardiography, or Myocardial Perfusion Imaging: Advice for High-Value Care From the American College of Physicians	2015
28	Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline From the American College of Physicians	2012
29	Evaluation of Patients With Suspected Acute Pulmonary Embolism: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians	2015
30	Nonpharmacologic Versus Pharmacologic Treatment of Adult Patients With Major Depressive Disorder: A Clinical Practice Guideline From the American College of Physicians	2016
	American Diabetes Association (ADA)	
31	Standards of Medical Care in Diabetes	2016
	American Geriatric Society (AGS)	

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32	Guidelines Abstracted from the American Geriatrics Society: Guidelines for Improving the Care of Older Adults with Diabetes Mellitus: 2013 Update	2013
33	American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults	2015
	American Psychiatric Association (APA)	
34	Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Third Edition	2010
	American Urological Association (AUA)	
35	Early Detection of Prostate Cancer	2013
	Centers for Disease Control (CDC)	
36	CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016	2016
	Department of Veterans Affairs/Department of Defense (VA/DoD)	
37	VA/DoD Clinical Practice Guideline for the Management of Dyslipidemia for Cardiovascular Risk Reduction	2014
38	VA/DoD Clinical Practice Guideline for the Diagnosis and Management of Hypertension in the Primary Care Setting	2014
39	VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder	2016
	Eighth Joint National Committee (JNC-8)	
40	2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults Report From the Panel Members Appointed to the Eighth Joint National Committee	2014
	National Institute for Health and Care Excellence (NICE) – Do not do recommendations	
41	Atrial fibrillation: the management of atrial fibrillation [CG]	2014
42	Lipid Modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease [CG181]	2014
43	Hypertension: The clinical management of primary hypertension in adults [CG127]	2011
44	MI-secondary prevention: Secondary prevention in primary and secondary care for patients following a myocardial infarction [update of CG48]	2013
45	Type 2 diabetes in adults: management [NG28]	2015

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46	Diabetic foot problems: prevention and management [NG19]	2015
47	Type 1 diabetes in adults: diagnosis and management [NG17]	2015
48	Common Mental Health Disorders: The NICE Guideline on Identification and pathways to care [CG123]	2011
49	Depression: The Treatment and Management of depression in adults [CPG90]	2009
50	Depression in Adults [QS8]	2011
51	Stable Angina: management [CG126]	2011
52	Advanced breast cancer: diagnosis and treatment	2009
53	Depression in Adults with a Chronic Physical Health Problem [CPG91]	2010
54	Hyperglycaemia in acute coronary syndromes: Management of hyperglycaemia in people with acute coronary syndromes [CG130]	2011
55	Self-harm: The NICE Guideline on Longer-term management [CG133]	2012
56	Prostate Cancer: Diagnosis and Treatment [CG]	2014
	U.S. Multi-Society Task Force (USMSTF)	
57	Colonoscopy surveillance after colorectal cancer resection: recommendations of the US multi-society task force on colorectal cancer	2016
58	Guidelines for Colonoscopy Surveillance After Screening and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer	2012
59	Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps, 2008: A Joint Guideline From the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology	2008
	U.S. Preventive Services Task Force (USPSTF)	
60	Screening for Coronary Heart Disease With Electrocardiography	2012
61	Screening for Abdominal Aortic Aneurysm	2014
62	Aspirin Use for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer	2016
63	Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: Preventive Medication	2015
64	Screening for Abnormal Blood Glucose and Type 2 Diabetes Mellitus	2015
65	Screening for Colorectal Cancer	2016
66	Screening for Prostate Cancer	2012

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67	Screening for Lung Cancer	2014
68	Screening for Breast Cancer	2016
69	Screening for Testicular Cancer	2011
70	Screening for Chronic Obstructive Pulmonary Disease	2016
71	Screening for Asymptomatic Bacteriuria in Adults	2008
72	Screening for Asymptomatic Carotid Artery Stenosis	2014
73	Vitamin D and Calcium Supplementation to Prevent Fractures in Adults	2013
74	Screening for Ovarian Cancer	2012
75	Screening for Osteoporosis	2011
76	Menopausal Hormone Therapy for the Primary Prevention of Chronic Conditions	2012
77	Screening for Chlamydia and Gonorrhea	2014
78	Screening for Cervical Cancer	2012
79	Screening for Hepatitis C Virus Infection in Adults	2013
80	Screening for HIV	2013
81	Screening for Hepatitis B Virus Infection in Nonpregnant Adolescents and Adults	2014
82	Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women	2014
83	Screening for Cognitive Impairment in Older Adults	2014
84	Vitamin, Mineral, and Multivitamin Supplements for the Primary Prevention of Cardiovascular Disease and Cancer	2014
85	Screening for High Blood Pressure in Adults	2015
86	Screening for Depression in Adults	2016

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eMethods 1. Recommendation extraction procedures

There is a growing interest in identifying overuse of care – care that exposes patients to services that are not beneficial or may cause harm and which may take scarce resources away from those who would benefit from them. The national Choosing Wisely campaign is one manifestation of this trend. While this campaign has garnered attention, it has not produced systematic or reproducible approaches to identify overuse. Moreover, we increasingly recognize instances where the marginal benefit of frequent or intensive care is either absent or outweighed by the potential for patient harm. At the same time, both providers and patients may have particular difficulty stopping routine testing and treatments once they have become part of a patient's regular care. One example of excessive care is intensive glycemic management among diabetic patients who are elderly or have major comorbidities.

Measuring and facilitating appropriate de-intensification will require first identifying and creating recommendations that capture opportunities for and successful implementation of de-intensification. Below are the main parameters that we used to define our inclusion criteria: (A) deintensification, (B) primary care, and (C) modalities of care.

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DEINTENSIFICATION: We aim to identify opportunities for de-intensification, which we define as decreasing the intensity or frequency of medical interventions that are currently part of a patient's *ongoing care* or *management*. Indications for de-intensification include: (1) screening, (2) testing, (3) treatment, and (4) surveillance and follow-up. While most overuse recommendations focus on "low-value" one-time diagnostic or treatment procedures, much of health care involves "routine" use of medical services for prevention or management of ongoing, chronic conditions that may or may not have been appropriate at some point in time.

Deintensification includes:

A. Category A: Services that are deemed inappropriate (for some or all patients) by the state of the art in clinical knowledge

1. **Screening that is done on a routine basis, often as a part of a regular health maintenance exam; examples:**
   a. *The USPSTF recommends against routine screening for AAA in women who have never smoked.* (**USPSTF**)
   b. *Don't screen for carotid artery stenosis in asymptomatic adult patients.* (**CW**)
   c. *Don't order coronary artery calcium scoring for screening purposes on low risk asymptomatic individuals except for those with a family history of premature coronary artery disease.* (**CW**)
   d. *The USPSTF recommends against the use of aspirin for stroke prevention in women younger than 55 years and for myocardial infarction prevention in men younger than 45 years. (Grade D)*
2. **Key words/indicators for category A deintensification recommendations**
   a. **USPSTF Grade D:** The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.
   b. **Choosing Wisely and NICE 'do not do':** these lists both are, by definition, explicit recommendations against a service and thus often fall into category A. However, many of the recommendations against a service are conditional upon certain patient factors (e.g., do not provide service X to patients between ages > 75), some CW and NICE recommendations should be graded categories B or C (see following sections).
   c. **VA:**
      i. **Strong Against, "We recommend against offering this option"**
      ii. **Weakly against.**
   d. **ACP**:
      i. **Scheme I:** does not formally grade an indicator as "appropriate" or "inappropriate" but does provide straightforward "guidance statements" that explicitly recommend against certain procedures

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1. **From ACP guidelines:** *Guidance statement: For surveillance evaluation in men and women with a history of Barrett esophagus. In men and women with Barrett esophagus and no dysplasia, surveillance examinations should occur at intervals no more frequently than 3 to 5 years. More frequent intervals are indicated in patients with Barrett esophagus and dysplasia*.
2. **From the ACP best practice advice:** *Best Practice Advice*: Clinicians should avoid targets less than 7.8 mmol/L (<140 mg/dL) because harms are likely to increase with lower blood glucose targets.
    a. *Guidance Statement 4: ACP recommends that clinicians stop screening for colorectal cancer in adults over the age of 75 years or in adults with a life expectancy of less than 10 years.*

ii. **Scheme II:**
1. **Grade D:** Moderate evidence against the use of a recommendation; clinicians "should not do this"
2. **Grade E:** Good evidence against the use of a recommendation; clinicians "should not do this"

e. **ACC/AHA class IIIa or IIIb:**
i. **Class IIIa** suggests "no benefit," where the procedure/test is not helpful, or the treatment has no proven benefit.
ii. **Class IIIb** suggests "harm," where the procedure/test has excess cost or is either harmful or without benefit, or the treatment is harmful to patients

B. **Category B: Services that are still deemed generally appropriate but have ceased to be indicated for particular patients due to changes in patient health or demographic factors (e.g. age, comorbidity).**

1. **"Aging out" of a clinical recommendation via increased age or decreased life expectancy; examples:**
    a. *ACP recommends that clinicians stop screening for colorectal cancer in adults over the age of 75 years or in adults with a life expectancy of less than 10 years.* (**ACP**)
    b. *Don't routinely prescribe lipid-lowering medications in individuals with a limited life expectancy.* (**CW**)
2. **Permanent changes to health conditions, e.g., increased comorbidity, example:**
    a. Onset of dementia
3. **Care that should be time-limited to an acute episode of care but is extended inappropriately; example:**
    a. *Don't treat with an anticoagulant for more than three months in a patient with a first venous thromboembolism (VTE) occurring in the setting of a major transient risk factor.* (**CW**)

C. **Category C: Services that are deemed appropriate at some particular intensity or frequency**

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1. **Services that are routinely conducted at inappropriately high frequencies or short intervals; examples:**
    a. *For surveillance evaluation in men and women with a history of Barrett esophagus. In men and women with Barrett esophagus and no dysplasia, surveillance examinations should occur at intervals no more frequently than 3 to 5 years. More frequent intervals are indicated in patients with Barrett esophagus and dysplasia.* (**ACP**)
    b. *In patients with AAAs smaller than 4.0 cm in diameter, monitoring by ultrasound examination every 2 to 3 years is reasonable.* (**ACC/AHA**)
2. **Medications or other services that are conducted at too high an intensity; example:**
    a. *Clinicians should avoid targets less than 7.8 mmol/L (<140 mg/dL) because harms are likely to increase with lower blood glucose levels.* (**ACP**)
3. **Other notes:**
    a. **Note: if a recommendation is category C, do not also label it category E**
        i. **ADA Dyslipidemia/lipid management Treatment Goal 4.** *In individuals without overt CVD, the goal is LDL cholesterol ≤100 mg/dL (2.6 mmol/L).*

D. **Category D: Services that are weakly recommended or deemed of marginal benefit, either for the general population or for specific sub-populations (*non-definitive statements*)**

1. **Examples**
    a. **USPSTF Grade C:** *Adults age 60-69: The decision to use low-dose aspirin to prevent CVD and colorectal cancer in adults ages 60 to 69 years who have a greater than 10% 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to use low-dose aspirin.*
    b. **ACC/AHA IIb, grade C:** *The effectiveness of the therapeutic use of folic acid and B12 vitamin supplements in individuals with lower extremity PAD and homocysteine levels greater than 14 micromoles per liter is not well established.*
    c. **ACC/AHA IIb, grade C:** *The effectiveness of ginkgo biloba to improve walking distance for patients with intermittent claudication is marginal and not well established.*
2. Key guideline indicators for category D recommendations
    a. **USPSTF Grade C:** The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small. Offer or provide this service for selected patients depending on individual circumstances.
    b. **ACC/AHA Grade C:** Poor evidence to support or to reject the use of a recommendation; clinicians "may or may not follow the recommendation**"**.
    c. **Weak (ACP, VA, AGS):**

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i. Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes
ii. Benefits finely balanced with risks and burden. Panel judged the evidence to be in favor of these interventions, but the current level of evidence or potential risks of the treatment did not support a strong recommendation.
iii. **VA**: Weak Against, "We suggest not offering this option"; Weak For, or "We suggest offering this option".

E. **Category E: Services that are deemed appropriate for restricted specific patient populations, implicitly recommending against providing the service to omitted patient populations, i.e., these explicitly recommend doing something, but with limited population parameters.**

1. **Examples**
   a. **USPSTF:** *Abnormal Blood Glucose and Type 2 Diabetes Mellitus Screening. The USPSTF recommends screening for abnormal blood glucose as part of cardiovascular risk assessment in adults aged 40 to 70 years who are overweight or obese. (implying no screening for those younger than 40 or older than 70)*
2. Key guideline indicators for category E recommendations
   a. Key words: combination of recommendation for service + specific denominator (by gender, age, risk level, comorbidity)
   b. **USPSTF Grade A/B:**
      i. **Grade A**: The USPSTF recommends the service. There is high certainty that the net benefit is substantial. Offer or provide this service.
      ii. **Grade B**: The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial. Offer or provide this service.
   c. **ACP/AGS:**
      i. **Strong:** Benefits clearly outweigh risks and burden, *or* risks and burden clearly outweigh benefits. Panel judged the evidence and determined that the benefits clearly outweighed harms or the potential harms clearly outweighed the benefits.
      ii. **High-Quality Evidence:** Evidence is considered high quality when it is obtained from one or more well-designed and well-executed randomized controlled trials (RCTs) that yield consistent and directly applicable results. This also means that further research is very unlikely to change our confidence in the estimate of effect.
      iii. **Moderate-Quality Evidence:** Evidence is considered moderate quality when it is obtained from RCTs with important limitations. In addition, evidence from well-designed controlled trials without randomization, well-designed cohort or case–control analytic studies, and multiple time series with or without intervention are in this category. Moderate-quality evidence also means that further research will

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probably have an important effect on our confidence in the estimate of effect and may change the estimate.

d. **VA: Strongly for, or "We recommend offering this option"**

3. **Additional notes for category E**
   a. **Note:** the existence of some specific denominator only changes our categorization of intensification (category E vs. I) and not de-intensification (category A) recommendations.
   b. **Note:** if a recommendation also falls into categories A, B or C, do not additionally give it a category ranking of E. Remember, *category E recommendations are purely intensification recommendations except for the fact that they are recommendation only for a specific subpopulation.*
      i. **Examples of recommendations that *are not* category E:**
         1. Category B/C and not A or E:
            a. **Glycemic Goals 3.** *Less stringent A1C goals (such as <8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with long-standing diabetes in whom the general goal is difficult to attain despite DSME, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.*
         2. Category A, not E:
            a. **Antiplatelet agents 2.** *Aspirin should not be recommended for CVD prevention for adults with diabetes at low CVD risk (10-year CVD risk <5%, such as in men aged <50 years and women aged <60 years with no major additional CVD risk factors), since the potential adverse effects from bleeding likely offset the potential benefits.*

F. **Category *: Recommendations that do not state whether or how to deliver a service and (e.g.) (1) claim that there is "insufficient" evidence to make a recommendation; (2) call for "patient preferences" or "shared decision making;" (3) simply recommend that "published guidelines be followed."**

1. Please see section (5) for summary of discussion of how to treat these recommendations in the ASSURES project.
2. **Services for which there is insufficient evidence**
   a. **Key guideline indicators**
      i. **USPSTF Grade I**
      ii. [Note: these recommendations are often better identified by key phrases (e.g., "patient preferences" or "shared decision making") than by any specific grade.]
   b. **Examples**

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i. **USPSTF Grade I**: The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years.

3. **Services for which "patient preference," "shared decision making," "clinical judgment," or "personalized" care is called for.**
   a. Examples
      i. **ACC/AHA**: *Diagnostic and therapeutic approaches to SVT should be individualized in patients more than 75 years of age to incorporate age, comorbid illness, physical and cognitive functions, patient preferences, and severity of symptoms.*
      ii. **VA**: *We suggest taking into consideration the patient's baseline blood pressure and presence of comorbidities, when deciding on either monotherapy or combination therapy (two drugs) when initiating drug therapy.*
      iii. **ACC/AHA**: *In individuals with clinical ASCVD >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects and drug–drug interactions and to consider patient preferences when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it.*
      iv. **ACC/AHA**: *In adults with LDL-C <190 mg/dL who are not otherwise identified in a statin benefit group, or for whom after quantitative risk assessment a risk-based treatment decision is uncertain, additional factors may be considered to inform treatment decision making. In these individuals, statin therapy for primary prevention may be considered after evaluation of the potential for ASCVD risk-reduction benefits, adverse effects, and drug–drug interactions and consider patient preferences*.

4. **Vague recommendations that simply call for "following guidelines."**
   a. **Example**
      i. **ACC/AHA**: *Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines.*

5. **For ASSURES: we may consider creating de-intensification recommendations using the following logic.**
   a. Suppose there is some service that, despite a "weak" evidence base (e.g., USPSTF Grade C), is mildly recommended for some subgroup (e.g., individuals 50-65 years of age). Suppose further that this service is deemed to have an "insufficient" (e.g. USPSTF Grade I) evidence base to recommend for or against a service for a different subgroup (e.g., individuals >65 years of age). Nonetheless, *because this second subgroup (age > 65) is even less likely to benefit from the service, we can deduce that it would be even less appropriate to provide that service that subgroup and create a de-intensification for the population that received an "I" recommendation*
   b. **Example: USPSTF Aspirin as primary prevention**

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iv. *Adults younger than age 50 years*: The current evidence is insufficient to assess the balance of benefits and harms of aspirin use to prevent CVD and colorectal cancer in adults younger than age 50 years. **(Grade I)**.
    1. → *Recommend against aspirin in adults younger than 50 years of age*
v. *Adults age 70 years and older*: The current evidence is insufficient to assess the balance of benefits and harms of aspirin use to prevent CVD and colorectal cancer in adults age 70 years and older. (**Grade I**).
    1. → *Recommend against aspirin in adults older than 70 years of age*
vi. What is the logic here?
    1. Because the USPSTF had already deemed there to be sufficient evidence to recommend aspirin only for specific populations of adults age 50-69 (Grades B and C), this implies that the Grade I was an even weaker recommendation (rather than just uncertain due to a lack of evidence) and could be a potential deintensification measure.
vii. **Final Potential deintensification measure:** *Recommend against low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer in those adults (1) younger than 50 years; (2) older than 69 years of age; (3) age 50-69 years with (a) less than 10% 10-year CVD risk, (b) with increased risk for bleeding, (c) life expectancy of less than 10 years, or (c) unwilling to take low-dose aspirin daily for at least 10 years.*

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Deintensification excludes:

A. **Acute, one-time care now deemed inappropriate**
   1. *MRI for acute chest pain when source of chest pain is known.* (**CW**)
      a. [Note: this can be difficult to distinguish from episodes that may be single episodes but extended for a sufficiently long period of time so as to allow for deintensification, e.g., when a patient is on blood thinners for >3 months after hospital discharge.]
   2. Pregnancy

B. **Recommendations pertaining to initial work-up**
   1. *Don't do work up for clotting disorder (order hypercoagulable testing) for patients who develop first episode of deep vein thrombosis (DVT) in the setting of a known cause.* (**CW**)
   2. *Don't use coronary computed tomography angiography in high risk emergency department patients presenting with acute chest pain (risk defined by the Thrombolysis In Myocardial Infarction (TIMI) risk score for unstable angina acute coronary syndromes).* (**CW**)
   3. *Don't test for thrombophilia in adult patients with venous thromboembolism (VTE) occurring in the setting of major transient risk factors (surgery, trauma or prolonged immobility).* (**CW**)

C. **Changes that occur over a very short episode of care.**
   1. *Don't administer plasma or prothrombin complex concentrates for non-emergent reversal of vitamin K antagonists (i.e. outside of the setting of major bleeding, intracranial hemorrhage or anticipated emergent surgery).* (**CW**)

D. **Any services related to preoperative care**
   1. *Don't perform routine pre-operative testing before low-risk surgical procedures. (CW)*

E. **Any services related to behavioral/lifestyle recommendations (diet, exercise)**
   1. ***Smoking Cessation 1.*** *Advise all patients not to smoke or use tobacco products.*

F. **Any services related to rehabilitation services**

G. **Counseling**

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PRIMARY CARE: To limit the scope of this project, we focus on only those indications relevant to adult ambulatory primary care. We define primary care in the following way:

A. Recommendations that primary care, family medicine, and general internists would be likely to do in an ambulatory care setting, i.e., no OB, pediatrics, or hospital-based decisions

2. Example of actions that *take place* in an ambulatory care setting
    a. *Don't order annual electrocardiograms (EKGs) or any other cardiac screening for low risk patients without symptoms* (CW).
3. Example of actions that *do not take place* in an ambulatory care setting
    a. *Avoid CT pulmonary angiography in emergency department patients with a low-pretest probability of pulmonary embolism and either a negative Pulmonary Embolism Rule-Out Criteria (PERC) or a negative D-dimer* (CW).

B. Clinical actions that PCPs can implement (i.e., order or carry out) without active specialty involvement

1. This includes:
    a. Actions that PCPs can carry out, i.e., do not involve a specialist
        i. *Don't initiate antihypertensive treatment in individuals 60 years of age for systolic blood pressure (SBP) <150 mm Hg or diastolic blood pressure (DBP) <90 mm Hg.* (**CW**)
    b. Actions that PCPs can carry out even if other PCPs would refer to a specialist, i.e., do not need to involve a specialist
        i. *Measurement of LV function with a technology such as echocardiography or radionuclide imaging is not recommended for routine periodic reassessment of patients who have not had a change in clinical status or who are at low risk of adverse cardiovascular events.* (**CW**)
    c. Referrals that a PCP would initiate for care that would then be performed by someone else, i.e., the specialist would largely automatically implement if referred.
        i. *Avoid using stress echocardiograms on asymptomatic patients who meet low risk scoring criteria for coronary disease.* (**CW**)
2. This excludes:
    a. Actions that PCPs cannot implement, where a PCP would not have sufficient information or expertise to act upon this independently
        i. *Avoid PCI in asymptomatic patients with stable SIHD without the demonstration of ischemia on adequate stress testing or with normal fractional reserve (FFR) testing.* (**CW**)
    b. Referrals that a PCP could initiate for care that would not automatically be performed (the specialist may or may not agree and carry out)
        i. *Avoid coronary angiography for risk assessment in patients with stable ischemic heart disease (IHD) who are unwilling to undergo revascularization or who are*

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not candidates for revascularization based on comorbidities or individual preferences. (**CW**)

c. The *majority* of invasive procedures. (Exceptions include those invasive procedures that are implemented largely automatically by specialists, e.g., colonoscopy.)

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MODALITIES. To assist in categorizing de-intensification recommendations, we defined recommendations along the following modalities.

[**Note:** In general, screening is a service performed in the absence of signs or symptoms. Surveillance is a service performed after a diagnosis has been reached. Colonoscopies illustrate how fuzzy the distinction between screening/surveillance can be. For instance, a routine colonoscopy that is done on the general population (anyone >50 years old) is a screening colonoscopy. However, if that colonoscopy reveals the presence of polyps (whether sessile or adenomas or hyperplastic), the subsequent follow-up colonoscopies are "surveillance colonoscopies," even though the patient may be asymptomatic and the true disease of concern – colorectal cancer – has not yet been diagnosed.]

A. Screening/Diagnosis/Testing (Anything done prior to a diagnosis)

a. **Example –screening:** *Don't order annual electrocardiograms, EKGs, or any other cardiac screening for low risk patients without symptoms.* (**CW**)

b. **Example -diagnosis***: Don't use coronary artery calcium scoring for patients with known coronary artery disease (including stents and bypass grafts).* (**CW**)

B. Treatment

a. **Example:** *Don't routinely prescribe lipid-lowering medications in individuals with a limited life expectancy.* (**CW**)

C. Surveillance/Monitoring (After a diagnosis)

a. **Example:** *Don't perform echocardiography as routine follow-up for mild, asymptomatic native valve disease in adult patients with no change in signs or symptoms.* (**CW**)

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USPSTF: Search and Information Capture	**De-intensification determination**	**Evidence grading and gathering**	**Discussion**
(A) Visually scan all USPSTF Published Recommendations for recommendations to pertinent condition (cardiovascular). (B) For each recommendation, begin at the recommendation summary page and then gather three documents: (1) Full recommendation statement (*Annals of Internal Medicine*) (2) evidence summary (*Annals of Internal Medicine*), and (3) the final evidence review. The summary page has a link to "read the full recommendation statement" and, under "supporting documents," to the "final evidence review" and "evidence summary" (4) Be sure to collect the *denominators (or populations)* for all USPSTF recommendations and include them in the excel spreadsheet. (C) For those recommendations published before 2011 (and thus considered out of date for the ASSURES project), determine whether there is a Recommendations in Progress , and, if so, whether it is in the 4th stage of development (i.e., those with draft recommendation statements). If it is in the 4th stage of development, repeat steps (A) and (B) for each recommendation with a complete draft recommendation statement.	USPSTF recommendations are ideal as they are under primary care control and explicitly recommend against specific services. **Grade A/B:** The USPSTF recommends the service. *These are generally category E or I.* **Grade C:** *These are generally category D*. **Grade D:** The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. - *These are category A* **Grade I:** The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined. - *These are category **	**Evidence grading:** **A = High:** The available evidence usually includes consistent results from well- designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies. **B = Moderate:** The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by factors such as: number, size or quality; inconsistency of findings; limited generalizability; lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion. **C= Low:** The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of limited number or size of studies; important flaws in study design or methods; inconsistency of findings; gaps in the chain of evidence; findings not generalizable; lack of information	*Although we won't collect the following in the excel spreadsheet, the following sections will prove useful at later stages of measure development.* **Rationale** section includes both an "importance" statement (pertaining to prevalence of practice under discussion), and an overview of the "benefits" and "harms" of the practice. **Clinical Considerations** section includes both a "costs" statement that includes aggregate costs (although the preface of each recommendation includes "*The USPSTF does not consider the costs of providing a service in this assessment*") and a "current practice" statement. **Discussion** section includes section on "potential harms of screening and treatment." **Recommendations of Others** section allows for quick reference of other pertinent guidelines. **Evidence Gathering**; provides two forms of evidence summaries (a more concise "evidence summary" in *Annals of Internal Medicine* and a longer "evidence review"), both of which are available on recommendation page under "supporting

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		on important health outcome(s). More information may allow estimation of effects on health outcomes.	documents” on the right hand side of the page

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CW: Search and Information Capture	**De-intensification determination**	**Evidence grading and gathering**	**Discussion**
Serially search: (A) Top-down approach: search Topic area (cardiology) (B) Bottom-up approach: search key words in complete pdf of all CW lists (ischemic, heart, cardio-, cardiac, coronary, stroke, dvt, stenosis, coag-, arrhythmia, echo-, EKG, stress, hypertens-, valv-, pressure) (C) Society approach: visually scan all lists from key primary care societies (American College of Physicians; Society of General Internal Medicine; American Academy of Family Physicians; American Geriatrics Society) as well as key condition-specific societies (this comprised ~ 20 societies for cardiology) (D) Repeat step (B) using new key words discovered in steps (A)-(C)	As CW specifically identifies clinical activities that are inappropriate (for all individuals or specific populations), identifying useful guidelines requires only determining whether the measure applies to "routine" care (vs. one-time, inappropriate care) and whether it is under primary care control in the adult ambulatory setting.	**Evidence Grading:** No explicit level of evidence given. Each society chooses its own list and does so idiosyncratically. Each list is followed by a page beginning with a section on "How This List Was Created" that describes how the society selected a workgroup, identified potential areas to be included on the list, and determined the final roster of measures. This section also includes a (rather unhelpful) link to society disclosure and conflict of interest policies. **Evidence Gathering:** The "How This List Was Created" page also lists the "Sources," with each recommendation having a corresponding list of citations. The sources generally include either primary literature or guideline references.	CW is not a monolith. Each society proposes its own list and CW largely accepts this list as is. Thus the quality and importance of each society's recommendations vary tremendously. Some recommendations do briefly discuss the prevalence and cost of the clinical activity under consideration.

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NQF: Search and Information Capture	**De-intensification determination**	**Evidence grading and gathering**
A) Begin at the Quality Positioning System. (B) On the left side of the page, under "narrow your search," serially select following filters: 1. Clinical condition: condition of interest (cardiovascular) → "select all" → gather recommendations → "clear" → clinical condition (prevention) → "select all" → gather recommendations → "clear" Repeat for 2. Cross-cutting area: overuse 3. Care setting: ambulatory care	NQF offers little guidance pertinent to finding de-intensification measures. While the "overuse" cross-cutting area filter may seem like a good place to start, I had little success with that filter. It seemed that the best way was to sort by clinical condition (cardiovascular) and then simply visually scan through the ~100 measures that seemed relevant to de-intensification. NQF had very few de-intensification measures, and does not provide any evidence relating to the rigor or importance of its recommendations. Rather, one needs to track the NQF measure backward to the society steward's guideline and the descriptions contained therein.	**Evidence Grading:** No explicit level of evidence given. However, NQF subjects each candidate measure to rigorous measure evaluation criteria. Thus, any measure endorsed by NQF that appears to relate to de-intensification should be a good measure candidate. **Evidence Gathering**: The NQF does not list any evidence for its recommendations (unless they are currently under review) and instead states "for additional measure specification information, please contact the Measure Steward." To track down the evidence, I searched online "[measure] + [measure steward] (e.g., American College of Cardiology)," found which specific clinical guideline that NQF measure came from, and then found the specific citations within the clinical guideline itself.

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NICE: Search and Information Capture	**De-intensification determination**	**Evidence grading and gathering**
(A) Begin at NICE conditions and diseases (B) Select overall condition (cardiovascular condition) (C) Select specific condition (heart failure) – we address conditions with broken web links in step (E) (D) Under "NICE guidelines" select specific guideline (chronic heart failure in adults: management) This page has two resources to gather: (1) Go to "Tools and resources," select "do not do" recommendations, which takes you to all 'do not do' recommendations affiliated with that guideline (chronic heart failure in adults: management). The list of recommendations is important but there is no reason to pursue any recommendation further than the page with the list of recommendations (2) Go to "Evidence," select "full guideline" under the "support evidence" section, and download the full guideline. Here is an example of the guideline for clinical management of primary hypertension in adults. This guideline contains the evidence underlying all recommendations. *After repeating this for all conditions:* (E) For conditions with broken links*: search related term (ischaemia) → select measure ("Do not use biochemical markers of myocardial ischaemia") → select guidance ("chest pain of recent onset") → tools and resources → `do not do' recommendations → total list of recommendations * this should be used as the secondary approach only for those conditions with broken guidelines, as this approach will miss large categories of measures if used alone.	As "do not do" list specifically identifies inappropriate clinical activities, identifying de-intensification requires determining whether the measure applies to "routine" care (vs. one-time, inappropriate care) and whether it is under primary care control in the adult ambulatory setting. *All "do not do" recommendations are category A* *We are not including recommendations that are just embedded in the guideline itself.* In other words, we are only including those recommendations that are considered "do not do" recommendations and not other recommendations that are included in the guidelines, even if they appear to recommend de-intensification.	**Evidence Grading:** NICE does not offer a specific level of evidence indicator alongside its recommendations. It does provide an exhaustive description of who developed the guideline and their process of guideline development, including the method for identifying areas in need updating, the research protocol, evidence gathering, appraising the evidence, distilling the evidence and developing recommendations, and how agreement was reached. **Evidence Gathering: The** 'do not do' cites the overall clinical guideline that pertains to the broader condition (e.g., "Full version of NICE Clinical Guideline No 108: Chronic heart failure**:** National clinical guideline for diagnosis and management in primary and secondary care"). This clinical guideline (>200 pages long) lists the 'do not do' recommendations and contains specific citations in the section that contains those 'do not do' recommendations. There are shorter summaries of the NICE clinical guidelines but these do not contain evidence citations, unfortunately. The complete clinical guidelines provide exhaustive descriptions of their path "from evidence to recommendations." This includes the relative value placed on the outcomes considered, quality of evidence, trade-off between clinical benefits and harms, and trade-off between net health benefits and resource use. It then provides a list of recommendations, some of which appear on its 'do not do' list.

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ACP: Search and Information Capture	**De-intensification determination**	**Evidence grading and gathering**
(A) Begin at ACP guideline page (B) Visually scan list for relevant conditions (C) Select condition (cardiac screening) Then either select: "high value care advice" or "current guideline" "High value care advice" links to the Annals of Internal Medicine Statement about inappropriate care. "Current guidelines" links to Annals of Internal Medicine clinical guideline with lists of recommendations that can be subjected to the de-intensification criteria listed above.	**Recommendations and clinical considerations (**Colorectal cancer screening, 2012) Guidance Statement 1: ACP recommends that clinicians perform individualized assessment of risk for colorectal cancer in all adults. Guidance Statement 2: ACP recommends that clinicians screen for colorectal cancer in average-risk adults starting at the age of 50 years and in high-risk adults starting at the age of 40 years or 10 years younger than the age at which the youngest affected relative was diagnosed with colorectal cancer. Guidance Statement 4: ACP recommends that clinicians stop screening for colorectal cancer in adults over the age of 75 years or in adults with a life expectancy of less than 10 years. Clinical Considerations: The screening interval for average-risk adults older than 50 y is 10 y for optical colonoscopy; 5 y for FS, DCBE, and CTC; annually for gFOBT and iFOBT; and uncertain for sDNA. **Recommendation strength** **Strong:** Benefits clearly outweigh risks and burden, *or* risks and burden clearly outweigh benefits. Panel judged the evidence and determined that the benefits clearly outweighed harms or the potential harms clearly outweighed the benefits. - *Strong against are category A* - *Strong for may be categories B, C, E, or I* **Weak:** Benefits finely balanced with risks and burden. Panel judged the evidence to be in favor of these interventions, but the current level of evidence or potential risks of the treatment did not support a strong recommendation. - *Weak against are category A* - *Weak for are category D* **Insufficient:** Insufficient evidence to determine net benefits or risks. Panel judged the evidence as warranting a recommendation statement to be made, but weighed the evidence as being insufficient to determine the net risks and benefits. Patient preferences may strongly influence the appropriate therapy. - *Insufficient are category **	**Quality of evidence** **High-Quality Evidence:** Evidence is considered high quality when it is obtained from 1 or more well-designed and well-executed randomized, controlled trials (RCTs) that yield consistent and directly applicable results. This also means that further research is very unlikely to change our confidence in the estimate of effect. **Moderate-Quality Evidence:** Evidence is considered moderate quality when it is obtained from RCTs with important limitations. In addition, evidence from well-designed controlled trials without randomization, well-designed cohort or case–control analytic studies, and multiple time series with or without intervention are in this category. Moderate-quality evidence also means that further research will probably have an important effect on our confidence in the estimate of effect and may change the estimate. **Low-Quality Evidence:** Evidence obtained from observational studies would typically be rated as low quality because of the risk for bias. Low-quality evidence means that further research is very likely to have an important effect on our confidence in the estimate of effect and will probably change the estimate. However, the quality of evidence may be rated as moderate or even high, depending on circumstances under which evidence is obtained from observational studies.

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AGS: Search and Information Capture	**De-intensification determination**	**Evidence grading and gathering**
(A) Begin at AGS Clinical Guidelines and Recommendations (B) Either register as a user on AGS or search pubmed for the guideline	Scheme used in (i) Clinical Practice Guideline for Postoperative Delirium in Older Adults (2014) and (ii) Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults (2012): **Strong, weak, insufficient scheme** **Strong:** Benefits clearly outweigh risks and burden, *or* risks and burden clearly outweigh benefits. Panel judged the evidence and determined that the benefits clearly outweighed harms or the potential harms clearly outweighed the benefits. - *Strong against are category A* - *Strong for may be categories B, C, E, or I* **Weak:** Benefits finely balanced with risks and burden. Panel judged the evidence to be in favor of these interventions, but the current level of evidence or potential risks of the treatment did not support a strong recommendation. - *Weak against are category A* - *Weak for are category D* **Insufficient:** Insufficient evidence to determine net benefits or risks. Panel judged the evidence as warranting a recommendation statement to be made, but weighed the evidence as being insufficient to determine the net risks and benefits. - *Insufficient are category ** **Not applicable:** No recommendation made. Panel determined that no recommendation could be made, that is, a statement could not be made either for or against a clinical practice**.** - *"Not applicable" are category ** **Scheme used in Guidelines for Improving the Care of Older Adults with Diabetes Mellitus: 2013 Update (2013)** **Grade A:** Good evidence to support the use of a recommendation; clinicians "should do this all the time" **Grade B:** Moderate evidence to support the use of a recommendation; clinicians "should do this most of the time" **Grade C:** Poor evidence to support or to reject the use of a recommendation; clinicians "may or may not follow the recommendation" **Grade D:** Moderate evidence against the use of a recommendation; clinicians "should not do this" **Grade E:** Good evidence against the use of a recommendation; clinicians "should not do this"	Scheme in (i) postop delirium (2014) and inappropriate medication (2012): **Level I, II, II** **Level I:** Evidence from at least one properly randomized controlled trial **Level II:** Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytical studies, from multiple time-series studies, or from dramatic results in uncontrolled experiments **Level III:** Evidence from respected authorities based on clinical experience, descriptive studies, or reports of expert committees Scheme used in (i) diabetes guideline (2013): **High, Moderate, Weak** **High:** Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (≥ 2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects) **Moderate:** Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (≥ 1 higher-quality trial with > 100 participants; ≥2 higher-quality trials with some inconsistency; ≥2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence **Weak:** Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes

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VA: Search and Information Capture	**De-intensification determination and evidence grading and gathering**	**Discussion**
(A). VA/DoD Clinical Practice Guidelines (B) Select Disease Category (Dyslipidemia) (C) Guideline links: select (1) Full Guideline, (2) LIPIDS Provider Summary, (3) Lipids in Peer Reviewed Publications (D) Select all recommendations	**For:** Strong Against, "We recommend against offering this option " - *Strong against are category A* Weak Against, "We suggest not offering this option" - *Weak against are category A* Strong For, or "We recommend offering this option" - *Strong for may be categories B, C, E, or I* Weak For, or "We suggest offering this option" - *Weak for are category D*	Tim and Eve have some concern that the VA guidelines are not sufficiently rigorous. We will need to discuss final inclusion/exclusion of VA guidelines. They are currently being included, however.

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AAFP: Search and Information Capture	**Discussion**
(A) Go to clinical guidelines by type (B) Select disease categories either developed or jointly developed by AAFP (these include dementia, post-MI depression, venous thromboembolism, atrial fibrillation) or endorsed by the AAFP and do not come from organizations already covered (e.g., select guidelines from The Joint National Committee but not the USPSTF) (C) Search for table summarizing recommendations (D) Scan recommendations for which the COR (class of recommendation) is IIIa (no benefit) or IIIb (harm) and also record the LOE (level of evidence). (E) Find the relevant citations by reading the text surrounding the summary recommendation tables.	**I recommend against using the AAFP**. There are no AAFP-developed guidelines from the past 5 years. In recent years, the AAFP largely adopts and adapts other guidelines. When they do so, they adapt the grading scheme followed by those guidelines. While the AAFP theoretically might offer us an opportunity to include new guidelines not already captured, the guidelines adopted by AAFP largely coincide with those already included in our search (USPSTF, CW).

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AHA/ACC Search and Information Capture	**De-intensification determination**	**Evidence grading and gathering**	**Discussion**
(A) AHA/ACC, select ACC/AHA joint guidelines (B) Download each guideline from 2010-onward (C) Search for table summarizing recommendations (D) Scan recommendations for which the COR (class of recommendation) is IIIa (no benefit) or IIIb (harm) and also record the LOE (level of evidence). (E) Find the relevant citations by reading the text surrounding the summary recommendation tables.	**Class IIIa** suggests "no benefit," where the procedure/test is not helpful or the treatment has no proven benefit. **Class IIIb** suggests "harm," where the procedure/test has excess cost and is either harmful or without benefit; or the treatment is harmful to patients	**A:** Data derived from multiple randomized clinical trials or meta-analyses. **B:** Data derived from a single randomized trial, or non- randomized studies. **C:** Consensus opinion of experts, case studies, or standard of care.	While the AHA/ACC guidelines are somewhat overwhelming at first, the process is made considerably more efficient by skimming quickly through the guidelines for the summary recommendation tables and then simply selecting those recommendations with Class IIIa or IIIb ratings (no benefit or harm, respectively).

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eTable 2. Examples of recommendations that could be reworded to form a specific de-intensification recommendation

	Example	
Recommendation included:	*Original wording of the recommendation*	*Reworded as a de-intensification recommendation*
1. Services that are deemed inappropriate for some or all patients by the state of the art in clinical knowledge	"We recommend against the use of more than one of the following three drug classes together in the same patient: angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, or direct renin inhibitors." (VA/DoD)	"Stop all but 1 class of the renin-angiotensin system agents in patients on combination therapy from two or more of the following classes: angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, or direct renin inhibitors"
2. Services that are still deemed generally appropriate but have ceased to be indicated for particular patients due to changes in patient health or demographic factors (e.g. age, comorbidity)	"Don't routinely prescribe lipid-lowering medications in individuals with a limited life expectancy." (CW)	"Stop lipid lowering therapy in patients who are on lipid lowering therapy with life expectancy <5 years"
3. Services that should be time-limited to an acute episode of care but are extended inappropriately	"Don't treat with an anticoagulant for more than three months in a patient with a first venous thromboembolism occurring in the setting of a major transient risk factor." (CW)	"Stop anticoagulant treatment in low-risk patients with a first venous thromboembolism after 3 months of treatment"
4. Services that are deemed appropriate at some particular intensity or frequency	"In patients treated with dual antiplatelet therapy, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended." (ACC/AHA)	"Decrease daily aspirin dose to <=100 mg in patients on dual antiplatelet therapy and daily aspirin dose >100mg"
5. Services that are weakly recommended or deemed of marginal benefit, either for the general population or for specific sub-populations	"The clinical effectiveness of pentoxifylline as therapy for claudication is marginal and not well established." (AHA/ACC*)*	"Stop the use of pentoxifylline in all patients"
6. Services that are deemed appropriate for restricted specific patient populations, implicitly recommending against providing the service to omitted patient populations, i.e., these explicitly recommend doing something, but with limited population parameters	"Clinicians should encourage colorectal cancer screening by 1 of 4 strategies: high-sensitivity fecal occult blood test or fecal immunochemical test (every year); sigmoidoscopy (every 5 years); combined high-sensitivity fecal occult blood test or fecal immunochemical test (every 3 years) plus sigmoidoscopy (every 5 years); or optical colonoscopy (every 10 years) in average-risk adults aged 50 to 75 years." (ACP)	"Don't screen more than every 10 years with colonoscopy, every 5 years with sigmoidoscopy, or yearly with high-sensitivity fecal occult blood test or fecal immunochemical test in patients with average-risk of colorectal cancer"

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7. Recommendations that do not state whether or how to deliver a service and (e.g.) (1) claim that there is "insufficient" evidence to make a recommendation; (2) call for "patient preferences" or "shared decision making;" or (3) simply recommend that "published guidelines be followed"	"The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for abdominal aortic aneurysm in women ages 65 to 75 years who have ever smoked." (USPSTF) "Offer prostate specific antigen screening for detecting prostate cancer only after engaging in shared decision-making." (AUA)	"Don't screen women for abdominal aortic aneurysm regardless of age and smoking status" "Don't offer prostate specific antigen screening without first engaging in shared decision-making"

Abbreviations: CW = Choosing Wisely; ACC = American College of Cardiology; ACP = American College of Physicians; AHA = American Health Association; AUA = American Urological Association; DoD = Department of Defense; USPSTF = U.S. Preventive Services Task Force; VA = Veterans Affairs

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eMethods 2. Review, Grouping, and Prioritization of Recommendations by Study Investigators and Advisory Council Members

First, two physician investigators (selected from the following investigators: EK, TH, JS, TC, LM, SS) reviewed each recommendation to assess its relevance to the study. A recommendation was dropped if both reviewers felt it did not focus on primary care (defined as care that primary care physicians would likely do in an ambulatory care setting [excludes pediatric, palliative, perioperative, and prenatal services] and clinical actions that primary care physicians can carry out or order without active specialty involvement), did not focus on routine care (defined as ongoing management for chronic conditions or prevention), or did not (or could not) represent de-intensification. For each recommendation that was not dropped based on these criteria, the same two investigators assessed, at a high-level, how likely it was that: 1) the available evidence would suggest that de-intensification is likely to improve patient outcomes, that continuing testing/treatment could cause harm in some patients, and that there would be an absence of evidence of benefit for continued/repeated intense treatment or testing; 2) the recommendation would affect a large number of patients or have a significant impact on a smaller number of patients; and 3) de-intensification could reliably be measured using administrative data, electronic health record data, or existing/new survey data. A recommendation was excluded from further consideration if both investigators felt it did not meet any of these criteria.

The two principal investigators (EK, TH) then grouped any recommendations that had similar intent, assigning one as the primary recommendation and the others as supporting recommendations. In assigning primary recommendations, priority was given to recommendations that more broadly covered the topic of interest. This step yielded 178 remaining recommendations, a larger number than would be feasible to assess through the planned expert panel process, which we estimated at approximately 30. Therefore, the two investigators independently rated the primary recommendations from 1-9, with 1 being a relatively unimportant target for de-intensification and 9 being an important target for de-intensification. A rating of 9 meant that the recommendation had high likelihood of improving patient outcomes, had a high opportunity for improvement, and was feasible to measure. Following the rating, the top-rated recommendations were revised to focus on de-intensification, if needed. For example, consider the following recommendation: "*The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at*

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least 10 years." The recommendation was rewritten as: *"Do not prescribe low dose aspirin for primary prevention of cardiovascular disease in adults under 50, or whose 10-year cardiovascular risk is <10%, or who are at increased risk of bleeding, or who have a life expectancy less than 10 years, or who are unlikely to be willing to take aspirin for at least 10 years."*

The top-rated 46 primary recommendations were distributed to the advisory council members for further prioritization, using the same importance scale as used by the principal investigators. For each primary recommendation, council members received a list of supporting recommendations (if any), rationale for the recommendation, a link to the actual recommendation or guideline, the evidence rating of the recommendation (if available), and a list of references supporting the evidence. Each member was asked to provide an importance rating and justification for that rating.

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eTable 3. Rapid Evidence Synthesis (RES) reports completed

Note: The actual rapid evidence synthesis reports are included in the expert panel booklets.

	RES Titles
1	Intensive Glycemic Control in Older Adults with Type 2 Diabetes Mellitus
2	Metformin Use in Older Adults with Type 2 Diabetes Mellitus
3	Routine Self-Monitoring of Blood Glucose in Adults with Type 2 Diabetes Mellitus Not Using Insulin
4	Systolic Blood Pressure Targets in Type 2 Diabetes Mellitus
5	Statin Combination Therapy Versus Monotherapy in Adults at Risk of Cardiovascular Disease
6	De-intensification Dual Antiplatelet Therapy (DAPT)
7	Echocardiography as Routine Follow-up for Asymptomatic Mild Native Valve Disease in Adults with No Change in Signs or Symptoms
8	Dual-energy X-ray absorptiometry (DXA) Screening
9	Screening for Cervical Cancer
10	Prostate-Specific Antigen-Based Screening for Prostate Cancer
11	High-Dose Opioid Therapy
12	Opioids and Benzodiazepines
13	Benzodiazepines and Other Sedative Hypnotics for Older Adults with Insomnia, Agitation, or Delirium
14	Use of Anticholinergic Drugs in Older Adults with Cognitive Impairment
15	Skeletal Muscle Relaxants for Older Adults
16	Inappropriate Antidepressant Use in Older Adults
17	Testosterone for Erectile Dysfunction in Men with Normal Serum Testosterone Levels
18	Estrogen and Progestin in Postmenopausal Women

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DEPARTMENT OF VETERANS AFFAIRS
CENTER FOR CLINICAL MANAGEMENT RESEARCH

De-intensification of routine medical services for patients with diabetes and/or cardiovascular disease

Expert Panel #1

Meeting 1: May 16, 2017
Meeting 2: June 20, 2017

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Background Information and Instructions

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Summary of Expert Panel Tasks

1. Review the attached booklet, answer the questions for each measure, and return answers to project staff prior to Meeting #1

Goal:	Have panel members become familiar with the proposed de-intensification measures, including the available evidence, for discussion during Meeting #1
Due Date:	**May 8, 2017**
Type:	Independent work
Instructions:	1. Review the attached booklet 2. Answer questions related to each measure directly into the booklet [see data entry fields] 3. Return your pdf, with answers to the questions, to Mandi.klamerus@va.gov by the above due date 4. Confirm your ThinkTank link works in preparation for meeting #1 (https://vha.thinktank.net/login.html?sessionID=85 (Session ID: 85; Passkey: 1234)). Contact Mandi if you cannot access the session.

2. Participate in Virtual Group Meeting #1

Goal:	Introduce panel members, outline the goals of the project, review the proposed measures, and collect suggestions for measure improvement
Meeting Date:	**May 16, 2017 (1-4pm Eastern)**
Type:	Virtual group meeting, using ThinkTank software + teleconference • ThinkTank access: https://vha.thinktank.net/login.html?sessionID=85 (Session ID: 85; Passkey: 1234) • Call-in information: 800-767-1750; access code: 01285#
Instructions:	Participate in a group discussion about the proposed measures

3. Conduct pre-rating of measures

Goal:	(Following Meeting #1, staff will make suggested revisions to the measures.) Rate the revised de-intensification measures using the following criteria: validity, improvement opportunity, and feasibility of implementation
Due Date:	**June 12, 2017**
Type:	Independent work, using ThinkTank software (Do not start until you receive instructions; these will be sent out after Meeting #1) • ThinkTank access: https://vha.thinktank.net/login.html?sessionID=85 (Session ID: 85; Passkey: 1234)
Instructions:	See pages 11-12 of the booklet for rating criteria

4. Participate in Virtual Group Meeting #2, including re-rating measures

Goal:	Discuss measures where there was clear disagreement in pre-rating and re-rate all measures using the following criteria: validity, improvement opportunity, and feasibility of implementation
Meeting Date:	**June 20, 2017 (1-4pm Eastern)**
Type:	Virtual group meeting, using ThinkTank software + teleconference • ThinkTank access: https://vha.thinktank.net/login.html?sessionID=85 (Session ID: 85; Passkey: 1234) • Call-in information: 800-767-1750; access code: 01285#
Instructions:	See pages 11-12 of the booklet for rating criteria

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Expert Panel Member Bios

R. Sacha Bhatia, MD, MBA

Dr. R. Sacha Bhatia is the Director of the Institute for Health System Solutions and Virtual Care at Women's College Hospital, where he is also a staff cardiologist. As Director of WIHV, Dr. Bhatia leads evaluation for Choosing Wisely Canada, a national initiative managed through the University of Toronto in collaboration with the CMA. He is also an Assistant Professor at the University of Toronto and an adjunct scientist at the Institute for Clinical Evaluative Sciences. Previously, he worked as a clinical and research fellow in cardiology at Massachusetts General Hospital and Harvard University. He received his medical degree and MBA at McGill University and his internal medicine and cardiology training in Toronto.

Paul R. Conlin, MD

Dr. Paul Conlin is Chief, Medical Service at VA Boston Healthcare System, Professor of Medicine at Harvard Medical School and Maurice Strauss Chair at Boston University School of Medicine. He is Director of the Clinical and Translational Research Academy in *Harvard Catalyst* - The Harvard Clinical and Translational Science Center. Dr. Conlin has been a practicing endocrinologist at VA Boston Healthcare System since 1989 and is Chair, VA Diabetes-Endocrinology Field Advisory Committee. His research uses clinical trials to study lifestyle changes, care management and telehealth technologies to improve diabetes care.

Sarah Garrison, MD

Dr. Sarah Garrison is the Chief of Staff of the James J Peters VA Medical Center, and is the Associate Dean of Veteran's Affairs for the Icahn School of Medicine at Mount Sinai. Dr. Garrison has a long standing interest in primary care, population health, preventive health, and understanding health disparities.

Peter Groeneveld, MD, MS

Dr. Peter Groeneveld is a VA Staff Physician at the Michael J. Crescenz (Philadelphia) VA Medical Center, and he is a core investigator at the VA's Center for Health Equity Research and Promotion (CHERP), a VA Center of Innovation, and he is an Associate Professor at the Perelman School of Medicine, University of Pennsylvania, where he directs Penn's Cardiovascular Outcomes, Quality, and Evaluative Research Center. Dr. Groeneveld's primary research interests are in the outcomes, costs, and societal implications of new medical technologies, with a particular focus on implantable devices.

Linda Humphrey, MD, MPH, MACP

Dr. Linda Humphrey is a staff physician at Portland's Veterans Affairs Medical Center and Professor of Medicine, Public Health and Preventive Medicine and Informatics and Clinical Epidemiology at OHSU. She is also the VA site director for the OHSU and VA preventive medicine residency program. Dr. Humphrey's area of research is in prevention and she has worked for the last 15 years on USPSTF systematic reviews, including breast cancer screening, medications to reduce breast cancer risk, menopausal hormone therapy, novel cardiovascular risk factors, ECG screening and most recently, lung cancer screening. She currently is the site director for a multicenter cardiovascular prevention trial.

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Devan Kasagara, MD, MCR

Dr. Devan Kansagara is the Director of the Evidence-based Synthesis Program at the VA Portland Healthcare System, and is Associate Professor of Medicine and of Medical Informatics and Clinical Epidemiology at Oregon Health Science University. His work, over the last ten years, has focused on synthesizing bodies of evidence and, more recently, on evidence-based health policy and clinical guideline development. He also has an interest in health systems redesign efforts, particularly in care transitions and the patient-centered medical home.

Grace Lin, MD, MAS

Dr. Grace Lin is Assistant Professor of Medicine and Health Policy in the Division of General Internal Medicine and the Philip R. Lee Institute of Health Policy Studies at the University of California, San Francisco. Her research focus is on appropriate utilization of healthcare resources and shared decision-making. Her most recent work is focused on the development of a patient-reported instrument to measure the quality of the decision-making process in patients with heart disease.

Rozalina McCoy, MD, MS

Dr. Rozalina McCoy is an endocrinologist, primary care physician, and health services researcher at the Mayo Clinic in Rochester, MN. The goal of Dr. McCoy's research is to individualize and optimize the care for people with diabetes, particularly in the context of multi-morbidity, by identifying and promoting patient-centered care that balances the benefits, harms, and burdens of treatment. Her recent work has included identifying risk factors for hypoglycemia, including potential overtreatment of high risk individuals.

Brahmajee K. Nallamothu, MD, MPH

Dr. Brahmajee Nallamothu is an interventional cardiologist and cardiovascular outcomes researcher at the University of Michigan in Ann Arbor. He is a nationally-recognized investigator whose work focuses on improving the delivery of specialized cardiovascular procedures, particularly primary PCI in ST-elevation myocardial infarction. Dr. Nallamothu has made important contributions using hospital- and population-level approaches to examine strategies for optimizing door-to-balloon times and the use of reperfusion therapies in STEMI systems of care. He was a member of the Steering and Research & Publications committees of the American College of Cardiology's D2B Alliance. He also has worked closely with the American Heart Associations' Mission: Lifeline program.

Eugene Oddone, MD, MHS

Dr. Eugene Oddone is a core investigator in the Durham, NC VA Center for Health Services Research in Primary Care, a VA Center of Innovation, and Professor of Internal Medicine at Duke University. His research interests have focused on improving chronic disease management in primary care, and supporting behaviors to improve prevention of cardiovascular disease.

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Lisa Rubenstein, MD, MPH

Dr. Lisa Rubenstein retired from VA at the end of April 2017, but was the founding Director of the HSR&D Center of Innovation at VA Greater Los Angeles Healthcare System and a practicing general internist. She led the VA Care Coordination QUERI Program: Improving Patient-Centered Care Coordination for High Risk Veterans in PACT, the Veterans Assessment and Improvement Laboratory (VAIL), a PACT Demonstration Laboratory, and the evaluation of the PACT Intensive Management Project. Dr. Rubenstein received the VA Health Services Research and Development Under Secretary for Health Award in 2000 and the John M Eisenberg award for career achievement in research from the Society of General Internal Medicine in 2016. Dr. Rubenstein is also a Professor of Medicine and Public Health Emeritus at UCLA.

Michael Steinman, MD

Dr. Michael Steinman is a Professor of Medicine in the UCSF Division of Geriatrics and Director of Research Training Programs for the Division. He also is co-chair of the American Geriatrics Society Beers Criteria Update Panel, a widely-used guideline about appropriate prescribing in older adults. His research interests focus on measuring and improving the quality of prescribing for clinically complex older adults, and on evaluating outcomes of medication use in this population.

Adam Tremblay, MD

Dr. Adam S. Tremblay is the Director of Primary Care and an Associate Chief of Medicine at the VA Ann Arbor Healthcare System and Clinical Assistant Professor and Associate Residency Program Director at the University of Michigan. Dr. Tremblay is responsible for overseeing the daily operations of the Primary Care Clinics at the VA Ann Arbor Healthcare System. In this role, he directs patient care and focuses on resident education, curriculum development, primary care performance improvement, and clinical operations. His areas of academic interest include the Patient Centered Medical Home and Ambulatory Internal Medicine resident education.

Sandeep Vijan, MD, MS

Dr. Sandeep Vijan is the Medical Director of Quality Analytics at the University of Michigan. Dr. Vijan directs a team of data managers, abstractors, and analysts who create quality reports, both mandated (e.g., MIPS, core measures, patient experience) and locally initiated measures for quality reporting and improvement. He is an internist and health services researcher with a primary interest in using statistical modeling to improve our delivery and measure personalized, high quality healthcare.

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Why is de-intensification important?

There is an increasing consensus that overtreatment and overtesting exposes some patients to services they may not need or prefer or that may even harm them; the Choosing Wisely campaign is the most obvious manifestation of this consensus. However, the majority of recommendations, from Choosing Wisely and others, focus on reducing overuse by avoiding one-time diagnostic procedures or treatment at the beginning of a discrete episode of care. They do not focus on stopping or scaling back the intensity or frequency of medical interventions that are currently part of a patient's ongoing management. We believe that *de-intensification of routine medical services* is the next frontier for improving care quality.

De-intensification: Decreasing the intensity or frequency of medical interventions that are currently part of a patient's routine ongoing management (e.g., not acute care, not an initial work-up, not pre-operative care).

What are the goals of this project?

The current research project, funded by the Department of Veterans Affairs, will identify and validate clinical indications and measures for de-intensification and will develop multi-component strategies to disseminate and implement de-intensification measures.

The specific goal of the national, expert panel is to review and validate indications for de-intensification of routine medical services for patients with diabetes and/or cardiovascular disease.

How were the indications for de-intensification identified and the proposed de-intensification measures developed for review by the expert panel?

The following steps map to one or more of the sections described under each measure. (Hover your mouse over 'Step' to see which sections.)

Step 1: Environmental scan

Project staff reviewed current, high-quality recommendations, guidelines, and measures to identify those that were primary-care related, routine-based, and de-intensification focused. The

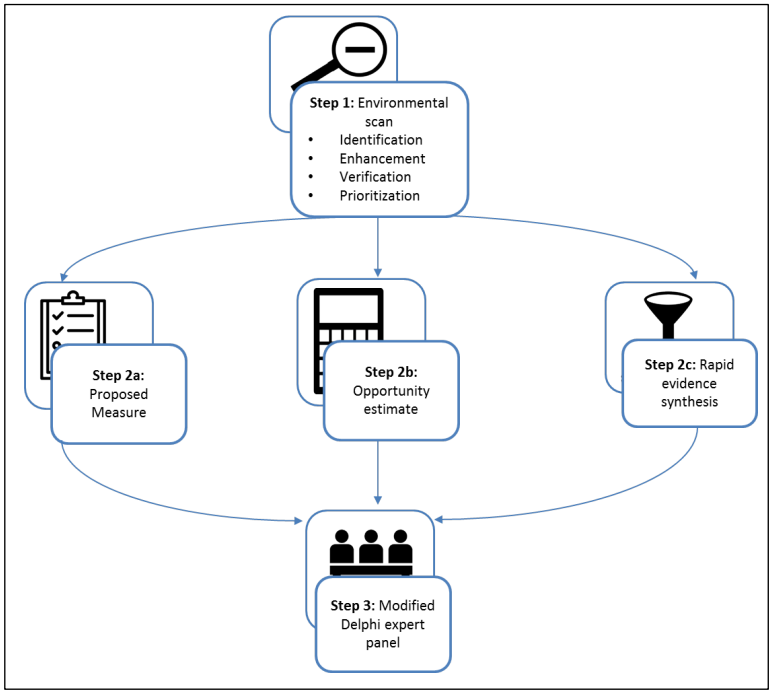

Figure 1: Steps to prepare for the expert panel

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list was enhanced by seeking nominations from our Advisory Council and their constituents.

Figure 2 provides details of Step 1's verification and prioritization process.

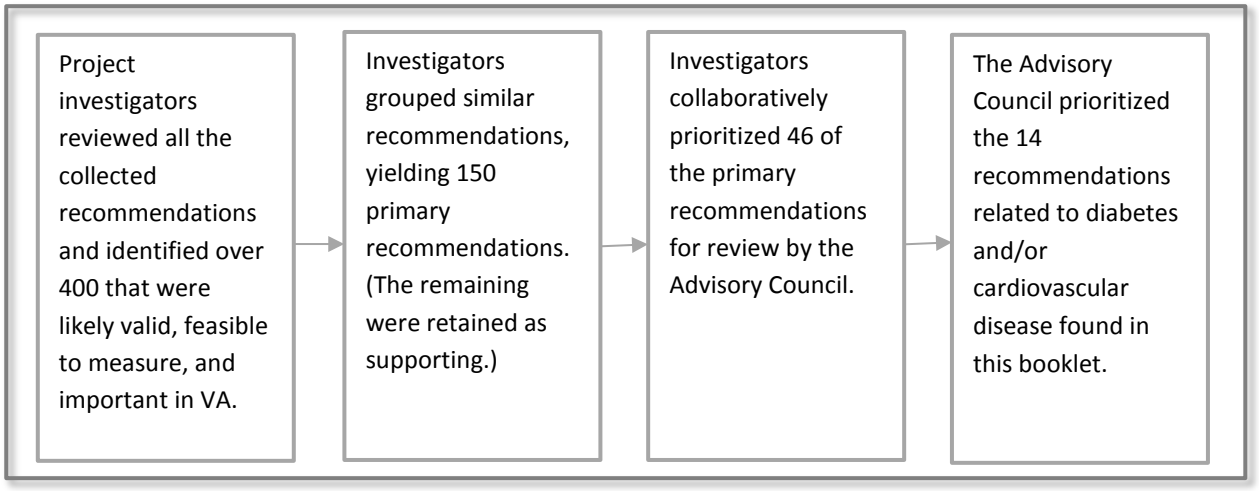


Figure 2: Environmental scan process: verification and prioritization

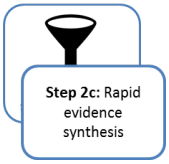
Step 2a: Proposed measure

Recommendations often do not include all the required components of a typical *measure* (e.g., denominator, numerator, exclusions); therefore, a proposed de-intensification measure was drafted by the principal investigators of the project. The draft included a population of interest (denominator) and de-intensification action (numerator), including a time period. You will have an opportunity to share your viewpoint on each measure.

Step 2b: Opportunity estimate

An opportunity estimate is a high-level prevalence estimate of potential opportunities for de-intensification. An estimate, for VA, has been included in the booklet for each of the proposed de-intensification measures. All opportunity estimates include active VA patients only (active is defined as having at least 1 visit in the year prior to the study year (any type) and at least 2 primary care visits during the combined period of the study year and year prior) and examined recent data (2013-2016). Note: Estimates for outside VA are included only if they are available from the literature.

Step 2c: Rapid evidence synthesis



A rapid evidence synthesis (RES) is a streamlined approach to synthesizing evidence in a timely manner to answer specific questions about a clinical problem. A RES was conducted by the Pacific Northwest Evidence-based Practice Center (EPC) in Portland, Oregon.

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De-intensification recommendations were selected for RES if they met any of the following criteria:

1. No related guideline or recent evidence synthesis/review currently existed; or
2. There appeared to be some disagreement in the primary/supporting recommendations or guidelines; or
3. Uncertainty or questions remained even with an existing guideline (e.g., some anecdotal evidence that providers weren't following the recommendation or didn't believe the recommendation).

Step 3: Modified Delphi expert panel

Two modified Delphi expert panels will be convened. The first panel, which you are a part of, focuses on diabetes and cardiovascular disease. A second panel, planned for later this year, will focus on cancer screening and surveillance, geriatric and mental health conditions. Each panel will use a modified Delphi process in order to prioritize the proposed measures of de-intensification.

As a member of the panel, you will rate each measure twice— after staff have revised the measures based on the discussion during virtual Meeting #1 and then again during virtual Meeting #2.
See page 5 for dates of all required tasks, including pre-rating and re-rating.

What criteria will the expert panel use to prioritize the proposed measures?

The expert panel is tasked with rating each presented de-intensification measure based on validity, improvement opportunity, and feasibility of implementation.

Ratings will be completed using the following 9 point scale, using validity as an exemplar:

Rating	Meaning
1-3	The indicator is not a valid criterion for evaluating quality
4-6	The indicator is an uncertain or equivocal criterion for evaluating quality.
7-9	The indicator is clearly a valid criterion for evaluating quality

On the next page (page 12) is a description of each criterion and components of the measure to consider during the rating process. When evaluating a measure, we ask you to utilize any presented information in this booklet, as well as your professional knowledge, to help assess the validity and improvement opportunity. There is no information presented to help you assess feasibility of implementation; this will require you to reflect on your prior experiences and knowledge of the topic.

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Rating Criteria	When should a measure receive a high rating?	Other Considerations	Related sections in the booklet
1. Validity	A measure is rated highly on validity if it is based on high quality scientific evidence that suggests that performance on the measure is likely to improve patient outcomes and is consistent with high quality care. A quality measure is considered valid if one or more of the following are true: 1. Evidence exists that de-intensification is likely to improve patient outcomes 2. Evidence exists that intense testing/treatment could cause harm in some patients 3. There is absence of evidence of benefit of continued/repeated intense treatment or testing 4. De-intensification is consistent with high quality care; providers who have higher rates of de-intensification would be considered higher quality providers	The source of the evidence should be clearly defined and reputable, such as a systematic review, clinical guideline, or high quality studies; and the evidence should be of high quality, quantity, and consistency. There should be specific links between the clinical recommendation in the evidence and the performance measure. The measure should have a numerator with a clearly defined, specific clinical action or clinical service that is supported by evidence. The time period of the clinical action should be specified (e.g., annually, within 6 weeks of diagnosis) and supported by the evidence whenever possible. The time interval presented in the numerator should be realistic and not promote overuse or underuse. The denominator should clearly define the eligible patient population and contain appropriate exclusions to make the eligible population specific to the action defined in the numerator.	• Proposed measure • Recommendation and supporting recommendations • Rapid evidence synthesis summary • Evidence base (if no RES was completed)
2. Improvement opportunity	A measure is rated highly on improvement opportunity if: 1. It is likely to affect a large number of patients or have a significant impact on a smaller number of patients 2. The current rate of de-intensification is low or likely to be low	The numerator should include a clinically significant population, and the denominator should not have unnecessary exclusions (which could minimize the potential scope and/or impact of the measure). *Please consider opportunities in VA (data presented) and outside VA (data not presented except when available in the literature) when you are rating	• Potential opportunity for improvement
3. Feasibility of implementation	A measure is rated highly on feasibility of implementation if: 1. De-intensification of this treatment/testing is under the control of the health professional or health organization	It is possible to imagine an intervention (e.g., clinical decision support, detailing, patient education or empowerment, pay for performance, etc.) that could promote de-intensification *Do not consider feasibility of measurement	None, please use your knowledge in this area in order to evaluate whether this measure would be feasible to implement

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What happens after the expert panel?

Following the two virtual expert panel meetings, project staff will determine what data source(s) (e.g., automated data, manual medical record abstraction, other) will be required for each measure that was rated highly. The measure specification (i.e., numerator, denominator, exclusions) will be refined and the measure will be generated. Then, the prevalence of de-intensification in VA will be assessed. The reliability of the measure, variation in de-intensification rates across sites, and predictors of de-intensification will also be examined.

In addition, project staff will be conducting collaborative decision-making sessions with patients and providers in order to identify gaps in understanding and potential barriers to deploying de-intensification measures and recommendations. Findings from all the work in this project, including from the expert panel, will be synthesized into practical intervention strategies.

What should you do next?

On the following pages [14-151], you will find the proposed de-intensification measures and information pertaining to the measures, including any rapid evidence synthesis reports [pages 63-151]. (*Note: If you choose to print the documents, we recommend that you only print pages 1-62.*)

At this time, we are asking you to review all of the provided information and answer the questions that follow each measure. (Example: Do you agree that the topic/measure is valid and that there is an opportunity for improvement?) Please just type your answers directly into the fields provided. **Then, save the pdf and e-mail it to Mandi.klamerus@va.gov by May 8th, 2017.** The information you provide will help guide the discussion during Meeting #1.

Note: You should also have this pdf, with your entries, open on your computer during the virtual meetings!

We thank you for your participation on the panel and look forward to discussing the proposed de-intensification measures with you over the next few weeks!

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Diabetes Measures

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Measure 1 – De-intensification of hypoglycemic agents other than metformin

Proposed de-intensification measure

Action: Stop or decrease hypoglycemic agents other than metformin within 6 months of a low A1c

Population: Older adults (>65 years old) with an **A1c <7**

Definitions

None

Existing recommendation that motivated the proposed de-intensification measure

Choosing Wisely- Glycemic Control: "Avoid using medications other than metformin to achieve hemoglobin A1c <7.5% in most older adults; moderate control is generally better."

- Source: Choosing Wisely
- Steward: American Geriatrics Society (AGS)
- Last Update: April 23, 2015

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields below each question.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

    a. In particular, should the definition of low A1c be modified?

    b. Is the definition of older adults correct?

    c. Should any other exclusions be added?

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Potential opportunity for improvement

In VA (estimate)

- [FY2015] **10%** (125,493/1,293,437) of patients **older than 65 with an A1c<7.0** were prescribed a diabetes medication other than metformin.
- [FY2015] **14%** (194,143/1,434,203) of patients **older than 65 with an A1c<7.5** were prescribed a diabetes medication other than metformin.
- Note: By comparison, the corresponding percentages are 7% and 10% **for the entire population (i.e. all ages).**

The following is extracted from: Sussman et al. Rates of De-intensification of Blood Pressure and Glycemic Medication Treatment Based on Levels of Control and Life Expectancy in Older Patients with Diabetes Mellitus. JAMA Int Med. 2015;175(12):1942-9.

- [2012] Participants (**older than 70 year**s) were eligible for de-intensification of treatment if they had a low hemoglobin A1c (HbA1c) level. Those with a:
  - Moderately low HbA1c, defined as **6.0% to 6.4%** (N=23,769), had a:
    - **20.9%** (20.3%-21.4%) chance of having glucose-lowering medicine de-intensified.
  - Very low HbA1c, defined as **less than 6.0%** (N=12,917), had a:
    - **27.0%** (26.2%-27.8%) chance of having glucose-lowering medicine de-intensified.

Outside VA

The following is extracted from: Lipska KJ, Ross JS, Miao Y, et al. Potential overtreatment of diabetes mellitus in older adults with tight glycemic control. JAMA Internal Medicine. 2015; 175(3): 356-62.

- [2001-2010] Among older adults (**≥65 years**) with diabetes who completed the National Health and Nutrition Examination Survey:
  - **61.5%** (95% CI, 57.5%-65.3%) had an **HbA_{1c} level of less than 7%** (3.8 million; 95% CI, 3.4-4.2). Of participants with an HbA1c less than 7%:
    - **54.9%** were treated with either insulin or sulfonylureas
    - **4.0%** were treated with both insulin and sulfonylureas
  - **41.9%** (95% CI, 37.9%-46.1%) had an **HbA_{1c} level of less than 6.5%** (2.6 million; 95% CI, 2.2-2.9). Of participants with an HbA_{1c} less than 6.5%:
    - **43.9%** of those relatively healthy; **52.3%** of those with complex, intermediate health; and **56.3%** of those with very complex/poor health were treated with insulin or sulfonylureas

Rapid evidence synthesis summary

1. Intensive Glycemic Control in Older Adults with Type 2 Diabetes Mellitus

(Review the entire rapid evidence synthesis report.)

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Why is intensive glycemic control in the elderly an issue?

There is uncertainty about ideal target glycated hemoglobin (HbA1c) levels in patients with type 2 diabetes mellitus, and clinical guidelines have discordant recommendations regarding optimal HbA1c thresholds. Potential benefits of more intensive glycemic control include reduced risk of macro- and microvascular complications; however, overly intensive glycemic control is also associated with increased risk of hypoglycemia. The benefits and harms of intensive glycemic control in older patients and/or those with multiple comorbidities and limited life expectancy is particularly uncertain. This rapid evidence review synthesizes the evidence on benefits and harms of continuation of intense glycemic control in people with diabetes, as well as the effect of de-intensification of glycemic control.

What is the evidence on evidence of potential benefits and harm from continued intense glycemic control in people with diabetes?

- There was no difference between intensive and standard glycemic control on all-cause or cardiovascular mortality, based on two systematic reviews and most individual trials.
    - One trial, ACCORD, found significantly increased incidence of all-cause mortality with intensive glycemic control (HbA1c <6.5%) in those under age 65 years (accounting for 66% of the study population) but not in those over age 65
    - ACCORD found no difference in risk of all-cause mortality between intensive and standard glycemic control when patients were stratified according to diabetes duration or baseline HbA1c.
- Intensive glycemic control was associated with a reduced risk of non-fatal MI, based on systematic reviews and the ACCORD trial.
- Intensive glycemic control increased risk of hypoglycemia ranging from RR 1.85 to 2.95; based on individual trials (HbA1c <6.4 to <8.4%) and systematic reviews.

What is the evidence on de-intensification?

There was no direct evidence on the benefits and harms of de-intensification of glycemic control.

What are the implications of our findings?

There was little evidence of benefit with intensive glycemic control, apart from HbA1c lowering and incidence of non-fatal MI, with increased risk of hypoglycemia.

Observational evidence suggests that the effects of intensive HbA1c can take over a decade to manifest; this may have implications for applying evidence on potential benefits of intensive glycemic control in persons with limited life expectancy due to older age or multiple or serious comorbidities.

2. Metformin Use in Older Adults with Type 2 Diabetes Mellitus

(Review the entire rapid evidence synthesis report.)

Why is diabetes treatment with metformin monotherapy in the elderly important?

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Metformin is recommended by the American Diabetes Association and other organizations as the first-line pharmacological therapy for treatment of type 2 diabetes mellitus. When metformin monotherapy does not result in adequate glucose control, additional glucose-lowering drugs can be added to metformin. However, this combination therapy can increase the risk of hypoglycemia, which can be especially devastating in older and frail patients. This rapid evidence review synthesizes the evidence on benefits and harms of intensification of glucose-lowering therapy in persons who do not achieve adequate control on metformin monotherapy, as well as on de-intensification of glucose-lowering therapy in persons on combination therapy that includes metformin.

What is the evidence on benefits and harms of using metformin versus metformin in combination with another noninsulin glucose-lowering agent to achieve glycemic control in older adults with type 2 diabetes?

- There was no clear difference between combination therapy with metformin and metformin monotherapy in risk of all-cause or cardiovascular mortality, or cardiovascular events, based on a large systematic review of primarily short-term (<1 year) randomized trials, but most estimates were imprecise.
- Longer-term evidence from a large observational study suggests decreased risk of all-cause mortality and cardiovascular events with certain combination therapies when compared with metformin monotherapy; findings are susceptible to residual confounding.
- Combination therapy with metformin was associated with modestly larger reductions in HbA1c compared with metformin monotherapy, based on a systematic review of short-term randomized trials and a large observational study.
- Combination therapy with metformin was associated with increased risk of mild/moderate hypoglycemia compared with metformin monotherapy in a systematic review of randomized trials, but there were too few cases of severe hypoglycemia with either combination therapy or monotherapy groups to determine risks.
- A large observational study found combination therapy consistently increased risk of severe hypoglycemia compared with metformin monotherapy.

What is the evidence on de-intensification?

There is no direct evidence on effects of de-intensification of non-metformin glucose-lowering medications in older patients on combination therapy including metformin for type 2 diabetes, versus continued combination therapy.

What are the implications of our findings?

Combination therapy with metformin was more effective than metformin monotherapy at lowering HbA1c, but combination therapy was associated with increased risk of hypoglycemia. There were no clear effects on clinical outcomes based on randomized trials, but estimates were imprecise. Evidence on how benefits and harms of combination therapy may differ in older adults is lacking.

Additional supporting recommendations

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Source	Recommendations
American Geriatrics Society, including BEERS Criteria	1. There is potential harm in lowering (Target goal) HbA1c to less than **6.5%** in older adults with type 2 DM. 2. Target goal for glycosylated hemoglobin (HbA1c) in older adults generally should be **7.5% to 8%.** HbA1c between **7% and 7.5%** may be appropriate if it can be safely achieved in healthy older adults with few comorbidities and good functional status. 3. Higher HbA1c targets **(8–9%)** are appropriate for older adults with multiple comorbidities, poor health, and limited life expectancy. 4. Avoid use of long-duration sulfonylureas (Chlorpropamide, Glyburide).
American Diabetes Association	1. Providers might reasonably suggest more stringent A1C goals (such as **<6.5%** [48 mmol/mol]) for selected individual patients if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate patients might include those with short duration of diabetes, type 2 diabetes treated with lifestyle or metformin only, long life expectancy, or no significant cardiovascular disease. 2. Less stringent A1C goals (such as **<8%** [64 mmol/mol]) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. 3. Glycemic goals for some older adults might reasonably be relaxed, using individual criteria, but hyperglycemia leading to symptoms or risk of acute hyperglycemic complications should be avoided in all patients. 4. Intensive glucose control is not advised for the improvement of poor cognitive function in hyperglycemic individuals with type 2 diabetes. 5. In individuals with poor cognitive function or severe hypoglycemia, glycemic therapy should be tailored to avoid significant hypoglycemia.
American College of Cardiology/ American Heart Association	1. A goal HbA1c between **7% and 9%** is reasonable for certain patients according to age, history of hypoglycemia, presence of microvascular or macrovascular complications, or presence of coexisting medical conditions. 2. For selected individual patients, such as those with a short duration of diabetes mellitus and a long life expectancy, a goal hemoglobin A1c (HbA1c) of **7%** or less is reasonable.

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	3. Less stringent HbA1c goals may be considered for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, or extensive comorbidities, or those in whom the goal is difficult to attain despite intensive therapeutic interventions.

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Measure 2 – De-intensification of home glucose testing

Proposed de-intensification measure

Action: Decrease the number of prescribed glucose test strips to 10 or fewer per month OR document patient preference for more frequent testing (i.e., more than 10 test strips per month) within 6 months of the last prescription issue date

Population: Patients with Type 2 diabetes not on insulin

Definitions

None

Existing recommendation that motivated the proposed de-intensification measure

Choosing Wisely - Glucose Testing: "Don't recommend daily home finger glucose testing in patients with Type 2 diabetes mellitus not using insulin."

- Source: Choosing Wisely
- Steward: Society of General Internal Medicine (SGIM)
- Last Update: September 12, 2013

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

    a. What is the usual number of test strips per month that should be decreased? (Note that in the VA the usual limit is 50 per 3 months for those not on insulin)

3. Do you agree with the population, including exclusions?

Potential opportunity for improvement

In VA (estimate)

- [FY2015] **6%** (38,501/669,978) of patients with diabetes, who were not on insulin, were prescribed more than **200** glucose test strips (in a one year period.)

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- [FY2015] **19%** (127,464/669,978) of patients with diabetes, who were not on insulin, were prescribed more than **120** glucose test strips (in a one year period.)

Outside VA

The following is extracted from: Johnson et al. Differences in diabetes self-care activities by race/ethnicity and insulin use. Diabetes Educ. 2014; 40(6): 767-77.

- [2011] Outlined below is the percentage of adults with diabetes (by race/ethnicity), not on insulin, reporting daily glucose monitoring. These percentages were obtained using data from the 2011 Behavioral Risk Factor Surveillance System (BRFSS) survey.
    - 53.5% [white]
    - 57.7% [black]
    - 42.5% [Asian/Native Hawaiian or other Pacific Islander]
    - 66.3% [American Indian/Alaskan Native]
    - 50.3% [Hispanic]

Rapid evidence synthesis summary (Review the entire rapid evidence synthesis report.)

Why is self-monitoring of blood glucose in patients not using insulin an issue?

- Self-Monitoring of Blood Glucose (SMBG) involves testing of blood sugar levels to monitor and manage diabetes mellitus. There are questions about whether SMBG is effective among people with type 2 diabetes mellitus who are not using insulin.
- SMBG requires resources (testing supplies, education, clinician visit time, and patient self-management activities), knowledge about how to conduct the testing, the ability to interpret the results, and the capacity to make changes based on these results.
- SMBG is currently performed by many people with type 2 diabetes who are not on insulin.

What is the evidence on benefits and harms of SMBG for people with Type 2 diabetes mellitus not using insulin?

- Systematic reviews summarizing randomized controlled trials of the effectiveness of SMBG (SMBG compared to no SMBG) have consistently found that routine SMBG results in small reductions (~ 0.3) in HbA1c when compared with no SMBG.
- The difference is greater (-0.54) for patients who have had a diabetes diagnosis for ≤ 1 year.
    - A 0.5 change in HbA1c is the minimum considered to be clinically meaningful.
- Studies have also reported either small or no differences in other physical outcomes (e.g., body mass index).
- There is insufficient evidence to determine the effects of SMBG on clinical outcomes such as mortality or cardiovascular morbidity.
- Studies that compare different frequencies and approaches to SMBG for these patients have been published or are due to be published soon. However, the interventions (i.e., frequency of SMBG and the interventions that accompany SMBG) differ across the studies, making it difficult to draw conclusions about comparative benefits or harms.

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What is the evidence on de-intensification?

No studies directly evaluated the impact of stopping SMBG or reducing its frequency among persons with type 2 diabetes mellitus performing SMBG.

What are the implications of our findings?

- Current evidence concludes SMBG has limited benefits (small reductions in HbA1c) for patients with type 2 diabetes who are not using insulin. This supports guideline recommendations against routine, frequent SMBG for these patients.
- Slightly larger reductions in HbA1c for patients who have had diabetes for less than a year suggest that SMBG might be more useful for subgroups of patients and providers using SMBG to inform changes in treatments and behaviors.

Additional supporting recommendations

Source	Recommendations
National Institute for Health Care and Excellence	1. Do not routinely offer self-monitoring of blood glucose levels for adults with type 2 diabetes unless the person is on insulin, there is evidence of hypoglycaemic episodes, the person is on oral medication that may increase their risk of hypoglycaemia while driving or operating machinery, or the person is pregnant, or is planning to become pregnant.
Choosing Wisely. American Association of Clinical Endocrinologists and the Endocrine Society	1. Avoid routine multiple daily self-glucose monitoring in adults with stable type 2 diabetes on agents that do not cause hypoglycemia.

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Measure 3 – De-intensification of antihypertensive medications

Proposed de-intensification measure

Action: Decrease the dose or number of antihypertensive medications within six months of the last prescription issue date

Population: Older adults with Type 2 diabetes on hypertension therapy who have a SBP<130 or DBP<70

Definitions

SBP: systolic blood pressure; DBP: diastolic blood pressure; Older adults: >65y; Dose: High, Medium, Low

Existing recommendation that motivated the proposed de-intensification measure

ADA Guideline Recommendation - Blood pressure control: "In older adults with Type 2 diabetes, pharmacological therapy to achieve treatment goals of <130/70 mmHg is not recommended. Treating to systolic blood pressure <130 has not been shown to improve cardiovascular outcomes and treating to diastolic blood pressure <70 has been associated with higher mortality."

- Source and Steward: American Diabetes Association (ADA)
- Last Update: January 1, 2016
- Level of Evidence**:** Category C (supportive evidence from poorly controlled or uncontrolled studies or conflicting evidence with the weight of evidence supporting the recommendation)

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

    a. Are there different blood pressure thresholds that would improve the measure?

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Potential opportunity for improvement

In VA

The following is extracted from: Sussman et al. Rates of De-intensification of Blood Pressure and Glycemic Medication Treatment Based on Levels of Control and Life Expectancy in Older Patients with Diabetes Mellitus. JAMA Int Med. 2015;175(12):1942-9.

- [2012] Participants (older than 70 years) were eligible for de-intensification of treatment if they had low blood pressure. Those with a:
  - Moderately low BP, defined as systolic BP of 120 to 129 mmHg or diastolic BP (DBP) less than 65 mmHg (N=25,955), had a:
    - 16.0% (15.5%-16.4%) chance of having a BP medication de-intensified
  - Very low BP, defined as less than 120/65 mmHg (N=81,226), had a:
    - 18.8% (18.5%-19.1%) chance of having a BP medication de-intensified

Outside VA

The following is extracted from: Min L et al. Net harm of overly-aggressive blood pressure (BP) control on cardiovascular (CV) and fall injury events in older Americans. Presentation at 2015 American Geriatrics Society Annual Meeting.

- [2008, 2010] Among 5,518 participants in the biennial Health and Retirement Study (HRS), age >=65, with self-reported hypertension and taking BP medications, who had BP measured by an enhanced HRS examine:
  - 18% were found to be overtreated (SBP<120).

Rapid evidence synthesis summary (Review the entire rapid evidence synthesis report.)

Why is de-intensification of antihypertensive medications in patients with type 2 diabetes mellitus important?

The 2010 Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial changed the focus of clinical practice guidelines for blood pressure (BP) management in patients with type 2 diabetes mellitus (DM) from intense to less intense targets, with many (including guidelines from the Department of Veterans Affairs/Department of Defense) recommending lowering of the BP target in diabetics from <130/80 to <140/85 or 140/90. However, de-intensification of antihypertensive therapy is uncommon even among those with BP well below target levels. This rapid evidence synthesis summarizes the evidence of benefits and harms for more versus less intensive BP control and of de-intensification of antihypertensive therapy.

What is the evidence on more intensive versus less intensive blood pressure control?

ACCORD provides the most direct evidence that is applicable to currently recommended BP targets on the benefits and harms of more intensive versus less intensive blood pressure control in people with diabetes. This rapid evidence review also evaluated three recent systematic reviews that included ACCORD and evaluated effects of intensive BP lowering.

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- ACCORD found that, compared to a systolic blood pressure (SBP) target of <140 mm Hg, a SBP target of <120 mm Hg was not associated with a statistically significant reduction in the rate of the composite outcome of fatal and nonfatal major cardiovascular events. Although the lower SBP target was associated with decreased risk of stroke, this benefit was offset by an increased risk of serious adverse events.
- A systematic review of more intensive versus less intensive BP targets that included ACCORD found more intensive BP targets associated with decreased risk of major cardiovascular events, but findings are difficult to interpret since the BP targets varied from trial to trial.
- Two other reviews that evaluated the effectiveness of antihypertensive treatment trials in persons with lower mean baseline BP and those that achieved lower BPs found that achieving SBP <130 mm Hg was associated with decreased risk of stroke, but they found no clear effects on major cardiovascular events or cardiovascular mortality.
- Neither ACCORD nor the systematic reviews evaluated effects of more versus less intensive BP lowering on quality of life, or how effects of intensive antihypertensive management varied in subgroups.

What is the evidence on de-intensification?

There is no direct evidence on effects of de-intensification of BP management in people with DM.

What are the implications of our findings?

Evidence from a large randomized trial supports a less intense SBP target (<140 mm Hg) in persons with DM. Studies did not address whether outcomes vary by differences in underlying risk of patient populations.

Additional supporting recommendations

Source	Recommendations
American College of Physicians and the American Academy of Family Physicians	1. ACP and AAFP recommend that clinicians initiate treatment in adults aged 60 years or older with systolic blood pressure persistently at or above 150 mm Hg to achieve a target systolic blood pressure of less than 150 mm Hg to reduce the risk for mortality, stroke, and cardiac events. ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on periodic discussion of the benefits and harms of specific blood pressure targets with the patient. 2. ACP and AAFP recommend that clinicians consider initiating or intensifying pharmacologic treatment in adults aged 60 years or older with a history of stroke or transient ischemic attack to achieve a target systolic blood pressure of less than 140 mm Hg to reduce the risk for recurrent stroke. ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on periodic discussion of the benefits and harms of specific blood pressure targets

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	with the patient. 3. ACP and AAFP recommend that clinicians consider initiating or intensifying pharmacologic treatment in some adults aged 60 years or older at high cardiovascular risk, based on individualized assessment, to achieve a target systolic blood pressure of less than 140 mm Hg to reduce the risk for stroke or cardiac events. ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on periodic discussion of the benefits and harms of specific blood pressure targets with the patient.

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Cardiovascular Disease Measures

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Measure 4 – De-intensification of non-statin adjunct therapy

Proposed de-intensification measure

Action: Stop the non-statin medications within 6 months of the last prescription issue date of niacin or fibrate

Population: All patients on combination lipid lowering therapy (i.e., stain/fibrate or statin/niacin); exclude men with diabetes and HDL<35 mg/dL

Definitions

HDL: high-density lipoprotein

Existing recommendation that motivated the proposed de-intensification measure

ADA Guideline Recommendation - De-intensification of non-statin adjunct therapy:
"Combination therapy (statin/fibrate) has not been shown to improve atherosclerotic cardiovascular disease outcomes and is generally not recommended. However, therapy with statin and fenofibrate may be considered for men with both triglyceride level >=204 mg/dL (2.3 mmol/L) and HDL cholesterol level <=34 mg/dL (0.9 mmol/L).

Combination therapy (statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone and may increase the risk of stroke and is not generally recommended."

- Source and Steward: American Diabetes Association (ADA)
- Last Update: January 1, 2016
- Level of Evidence:
  - Statin/Fibrate: Category B (supportive evidence from well-conducted cohort studies or supportive evidence from a well-conducted case-control study)
  - Statin/Niacin: Category A (clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, compelling nonexperimental evidence, or supportive evidence from well-conducted randomized controlled trials that are adequately powered)

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement? Question?

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2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

    a. Should the population be all patients? Should we exclude men with diabetes and low HDL?

Potential opportunity for improvement

In VA (estimate)

- [FY2015] 47,833 patients were on a statin and fibrate OR a statin and niacin. (Patients on a statin and fibrate, with a HDL<35, were excluded.)

Outside VA

The following is extracted from: Bittner et al. Trends in the Use of Nonstatin Lipid-Lowering Therapy Among Patients With Coronary Heart Disease: A Retrospective Cohort Study in the Medicare Population 2007 to 2011. J Am Coll Cardiol. 2015; 66(17): 1864-72.

- [2011] In a retrospective cohort study of Medicare Beneficiaries, with CHD, on a statin:
    - Approximately 5% were also on fibrate.
    - Approximately 3% were also on niacin.

Rapid evidence synthesis summary (Review the entire rapid evidence synthesis report.)

Why is de-intensification of statin combination therapy in adults at risk of cardiovascular disease important?

- Statin monotherapy is effective at reducing risk of cardiovascular events and mortality for primary and secondary prevention. The addition of fibrates or niacin to statin therapy may further lower lipid levels and result in additional reductions in risk of cardiovascular outcomes, which may be particularly relevant for persons at high cardiovascular risk or who cannot achieve adequate lipid lowering with a statin alone.
- This rapid evidence review summarizes the evidence on benefits and harms of combination therapy with a statin plus a fibrate or niacin versus a statin alone, and on de-intensification of combination therapy to statin monotherapy.

What is the evidence on potential benefits and harms from statin combination therapy with a fibrate or niacin versus statin monotherapy in adults at risk of cardiovascular disease?

- Five trials of statin combination therapy with a fibrate (three trials) or niacin (two trials) found no significant reductions in all-cause mortality or cardiovascular outcomes with combination

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therapy versus statin monotherapy.

- Statin and fibrate combination therapy was associated with increased risk of renal events versus statin monotherapy, though evidence was imprecise and limited to two trials.
- Statin and niacin combination therapy was associated with an increased risk of new-onset diabetes versus statin monotherapy, and a non-significant increase in risk of ischemic stroke (three trials).

What is the evidence on benefits and harms of de-intensification of statin combination therapy with a fibrate or niacin?

No trial evaluated benefits and harms of de intensification of statin combination therapy.

What are the implications of our findings?

Statin combination therapy with a fibrate or niacin was not associated with reduced risk of mortality or cardiovascular outcomes versus statin monotherapy, but was associated with increased risk of adverse events including renal dysfunction (fibrates) and incident diabetes (niacin).

Additional supporting recommendations

Source	Recommendations
National Institute for Health and Care Excellence	1. Do not offer the combination of a bile acid sequestrant (anion exchange resin), fibrate, nicotinic acid or omega-3 fatty acid compound with a statin for the primary or secondary prevention of CVD. 2. Do not routinely offer fibrates for the prevention of CVD to any of the following: people who are being treated for primary prevention; people who are being treated for secondary prevention; people with CKD; people with type 1 diabetes; people with type 2 diabetes. 3. Do not offer nicotinic acid (niacin) for the prevention of CVD to any of the following: people who are being treated for primary prevention; people who are being treated for secondary prevention; people with CKD; people with type 1 diabetes; people with type 2 diabetes
American College of Cardiology/ American Heart Association	1. Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis.

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Measure 5 – De-intensification of lipid-lowering medications

Proposed de-intensification measure 1

Action 1: Stop lipid lowering therapy within 6 months of the last prescription issue date

Population 1: Patients who are on lipid lowering therapy with life expectancy <5 years

Proposed de-intensification measure 2

Action 2: Stop lipid lowering therapy within 6 months of the last prescription issue date

Population 2: Patients who are on lipid lowering therapy with life expectancy <5 years due to non-cardiovascular disease

Definitions

None

Existing recommendation that motivated the proposed de-intensification measure

Choosing Wisely - De-intensification of lipid-lowering medications: "Don't routinely prescribe lipid-lowering medications in individuals with a limited life expectancy."

- Source: Choosing Wisely
- Steward: AMDA - The Society for Post-Acute and Long-Term Care Medicine
- Last Update: September 4, 2013

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

    a. How should life expectancy be defined?

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b. Should the measure be limited only to those whose life-expectancy is limited by non-cardiovascular disease (as in proposed measure 2)?

Potential opportunity for improvement

In VA (estimate)

- [FY2015] 49% (125,684/254,985) of patients with a limited life expectancy filled a prescription for a lipid lowering drug.
- **Limited life expectancy** was defined as 60% or below cumulative survival based on age and comorbidity status, or with a note in the medical record of less than 5 year life expectancy, or with an indication of metastatic carcinoma (as coded in Charlson comorbidity index) at any age.

Outside VA

The following is extracted from: Bayliss et al. Statin prescribing patterns in a cohort of cancer patients with poor prognosis. J Palliat Med. 2013; 16(4): 412-8.

- [2001-2008] In a retrospective cohort analysis of 539 members of Kaiser Permanente Colorado who were receiving statins at diagnosis of a cancer with 0% to 25% predicted 5-year survival:
    - 59% had a statin refill after their diagnosis.

The following is extracted from: Poudel et al. Use of Preventive Medication in Patients With Limited Life Expectancy: A Systematic Review. J Pain Symptom Manage. 2017 Feb 9.

- [1995-2015] A recent systematic review, which examined the use of preventive medication in patients with reduced life expectancy, found that "lipid-lowering medications, especially the statins, were frequently prescribed preventive medications."

Evidence-base

Rationale

The following information is extracted directly and verbatim from Choosing Wisely.

There is no evidence that hypercholesterolemia, or low HDL-C, is an important risk factor for all-cause mortality, coronary heart disease mortality, hospitalization for myocardial infarction or unstable angina in persons older than 70 years. In fact, studies show that elderly patients with the lowest cholesterol have the highest mortality after adjusting other risk factors. In addition, a less favorable risk-benefit ratio may be seen for patients older than 85, where benefits may be more diminished and risks from statin drugs more increased (cognitive impairment, falls, neuropathy and muscle damage).

Citation(s) provided for the evidence

Dalleur O, Spinewine A, Henrard S, Losseau C, Speybroeck N, Boland B. Inappropriate prescribing and related hospital admissions in frail older persons according to the STOPP and START criteria. Drugs

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Aging. 2012 Oct;29(10):829-37.

Krumholz HM, Seeman TE, Merrill SS, Mendes de Leon CF, Vaccarino V, Silverman DI, Tsukahara R, Ostfeld, AM, Berman LF. Lack of association between cholesterol and coronary heart disease mortality and morbidity and all-cause morality in persons older than 70 years. JAMA. 1994 Nov 2;272(17):1335-40.

Maraldi C, Lattanzio F, Onder G, Gallerani M, Bustacchini S, De Tommaso G, Volpato S. Variability in the prescription of cardiovascular medications in older patients: correlates and potential explanations. Drugs Aging. 2009 Dec;26 Suppl 1:41-51

Schatz IJ, Masaki K, Yano K, Chen R, Rodriguez BL, Curb JD. Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study. Lancet. 2001 Aug 4;358(9279):351-5.

Schiattarella GG, Perrino C, Magliulo F, Ilardi F, Serino F, Trimarco V, Izzo R, Amato B, Terranova C, Cardin F, Militello C, Leosco D, Trimarco B, Esposito G. Statins and the elderly: recent evidence and current indications. Aging Clin Exp Res. 2012 Jun;24(3 Suppl):47-55.

Weverling-Rijnsburger AW, Blauw GJ, Lagaay AM, Knook DL, Meinders AE, Westendorp RG. Total cholesterol and risk of mortality in the oldest old. Lancet. 1997 Oct 18;350(9085):1119-23.

Additional supporting recommendations

Source	Recommendations
U.S. Preventive Services Task Force	1. The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of statin use for the prevention of CVD events in adults age 76 years and older without a history of heart attack or stroke.
American Diabetes Association	1. For patients with diabetes aged 40–75 years without additional atherosclerotic cardiovascular disease risk factors, consider using moderate-intensity statin and lifestyle therapy. 2. For patients with diabetes aged 40–75 years with additional atherosclerotic cardiovascular disease risk factors, consider using high-intensity statin and lifestyle therapy. 3. Other cardiovascular risk factors should be treated in older adults with consideration of the time frame of benefit and the individual patient. Treatment of hypertension is indicated in virtually all older adults, and lipid-lowering and aspirin therapy may benefit those with life expectancy at least equal to the time frame of primary or secondary prevention trials.

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Measure 6 – De-intensification of RA system combination therapy for blood pressure reduction

Proposed de-intensification measure

Action: Stop all but 1 class of the renin-angiotensin system agents (i.e., ACEIs, ARBs, or DRIs) within 6 months of the last prescription issue date

Population: Patients on combination therapy from two or more of the following classes: ACEIs, ARBs, or DRIs

Definitions

ACEI: angiotensin-converting-enzyme inhibitor; ARB: angiotensin II receptor blocker; DRI: direct renin inhibitor; RA: renin-angiotensin

Existing recommendation that motivated the proposed de-intensification measure

VA/DoD Guideline Recommendation - Combination therapy for blood pressure reduction: "We recommend against the use of more than one of the following three drug classes together in the same patient: angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, or direct renin inhibitors."

- Source and Steward: Veterans Affairs and Department of Defense (VA/DoD)
- Last Update: October 1, 2014
- Strength of Recommendation: Strongly against (The guideline panel recommends against offering this option.)

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

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Potential opportunity for improvement

In VA (estimate)

- [July 2014 - June 2015] 0.2% (3,378/1,770,003) of patients had concurrent prescriptions in more than one of the following classes: an angiotensin-converting-enzyme inhibitor, an angiotensin II receptor blocker, or a direct renin inhibitor.

Outside VA

The following is extracted from: Albert et al. Use of aldosterone antagonists in heart failure. JAMA. 2009; 302(15): 1658-65.

- [2005-2007] In an observational analysis of 47,706 patients with heart failure who were discharged to home, 8,610 received an aldosterone antagonist prescription.
  Of these 8,610:
  - 194 (2.3%) also received the ACC/AHA guideline–proscribed (class III recommendation) combination of ACE inhibitor and ARB therapy.

Evidence-base

Rationale 1

The following information is extracted directly and verbatim from the VA/DoD Clinical Practice Guideline for the Diagnosis and Management of Hypertension (see above).

Despite the potential for additional blood pressure reduction with combination therapy of agents that act at the renin-angiotensin system (ACEIs, ARBs, and DRIs), data from recent clinical trials have reported an increased risk for harm (including hypotensive symptoms, renal dysfunction or acute kidney injury events, or hyperkalemia) without long-term cardiovascular or renal outcome benefit in patients treated with combination therapy with two or more of these three classes, compared to monotherapy. Although these trials primarily studied high-risk patients with at least one of the following conditions including vascular disease, diabetes mellitus, kidney disease, or diabetic nephropathy, the majority of patients either had a diagnosis of hypertension or were being treated with antihypertensive medications.

Citation(s) provided for the evidence

Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med. Nov 14 2013;369(20):1892-1903.

Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med. Dec 6 2012;367(23):2204-2213.

Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med. Apr 10 2008;358(15):1547-1559.

Rationale 2

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The following information is extracted directly and verbatim from: Makani H, Bangalore S, Desouza KA, Shah A, Messerli FH. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomized trials. BMJ. 2013 Jan 28;346:f360.

Although dual blockade of the renin-angiotensin system may have seemingly beneficial effects on certain surrogate endpoints, it failed to reduce mortality and was associated with an excessive risk of adverse events such as hyperkalaemia, hypotension, and renal failure compared with monotherapy. The risk to benefit ratio argues against the use of dual therapy.

Additional supporting recommendations

Source	Recommendations
National Institute for Health and Care Excellence	1. Do not combine an ACE inhibitor with an ARB to treat hypertension. 2. Do not combine an ACE inhibitor with an angiotensin II-receptor antagonist to treat hypertension in adults with type 2 diabetes. 3. Do not offer combined treatment with an ACE inhibitor and an angiotensin II receptor blocker (ARB) to people after an MI, unless there are other reasons to use this combination.
American College of Cardiology/ American Heart Association	1. Routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful for patients with heart failure with reduced ejection fraction.

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Measure 7 – De-intensification of aldosterone receptor antagonists

Proposed de-intensification measure

Action: Reduce dose or stop aldosterone receptor antagonists within 6 months of the last prescription issue date

Population: Patients on aldosterone receptor antagonists with renal insufficiency (estimated glomerular filtration rate <30 mL/min/1.73 m2) and/or potassium greater than 5.0 mEq/L

Definitions

None

Existing recommendation that motivated the proposed de-intensification measure

AHA/ACC Guideline Recommendation - De-intensification of aldosterone receptor antagonists:

"Inappropriate use of aldosterone receptor antagonists is potentially harmful because of life-threatening hyperkalemia or renal insufficiency when serum creatinine is greater than 2.5 mg/dL in men or greater than 2.0 mg/dL in women (or estimated glomerular filtration rate <30 mL/min/1.73 m^2), and/or potassium greater than 5.0 mEq/L."

- Source and Steward: American Heart Association/American College of Cardiology (AHA/ACC)
- Last Update: October 15, 2013
- Strength of Recommendation: Class III Harm (suggests "harm," where the procedure/tests has excess cost and is either harmful or without benefit; or treatment is harmful to patients)
- Level of Evidence: Category B (data derived from a single randomized trial, or non-randomized studies)

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

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Potential opportunity for improvement

In VA (estimate)

- [FY2015] 7.5% (7,422/98,792) of patients prescribed an aldosterone receptor antagonist had at least two high potassium measurements, two high serum creatinine measurements, two low estimated glomerular filtration rates, or one high serum creatinine measurement and one low estimated glomerular filtration rate.

Outside VA

The following is extracted from: Albert et al. Use of aldosterone antagonists in heart failure. JAMA. 2009; 302(15): 1658-65.

- [2005-2007] In an observational analysis of 47,706 patients with heart failure who were discharged to home, 8,610 received an aldosterone antagonist prescription.
  Of these 8,610:
  - 269 (3.1%) met at least 1 criterion for inappropriate use (listed below)
    - Documented contraindication (N=46)
    - Serum potassium >6.0 mEq/L (N=6)
    - Serum creatinine ≥3.0 mg/dL (N=232)
  - 640 (7.4%) met at least 1 criterion for potentially inappropriate use (listed below)
    - Serum potassium >5.5 and <6.0 mEq/L (N=18)
    - Serum creatinine ≥2.5 and <3.0 mg/dL (N=233)
    - Ejection fraction >40% and without hypertension (N=396)

Evidence-base

Rationale

The following information is extracted directly and verbatim from the 2013 ACCF/AHA Guideline for the Management of Heart Failure.

The major risk associated with use of aldosterone receptor antagonists is hyperkalemia due to inhibition of potassium excretion, ranging from 2% to 5% in large clinical trials to 24% to 36% in population-based registries. Routine triple combination of an ACE inhibitor, ARB, and aldosterone receptor antagonist should be avoided.

The development of potassium levels >5.5 mEq/L (approximately 12% in EMPHASIS-HF) should generally trigger discontinuation or dose reduction of the aldosterone receptor antagonist unless other causes are identified. The development of worsening renal function should lead to careful evaluation of the entire medical regimen and consideration for stopping the aldosterone receptor antagonist. Patients should be instructed specifically to stop the aldosterone receptor antagonist during an episode of diarrhea or dehydration or while loop diuretic therapy is interrupted.

Citation(s) provided for the evidence

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Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med 2004;351:543–51.

Bozkurt B, Agoston I, Knowlton AA. Complications of inappropriate use of spironolactone in heart failure: when an old medicine spirals out of new guidelines. J Am Coll Cardiol 2003;41:211–4.

Additional supporting recommendations

Source	Recommendations
American College of Cardiology/ American Heart Association	1. Aldosterone receptor antagonists (or mineralocorticoid receptor antagonists) are recommended in patients with New York Heart Association (NYHA) class II–IV heart failure (HF) and who have left ventricular ejection fraction (LVEF) of 35% or less, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II HF should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. Creatinine should be 2.5 mg/dL or less in men or 2.0 mg/dL or less in women (or estimated glomerular filtration rate >30 mL/min/1.73 m2), and potassium should be less than 5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency. 2. Aldosterone receptor antagonists are recommended to reduce morbidity and mortality following an acute MI in patients who have LVEF of 40% or less who develop symptoms of HF or who have a history of diabetes mellitus, unless contraindicated.

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Measure 8 – De-intensification of medication treatment for claudication

Proposed de-intensification measure

Action: Stop the use of pentoxifylline within 6 months of the last prescription issue date

Population: All patients

Definitions

None

Existing recommendation that motivated the proposed de-intensification measure

AHA/ACC Guideline Recommendation - Treatment for claudication: "The clinical effectiveness of pentoxifylline as therapy for claudication is marginal and not well established."

- Source and Steward: American Heart Association/American College of Cardiology (AHA/ACC)
- Last Update: April 9, 2013
- Level of Evidence: Category C (consensus opinion of experts, case studies, or standard of care)

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

Potential opportunity for improvement

In VA (estimate)

- [FY2016] 3,757 patients were prescribed pentoxifylline.

Outside VA

- Estimate for improvement opportunity outside VA not found in the literature

Evidence-base

Rationale

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The following information is extracted directly and verbatim from the Cochrane Review – Pentoxifylline for intermittent claudication.

Atherosclerosis or hardening of the arteries results in narrowing and blockages in the arteries and can reduce the blood supply to the legs causing peripheral arterial occlusive disease. Intermittent claudication (IC) is a cramp-like pain felt in the leg muscles that is brought on by walking and relieved by standing still or resting. Pentoxifylline is a drug that is used to relieve IC and to improve people's walking capacity. It decreases blood viscosity and improves red blood cell flexibility, increasing microcirculatory blood flow and the amount of oxygen in the tissues. This review looked at all available evidence from randomised controlled trials on the efficiency of pentoxifylline in the treatment of IC.

Twenty-three trials with a total of 2816 participants were included. A majority of the included studies suggested a mild to moderate improvement in pain-free walking distance and total walking distance for pentoxifylline over placebo (and other treatments, which included Ginkgo biloba, buflomedil, iloprost, nylidrin and aspirin). The statistical significance of the findings from the individual trials was unclear and there was large variability in the effect of pentoxifylline between the different studies. The ankle brachial pressure index was not improved with pentoxifylline. The most commonly reported side effects were gastrointestinal symptoms, mainly nausea, and the drug was well tolerated.

The duration of trials, the dose of pentoxifylline and the distances that participants could walk at the start of the trials varied. The quality of the included studies was generally low.

Given all these factors, the role of pentoxifylline in intermittent claudication remains uncertain, and although it may have some beneficial effect for improving the walking distance of patients with IC, the response to pentoxifylline should be assessed on an individual basis.

Citation(s) provided for the evidence

Salhiyyah K, Senanayake E, Abdel-Hadi M, Booth A, Michaels HA. Pentoxifylline for intermittent claudication. Cochrane Database Syst Rev. 2012 Jan 18.

Additional supporting recommendations

Source	Recommendations
	None

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Measure 9 – De-intensification of DAPT

Proposed de-intensification measure

Action: Stop either aspirin or alternate antiplatelet therapy within 6 months of the last prescription issue date

Population: Patients on DAPT (*dual anti-platelet regimen*) with stable IHD without prior history (in the last 12 months) of ACS, coronary stent implantation, or CABG

Definitions

DAPT: dual antiplatelet therapy; IHD: ischemic heart disease; ACS: acute coronary syndrome; CABG: coronary artery bypass graft; SIHD: stable ischemic heart disease

Existing recommendation that motivated the proposed de-intensification measure

ACC/AHA Guideline Recommendation - De-intensification of DAPT: "In patients with SIHD without prior history of ACS, coronary stent implantation, or recent (within 12 months) CABG, treatment with DAPT is not beneficial."

- Source and Steward: American Heart Association/American College of Cardiology (AHA/ACC)
- Last Update: March 1, 2016
- Strength of Recommendation: Class III No Benefit (suggests "no benefit," where the procedure/test is not helpful or the treatment has proven no benefit)
- Level of Evidence: Category B-R (moderate quality evidence from 1 or more RCTS or meta-analyses of moderate-quality RCTs)

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

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Potential opportunity for improvement

In VA (estimate)

- [FY2015] 3.7% (34,158/912,350) of patients with stable IHD without prior history of ACS, coronary stent implantations, or recent CABG were treated with DAPT.

Outside VA

The following is extracted from: Goldsweig AM, Reid KJ, Gosch K, et al. Contemporary use of dual antiplatelet therapy for preventing cardiovascular events. Am J Manag Care. 2014; 20(8): 659-65.

- [2008-2011] In a retrospective analysis of 5,100 patients with multiple CVD risk factors but no known cardiovascular disease:
  - 4.6% were prescribed both aspirin and clopidogrel.

Rapid evidence synthesis summary (Review the entire rapid evidence synthesis report.)

Why is de-intensification of DAPT in SIHD patients important?

- Dual antiplatelet therapy (DAPT) can decrease ischemic risk versus single antiplatelet therapy but is associated with increased bleeding risk.
- The American College of Cardiology and the American Heart Association do not recommend DAPT in people with stable ischemic heart disease (SIHD) without stent implantation and no history of acute coronary syndrome (ACS) or myocardial infarction (MI).
- Despite guideline recommendations, DAPT is still used in some patients with SIHD.
- This rapid evidence synthesis summarizes the evidence of the benefits and harms of DAPT in SIHD patients compared with single antiplatelet therapy, and de-intensification of DAPT.

What is the evidence on benefits versus harms of DAPT in SIHD patients?

- Two trials evaluated DAPT versus aspirin in persons with SIHD or who were at high cardiovascular risk without a clear indication for DAPT.
  - The CHARISMA trial found no difference between DAPT versus aspirin in risk of all-cause mortality, cardiovascular (CV) mortality, myocardial infarction, or the primary CV composite outcome (MI, stroke, or death); DAPT was associated with a slight (not statistically significant) increase in risk of severe bleeding and an increased risk of moderate bleeding.
  - The PEGASUS-TIMI 54 trial found no difference between DAPT versus aspirin in risk of all-cause mortality or cardiovascular mortality. DAPT was associated with decreased risk of the primary composite outcome of CV death, MI, or stroke, but these effects were offset by a similar increase in the risk of severe bleeding.

What is the evidence on de-intensification?

No study evaluated effects of de-intensification of DAPT in persons with SIHD.

What are the implications of our findings?

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DAPT does not reduce risk of mortality or CV mortality in persons with SIHD; any beneficial effects on cardiovascular outcomes are offset by increases in bleeding.

Additional supporting recommendations

Source	Recommendations
American Heart Association/American College of Cardiology	1. In patients with SIHD, treatment with DAPT (with clopidogrel initiated early postoperatively) for 12 months after CABG may be reasonable to improve vein graft patency.
American Diabetes Association	1. Dual antiplatelet therapy is reasonable for up to a year after an acute coronary syndrome.

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Measure 10 – De-intensification of high dose aspirin

Proposed de-intensification measure

Action: Decrease daily aspirin dose to <=100 mg within 6 months of the last prescription issue date

Population: Patients with DAPT and daily aspirin dose>100 mg

Definitions

DAPT: dual antiplatelet therapy

Existing recommendation that motivated the proposed de-intensification measure

ACC/AHA Guideline Recommendation - Aspirin dosing in patients treated with DAPT**:** "In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended."

- Source and Steward: American College of Cardiology/ American Heart Association (ACC/AHA)
- Last Update: March 1, 2016
- Strength of Recommendation: Class I Strong (the procedure/treatment should be performed/administered)
- Level of Evidence: Category B-NR (Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies or meta-analyses of such studies)

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

Potential opportunity for improvement

In VA (estimate)

- During FY15, 5.5% (14,260/258,500) of patients treated with DAPT were prescribed a daily aspirin dose greater than 81mg.

Outside VA

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- Estimate for improvement opportunity outside VA not found in the literature

Evidence-base

Rationale

The following information is extracted directly and verbatim from the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease.

Lower daily doses of aspirin, including in patients treated with DAPT, are associated with lower bleeding complications and comparable ischemic protection than are higher doses of aspirin.

Citation(s) provided for the evidence

Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324:71–86.

Jolly SS, Pogue J, Haladyn K, et al. Effects of aspirin dose on ischaemic events and bleeding after percutaneous coronary intervention: insights from the PCI-CURE study. Eur Heart J. 2009;30:900–7.

Lorenz RL, Schacky CV, Weber M, et al. Improved aortocoronary bypass patency by low-dose aspirin (100 mg daily): effects on platelet aggregation and thromboxane formation. Lancet. 1984;1:1261–4.

Mehta SR, Tanguay J-F, Eikelboom JW, et al. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomized factorial trial. Lancet. 2010;376:1233–43.

Patrono C, Baigent C, Hirsh J, et al. Antiplatelet drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest.2008;133:199S–233S.

Peters RJG, Mehta SR, Fox KAA, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. Circulation.2003;108:1682–7.

Serebruany VL, Steinhubl SR, Berger PB, et al. Analysis of risk of bleeding complications after different doses of aspirin in 192,036 patients enrolled in 31 randomized controlled trials. Am J Cardiol. 2005;95:1218–22.

Steinhubl SR, Bhatt DL, Brennan DM, et al. Aspirin to prevent cardiovascular disease: the association of aspirin dose and clopidogrel with thrombosis and bleeding. Ann Intern Med. 2009;150:379–86.

Xian Y, Wang TY, McCoy LA, et al. Association of discharge aspirin dose with outcomes after acute myocardial infarction: insights from the Treatment with ADP Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome (TRANSLATE-ACS) Study. Circulation.2015;132:174–81.

Additional supporting recommendations

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Source	Recommendations
American College of Cardiology/ American Heart Association	1. Recommendations for duration of DAPT in patients with stable ischemic heart disease (SIHD): In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended. 2. Recommendations for duration of DAPT in patients with ACS treated with percutaneous coronary intervention (PCI): In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended. 3. Recommendations for duration of DAPT in patients undergoing coronary artery bypass grafting (CABG): In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended. 4. Recommendations for duration of DAPT in patients with SIHD treated with PCI: In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended. 5. Recommendations for Duration of DAPT in Patients with acute coronary syndrome (ACS) Treated with Medical Therapy Alone: In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended.

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Measure 11 – De-intensification of resting or exercise electrocardiography, stress echocardiography, and stress myocardial perfusion imaging for screening

Proposed de-intensification measure

Action: Stop annual (or more frequent) screening with resting or stress electrocardiography, stress echocardiography, or stress myocardial perfusion imaging

Population: Asymptomatic adults at low risk for CHD events

Definitions

ECG: electrocardiography/electrocardiogram; MPI: myocardial perfusion imaging

Existing recommendations that motivated the proposed de-intensification measure

USPSTF Recommendation - De-intensification of screening ECG: "The USPSTF recommends against screening with resting or exercise electrocardiography (ECG) for the prediction of coronary heart disease (CHD) events in asymptomatic adults at low risk for CHD events."

- Source and Steward: U.S. Preventive Services Task Force (USPSTF)
- Last Update: September 20, 2011
- Level of Evidence: Grade D (The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.)

ACP Guideline Recommendation- De-intensification screening ECG, stress echocardiography, stress MPI: "Clinicians should not screen for cardiac disease in asymptomatic, low-risk adults with resting or stress electrocardiography, stress echocardiography, or stress myocardial perfusion imaging."

- Source and Steward: American College of Physicians (ACP)
- Last Update: March 17, 2015

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

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3. Do you agree with the population, including exclusions?

Potential opportunity for improvement

In VA (estimate)

- [**October 2014 – September 2015** (12 months)] **1.8%** (13,717/763,638) of patients at low risk for CHD events and asymptomatic (i.e., no chest pain or angina) had more than one resting or exercise ECG, MPI, or stress echo.
- [**July 2014 - September 2015** (15 months)] **2.5%** (18,672/755,758) of patients at low risk for CHD events and asymptomatic (i.e., no chest pain or angina) had more than one resting or exercise ECG, MPI, or stress echo.
- Low risk for CHD events was defined as an ASCVD score less than 5%, and no indication of ASCVD during the study year or year prior.

Outside VA

The following information is extracted from: Chou R ; High Value Care Task Force of the American College of Physicians.Cardiac screening with electrocardiography, stress echocardiography, or myocardial perfusion imaging: advice for high-value care from the American College of Physicians. Ann Intern Med. 2015 Mar 17;162(6):438-47.

- One study of national survey data found that screening ECG use at general medical examination visits increased from 6.1% to 11.3% from 1999 to 2009 (Kale 2013).
- A systematic review found overuse rates of 9.2% for ECG and 3.0% to 52% for cardiac stress tests (Korenstein 2012).
- In a Consumer Reports survey, 39% of asymptomatic adults without high blood pressure or a high cholesterol level reported having ECG within the past 5 years, and 12% reported undergoing exercise ECG. More than half reported that their physician recommended it as part of their routine health care (Schwartz 2010).
- For cardiac stress imaging, 3 studies found that about 15% of stress MPI and echocardiography examinations did not meet appropriateness criteria, with evaluation of low-risk, asymptomatic patients accounting for about half of the cases in 2 studies and 25% in the other (Hendel 2010; Gibbons 2008; Winchester 2013).

Evidence-base

Rationale 1

The following information is extracted directly and verbatim from the U.S. Preventive Services Task Force Evidence Synthesis for Screening Asymptomatic Adults for Coronary Heart Disease With Resting or Exercise Electrocardiography.

For asymptomatic adults at low risk for CHD events, the USPSTF found adequate evidence that the

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incremental information offered by resting or exercise ECG (beyond that obtained with conventional CHD risk factors) is highly unlikely to result in changes in risk stratification that would prompt interventions and ultimately reduce CHD-related events. The USPSTF based this conclusion on the epidemiology of CHD, the natural history of CHD, and established treatment strategies based on risk stratification.

USPSTF - Evidence summary

USPSTF - Clinical Summary

Rationale 2

The following information is extracted directly and verbatim from Cardiac Screening With Electrocardiography, Stress Echocardiography, or Myocardial Perfusion Imaging: Advice for High-Value Care From the American College of Physicians.

Cardiac screening has not been shown to improve patient outcomes. It is also associated with potential harms due to false-positive results because they can lead to subsequent, potentially unnecessary tests and procedures. Cardiac screening is likely to be particularly inefficient in adults at low risk for coronary heart disease given the low prevalence and predictive values of testing in this population and the low likelihood that positive findings will affect treatment decisions. In this patient population, clinicians should focus on strategies for mitigating cardiovascular risk by treating modifiable risk factors (such as smoking, diabetes, hypertension, hyperlipidemia, and overweight) and encouraging healthy levels of exercise.

Additional supporting recommendations

Source	Recommendations
Choosing Wisely. American Academy of Family Physicians	1. Don't order annual electrocardiograms (EKGs) or any other cardiac screening for low risk patients without symptoms.
Choosing Wisely. American College of Physicians	1. Don't obtain screening exercise electrocardiogram testing in individuals who are asymptomatic and at low risk for coronary heart disease.
Choosing Wisely. American Society of Echocardiography	1. Avoid using stress echocardiograms on asymptomatic patients who meet low risk scoring criteria for coronary disease.
Choosing Wisely. American Society of Nuclear Cardiology	1. Don't perform stress cardiac imaging or advanced non-invasive imaging in the initial evaluation of patients without cardiac symptoms unless high-risk markers are present. 2. Don't perform radionuclide imaging as part of routine follow-up in asymptomatic patients.
Choosing Wisely. American College of	1. Don't perform annual stress cardiac imaging or advanced non-invasive imaging as part of routine follow-up in asymptomatic patients.

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Cardiology	
American College of Cardiology	1. Percentage of all stress SPECT myocardial perfusion imaging (MPI), stress echo, cardiac computed tomography angiography (CCTA), and cardiac magnetic resonance (CMR) performed in asymptomatic, low coronary heart disease (CHD) risk patients for initial detection and risk assessment. [NQF Measure]

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Measure 12 – De-intensification of annual surveillance exercise electrocardiography

Proposed de-intensification measure

Action: Stop annual surveillance testing using exercise ECG

Population: Patients with IHD who are asymptomatic

Definitions

ECG: electrocardiography/electrocardiogram; IHD: ischemic heart disease also called coronary heart disease (CHD), coronary artery disease (CAD) or atherosclerotic heart disease.

Existing recommendation that motivated the proposed de-intensification measure

AHA/ACC Recommendation – De-intensification surveillance exercise ECG: "In patients who have no new or worsening symptoms or no prior evidence of silent ischemia and are not at high risk for a recurrent cardiac event, the usefulness of annual surveillance exercise ECG testing is not well established."

- Source: American Heart Association/American College of Cardiology (AHA/ACC)
- Steward: ACCF/AHA/ACP/AATS/PCNA/SCAI/STS
- Last Update: December 18, 2012
- Strength of Recommendation: Class IIB (additional studies with broad objectives needed, and additional registry data would be helpful; procedure/treatment may be considered)
- Level of Evidence: Category C (consensus opinion of experts, case studies, or standard of care)

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

    a. Silent ischemia and high risk for a recurrent cardiac event are listed as possible reasons for surveillance in asymptomatic adults. How important would it be to include these as

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exclusions?

Potential opportunity for improvement

In VA (estimate)

- [FY2014-FY2015] **0.2%** (1,782/737,303) of patients with IHD who were asymptomatic (i.e., no angina, shortness of breath, or chest pain in two year window) received two exercise ECGS.

- [FY2014-FY2015] **0.5%** (95/18,098) of patients with IHD who were asymptomatic (i.e. no angina, shortness of breath, or chest pain in two year window) and **not at high risk for recurrent cardiac event** received two exercise ECGs.

Outside VA

The following is extracted from: Schwartz et al. Measuring low-value care in Medicare. JAMA Intern Med. 2014; 174(7): 1067-76.

- [2008-2009] Using claims data from Medicare beneficiaries, as well as demographic information from enrollment files and chronic conditions from the Chronic Conditions Data Warehouse:
  - **7.3%** of beneficiaries received stress testing for stable coronary artery disease – using a **more sensitive measure**.
    - More sensitive, less specific (base definition): Stress testing for patients with an established diagnosis of ischemic heart disease or angina (at least 6 months prior to the stress test) and thus not done for screening purposes
  - **0.8%** of beneficiaries received stress testing for stable coronary artery disease – using a **more specific measure**.
    - Less sensitive, more specific (additional restrictions): Test not associated with inpatient or emergency care, which might be indicative of unstable angina. Only patients with a past diagnosis of myocardial infarction in order to exclude patients with a history of non-cardiac chest pain inaccurately coded as angina (i.e., those with no underlying ischemic heart disease who might benefit from screening and optimization of medical management)

Evidence-base

Rationale

The following information is extracted directly and verbatim from Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease.

The appropriateness of performing noninvasive testing in patients who either are asymptomatic or have stable symptoms (i.e., routine surveillance testing) depends on factors related to the likelihood of significant findings, such as the patient's risk for rapidly advancing disease, propensity to have silent ischemia, and length of time since revascularization. The data supporting follow-up testing are sparse

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and insufficient to support routine, repeat testing in asymptomatic individuals.

There are, however, several circumstances in which a decision to perform follow-up testing is thought to be warranted in the absence of a change in clinical status, although data supporting this approach are limited. These circumstances include, but are not limited to, evaluation of incomplete revascularization, assessment of the adequacy of medical therapy by provocative exercise testing, a substantial change in risk profile, or the need to reevaluate coronary status in anticipation of major noncardiovascular surgery when the patient's exercise capacity is limited or unknown (although revascularization in this circumstance has not been shown to reduce the risk of perioperative cardiovascular complications.

In the absence of a change in clinical status, patients with a low projected annual mortality rate (<1%) are those with low-risk Duke treadmill scores, either without imaging or with negative imaging findings, whose 4-year cardiovascular survival rate approximates 99%. The low-risk category also includes patients with normal stress imaging who lack adverse prognostic characteristics, such as diabetes mellitus or prior MI. Younger women without diabetes mellitus or a prior MI who have normal stress nuclear MPI remain at very low risk for as long as 7 to 9 years, depending on specific clinical characteristics, and probably do not require repeat stress imaging during that period in the absence of changes in clinical status. (307)

Data are more limited with regard to the value of serial testing strategies in patients at intermediate risk of cardiac mortality (1% to 3% per year). Follow-up testing probably should be performed only if decisions about a change in pharmacological management, level of exercise, or revascularization will be influenced directly by the test result or if the patient has persistent symptoms despite adequate GDMT. Thus, in the patient with known SIHD, the goal of repeat testing is the assessment of residual ischemic burden after optimization of GDMT or the consideration of revascularization as a result of failed optimal medical management.

Even for high-risk patients, the value of annual exercise testing (or serial exercise testing at alternative intervals) in the absence of a change in symptoms has not been studied adequately. Yearly exercise testing could be useful in patients with SIHD who have >3% risk of mortality per year, because a marked decrease in exercise capacity or a marked increase in ischemic burden can warrant reevaluation of the medical regimen or interventional plan. Examples of such patients are those with a high-risk Duke treadmill score, patients with an EF<50% and significant CAD in 1 major vessel, patients with diabetes mellitus, and those with multivessel disease who have not undergone CABG. Some data also suggest that ischemic burden might be useful in targeting ischemia-guided revascularization.

Citation(s) provided for the evidence

Hachamovitch R, Hayes S, Friedman JD, et al. Determinants of risk and its temporal variation in patients with normal stress myocardial perfusion scans: what is the warranty period of a normal scan? J Am Coll Cardiol. 2003; 41: 1329–40.

Additional supporting recommendations

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Source	Recommendations
American College of Cardiology/ American Heart Association	1. Standard exercise ECG testing performed at 1-year or longer intervals might be considered for follow-up assessment in patients with SIHD who have had prior evidence of silent ischemia or are at high risk for a recurrent cardiac event and are able to exercise to an adequate workload and have an interpretable ECG. 2. Nuclear MPI, echocardiography, or cardiac magnetic resonance (CMR) with either exercise or pharmacological stress can be useful for follow-up assessment at 2-year or longer intervals in patients with SIHD with prior evidence of silent ischemia or who are at high risk for a recurrent cardiac event and a) are unable to exercise to an adequate workload, b) have an uninterpretable ECG, or c) have a history of incomplete coronary revascularization 3. Nuclear MPI, echocardiography, or CMR, with either exercise or pharmacological stress or CCTA, is not recommended for follow-up assessment in patients with SIHD, if performed more frequently than at a) 5-year intervals after CABG or b) 2-year intervals after PCI

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Measure 13 – De-intensification of echocardiography for routine follow-up

Proposed de-intensification measure
Action: Stop annual echocardiography

Population: Adult patients with asymptomatic native valve disease

Definitions
None

Existing recommendation that motivated the proposed de-intensification measure
Choosing Wisely - Routine echocardiography: "Don't perform echocardiography as routine follow-up for mild, asymptomatic native valve disease in adult patients with no change in signs or symptoms."

- Source: Choosing Wisely
- Steward: American College of Cardiology (ACC)
- Last Update: April 4, 2012

See all additional supporting recommendations.

Questions to consider
Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

Potential opportunity for improvement
In VA (estimate)

- [FY2015] 4% (4,190/116,600) of adult patients with asymptomatic native valve disease had more than one echocardiogram during the study year.

Outside VA
The following is extracted from: Ward et al. Prospective evaluation of the clinical application of the American College of Cardiology Foundation/American Society of Echocardiography Appropriateness

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Criteria for transthoracic echocardiography. JACC Cardiovasc Imaging. 2008; 1(5): 663-71.

- [2007] In a prospective evaluation designed to evaluate the clinical application of the American College of Cardiology Foundation/American Society of Echocardiography Appropriateness Criteria (AC) for transthoracic echocardiography:
  - 11.3% (N=157) were found to be ordered for inappropriate indications.
    - Routine (yearly) re-evaluation of an asymptomatic patient with mild native aortic stenosis or mild-moderate native mitral stenosis and no change in clinical status (N=18)
    - Routine (yearly) evaluation of native valvular regurgitation in an asymptomatic patient with mild regurgitation, no change in clinical status, and normal LV size (N=9)
    - Other inappropriate indications (N=130)

Rapid evidence synthesis summary (Review the entire rapid evidence synthesis report.)

Why is de-intensification of routine surveillance with echocardiography for asymptomatic mild AS or MR in adults important?

Asymptomatic mild aortic stenosis (AS) or mitral regurgitation (MR) may progress to more severe disease. The benefits and harms of echocardiographic surveillance of persons with asymptomatic mild AS or MR is uncertain.

What is the evidence on benefits versus harms of routine surveillance with echocardiography for asymptomatic mild AS or MR in adults with no change in signs or symptoms?

- No study directly evaluated benefit or harms of surveillance with echocardiography in persons with asymptomatic mild AS or MR.
- Natural history studies indicate that mild AS and MR progress to more severe valvular disease over time, though there is individual variability in the rate of progression; no study reported the proportion of patients who progress to severe AS or MR without developing symptoms.
- The effectiveness of surgical or other interventions among persons with asymptomatic AS or MR, even when severe, is uncertain.
- Harms may include the potential for unnecessary and potentially harmful tests and treatments as a result of surveillance, due to over diagnosis, overtreatment, or incidental echocardiographic findings.

What is the evidence on de-intensification?

No study evaluated benefits and harms of de-intensification of surveillance echocardiography for mild asymptomatic AS or MR.

What are the implications of our findings?

There is no direct evidence on potential benefits or harms of echocardiographic surveillance in patients with asymptomatic mild AS or MR, or of de-intensification of surveillance. Although mild AS and MR progress to more severe disease over time and severe valvular disease is associated with poorer clinical outcomes, it is unclear how many patients progress to severe AS or MR without developing symptoms.

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Research is needed to clarify effects of interventions in persons with asymptomatic severe AS or MR.

Additional supporting recommendations

Source	Recommendations
Choosing Wisely. American Society of Echocardiography	1. Don't order follow up or serial echocardiograms for surveillance after a finding of trace valvular regurgitation on an initial echocardiogram. 2. Don't repeat echocardiograms in stable, asymptomatic patients with a murmur click where a previous exam revealed no significant pathology.
American College of Cardiology/ American Heart Association	1. Frequency of Echocardiograms in Asymptomatic Patients with valvular heart disease (VHD) and Normal Left Ventricular Function: Aortic stenosis with known VHD and normal left ventricular function. Stage B: 3-5 y (mild severity Vmax 2.0–2.9 m/s) or every 1–2 y (moderate severity Vmax 3.0–3.9 m/s); stage C: every 6–12 mo (Vmax ≥4 m/s) 2. Frequency of Echocardiograms in Asymptomatic Patients with VHD and Normal Left Ventricular Function: Mitral valve stenosis (MS) with known VHD and normal left ventricular function. Stage B: every 3–5 y (MVA >1.5 cm2); stage C: every 1–2 y (MVA 1.0–1.5 cm2) once every year (MVA <1.0 cm2) 3. Frequency of Echocardiograms in Asymptomatic Patients with VHD and Normal Left Ventricular Function: Aortic regurgitation (AR) with known VHD and normal left ventricular function. Stage B: every 3–5 y (mild severity) every 1–2 y (moderate severity); stage C: every 6–12 mo, Dilating LV: more frequently 4. Frequency of Echocardiograms in Asymptomatic Patients with VHD and Normal Left Ventricular Function: Mitral regurgitation (MR) with known VHD and normal left ventricular function. Stage B: every 3–5 y (mild severity), every 1–2 y (moderate severity); Stage C: every 6–12 mo, Dilating LV: more frequently 5. TTE should be performed to re-evaluate asymptomatic patients with MS and stable clinical findings to assess pulmonary artery pressure and valve gradient. Very severe MS with mitral valve area <1.0 cm2 every year; Severe MS with mitral valve area ≤1.5 cm2 every 1 to 2 years; Progressive MS with mitral valve area >1.5 cm2 every 3 to 5 years)

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Measure 14 – De-intensification of screening for carotid artery stenosis

Proposed de-intensification measure

Action: Stop screening for carotid artery stenosis

Population: Asymptomatic adult patients without a history of cerebrovascular disease

Definitions

None

Existing recommendation that motivated the proposed de-intensification measure

Choosing Wisely - Screening for Carotid Artery Stenosis: "Don't screen for carotid artery stenosis (CAS) in asymptomatic adult patients."

- Source: Choosing Wisely
- Steward: American Academy of Family Physicians (AAFP)
- Last Update: February 21, 2013

See all additional supporting recommendations

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

Potential opportunity for improvement

In VA (estimate)

- [FY2015] 1% (49,824/4,828,276) of asymptomatic patients (i.e., no record of stroke or TIA) had a diagnostic study/image of the carotid arteries.

Outside VA

The following is extracted from: Schwartz et al. Measuring low-value care in Medicare. JAMA Intern Med. 2014 Jul;174(7):1067-76.

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- [2008-2009] Using claims data from Medicare beneficiaries, as well as demographic information from enrollment files and chronic conditions from the Chronic Conditions Data Warehouse:
  - 6.0% of asymptomatic patients received carotid artery disease screening – using a more sensitive measure.
    - More sensitive, less specific (base definition): Carotid imaging for patients without a history of stroke or TIA and without a diagnosis of stroke, TIA, or focal neurological symptoms in claim
  - 5.1% of asymptomatic patients received carotid artery disease screening – using a more specific measure.
    - Less sensitive, more specific (additional restrictions): Test not associated with inpatient or emergency care

The following is extracted from: Segal et al. Identifying possible indicators of systematic overuse of health care procedures with claims data. Med Care. 2014; 52(2): 157-63.

- [2008] Using a 5% sample of fee-for-services patients insured by Medicare:
  - 12.5 per 1000 beneficiaries received screening for asymptomatic carotid artery stenosis in the general adult population.

Evidence-base

Rationale

The following information is extracted directly and verbatim from Choosing Wisely.

There is good evidence that for adult patients with no symptoms of carotid artery stenosis, the harms of screening outweigh the benefits. Screening could lead to non-indicated surgeries that result in serious harms, including death, stroke and myocardial infarction.

Citation(s) provided for the evidence

American Academy of Family Physicians. Carotid Artery Stenosis [Internet]. 2007[cited 2012 Oct 10].

U.S. Preventive Services Task Force. Screening for Carotid Artery Stenosis [Internet]. 2007 Dec. [Cited 2012 Oct 10].

Wolff T, Guirguis-Blake J, Miller T, et al. Screening For Asymptomatic Carotid Artery Stenosis. Rockville (MD): Agency for Healthcare Research and Quality (US); 2007 Dec. (Evidence Syntheses, No. 50).

Additional supporting recommendations

Source	Recommendations
U.S. Preventive Services Task Force (link above under	1. The USPSTF recommends against screening for asymptomatic carotid artery stenosis in the general adult population.

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citations)	
American College of Cardiology/ American Heart Association	1. In patients who have undergone vertebral artery revascularization, serial noninvasive imaging of the extracranial vertebral arteries is reasonable at intervals similar to those for carotid revascularization. 2. Carotid duplex ultrasonography is not recommended for routine screening of asymptomatic patients who have no clinical manifestations of or risk factors for atherosclerosis. 3. Duplex ultrasonography might be considered to detect carotid stenosis in asymptomatic patients without clinical evidence of atherosclerosis who have 2 or more of the following risk factors: hypertension, hyperlipidemia, tobacco smoking, a family history in a first-degree relative of atherosclerosis manifested before age 60 years, or a family history of ischemic stroke. However, it is unclear whether establishing a diagnosis of ECVD would justify actions that affect clinical outcomes. 4. Duplex ultrasonography to detect hemodynamically significant carotid stenosis may be considered in asymptomatic patients with symptomatic peripheral artery disease (PAD), coronary artery disease (CAD), or atherosclerotic aortic aneurysm, but because such patients already have an indication for medical therapy to prevent ischemic symptoms, it is unclear whether establishing the additional diagnosis of extracranial carotid and vertebral artery disease (ECVD) in those without carotid bruit would justify actions that affect clinical outcomes.

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Rapid Evidence Synthesis Reports

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Intensive Glycemic Control in Older Adults with Type 2 Diabetes Mellitus: Rapid Evidence Synthesis

This report was prepared by the Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University, under Contract No. VA268-16-Q-0140, in support of an HSR&D research study focused on Identifying, Measuring, and Facilitating Opportunities for De-Intensification of Medical Services.

KEY MESSAGES

Why is this important?

- There is uncertainty about ideal target glycated hemoglobin (HbA1c) levels in patients with type 2 diabetes mellitus, and clinical guidelines have discordant recommendations regarding optimal HbA1c thresholds. Potential benefits of more intensive glycemic control include reduced risk of macro- and microvascular complications; however, overly intensive glycemic control is also associated with increased risk of hypoglycemia. The benefits and harms of intensive glycemic control in older patients and/or those with multiple comorbidities and limited life expectancy is particularly uncertain. This rapid evidence review synthesizes the evidence on benefits and harms of continuation of intense glycemic control in people with diabetes, as well as the effect of de-intensification of glycemic control.

What is the evidence on evidence of potential benefits and harm from continued intense glycemic control in people with diabetes?

- There was no difference between intensive and standard glycemic control on all-cause or cardiovascular mortality, based on two systematic reviews and most individual trials.
    - One trial, ACCORD, found significantly increased incidence of all-cause mortality with intensive glycemic control (HbA1c <6.5%) in those under age 65 years (accounting for 66% of the study population) but not in those over age 65.
    - ACCORD found no difference in risk of all-cause mortality between intensive and standard glycemic control when patients were stratified according to diabetes duration or baseline HbA1c.
- Intensive glycemic control was associated with a reduced risk of non-fatal MI, based on systematic reviews and the ACCORD trial.
- Intensive glycemic control increased risk of hypoglycemia ranging from RR 1.85 to 2.95; based on individual trials (HbA1c <6.4 to <8.4%) and systematic reviews.

What is the evidence on de-intensification?

- There was no direct evidence on the benefits and harms of de-intensification of glycemic control.

What are the implications of our findings?

- There was little evidence of benefit with intensive glycemic control apart, from HbA1c lowering and incidence of non-fatal MI, with increased risk of hypoglycemia.
- Observational evidence suggests that the effects of intensive HbA1c can take over a decade to manifest; this may have implications for applying evidence on potential benefits of intensive glycemic control in persons with limited life expectancy due to older age or multiple or serious comorbidities.

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Background

The Centers for Disease Control and Prevention estimates that 16% of adults age 45 to 64 years and 26% of adults over age 65 have diagnosed or undiagnosed diabetes;[1] among U.S. Veterans, the rate of diabetes is about 25%.[2] There is significant burden of disease associated with type 2 diabetes mellitus (DM), particularly in those over age 65 years, including increased risk of macrovascular (e.g., fatal and nonfatal cardiovascular disease) and microvascular (e.g., nephropathy, retinopathy, neuropathy) sequelae.[3] Optimizing glycemic control is vital to clinical management of DM, in order to improve quality of life and minimize the negative health consequences associated with this condition.[3,4]

There has been considerable debate and uncertainty about ideal target glycated hemoglobin (HbA1c) levels in patients with DM.[5] Clinical guidelines have discordant recommendations regarding optimal HbA1c thresholds. Over time, HbA1c levels ranging from <6.0% to <7.0% have been recommended by various organizations for people with DM, with higher targets often recommended for older and/or frail patients.[5-9] The benefits and harms of intensive glycemic control in older patients and/or those with multiple comorbidities and limited life expectancy is particularly uncertain.[3] Potential benefits of more intensive glycemic control include reduced risk of macro- and microvascular complications. However, overly intensive glycemic control is also associated with increased risk of hypoglycemia, which can lead to falls, fractures, coma, and even death.[4] Studies indicate that more than 50% of older adults with diabetes may have overly intensive glycemic lowering, based on HbA1c levels of <7%, suggesting a need for de-intensificatoin.[10,11] Overly frequent HbA1c testing is also common among older adults, with >60% receiving testing more than twice a year; those with the highest number of tests per year are at increased risk of treatment intensification.[12]

This rapid evidence review synthesizes the evidence on benefits and harms of continuation of intense glycemic control in people with diabetes, as well as the effect of de-intensification of glycemic control.

Current Guidelines

Selected current practice guidelines on glycemic control are summarized in **Table 1**. Generally, in patients with DM, HbA1c targets recommended in guidelines range from 7% to less than 9%, depending on the number of comorbidities and life expectancy. The highest HbA1c targets (≥8 to <12% in asymptomatic patients) are those recommended by the Diabetes Care Program of Nova Scotia and the Palliative and Therapeutic Harmonization (PATH) Program.[9] These recommendations are the only ones specifically developed for frail, older adults.

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Table 1. Summary of current guidelines on glycemic control

Guideline	Recommendations

American Geriatrics Society[6,13]	• HbA1c target goals:
	  ○ 7.0 – 7.5% in healthy older adults with few comorbidities and good functional status (Level IA evidence)
	  ○ 7.5 – 8.0% in those with moderate comorbidity and a life expectancy <10 years (Level IA evidence)
	  ○ 8.0 – 9.0% in those with multiple morbidities, poor health and limited life expectancy. (Level IIA evidence)
	• There is no evidence that using medications to achieve tight glycemic control in most older adults with type 2 diabetes is beneficial.
	• Tight control has been consistently shown to produce higher rates of hypoglycemia in older adults.
	• Given the long time frame to achieve theorized microvascular benefits of tight control, glycemic targets should reflect patient goals, health status and life expectancy.

American Diabetes Association[7]	• For many nonpregnant adults a reasonable HbA1c goal is <7% (53 mmol/mol). (Level A evidence) • Providers might reasonably suggest more stringent HbA1c goals (such as <6.5% [48 mmol/mol]) for selected individual patients if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate patients might include those with short duration of diabetes, type 2 diabetes treated with lifestyle or metformin only, long life expectancy, or no significant cardiovascular disease. (Level C evidence) • Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. (Level B evidence)
VA/DoD[8]	• HbA1c target of <7%, if it can be achieved without risk in patients with a life expectancy of at least 10-15 years; no or very mild microvascular complications of diabetes; and no major concurrent illnesses. (Level A evidence) • HbA1c target of <8% in patients with longer duration diabetes (more than10 years) or with comorbid conditions, and who require combination medication regimen including insulin. (Level A evidence) • HbA1c target of 8-9% in patients with advanced microvascular complications and/or major comorbid illness, and/or a life expectancy of less than 5 years is as these patients are unlikely to benefit from aggressive glucose lowering management. (Level A evidence) • HbA1c target <9% in patients with diabetes to reduce symptoms of hyperglycemia. (Level C evidence) • Risk of hypoglycemia should be considered in recommending a target goal. (Level B evidence)

Diabetes Care Program of Nova Scotia and the Palliative and Therapeutic Harmonization (PATH) Program[9]	• Committee-based recommendations developed specifically for frail, older adults (frailty based on validated assessments and/or presence of multiple debilitating comorbidities)
	  ○ HbA1c <8%: Decrease or discontinue diabetes treatment
	  ○ HbA1c ≥8% to <12%: Acceptable if asymptomatic
	  ○ HbA1c >12%: Consider increasing diabetes treatment

Abbreviations: HbA1c=glycated hemoglobin

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Methods

Topic Selection and Scope Development

Key Questions

This review includes studies relevant the following Key Questions and Eligibility Criteria:

1) What is the evidence of potential benefits and harm from continued intense glycemic control in people with diabetes?
2) What is the evidence that de-intensification of glycemic control would not cause harm or may benefit specific patient populations?

Eligibility Criteria

- Population: Adults with diabetes, focusing on evidence in older persons
- Intervention: Intensive glycemic control based on target HbA1c measures
- Comparator: Standard or non-targeted glycemic control
- Outcomes: All-cause and CV mortality, serious CV events, serious adverse events attributed to glucose-lowering medication
- Timing: Any
- Setting: Any
- Study design: high-quality systematic reviews and randomized controlled trials

Searching and Study Selection

The RES research librarian conducted searches of Ovid MEDLINE®, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews through November 2016. We used a best evidence approach when reviewing abstracts and selecting studies for inclusion that involves using the most relevant studies with the strongest methodologies.[14,15] We included good-quality systematic reviews that provided direct evidence on glycemic control in older adults. We included randomized controlled trials (RCTs) that were published subsequent to included systematic reviews, or when no good-quality systematic reviews meeting inclusion criteria were available.

Data Synthesis and Quality Assessment

Data abstraction was conducted using standard, prespecified criteria based on Agency for Healthcare Research and Quality guidance.[16] After studies were selected for inclusion, data was abstracted into predetermined table templates. Quality assessment of systematic reviews was based on the ROBIS tool.[17] We qualitatively summarized the evidence based on the overall quality, consistency, precision, and directness of the evidence.[16]

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Results

Key Question 1. What is the evidence of potential benefits and harm from continued intense glycemic control in people with diabetes?

Evidence from Systematic Reviews

Numerous systematic reviews have assessed the benefits and harms of intensive versus standard glycemic control,[18-22] largely drawing from the same evidence base with consistent risk estimates.[23] Evidence from one of the largest (Boussageon)[24] and one of the most recent (Sardar)[25] good-quality reviews is summarized in **Table 2; Appendix A**. The reviews included 13 and 17 trials, respectively, comparing >18,000 patients receiving intensive glycemic control interventions and >16,000 receiving standard glycemic control interventions. Intensive glycemic control interventions were variably defined among the included studies in both reviews, ranging from HbA1c targets of <6.0% to <8.0%, FPG glucose targets of 4.0 to <7.0 mmol/L, or the addition of insulin or other glucose-lowering drugs to standard care; details about intensive and standard interventions appear in **Appendix A**. The mean age in the studies included in the reviews was 57 and 62 years (range 49 to 66 years), and the duration of diabetes was four and five years (range from newly diagnosed to 12 years). Mean baseline HbA1c was 7.9% and 9%.

Table 2. Characteristics of systematic reviews of intensive glycemic control

Author, Year	Countries	Types of Studies Included	Intervention Characteristics	Patient characteristics
Boussageon 2011[24]		13 RCTs	Intensive glycemic control (n=18,315) Standard glycemic control (n=16,218)	n=34,533 Mean age 62 years (range 49 to 66 years) 40% female (range 0 to 69%) Mean duration of diabetes 8 years (range 0 to 12 years) Mean baseline HbA1c 7.9% (range 7.1 to 9.5%) Mean duration of followup 5 years (range 1 to 10 years)
Sardar 2015[25]	United States Canada	17 RCTs (7 North America; 10 rest of the world [ROW]) of patients age ≥18 years with type 2 DM comparing intensive glycemic control with standard treatment (placebo or less intensive control)	Intensive glycemic control (n=18,603) Standard glycemic control (n=16,364)	n=34,967 Mean age 57 years (range 49 to 66 years) 43 % female (range 0 to 78%) Mean duration of diabetes 5 years (range newly diagnosed to 12 years) Mean baseline HbA1c 9.0% (range 7.1 to 11.9) Mean baseline FPG 8.7 mmol/L (range 7.9 to 13.5) Duration of followup 4 years (range 4 months to 20 years)

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The reviews found no difference between intensive and standard glycemic control and risk of all-cause (9 trials, relative risk [RR] 1.04, 95% CI 0.91 to 1.19; I^2=42%; and 12 trials, odds ratio [OR] 1.03, 95% CI 0.93 to 1.13; I^2=20%) or cardiovascular mortality (10 trials, RR 1.11, 95% CI 0.86 to 1.43; I^2=61%; and 12 trials, OR 1.90, 95% CI 0.90 to 1.32; I^2=53%; **Table 3**).[24,25] The Boussageon review also found no difference between groups in fatal or nonfatal myocardial infarction (MI) (8 trials; RR 0.90, 95% CI 0.81 to 1.01; I^2=0%), stroke (8 trials; RR 0.96, 95% CI 0.83 to 1.13; I^2=0%), retinopathy (8 trials; RR 0.85, 95% CI 0.71 to 1.03; I2=54%) or neuropathy (6 trials; RR 0.99, 95% CI 0.95 to 1.03; I^2=0%),[24] though intensive glucose lowering was associated with decreased risk of nonfatal MI (8 trials; RR 0.85, 95% CI 0.74 to 0.96; I^2=0%). Intensive glucose lowering was associated with increased risk of severe hypoglycemia (5 trials; RR 2.33, 95% CI 1.62 to 3.36; I^2=63%).

For some outcomes, pooled estimates were characterized by the presence of moderate to high statistical heterogeneity. The Sardar review attempted to account for this heterogeneity by subgrouping the included trials into those conducted in North America and those conducted in the rest of the world (ROW; **Appendix B**).[25] Stratification of trials in this manner reduced heterogeneity, with intensive glucose lowering associated with increased risk of all-cause (5 trials; OR 1.21, 95% CI 1.05 to 1.90; I^2=0%) and cardiovascular (7 trials; OR 1.41, 95% CI 1.05 to 1.90; I^2=36%) mortality in the North American studies, but not in the ROW studies (7 trials; OR 0.93, 95% CI 0.85 to 1.03; I^2=0% and OR 0.89, 95% CI 0.73 to 1.03; I^2=0%). It is unclear if these findings are a result of differences in study designs, patient populations or systemic health care variations, although it is notable that the mean reduction in HbA1c in the North American studies was 2.2%, versus 0.8% in the ROW studies. In addition, results of the North American studies were highly influenced by the large Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which accounted for 77% of the total population of the North American studies.

Table 3. Summary of findings of systematic reviews of intensive glycemic control

Author, Year	Findings: Intensive vs. Standard Glycemic Control
Boussageon 2011[24]	All-cause mortality (9 trials): RR 1.04 (95% CI 0.91 to 1.19; I^2=42%) CV mortality (10 trials): RR 1.11 (95% CI 0.86 to 1.43; I^2=61%) Nonfatal MI (8 trials): RR 0.85 (95% CI 0.74 to 0.96; I^2=0%) Fatal or nonfatal MI (8 trials): RR 0.90 (95% CI 0.81 to 1.01; I^2=0%) Nonfatal stroke (5 trials): RR 1.00 (95% CI 0.83 to 1.21; I^2=0%) Fatal or nonfatal stroke (8 trials): RR 0.96 (95% CI 0.83 to 1.13; I^2=0%) Retinopathy (8 trials): RR 0.85 (95% CI 0.71 to 1.03; I^2=54%) Neuropathy (6 trials): RR 0.99 (95% CI 0.95 to 1.03; I^2=0%) Peripheral vascular events (8 trials): RR 0.98 (95% CI 0.84 to 1.13; I^2=34%) Severe hypoglycemia (5 trials): RR 2.33 (95% CI 1.62 to 3.36; I^2=63%)
Sardar 2015[25]	All-cause mortality (12 trials): OR 1.03 (95% CI 0.93 to 1.13; I^2=20%) CV mortality (12 trials): OR 1.09 (95% CI 0.90 to 1.32; I^2=53%) Nonfatal MI: North America only (5 trials): OR 0.80 (95% CI 0.68 to 0.93; I^2=0%); ROW only (5 trials): OR 0.83 (95% CI 0.67 to 1.03; I^2=44%)

Evidence from Randomized Controlled Trials

Literature searches did not identify any new RCTs of intensive versus standard glycemic control published since the most recent systematic review described above. Three large individual trials (ACCORD, the Action in Diabetes and Vascular Disease: Preterax and Diamicrom Modified Release

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Controlled Evaluation [ADVANCE] trial, and the Veterans Affairs Diabetes Trial [VADT]), all included in the systematic reviews and accounting for about two-thirds of the total sample in the reviews, enrolled patients with mean age of 60 years or older (**Table 4**).[26-29] The ACCORD trial conducted separate subgroup analyses according to age, duration of diabetes and baseline HbA1c, the ADVANCE trial enrolled the oldest population, although with the shortest duration of diabetes, and the VADT study enrolled a population with the longest duration of diabetes and the highest achieved HbA1c level. The three trials defined intensive glycemic control as target HbA1c levels of less than 6% in ACCORD, less than 6.5% in ADVANCE and an absolute HbA1c reduction of 1.5% in VADT.

Table 4. Patient characteristics and HbA1c levels in the ACCORD, ADVANCE and VADT trials

Study Name n= Study Duration	Mean Age	Duration of Diabetes	History of Prior Cardiovascular Event	Baseline HbA1c	HbA1c Target in Intensive Control Group	Achieved HbA1c: Intensive vs. Standard Control
ACCORD[26] n=10,251 4 years	62 years	10 years	35%	8.3%	<6.0%	6.4 vs. 7.5%
ADVANCE[28] n=11,140 5 years	66 years	8 years	32%	7.5%	<6.5%	6.5 vs. 7.2%
VADT[29] n=1,791 6 years	60 years	12 years	40%	9.4%	Reduction of 1.5% from baseline value	6.9% vs. 8.4%

All-Cause Mortality

Overall risk of all-cause mortality in ACCORD was 5% in the intensive glycemic control group and 4% in the standard control group (hazard ratio [HR] 1.22, 95% CI 1.01 to 1.46).[26] Post-hoc subgroup analysis according to age found a nonsignificant decreased risk of all-cause mortality with intensive glycemic control versus standard control in study participants over age 75 years, while longer duration of diabetes (>10 years) was associated with a nonsignificant increased risk of all-cause mortality (**Table 5**). Those with the highest HbA1c values at baseline had a higher risk of death with intensive treatment, while the mortality rate for those with lower levels at baseline and in the standard treatment group were relatively stable during the study's 3.5 years followup (**Table 5**).

Table 5. Intensive glycemic lowering versus standard care and all-cause mortality in ACCORD subgroups

	Mortality Rate	Hazard Ratio, 95% CI
Age		
<65 years	4% (125/3397) vs 3% (87/3382)	1.39, 1.05 to 1.82
65 to 69 years	6% (57/938) vs 5% (46/947)	1.23, 0.84 to 1.82
70 to 74 years	8% (40/516) vs 7% (38/537)	1.01, 0.65 to 1.59
≥75 years	13% (35/277) vs 12% (32/257)	0.90, 0.55 to 1.47
Duration of Diabetes		
0-5 years	4% (64/1474) vs 4% (62/1455)	0.97, 0.68 to 1.38
6-10 years	5% (68/1472) vs 3% (46/1459)	1.39, 0.96 to 2.02
11-15 years	4% (42/971) vs 3% (33/987)	1.22, 0.77 to 1.92
≥16 years	7% (80/1163) vs 5% (61/1178)	1.35, 0.97 to 1.89
Baseline HbA1c		
<7.5%	5% (50/1036) vs 4% (45/1022)	1.00, 0.67 to 1.50
7.4 to 8.4	4% (93/2226) vs 4% (90/2200)	1.00, 0.75 to 1.34
>8.5%	6% (114/1857) vs 4% (68/1887)	1.64, 1.22 to 2.22

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Achieved HbA1c level in the ADVANCE trial was similar to that in ACCORD, while HbA1c levels were higher in the VADT (**Table 4**, above). Neither the ADVANCE nor VADT studies conducted subgroup analysis according to age, diabetes duration or baseline HbA1c.[28,29]

Other Outcomes

Composite cardiovascular outcomes. ACCORD, ADVANCE and VADT all included a combination of fatal and nonfatal cardiovascular events as a primary outcome. In ACCORD and VADT, there was a nonsignificant effect on the primary outcome in favor of intensive treatment (HR 0.90, 95% CI 0.78 to 1.04 and HR 0.88, 95% CI 0.74 to 1.05).[26,29] The risk estimate in ADVANCE was similar, and marginally significant (HR 0.90, 95% CI 0.82 to 0.98).[28] Subgroup analyses from ACCORD and ADVANCE found no differential effect when patients were stratified according to patient age <65 years and ≥65 years. In ACCORD, higher baseline HbA1c (>8.0%) was associated with increased risk in the intensive group compared with lower HbA1c (≤8.0%) at baseline (p=0.03),[26] but there was no difference in ADVANCE in patients with baseline HbA1c <7.2% and ≥7.2%.[28]

Nonfatal MI and other cardiovascular outcomes. Only the ACCORD trial found intensive glycemic control associated with significantly reduced risk of nonfatal MI (HR 0.76, 95% CI 0.62 to 0.92), but when limited to patients over age 65 years, the risk estimate was not significant (HR 0.89, 95% CI 0.68 to 1.16).[30] Neither ADVANCE nor VADT found intensive glycemic control associated with significant effects on nonfatal MI, and neither reported risk of nonfatal MI in subgroups.[26]

Subgroup analysis from ACCORD according to patients age less than 65 years and those age 65 years or older found no significant differences between groups in risk of fatal or nonfatal stroke, fatal or nonfatal congestive heart failure, or cardiovascular mortality.[30]

Severe hypoglycemia. Risk of severe hypoglycemia was significantly higher with intensive glycemic control in all three trials, ranging from RR 1.85 (95% CI 1.30 to 2.63) in ADVANCE, RR 2.74 (95% CI 1.57 to 4.77) in VADT and RR 2.95 (95% CI 2.51 to 3.46) in ACCORD.[24,30] In ACCORD, risk was similar in those age 65 years and older (RR 2.96. 95% CI 2.35 to 3.73) than those less than age 65 (RR 2.95, 95% CI 2.36 to 3.68).[30]

Key Question 2. What is the evidence that de-intensification of glycemic control would not cause harm or may benefit specific patient populations?

We identified no trials that directly evaluated benefits and harms of de-intensification of glycemic control.

Discussion

Table 6 summarizes the benefits and harms of continuing intensive glycemic control versus de-intensifying glycemic control. Intensive glycemic control did not reduce incidence of all-cause or cardiovascular mortality based on evidence from good-quality systematic reviews, though intensive glycemic control was associated with decreased risk of nonfatal MI. All-cause mortality was significantly increased in the ACCORD trial, in which patients in the intensive control group achieved a mean HbA1c of 6.4%. The ACCORD trial also found reduced intensive glycemic control associated with decreased risk of nonfatal MI. Intensive glycemic control also increased risk of severe hypoglycemia. Due to lack of direct evidence, the benefits and harms of de-intensification are unclear.

There is some evidence that intensive glycemic control may be most beneficial when initiated early in the DM course, and that the positive effects of intensive glycemic control can take many years to manifest, based on observational evidence from the UK Prospective Diabetes Study (UKPDS).[31] In UKPDS, which enrolled patients with newly diagnosed DM (mean age 54 years), median baseline HbA1c was 8.0%, and although the intensive treatment groups had some initial reduction in HbA1c (median

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6.6% versus 7.9% in the standard treatment group), at one year HbA1c levels had stabilized and were similar in both the intensive and standard groups (about 7.8 to 8.0%).[32,33] Observational 20-year followup data (10 years post-treatment) found significant reductions in all-cause and diabetes-related mortality and MI in people treated with intensive glycemic control.[33] These positive effects of intensive glycemic control were not observed during the ten years of the UKPDS trial, and six-year post-treatment followup from the ADVANCE trial also found no positive effect on all-cause or cardiovascular mortality or nonfatal MI or stroke.[34] This observational evidence suggests that the effects of intensive HbA1c can take over a decade to manifest; this may have implications for applying evidence on potential benefits of intensive glycemic control in persons with limited life expectancy due to older age or multiple or serious comorbidities.

Table 6. Summary of benefits and harms of both continuing intensive glycemic control and de-intensifying glycemic control

Action	Benefits	Harms
Intensive glycemic control	• Potentially reduced risk of non-fatal MI, based on the results of the ACCORD trial (HbA1c <6.5%) • No clear benefit for other outcomes, including all-cause or cardiovascular mortality, based on systematic reviews and individual trials • Observational evidence suggests the benefits of intensive glycemic control can take 10+ years to manifest	• Increased risk of all-cause mortality; based on the ACCORD trial (HbA1c <6.5%). Pooled estimates from systematic reviews were not significant for this outcome. • Increased risk of hypoglycemia ranging from RR 1.85 to 2.95; based on individual trials (HbA1c <6.4 to <8.4%) and systematic reviews
Discontinuing or De-intensifying intensive glycemic control	• No direct evidence	• No direct evidence

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Appendix

Appendix A. Characteristics of systematic reviews of intensive glycemic control and summary of findings

Author, Year	Types of Studies Included	Interventions*	Patient Characteristics	Intensive vs. Standard Glucose Control	Limitations
Boussageon 2011[24]	13 RCTs	Intensive glycemic control (n=18,315) Standard glucose control (n= 16,218)	n=34,533 Mean age 62 years (range 49 to 66 years) 40% female (range 0 to 69%) Mean duration of diabetes 8 years (range 0 to 12 years) Mean baseline HbA1c 7.9% (range 7.1 to 9.5%) Mean duration of followup 5 years (range 1 to 10 years)	All-cause mortality (9 trials): RR 1.04 (95% CI 0.91 to 1.19; I^2=42%) CV mortality (10 trials): RR 1.11 (95% CI 0.86 to 1.43; I^2=61%) Nonfatal MI (8 trials): RR 0.85 (95% CI 0.74 to 0.96; I^2=0%) Fatal or nonfatal MI (8 trials): RR 0.90 (95% CI 0.81 to 1.01; I^2=0%) Nonfatal stroke (5 trials): RR 1.00 (95% CI 0.83 to 1.21; I^2=0%) Fatal or nonfatal stroke (8 trials): RR 0.96 (95% CI 0.83 to 1.13; I^2=0%) Retinopathy (8 trials): RR 0.85 (95% CI 0.71 to 1.03; I^2=54%) Neuropathy (6 trials): RR 0.99 (95% CI 0.95 to 1.03; I^2=0%) Peripheral vascular events (8 trials): RR 0.98 (95% CI 0.84 to 1.13; I^2=34%) Severe hypoglycemia (5 trials): RR 2.33 (95% CI 1.62 to 3.36; I^2=63%)	• No studies conducted in older adults • Varying definitions among included studies of intensive and standard glucose control • Variation in patient characteristics, particularly duration of diabetes at time of study entry
Sardar 2015[25]	17 RCTs (7 North America; 10 rest of the world [ROW])	Intensive glycemic control (n=18,603) Standard glycemic control (n=16,364)	n=34,967 Mean age 57 years (range 49 to 66 years) 43 % female (range 0 to 78%) Mean duration of diabetes 5 years (range newly diagnosed to 12 years) Mean baseline HbA1c 9.0% (range 7.1 to 11.9) Mean baseline FPG 8.7 mmol/L (range 7.9 to 13.5) Duration of followup 4 years (range 4 months to 20 years)	All-cause mortality (12 trials): OR 1.03 (95% CI 0.93 to 1.13; I^2=20%) CV mortality (12 trials): OR 1.09 (95% CI 0.90 to 1.32; I^2=53%)	• No studies conducted in older adults • Varying definitions among included studies of intensive and standard glucose control • Variation in patient characteristics, particularly duration of diabetes at time of study entry

*Intensive and standard interventions were variably defined:

Boussageon 2011

- Intensive glycemic control: HbA1c target <6% (2 trials), <6.5% (1 trial), <7% (1 trial); FPG <6 mmol/L (1 trial), <7.8 (1 trial); standard treatment + TZD (2 trials); use of tolbutamide or phenformin (1 trial) or insulin (1 trial); insulin + metformin (1 trial)
- Standard glycemic control: HbA1c 7.0 to 7.9% (1 trial), <9% (1 trial); FPG <15 mmol/L (1 trial); standard glucose control (1 trial); placebo with or without insulin (4 trials); insulin (3 trials)

Sardar 2015

- Intensive glycemic control: HbA1c target <6% (2 trials), ≤6.5% (3 trials), range 6.5 to 7.0% (1 trial), <7.0% (3 trials), <7.5% (1 trial), "normal range" (1 trial); FPG ≤6.6 mmol/L (2 trials), range 4.0 to 7.0 mmol/L (1 trial); use of tolbutamide or phenformin (1 trial) or insulin (1 trial); insulin + metformin (1 trial)
- Standard glycemic control: HbA1c target <7.5% (1 trial), 7.0 to 7.9% (1 trial), no target (6 trials), locally defined target (1 trial); FPG <7.8 mmol/L (1 trial), <15 mmol/L (1 trial); elimination of symptoms (2 trials); insulin + placebo (1 trial); not reported (2 trials)

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Appendix B. Intensive glycemic control summary of findings according to region of the world

	Patient Characteristics	Summary of Findings
Sardar 2015[25] - Findings according to region of the world	North America n=13,287 Mean age 57 years (range 51 to 62 years) 42% female (range 0 to 78%) Mean duration of diabetes 5 years (range 6 months to 12 years) Mean baseline HbA1c 10.6% (range 8.1 to 11.9; not reported in 2 trials) Mean baseline FPG 9.9 mmol/L (range 7.9 to 12) Duration of followup 5 years (range 4 months to 13 years)	North America All-cause mortality (5 trials): OR 1.21 (95% CI 1.05 to 1.90; I^2=0%) CV mortality (7 trials): OR 1.41 (95% CI 1.05 to 1.90; I^2=36%) Macrovascular events (3 trials): OR 0.95 (95% CI 0.77 to 1.17; I^2=50%) Nonfatal MI (5 trials): OR 0.80 (95% CI 0.68 to 0.93; I^2=0%) Nonfatal stroke (2 trials): OR 0.91 (95% CI 0.58 to 1.43; I^2=50%) Microvascular events (1 trial): OR 0.94 (95% CI 0.87 to 1.02) Nephropathy (4 trials): OR 1.02 (95% CI 0.74 to 1.41; I^2=55%) Retinopathy (5 trials): OR 0.74 (95% CI 0.63 to 0.87; I^2=0%) Neuropathy (3 trials): OR 0.92 (95% CI 0.83 to 1.01; I^2=0%) Peripheral vascular disease (4 trials): OR 1.03 (95% CI 0.62 to 1.69; I^2=57%) Severe hypoglycemia (4 trials): OR 3.52 (95% CI 3.07 to 4.03; I^2=0%)
	Rest of the World (Outside North America) n=21,680 Mean age 57 years (range 49 to 66 years) 43% female (range 30 to 57%) Mean duration of diabetes 5 years (range newly diagnosed to 12 years) Mean baseline HbA1c 8.1% (range 7.1 to 10.7) Mean baseline FPG 8.0 mmol/L (range 8.8 to 13.5) Duration of followup 4 years (range 5 months to 20 years)	Rest of the World (Outside North America) All-cause mortality (7 trials): OR 0.93 (95% CI 0.85 to 1.03; I^2=0%) CV mortality (7 trials): OR 0.89 (95% CI 0.73 to 1.03; I^2=0%) Macrovascular events (4 trials): OR 0.90 (95% CI 0.73 to 1.10; I^2=38%) Nonfatal MI (5 trials): OR 0.83 (95% CI 0.67 to 1.03; I^2=44%) Nonfatal stroke (6 trials): OR 0.83 (95% CI 0.59 to 1.17; I^2=64%) Microvascular events (2 trials): OR 0.82 (95% CI 0.73 to 0.93; I^2=14%) Nephropathy (5 trials): OR 0.53 (95% CI 0.29 to 0.96; I^2=69%) Retinopathy (5 trials): OR 0.78 (95% CI 0.60 to 1.03; I^2=59%) Neuropathy (4 trials): OR 1.02 (95% CI 0.95 to 1.09; I^2=0%) Peripheral vascular disease (4 trials): OR 0.97 (95% CI 0.81 to 1.17; I^2=17%) Severe hypoglycemia (4 trials): OR 1.45 (95% CI 0.85 to 2.47; I^2=62%)

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Metformin Use in Older Adults with Type 2 Diabetes Mellitus: Rapid Evidence Synthesis

This report was prepared by the Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University, under Contract No. VA268-16-Q-0140, in support of an HSR&D research study focused on Identifying, Measuring, and Facilitating Opportunities for De-Intensification of Medical Services.

KEY MESSAGES

Why is this important?

- Metformin is recommended by the American Diabetes Association and other organizations as the first-line pharmacological therapy for treatment of type 2 diabetes mellitus. When metformin monotherapy does not result in adequate glucose control, additional glucose-lowering drugs can be added to metformin. However, this combination therapy can increase the risk of hypoglycemia, which can be especially devastating in older and frail patients. This rapid evidence review synthesizes the evidence on benefits and harms of intensification of glucose-lowering therapy in persons who do not achieve adequate control on metformin monotherapy, as well as on de-intensification of glucose-lowering therapy in persons on combination therapy that includes metformin.

What is the evidence on benefits and harms of using metformin versus metformin in combination with another noninsulin glucose-lowering agent to achieve glycemic control in older adults with type 2 diabetes?

- There was no clear difference between combination therapy with metformin and metformin monotherapy in risk of all-cause or cardiovascular mortality, or cardiovascular events, based on a large systematic review of primarily short-term (<1 year) randomized trials, but most estimates were imprecise.
- Longer-term evidence from a large observational study suggests decreased risk of all-cause mortality and cardiovascular events with certain combination therapies when compared with metformin monotherapy; findings are susceptible to residual confounding.
- Combination therapy with metformin was associated with modestly larger reductions in HbA1c compared with metformin monotherapy, based on a systematic review of short-term randomized trials and a large observational study.
- Combination therapy with metformin was associated with increased risk of mild/moderate hypoglycemia compared with metformin monotherapy in a systematic review of randomized trials, but there were too few cases of severe hypoglycemia with either combination therapy or monotherapy groups to determine risks.
- A large observational study found combination therapy consistently increased risk of severe hypoglycemia compared with metformin monotherapy.

What is the evidence on de-intensification?

- There is no direct evidence on effects of de-intensification of non-metformin glucose-lowering medications in older patients on combination therapy including metformin for type 2 diabetes, versus continued combination therapy.

What are the implications of our findings?

- Combination therapy with metformin was more effective than metformin monotherapy at lowering HbA1c, but combination therapy was associated with increased risk of hypoglycemia. There were no clear effects on clinical outcomes based on randomized trials, but estimates were imprecise. Evidence on how benefits and harms of combination therapy may differ in older adults is lacking.

Background

Metformin is recommended by the American Diabetes Association and numerous other organizations as the consensus first-line pharmacological therapy for treatment of type 2 diabetes

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mellitus (DM), based on glycemic efficiency, absence of weight gain, absence of hypoglycemia, favorable tolerability profile, and relatively low costs.[1] In addition, metformin was associated with decreased risk of cardiovascular outcomes in two randomized trials. In the United Kingdom Prospective Diabetes Study (UKPDS), metformin was associated with a 30% reduction (95% CI 5% to 48%) in composite cardiovascular outcomes versus usual care.[2] However, UKPDS enrolled patients from 1977 to 1991, and the control group received less intense glycemic control than current standards. The more recent Study on the Prognosis and Effect of Antidiabetic Drugs on Type 2 Diabetes Mellitus with Coronary Artery Disease (SPREAD DIMCAD) found metformin associated with lower risk of cardiovascular outcomes than sulfonylurea (hazard ratio [HR] 0.54, 95% CI 0.30 to 0.90).[3] SPREAD DIMCAD was not designed to distinguish benefit of metformin from harm from sulfonylurea. Evidence on cardiovascular benefits of other diabetes medications is limited.

Despite recommendations for metformin as the first-line pharmacological treatment for DM, clinicians face some challenges in selecting the appropriate therapy for some patients with DM, including older patients and those with multiple comorbidities. Contraindications to metformin include renal failure and hypersensitivity to metformin; renal failure is more common among older persons. In addition, metformin monotherapy does not achieve HbA1c targets in some patients, particularly those with higher HbA1c levels at baseline.[4] Several classes of glucose-lowering drugs can be added to metformin therapy, including sulfonylureas, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, and others. However, combination therapy can increase the risk of hypoglycemia.[5] Hypoglycemia can be especially devastating in older and frail patients, leading to increased risk of falls, cognitive dysfunction, and, potentially, death.[6] Thus, combination therapy may not always be an appropriate choice for some patients, even if their DM has previously been managed with such a treatment strategy. In addition, although older patients with very low HbA1c may especially benefit from de-intensification of glycemic control, in clinical practice de-intensification in these patients is infrequently achieved.[7-9] This may be due to local patient management practices or due to the lack of clear guidance on when to initiate de-intensification.[7]

Data indicate that noninsulin medications other than metformin are commonly prescribed. In 2014, about 53% of Medicare claims for noninsulin diabetes drugs were for metformin, 30% for sulfonylureas, 13% for DPP-4 inhibitors, 5% for TZDs, 2% for GLP-1 agonists, and 1% for sodium-glucose cotransporter 2 (SGLT-2) inhibitors.[10]

The purpose of this rapid evidence review is to synthesize the evidence on benefits and harms of intensification of glucose-lowering therapy in persons who do not achieve adequate control on metformin monotherapy, as well as on de-intensification of glucose-lowering therapy in persons on combination therapy that includes metformin.

Current Guidelines

Current clinical practice guidelines on the use of glucose-lowering medications in older adults are summarized in **Table 1**. Direct evidence on how best to balance the need for adequate glucose lowering while avoiding hypoglycemia in these patients is lacking, and most guidelines that address these populations rely on clinical expertise.[15] Still, metformin remains the first-choice therapy in older patients with diabetes, and certain other glucose-lowering drugs should be avoided (e.g., chlorpropamide and glyburide, due to risk of prolonged hypoglycemia).

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Table 1. Summary of recommendations on the use of specific glucose-lowering medications in older adults

Guideline	Recommendations

American Diabetes Association[16]	Hypoglycemia should be avoided in older adults; it should be screened for and managed by adjusting glycemic targets and pharmacological interventions. (B grade level of evidence)
	Intervention recommendations:
	• Recommended: Metformin
	  ○ First-line medication, except in patients with renal insufficiency or significant heart failure
	• Use with caution: Sulfonylureas and other insulin secretagogues
	  ○ Insulin can cause hypoglycemia; patients or caregivers should have good visual and motor skills and cognitive ability
	  ○ Glyburide use is contraindicated
	• Other agents and considerations
	  ○ Glucagon-like peptide 1 receptor agonists and dipeptidyl peptidase 4 inhibitors have few side effects but may be cost-prohibitive; patients or caregivers should have good visual and motor skills and cognitive ability
	  ○ Sodium glucose cotransporter 2 inhibitors have limited long-term evidence of efficacy and harms

American Geriatrics Society[17,18]	Avoid using medications other than metformin to achieve HbA1c <7.5% in most older adults; moderate control is generally better • Avoid chlorpropamide and glyburide due to risk of prolonged hypoglycemia. (Strong recommendation)
American College of Physicians[19]	Prescribe metformin to patients with type 2 diabetes when pharmacologic therapy is needed to improve glycemic control (strong recommendation; moderate level of evidence). Note: not age specific • Metformin is considered safe for patients with mild chronic kidney disease and some patients with moderate kidney impairment

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Methods

Topic Selection and Scope Development

This review included studies relevant to the following Key Questions and Eligibility Criteria.

Key Questions

1. What are the benefits and harms of using metformin in combination with another noninsulin glucose-lowering agent versus metformin monotherapy to achieve glycemic control in older adults with type 2 diabetes?
2. What are the benefits and harms of de-intensification of non-metformin glucose-lowering medications in older patients on combination therapy including metformin for type 2 diabetes, versus continued combination therapy?

Eligibility Criteria

- Population: Older adults with diabetes
- Intervention: Metformin
- Comparator: Other glucose-lowering medications
- Outcomes: All-cause and cardiovascular mortality, serious cardiovascular events, serious adverse events attributed to glucose-lowering medication, including severe hypoglycemia
- Timing: Any
- Setting: Any
- Study design: High-quality systematic reviews and randomized controlled trials (RCTs)

Searching and Study Selection

The research librarian conducted searches of Ovid MEDLINE®, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews through November 2016. We used a best evidence approach when reviewing abstracts and selecting studies for inclusion that involves using the most relevant studies with the strongest methodologies.[11,12] We included good-quality systematic reviews and key studies not included in the reviews that provided direct evidence on the incremental benefits and harms of additional glucose lowering agents in older adults with type 2 DM who were prescribed metformin. We also included studies on benefits and harms of de-intensification of glucose-lowering medications in older adults with type 2 DM by discontinuation of non-metformin agents versus continued combination therapy.

Data Synthesis and Quality Assessment

Data abstraction was conducted using standard, prespecified criteria based on Agency for Healthcare Research and Quality guidance.[13] After studies were selected for inclusion, data was abstracted into predetermined table templates. Quality assessment of included studies was based on the ROBIS tool for systematic reviews.[14]

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Results

Key Question 1. What are the benefits and harms of using metformin in combination with another noninsulin glucose-lowering agent versus metformin monotherapy to achieve glycemic control in older adults with type 2 diabetes?

Evidence from Systematic Reviews

A large, good-quality 2016 systematic review compared the effectiveness and harms of metformin combination therapy of metformin plus sulfonylureas (glimepiride, glyburide/glibenclamide, glipizide), TZDs (rosiglitazone, pioglitazone), DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin), SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin), and GLP-1 receptor agonists (exenatide, liraglutide, dulaglutide, and albiglutide) with metformin monotherapy (**Table 2;** quality assessment in **Appendix A)**.[20] The review included 177 trials, most with a duration of less than one year. The populations were described as mostly overweight, and mean age of participants ranged from 50 to 60 years in most studies.

Table 2. Systematic review characteristics

Author, Year	Intervention Characteristics	Included Studies Characteristics	Population Characteristics	Limitations
Bolen, 2016	Metformin +: • Sulfonylureas • TZDs • DPP-4 inhibitors • SGLT-2 inhibitors • Basal insulin • GLP-1 receptor agonists Metformin monotherapy	177 RCTs Duration of follow up: 12 weeks to 6 years; 83% had <1 year duration 58% of studies excluded older patients (over age 75 or 80 years)	Total n not reported Mean age not reported; populations of included studies described as mostly middle aged and overweight Mean duration of diabetes 3 to 7 years	• Only RCTs were included in the systematic review with widely variable duration of follow up • Limited incidence in the included RCTs for some important outcomes, most notably severe hypoglycemia

RCT=randomized controlled trial, TZDs=thiazolidinediones

The review found no difference between any metformin combination therapy versus metformin monotherapy in risk of all-cause and cardiovascular mortality or serious cardiovascular events, although some estimates were imprecise and/or based on single studies (**Table 3**). Combination therapy with metformin plus sulfonylureas was associated with greater risk of mild/moderate hypoglycemia than metformin monotherapy (odds ratio [OR] ranged from 2.15 to 29 in 9 RCTs), although the results were not pooled due to heterogeneity. For combinations involving drugs other than sulfonylureas, there were no clear differences between combination therapy and metformin monotherapy in risk of mild/moderate hyperglycemia. Evidence on the incidence of severe hypoglycemia was limited, with no cases reported in studies of metformin plus sulfonylureas (2 RCTs), SLGT-2 inhibitors (6 RCTs), or GLP-1 receptor agonists (2 RCTs) versus monotherapy. Among 13 trials of metformin plus DPP-4 inhibitors versus metformin monotherapy, ten trials reported no cases of severe hypoglycemia. In the remaining three trials, there was no difference in incidence of severe hypoglycemia between metformin combination therapy and monotherapy, but there were few events across studies and risk estimates were imprecise. Combination therapy with metformin was associated with greater reduction in HbA1c than metformin monotherapy, although statistical heterogeneity was high for most estimates. Effects generally ranged from a reduction in HbA1c level of 0.5% to 1%.

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Table 3. Systematic review summary of findings: metformin combination therapy versus monotherapy

	Metformin Combination Therapy Versus Monotherapy				
Outcome	**Sulfonylureas**	**TZDs**	**DPP-4 Inhibitors**	**SGLT-2 Inhibitors**	**GLP-1 Receptor Agonists**
All-Cause Mortality	2 RCTs; OR* 1.32; 0.09 to 19; I^2=30%	5 RCTs; OR 2.51, 0.66 to 9.52; I^2=0%	6 RCTs; OR 0.89, 0.28 to 2.86; I^2=0%	3 RCTs; OR 1.14, 0.18 to 7.27; I^2=0%	1 RCT; OR 1.00, 0.10 to 9.69
Cardiovascular Mortality		3 RCTs; OR 2.68, 0.42 to 17; I^2=0%	4 RCTs; OR 0.51, 0.15 to 1.73; I^2=0%	1 RCT; OR 3.01, 0.19 to 49	1 RCT; OR 1.14, 0.05 to 28
Cardiovascular Events	1 RCT; OR 0.34 (0.07 to 1.66)	5 RCTs; OR 1.59, 0.60 to 4.25; I^2=0%	6 RCTs; OR 1.90, 0.57 to 6.36; I^2=0%	1 RCT; OR 0.20, 0.01 to 4.13	
Mild or moderate hypoglycemia	9 RCTs†; OR range 2.15 to 29; all estimates favored metformin monotherapy, in 2 RCTs the confidence interval was not statistically significant and all estimates were imprecise.	8 RCTs; OR 1.59, 0.99 to 2.44; I^2=0%	14 RCTs; OR 0.97, 0.63 to 1.51; I^2=8%	1 RCT; OR 1.00, 0.24 to 4.13	No difference between groups in 2 studies; a third methodologically flawed study found lower risk with metformin
Severe hypoglycemia	2 RCTs; no events reported		13 RCTs†; no events in 10 RCTs, estimates imprecise and not significant in 3 RCTs	6 short-term RCTs and one long-term RCT; no events reported	2 RCTs; no events reported
Any hypoglycemia			9 RCTs; OR 0.96, 0.55 to 1.67; I^2=23%	6 RCTs; OR 1.74, 0.83 to 3.66; I^2=0%	
HbA1c	15 RCTs; ES‡ 0.94%, 0.68 to 1.19%; I^2=88%	HbA1c <8% at baseline: WMD 0.43%, 0.23 to 0.63%; I^2=79% HbA1c ≥8% at baseline: WMD 0.88%, 0.73 to 1.04%; I^2=18%	Study duration <1 yr: 27 RCTs; ES 0.65%, 0.60 to 0.70%; I^2=49% Study duration >1 yr: 4 RCTs; ES 0.53%, 0.47 to 0.59%; I^2=0%	9 RCTs; ES 0.61%, 0.52 to 0.71%; I^2=55%	5 RCTs†; all estimates favored combination therapy, between-group differences ranged from 0.5% to 1.3%

*OR <1 favors combination therapy, >1 favors metformin monotherapy

†Studies not pooled due to variability in baseline patient characteristics, outcome definition, drug doses, and/or lack of events

‡ES represents mean between-group difference in change from baseline; ES <0 favors metformin, >0 favors combination therapy

ES=effect size; HbA1c=glycated hemoglobin; OR=odds ratio; RCT=randomized controlled trial; TZDs=thiazolidinediones; WMD=weighted mean difference; yr=year

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Evidence from Observational Studies

Results from a large (n=469,688) observational study (**Table 4**)[21,22] are somewhat inconsistent with the systematic review of randomized trials. In this retrospective database study conducted in the United Kingdom, most patients were in their 60s and 58% were men. Hypertension was present in about 60% of patients and baseline HbA1c ranged from 7.8 to 9%.

The study found that relative to metformin monotherapy, combination therapy of metformin plus DPP-4 inhibitors and metformin plus other drugs (non-sulfonylurea, TZD, or DPP-4 inhibitor) was associated with reduced risk of all-cause mortality (adjusted hazard ratio [aHR] 0.80, 95% CI 0.71 to 0.91 and 0.72, 95% CI 0.58 to 0.89, respectively). Metformin plus TZDs and metformin plus DPP-4 inhibitors was associated with decreased risk of cardiovascular events versus metformin monotherapy (aHR 0.60, 95% CI 0.51 to 0.70 and aHR 0.87, 95% CI 0.77 to 0.99 respectively). Metformin plus TZDs was associated with reduced risk of heart failure versus metformin monotherapy (aHR 0.74, 95% CI 0.58 to 0.93).[21] This finding differs from randomized trials that found TZDs associated with increased risk of heart failure.[23] The predominant TZD in the observational study was pioglitazone, which appears to be associated with higher risk of heart failure than rosiglitazone.[24] In addition, patients with signs or symptoms of heart failure, or who were at risk for heart failure, may not have been prescribed a TZD following widespread dissemination of reports regarding heart failure risk. Metformin plus sulfonylureas (aHR 6.03, 95% CI 5.47 to 6.63) and metformin plus other (non-sulfonylurea, TZD, or DPP-4 inhibitor) drugs (aHR 2.77, 95% CI 1.92 to 4.01) were both associated with increased risk of serious hypoglycemia versus metformin monotherapy.[22]

Table 4. Clinical outcomes in a large observational study of metformin monotherapy versus combination therapy

	Metformin Combination Therapy Versus Monotherapy HR*, 95% CI			
Outcome	**Sulfonylureas**	**TZDs**	**DPP-4 Inhibitors**	**Other Drugs†**
All-Cause Mortality	0.96 (0.93 to 0.99)‡	0.86 (0.74 to 1.00)	0.80 (0.71 to 0.91)	0.72 (0.58 to 0.89)
Cardiovascular Events§	0.99 (0.95 to 1.03)	0.60 (0.51 to 0.70)	0.87 (0.77 to 0.99)	0.96 (0.80 to 1.15)
Heart Failure	1.09 (1.03 to 1.15)	0.74 (0.58 to 0.93)	0.91 (0.76 to 1.10)	1.08 (0.84 to 1.40)
Serious Hypoglycemia	6.03 (5.47 to 6.63)	1.35 (0.89 to 2.05)	1.23 (0.84 to 1.80)	2.77 (1.92 to 4.01)

*Adjusted for sex, age, year, duration of diabetes, ethnicity, Townsend deprivation score, smoking, use of other diabetes drugs and other medications, previous complications, comorbidities, body mass index, systolic blood pressure, HbA1c, serum creatinine level, TC/HDL ratio.
†"Other drugs" includes SGLT-2 inhibitors, alpha-glucosidase inhibitors, and meglitinides.
‡Result described as not statistically significant.
§Cardiovascular disease defined as angina, myocardial infarction, stroke, or transient ischemic attack
HR=hazard ratio

There are a number of possible explanations for the discrepancies between the systematic review findings and the observational evidence. The systematic review was restricted to randomized trials; in addition, most studies included in the systematic review had a duration of less than one year, and they may not have been designed to assess for clinical outcomes or powered to detect differences. The patient populations also differed. Among the trials included in the systematic review, the mean duration of diabetes in the study populations ranged from three to seven years, and the populations included in the systematic review were slightly younger (age range 50 to 60 years versus 60 to 66 years in the observational study). While patients in the observational study had 5 to 6 years of exposure to

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glucose-lowering drugs, those with previous TZD, DPP-4 inhibitor, or insulin exposure in the 12 months preceding study entry were excluded. Finally, although the observational study adjusted for confounders, residual confounding could have impacted findings.

Special Populations

There was very limited evidence on benefits and harms of metformin combination therapy versus monotherapy specifically in older adults. A large systematic review found no differential effect on HbA1c lowering according to age for comparisons of metformin combination therapy with DPP-4 inhibitors (10 trials) or sulfonylureas (3 trials) versus monotherapy.[20] Other outcomes were not reported.

A large (n=91,521) observational study conducted sensitivity analysis according to age ≤65 versus >65 years.[25] Compared with metformin monotherapy, there was an increased incidence of congestive heart failure with rosiglitazone combination therapy in those over age >65 (aHR 1.32, 95% CI 1.07 to 1.63) but not in patients ≤65 years (aHR 1.14, 95% CI 0.76 to 1.71). There were no differences between groups for all-cause mortality or myocardial infarction in this study, and evidence for other drug comparisons was not reported.

Key Question 2. What are the benefits and harms of de-intensification of non-metformin glucose-lowering medications in older patients on combination therapy including metformin for type 2 diabetes, versus continued combination therapy?

We identified no studies that directly evaluated the effect of limiting the use of non-metformin glucose-lowering medications in older adults with diabetes. Observational studies of de-intensification of glucose control have focused on the rate of de-intensification, rather than the effect of de-intensification on clinical outcomes.[7] Neither life expectancy nor HbA1c were predictive of de-intensification, suggesting that even in patients who are suitable candidates, de-intensification is not always accomplished in clinical settings.

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Discussion

Table 5 summarizes the benefits and harms of metformin combination therapy versus monotherapy and the effect of limiting the use of non-metformin glucose-lowering medications. A large, good-quality systematic review found no difference in risk of mortality or cardiovascular events between metformin combination therapy and monotherapy, though findings were limited by the relatively short duration of most trials and imprecise estimates.[20] Combination therapy was generally more effective than monotherapy at lowering HbA1c (average effect about 0.5 to 1.0%), or lower than the additive effects of the individual therapies. Incidence of severe hypoglycemia was rare, although most studies found the combination of metformin plus a sulfonylurea associated with increased risk of hypoglycemia (any severity) versus metformin monotherapy. However, a large observational study found some combinations of therapy with metformin associated with decreased risk of mortality or cardiovascular disease events versus metformin monotherapy.[21] Direct evidence on the effect of combination therapy in older adults was extremely limited, with one observational study finding elevated risk of heart failure in older (>age 65) but not younger patients taking combination metformin and rosiglitazone compared with metformin monotherapy.[25] Combination therapy was consistently associated with increased risk of severe hypoglycemia in a large observational study.[22]

Evidence on the effect of de-intensification of combination therapy for DM to metformin alone is lacking. Several studies suggest a higher threshold for HbA1c targets in older persons compared with younger persons.[16,18,26] There is evidence that use of additional glucose-lowering medications does not result in proportional lowering of HbA1c levels relative to monotherapy of the same medications, and that polypharmacy increases the risk of adverse events, including severe hypoglycemia.[27] However, even in patients at risk of hypoglycemia and associated negative outcomes, de-intensification of treatment is infrequently achieved.[7-9]

Table 5. Summary of benefits and harms of continuing metformin combination therapy and de-intensifying therapy to metformin monotherapy

Action	Benefits	Harms
Combination therapy versus metformin monotherapy	• Modest benefit with combination therapy compared with metformin monotherapy for HbA1c lowering, based on a large systematic review and observational study • No clear benefit for other outcomes, including all-cause or cardiovascular mortality, based on a large systematic review of primarily short-term (<1 year) studies. Observational evidence suggests decreased risk of all-cause mortality and cardiovascular disease with certain combinations.	• Increased risk of hypoglycemia with combination therapy, particularly metformin + sulfonylureas, versus metformin monotherapy
De-intensification to metformin monotherapy versus continued combination therapy	• No direct evidence	• No direct evidence

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Appendix A. Systematic review ROBIS quality rating*

Review	Study eligibility criteria	Identification and selection of studies	Data collection and study appraisal	Synthesis and findings	Overall risk of bias
	Judgement Concerns regarding specification of study eligibility criteria (Low, Moderate, High, Unclear)	**Judgement** Concerns regarding methods used to identify or select studies (Low, Moderate, High, Unclear)	**Judgement** Concerns regarding methods used to collect data and appraise studies (Low, Moderate, High, Unclear)	**Judgement** Concerns regarding the synthesis (Low, Moderate, High, Unclear)	**Judgement** Risk of bias in the review
Bolen 2016[20]	Low	Low	Low	Low	Low

*Modified ROBIS ratings to include Low, Moderate, High or Unclear.

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Routine Self-Monitoring of Blood Glucose in Adults with Type 2 Diabetes Mellitus Not Using Insulin: Rapid Evidence Synthesis

This report was prepared by the Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University, under Contract No. VA268-16-Q-0140, in support of an HSR&D research study focused on Identifying, Measuring, and Facilitating Opportunities for De-Intensification of Medical Services.

KEY MESSAGES

Why is this important?

- Self-Monitoring of Blood Glucose (SMBG) involves testing of blood sugar levels to monitor and manage diabetes mellitus. There are questions about whether SMBG is effective among people with type 2 diabetes mellitus who are not using insulin.
- SMBG requires resources (testing supplies, education, clinician visit time, and patient self-management activities), knowledge about how to conduct the testing, the ability to interpret the results, and the capacity to make changes based on these results.
- SMBG is currently performed by many people with type 2 diabetes who are not on insulin.

What is the evidence on benefits and harms of SMBG for people with Type 2 diabetes mellitus not using insulin?

- Systematic reviews summarizing randomized controlled trials of the effectiveness of SMBG (SMBG compared to no SMBG) have consistently found that routine SMBG results in small reductions (~ 0.3) in HbA1c when compared with no SMBG.
- The difference is greater (-0.54) for patients who have had a diabetes diagnosis for ≤ 1 year.
    - A 0.5 change in HbA1c is the minimum considered to be clinically meaningful.
- Studies have also reported either small or no differences in other physical outcomes (e.g., body mass index).
- There is insufficient evidence to determine the effects of SMBG on clinical outcomes such as mortality or cardiovascular morbidity.
- Studies that compare different frequencies and approaches to SMBG for these patients have been published or are due to be published soon. However, the interventions (i.e., frequency of SMBG and the interventions that accompany SMBG) differ across the studies, making it difficult to draw conclusions about comparative benefits or harms.

What is the evidence on de-intensification?

- No studies directly evaluated the impact of stopping SMBG or reducing its frequency among persons with type 2 diabetes mellitus performing SMBG.

What are the implications of our findings?

- Current evidence concludes SMBG has limited benefits (small reductions in HbA1c) for patients with type 2 diabetes who are not using insulin. This supports guideline recommendations against routine, frequent SMBG for these patients.
- Slightly larger reductions in HbA1c for patients who have had diabetes for less than a year suggest that SMBG might be more useful for subgroups of patients and providers using SMBG to inform changes in treatments and behaviors.

Background

Approximately 21 million people in the United States have been diagnosed with diabetes mellitus. Of these, 16% are 45 to 64 years of age and 26% are 65 years of age or older.[1] Estimates are that one-

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quarter of Veterans receiving health care from the U.S. Department of Veteran's Affairs (VA) have diabetes.[2] In adults, type 2 diabetes mellitus accounts for 90% to 95% of all diagnosed cases of diabetes.[1] The goal of treatment is to control blood glucose in order to avoid acute hypoglycemic or hyperglycemic episodes in the short term and to reduce longer-term macrovascular and microvascular damage that can result in cardiovascular disease, kidney disease, neuropathy, or retinopathy. Most adults with type 2 diabetes mellitus are treated with oral medications only (approximately 57%) or with no medication (approximately 14%).[1]

Self-monitoring of blood glucose (SMBG) involves patients testing a drop of their blood using a monitor and test strips. When a patient is being treated with insulin, the information from SMBG can be useful for adjusting the timing and dose of insulin to attain better control of blood glucose levels and reduce the risk of serious hypoglycemia due to insulin. In people who are not on insulin, diabetes may be managed by non-insulin medications and lifestyle interventions. In general, the risk of severe hyperglycemia is lower with type 2 diabetes mellitus and the risk of hypoglycemia is lower with non-insulin management than with insulin. Nonetheless, SMBG may help assess the impact of and encourage adherence to medication or lifestyle changes and may also provide information that can be used to inform treatment changes.

Questions have been raised about whether SMBG is effective for these purposes. Determining whether SMBG is effective is important because SMBG is common and costly. A national survey found that 35% of diabetics on no medication and 63% on oral medications only performed daily SMBG.[3] SMBG requires resources (testing supplies, education, clinician visit time, and patient self-management activities), knowledge about how to conduct the testing, the ability to interpret the results, and the capacity to make changes based on these results. In the VA, approximately $50 million per year is spent on test strips for blood glucose testing. An analysis of test strip dispensing reported 363,996 veterans 65 years of age or older received test strips in Fiscal Year 2009 and that 157.1 million strips were dispensed to all veterans. The analysis considered treatments and current practice guidelines and based on these, the authors estimated that 1 in 5 or more than 30 million strips were potentially unnecessary.[4]

The VA Evidence Synthesis Program (ESP) published a review in September 2007 titled, *Self-Monitoring of Blood Glucose in Patients with Type 2 Diabetes Mellitus: Meta Analysis of Effectiveness.*[5] This VA review found little evidence about the effect of SMBG on achieving target A1c levels and moderate evidence that SMBG results in a small decline (0.21%) in A1c levels at 6 months.

The purpose of this rapid evidence review is to identify and summarize evidence, including evidence published after 2006 (the end date for the search that informed the 2007 VA report), on the effectiveness of SMBG and for de-intensification of SMBG for patients with type 2 diabetes mellitus who are not using insulin.

Current Guidelines

Current clinical practice guidelines are summarized in **Table 1**. The guidelines vary somewhat, but are generally consistent. Most recommend against routine SMBG in patients at low risk of hypoglycemia or who have achieved their HbA1c goal. SMBG is generally recommended if patients have a high risk of hypoglycemia, if their glucose levels are fluctuating for some reason (e.g., illness), or if their medications or diet and exercise are changing.

Table 1. Summary of current guidelines on self-monitoring of blood glucose

Publication	Guidelines
American Diabetes Association[6]	• When prescribed as part of a broad educational program, SMBG may help to guide treatment decisions and/or self-management for patients taking less frequent insulin injections (B) or noninsulin therapies (E).

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2017	• When prescribing SMBG, ensure that patients receive ongoing instruction and regular evaluation of SMBG technique, SMBG results, and their ability to use SMBG data to adjust therapy (E). E = Expert consensus or clinical experience B = Supportive evidence from well-conducted cohort studies
*American Association of Clinical Endocrinologists and American College of Endocrinology Consensus Statement[7] 2016	Type 2 - Low risk of hypoglycemia • Daily BGM not recommended. • Initial periodic structured BGM (e.g., at meals and bedtime) may be useful in helping patients understand effectiveness of medical nutrition therapy/lifestyle therapy. • Once at A1C goal, less frequent monitoring is acceptable.
Endocrine Society (Choosing Wisely)[8] 2013	• Avoid routine multiple daily self-glucose monitoring in adults with stable type 2 diabetes mellitus on agents that do not cause hypoglycemia. ○ Once target control is achieved and the results of self-monitoring become quite predictable, there is little gained in most individuals from repeatedly confirming. ○ There are many exceptions, such as for acute illness, when new medications are added, when weight fluctuates significantly, when A1c targets drift off course, and in individuals who need monitoring to maintain targets. Self-monitoring is beneficial as long as one is learning and adjusting therapy based on the result of the monitoring.
Society of General Internal Medicine (Choosing Wisely)[9] 2013	• Don't recommend daily home finger glucose testing in patients with type 2 diabetes mellitus not using insulin. ○ SMBG is an integral part of patient self-management in maintaining safe and target-driven glucose control in type 1 diabetes. However, there is no benefit to daily finger glucose testing in patients with type 2 diabetes mellitus who are not on insulin or medications associated with hypoglycemia, and there is negative economic impact and potential negative clinical impact of daily glucose testing. ○ SMBG should be reserved for patients during the titration of their medication doses or during periods of changes in patients' diet and exercise routines
International Diabetes Federation Global Guideline for Managing Older People with Type 2 Diabetes[10] 2013	• Consider an individualized blood glucose monitoring plan for people on insulin and some oral glucose lowering therapy. • Monitoring of blood glucose could be considered for others as an optional component of self-management where there is an agreed purpose for testing. • Monitoring of blood glucose should only be used within a care package, accompanied by structured education on how the results can be used to reinforce lifestyle change, adjust therapy, or alert healthcare professionals to changes.

*Originally participated in Choosing Wisely and contributed to recommendation with Endocrine Society. Withdrew from Choosing Wisely in 2015.
Abbreviations: BGM = blood glucose monitoring; HbA1c = glycated hemoglobin; SMBG = self-monitoring of blood glucose.

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Methods

To conduct this rapid review we based our approach on the methods routinely used in conducting systematic reviews and then modified these to correspond to the timeline and purpose of these rapid reviews. The modifications are outlined in the next sections.

Topic Selection and Scope Development

The scope was limited to evidence of the overall effectiveness of routine SMBG in the population of interest and evidence of the impact of de-intensification.

Key Questions

1. What are the benefits and harms of routine self-monitoring (SMBG) compared to no SMBG in adults with type 2 diabetes mellitus who are not using insulin?
2. What are the benefits and harms of de-intensification of SMBG (reducing the frequency of or stopping SMBG) in adults with type 2 diabetes mellitus who are not using insulin?

Eligibility Criteria

- Population: Adults with type 2 diabetes mellitus who are not using insulin
- Intervention: Self-monitoring of blood glucose (SMBG)
- Comparator: No SMBG or less frequent SMBG
- Outcomes: HbA1c level; mortality or morbidity; cost; quality of life
- Timing: Daily or multiple times a day
- Setting: Out-patient care; home
- Included study designs: High-quality systematic reviews and randomized controlled trials.

Searching and Study Selection

The research librarian conducted searches of Ovid MEDLINE®, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews from 2006 through November 2016. We also searched PROSPERO and ClinicalTrials.gov for 2015 and 2016 to identify ongoing but not yet published reviews and trials. We first selected systematic reviews and then identified any randomized controlled trials (RCTs) that were published subsequent to the search dates of the most recent systematic review.

Data Synthesis and Quality Assessment

Quality assessment of systematic reviews was based on the ROBIS tool.[11] Data abstraction was conducted using standard, prespecified criteria based on AHRQ guidance.[12] After studies were selected for inclusion, data was abstracted into predetermined table templates.[11] We qualitatively summarized the evidence based on the overall quality, consistency, precision, and directness of the evidence.[12]

Results

Key Question 1. What are the benefits and harms of routine self-monitoring of blood glucose (SMBG) compared to no SMBG in adults with type 2 diabetes mellitus who are not using insulin?

Evidence from Systematic Reviews of Randomized Controlled Trials

Description of Recent Reviews

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Since the publication of the VA-sponsored review (Shekelle) in 2007,[5] a high-quality systematic review was published in 2012[13] and updated in 2016.[14] Both the VA review and the more recent review and update focused on benefits and harms of routine SMBG versus no SMBG. The systematic review and update as well as the VA report all required trials to include SMBG as the primary intervention and to compare routine SMBG to no SMBG/usual care. Studies in which all patients were engaged in SMBG were excluded. The limitations of this approach are outlined in the Discussion section below.

A Cochrane Review (Malanda)[13] was published in 2012 and an update was conducted and published by another research team (Zhu) in 2016.[14] The characteristics of these are summarized in **Table 2**. Since both estimate the impact of SMBG on HbA1c, our focus is on the update for this outcome as it contains the most recent data. However, since some subgroup analyses and inclusion of other outcomes differed between the reviews, both the initial review and the update are described below.

The 2012 Cochrane Review was based on searches of published literature through July 2011 and identified 12 RCTs[15-26] that included 3259 patients. This review identified and included six trials published since the VA review;[15,16,18,21,23,25] it also included six[17,19,20,22,24,26] of the 10[17,19,20,22,24,26-30] RCTs that were in the 2007 VA review. Four trials from the VA review[27-30] were excluded because they included some patients using insulin or it was unclear whether patients were using insulin. Studies had to report changes in glycemic control measured by glycated hemoglobin (HbA1c). Health-related quality of life and patient satisfaction were also included as primary outcomes. Whether information on the number of deaths and hypoglycemic events was reported in the included trials and their frequency were listed in an appendix on adverse events, but were not analyzed.

The 2016 update (Zhu) added 4 new trials[31-34] and included 11 that were in the Cochrane Review (10 based on the same publications;[16,17,19-26] and 1 new publication[35] about a trial that was included using an earlier publication[18]), for a total of 15 RCTs and 3383 patients. The included trials were conducted in several countries (United States [2 studies], European countries [11 studies], China [1 study] and Japan [1 study]) and publication dates ranged from 1989 to 2015. The trials evaluated outcomes at 6- and/or 12-month follow-up. Baseline HbA1c varied, with half of the studies reporting mean values less than 8% and half greater than or equal to 8%. The update also analyzed data on other physiologic measures, if these were reported, and conducted subgroup analysis based on trial sample size and geographic location.

The trials were evaluated using the Cochrane risk of bias tool.[36] Just under half of the trials provided inadequate information on random sequence generation (7 of 15 trials) and allocation concealment (6 of 15). Patients and care providers could not be blinded and outcome assessment was blinded in only 4 of the 15 studies. Most studies were rated as low risk of attrition bias (11 of 15) and the trials were rated as either low (8) or unclear (7) risk of reporting bias.

Table 2. Characteristics of recent systematic reviews

Author, Year	Number of Studies (Patients)	Search Dates (Databases)	Overlap with Prior Review	Outcomes	Subgroups
Zhu, 2016[14]	15 RCTs (3383)	Inception through 10/26/15 (PubMed, Cochrane Library, Web of Science, ScienceDirect, ClinicalTrials.gov)	Prior Review is Malanda[1] 4 additions 1 new report from previously included trial 10 same	HbA1c Fasting plasma glucose Body mass index Diastolic BP Systolic BP High-density lipoprotein Low-density lipoprotein Triglycerides	n>99 Asia vs. United States/Europe Follow-up period Diabetes History

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Author, Year	Number of Studies (Patients)	Search Dates (Databases)	Overlap with Prior Review	Outcomes	Subgroups
			1 excluded	Total cholesterol Waist circumference Weight	
Malanda, 2012[13]	12 RCTs (3259)	Inception through 7/2011 (MEDLINE, Cochrane Library, EMBASE, PsycINFO)	Prior Review is Shekelle (VA)[5] 6 additions 6 same 4 excluded	HbA1c Health-Related Quality of Life Patient Satisfaction	Diabetes Duration Length of follow-up

Effect of SMBG on HbA1c

The mean differences in HbA1c for the comparisons are reported in **Table 3**. The results are similar but not exactly equivalent because the two reviews grouped the studies differently for analysis.

The most current review by Zhu et.al.[14] calculated an overall effect across all subgroups and reported a reduction of 0.33% (95% CI -0.45 to -0.22) in HbA1c, which is smaller than the standard threshold for clinical significance (i.e., a change in HbA1c of 0.5 or more). The only subgroup analysis that found a reduction that crossed this threshold was when the results were stratified by how long patients were diagnosed with diabetes. In patients who had a diabetes diagnosis for less than 1 year, SMBG was associated with a -0.54% change (95% CI -0.75 to -0.33) in HbA1c compared to the control patients. In analyses stratified according to follow-up duration (6 months or 12 months), mean HbA1c before the SMBG intervention, and the geographic location of the study, the mean difference in HbA1c associated with SMBG for other subgroups were all less than 0.5 (**Table 3**). The results from a sensitivity analysis (which included only the nine studies with sample sizes over 99) were not meaningfully different from the overall estimate.

The results of the Zhu[14] update are consistent with those of the earlier Malanda review.[13] Malanda et al. did not estimate an overall effect, rather they split the results first by the diabetes duration (less than 1 year and 1 year or greater) and then by length of follow-up period (6 months and 12 months). The overall effect of SMBG versus no SMBG for people who had diabetes for less than 1 year was a reduction in HbA1c that just crossed the threshold of clinical significance (-0.52, 95% CI -0.89 to -0.42), while, similar to Zhu, the changes when patients had diabetes for more than 1 year were smaller (-0.26, 95% CI -0.39 to -0.13 at 12 months and -0.13, 95% CI -0.31 to 0.04 at 6 months) and unlikely to be clinically important. The authors did not conduct subgroup analysis by age, gender, patient complications, types of treatment, or baseline HbA1c.

Table 3. Differences in HbA1c reported in recent systematic reviews

	Mean Difference in HbA1c (95% CI) [number of studies or subgroups included]*		
Zhu, 2016[14]	**Results**	**Malanda, 2012[13]**	**Results**
Overall	**-0.33 (-0.45 to -0.22)**†		Not reported
Follow-up 6 months vs. ≥12 months	**-0.36 (-0.47 to -0.25) [11]** **-0.28 (-0.48 to -0.08) [9]**	For diabetes duration >1 year 6 months vs. 12 months	-**0.26 (-0.39 to -0.13) [9]** -0.13 (-0.31 to 0.04) [2]‡

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Diabetes duration >1 year ≤1 year	**-0.28 (-0.40 to -0.17) [15]** **-0.54 (-0.75 to -0.33) [3]**	For diabetes duration ≤1 year 12-month follow-up	-**0.52 (-0.89 to -0.14) [2]**
Pre-intervention HbA1c ≥8% <8%	**-0.28 (-0.41 to -0.16) [8]** **-0.35 (-0.52 to -0.180 [10]**		Not reported
Asia US/Europe	**-0.41 (-0.58 to -0.24) [4]** **-0.30 (-0.45 to -0.16) [14]**		Not reported
Overall Study n>99	**-0.29 (-0.44 to -0.13) [11]**		Not estimated

* The total subgroups in brackets may exceed the number of included trials because studies may include multiple arms (i.e., two different SMBG protocols and a control group) and the subgroup comparisons are included separately in the pooled estimates.

† **Bold**=statistically significant

‡ Not statistically significant

Effect of SMBG on Other Outcomes

The Zhu[14] review update reported that the SMBG group experienced statistically significant difference in mean body mass index (-0.65 kg/m^2, 95% CI -1.18 to -0.12), total cholesterol (-0.12 mmol/L, 95% CI -0.20 to -0.04), and waist circumference (-2.22 cm, 95% CI -4.40 to -0.03) compared to the no SMBG group. There were no statistically significant effects of SMBG on diastolic blood pressure, systolic blood pressure, high-density lipoprotein, low-density lipoprotein, triglycerides, or weight.

The Malanda review[13] also investigated the effects of SMBG on health-related quality of life, well-being, and patient satisfaction. The five studies that reported these outcomes used different measures and scoring, so quantitative synthesis was not possible. Based on a qualitative synthesis the review found no clear evidence that SMBG had any effect on these outcomes. Total hypoglycemia periods (symptomatic and asymptomatic) were reported in six studies. While hypoglycemia was more frequent with SMBG, data were not pooled because the studies did not use consistent definitions of hypoglycemia and there was high potential for reporting bias since SMBG allows detection of hypoglycemia that may not be noticed by patients in the non-SMBG groups.

The systematic reviews did not report effect estimates for macrovascular or microvascular complications or mortality. The included trials did not include the longer-term follow-up periods needed to detect the vascular complications, and while mortality during the studies was reported in two trials, it was reported to provide detail on study attrition and was not considered an outcome of SMBG.

Search for Additional Trials

Our search of MEDLINE and ClinicalTrials.gov from October 2015 (end of the search of the most recent review) through December 2016 did not identify any additional published RCTs, uncontrolled trials, or observational studies that evaluated the effectiveness of SMBG.

Key Question 2. What are the benefits and harms of de-intensification of SMBG (reducing the frequency of or stopping SMBG) in adults with type 2 diabetes mellitus who are not using insulin?

No identified studies directly tested the effects of stopping or reducing the frequency of SMBG in patients who had been routinely using SMBG.

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Discussion

Fifteen RCTs with over 3000 patients represent a substantial body of evidence that currently demonstrate the limited impact of SMBG testing for people with type 2 diabetes who are not using insulin. However, the evidence has potential limitations that are important to consider. These limitations include lack of detailed information on the processes that link SMBG to patient outcomes, the fact that summary results may mask differences in effect across individual patients, and variation in the timing and intensity of SMBG across the trials.

SMBG monitors blood glucose levels, but it is not a treatment for diabetes. Whether SMBG impacts patient outcomes depends on the ability of patients and clinicians to interpret the data and their willingness and ability to use the information to inform changes in behaviors and treatment. A common critique of the systematic reviews and the conclusion that the effectiveness of SMBG is limited for adults with type 2 diabetes mellitus not using insulin[37-41] is that the included trials have not sufficiently addressed either the steps between monitoring and outcomes or variations in medications, comorbidities, diet, exercise, and other lifestyle factors.

Another issue is that the pooled effects reported in the systematic reviews combine mean values and can mask variation in effect across different types of patients in the included trials. In an attempt to gain more insight into what types of patients might be more likely to benefit from SMBG, a meta-analysis of individual patient data[42] from five trials[16,17,19,22,25,26] was conducted with pre-planned subgroup analyses by age, gender, duration of diabetes, and baseline levels of HbA1c. This analysis included data from trials with at least 80 participants that were published between 2000 and 2012. The five trials were all also included in the Mandela review.[13] This analysis produced results similar to those reported in the other analysis, finding small reductions in HbA1c with SMBG (-0.25 at 3 months and -0.35 at 12 months) that are unlikely to be clinically meaningful. Imputing missing data and separating trials by loss to follow-up or differences in concurrent interventions did not change the results. Additionally, the differences in HbA1c levels were consistent across baseline levels, duration of diabetes, sex, and age.

Another limitation is that it is not possible from existing evidence to determine optimal SMBG strategies (e.g., frequency of testing, type of feedback, training, diabetes mellitus interventions), due to variability across studies. **Table 4** provides information on five examples to illustrate the variation across studies. The most current trial we identified was recently completed, but the results have not yet been published (Donahue, NCT02033499).[43] This study compared daily SMBG but with two different types of feedback to no SMBG. The St Carlos study conducted by Garcia de la Torre et al.[35] also included three arms but compared using SMBG profiles (six measurements per day every 3 days tapering to every 1 to 2 weeks) with lifestyle counseling or with supervised exercise, to no SMBG. In the trial by Farmer et al.,[19] the three arms were no SMBG, SMBG 3 times a week, and SMBG with training in which patients were encouraged to experiment with different frequencies and times. In a trial by Bosi et al.,[44] patients in the intensive monitoring arm completed profiles (4 measurements per day) 3 days a week, while patients in the active control arm completed profiles at baseline and at 6- and 12-month follow-up points. In a cluster randomized trial, primary care practices were assigned to either a structured SMBG arm in which patients completed 7-point profiles for 3 consecutive days in months 1, 3, 6, and 12 of the study or to an active control group in which patients used SMBG as directed by their physician.[45]

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Table 4. Examples of trials comparing different approaches to self-monitoring of blood glucose in patients with type 2 diabetes mellitus who are not using insulin

Author, Year Study Design	Sample Size	Follow-Up	Arms: Intervention	Arms: SMBG Frequency
Donahue (NCT02033499)[43] Expected to be released June 2017 RCT	450	52 weeks	1: SMBG testing with standard feedback 2: SMBG testing with enhanced, personalized feedback 3: No SMBG	1 and 2: Once daily
Bosi, 2013[44] RCT	1,024	12 months	1: Intense structured monitoring 2: Active control	1: 4-point profiles 3 days per week 2: 4-point profiles at baseline, 6 months and 12 months
Garcia de la Torre, 2013[35] RCT	195	3 years	1: SMBG and lifestyle 2: SMBG plus supervised exercise 3: No SMBG; treatment based on HbA1c	1 and 2: 6-point profiles every 3 days then a profile every 1 or 2 weeks depending on treatment
Polonsky, 2011[45] Cluster RCT	483	12 months	1: Structured Testing Group: Enhanced Usual Care and structured SMBG 2: Active Control: Enhanced Usual Care	1: 7-point profile for 3 consecutive days in months 1, 3, 6, 9 and 12 before visits with clinician 2: Use meter following physicians' recommendations
Farmer, 2007[19] RCT	453	12 months	1: SMBG 2: SMBG with training 3: No SMBG	1: Three values 2 days per week 2: Encouraged to experiment and customize monitoring

Given the high prevalence of type 2 diabetes mellitus and the frequency of SMBG, it is important to understand whether or not SMBG is effective in contributing to glucose control and identify both patients in whom it is most effective and optimal SMBG strategies (e.g., frequency of testing, complementary interventions). While technology makes SMBG possible and less painful than previously, SMBG requires training, learning, and commitment from patients and clinicians. This represents time and effort that patients and clinicians could spend on other activities. Another reason considering the effectiveness of SMBG is important is that the costs are substantial. A cost-effective analysis conducted for the Canadian government concluded that frequent testing, seven or more times per week, is unlikely to be cost effective. This analysis assumed a modest reduction in HbA1c (-0.25%) and used the United Kingdome Prospective Diabetes Study (UKPDS) model to estimate case complications and their impact on quality of life and costs. The analysis suggests less frequent testing (1-2 times per week) could be cost

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effective, while noting that changes in the cost of test strips and well as level of usage would affect this assessment.[46]

Summary

Since the VA-sponsored review published in 2007,[5] a systematic review and an update[13,14] including 10 new trials[15,16,21,23,25,31-35] has been added to the body of evidence assessing the effectiveness of routine SMBG for people with type 2 diabetes mellitus who are not using insulin. Overall the effects on SMBG are small and probably not clinically significant, with the possible exception of patients diagnosed with diabetes mellitus for a year or less (**Table 5**).

Table 5. Summary of benefits and harms of continuing or de-intensifying routine self-monitoring of blood glucose

Action	Benefits	Harms
Routine or Daily SMBG	• No or small potential benefit: Consistent, statistically significant reductions in HbA1c that are unlikely to be clinically relevant. • No consistent evidence of impact on other outcomes.	• No consistent, direct evidence of harms from testing
Discontinuing or De-intensifying SMBG	• No evidence identified	• No evidence identified

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Systolic Blood Pressure Targets in Type 2 Diabetes Mellitus: Rapid Evidence Synthesis

This report was prepared by the Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University, under Contract No. VA268-16-Q-0140, in support of an HSR&D research study focused on Identifying, Measuring, and Facilitating Opportunities for De-Intensification of Medical Services.

KEY MESSAGES

Why is this important?

- The 2010 Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial changed the focus of clinical practice guidelines for blood pressure (BP) management in patients with type 2 diabetes mellitus (DM) from intense to less intense targets, with many (including guidelines from the Department of Veterans Affairs/Department of Defense) recommending lowering of the BP target in diabetics from <130/80 to <140/85 or 140/90. However, de-intensification of antihypertensive therapy is uncommon even among those with BP well below target levels. This rapid evidence synthesis summarizes the evidence of benefits and harms for more versus less intensive BP control and of de-intensification of antihypertensive therapy.

What is the evidence on more intensive versus less intensive blood pressure control?

- ACCORD provides the most direct evidence that is applicable to currently recommended BP targets on the benefits and harms of more intensive versus less intensive blood pressure control in people with diabetes. This rapid evidence review also evaluated three recent systematic reviews that included ACCORD and evaluated effects of intensive BP lowering.
    - ACCORD found that, compared to a systolic blood pressure (SBP) target of <140 mm Hg, a SBP target of <120 mm Hg was not associated with a statistically significant reduction in the rate of the composite outcome of fatal and nonfatal major cardiovascular events. Although the lower SBP target was associated with decreased risk of stroke, this benefit was offset by an increased risk of serious adverse events.
    - A systematic review of more intensive versus less intensive BP targets that included ACCORD found more intensive BP targets associated with decreased risk of major cardiovascular events, but findings are difficult to interpret since the BP targets varied from trial to trial.
    - Two other reviews that evaluated the effectiveness of antihypertensive treatment trials in persons with lower mean baseline BP and those that achieved lower BPs found that achieving SBP <130 mm Hg was associated with decreased risk of stroke, but they found no clear effects on major cardiovascular events or cardiovascular mortality.
    - Neither ACCORD nor the systematic reviews evaluated effects of more versus less intensive BP lowering on quality of life, or how effects of intensive antihypertensive management varied in subgroups.

What is the evidence on de-intensification?

- There is no direct evidence on effects of de-intensification of BP management in people with DM.

What are the implications of our findings?

- Evidence from a large randomized trial supports a less intense SBP target (<140 mm Hg) in persons with DM. Studies did not address whether outcomes vary by differences in underlying risk of patient populations.

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Background

Diabetes and hypertension are both risk factors for cardiovascular disease and have additive or synergistic effects. Until recently, many hypertension clinical practice guidelines recommended that people with diabetes have a more intense blood pressure (BP) target (<130/80 mm Hg) than in the general population, in order to reduce cardiovascular risks.[1] However, results of the 2010 Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[2] suggested that intensive BP management in patients with type 2 diabetes mellitus (DM) may not be beneficial, and it may increase risks.[3,4] Compared with a systolic BP (SBP) target of <140 mm Hg, ACCORD found that an SBP target of <120 mm Hg was not associated with a statistically lower risk of the composite outcome of fatal and nonfatal major cardiovascular events. Although ACCORD found that the <120 mm Hg target reduced the risk of total stroke, the magnitude of benefit was small and offset by an increased risk of serious adverse events.[2,5] Following ACCORD, many practice guidelines (including those from the Department of Veterans Affairs/Department of Defense) relaxed the BP target in diabetics from <130/80 to <140/85 or 140/90 (see **Table 1**).[6-11]

Evidence on the frequency of and processes used to implement treatment de-intensification consistent with these new BP targets is limited. A retrospective cohort study of 211,667 veterans older than 70 years with diabetes who were treated in 2012 found that de-intensification of therapy was uncommon even among those whose BP was well below recommended levels (19%).[12] Study authors suggested this finding demonstrated a need for development of performance incentives to motivate appropriate treatment.

Additionally, the relaxing of the recommended BP targets has sparked much debate,[1] in part due to the publication of discordant systematic reviews regarding benefits of more intensive BP targets.[4,13,14] To assist the Veterans Health Administration in assessing BP targets in diabetes as potential indications for de-intensification, we performed a rapid evidence-based synthesis of recent discordant systematic reviews[4,13,14] and subsequent randomized trials on effects of different BP targets on clinical outcomes in patients with diabetes.

Current Guidelines

Table 1 summarizes BP targets in people with diabetes from five recent (2014 or after) clinical practice guidelines. Guidelines generally recommend a target of <140/90 mm Hg for most people with diabetes, with a few suggesting consideration of lower targets in persons with increased stroke risk[8] or albuminuria.[11]

Table 1. Summary of clinical practice guidelines from 2014 to present

Guideline	BP Targets In People with Diabetes	Cited Support for Recommendation
American College of Physicians (ACP) / American Academy of Family Physicians (AAFP)[7]	For adults aged 60 years or older, SBP of < 150 mm Hg, regardless of diabetes	Weiss et. al. VA Evidence-based Synthesis Program systematic review[15]
American Diabetes Association (ADA)[8]	<140/90 mm Hg; except "individuals in whom stroke risk is a concern may, as part of shared decision making, have lower systolic targets such as <130 mm Hg"	ACCORD 2010[2], McBrien 2012 meta-analysis,[16] Arguedas 2013 Cochrane review,[5] and Emdin 2015 systematic review[13]

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Guideline	BP Targets In People with Diabetes	Cited Support for Recommendation
American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention (AHA / ACC / CDC)[9]	For most people, the goal is <140 mmHg and <90 mmHg; however, lower targets may be appropriate for people with diabetes	JNC-7[17]
American Society of Hypertension / International Society of Hypertension (ASH / ISH)[10]	<140/90 mm Hg	None provided
Eighth Joint National Committee (JNC-8)[11]	< 140/90 mm Hg, "although some experts still recommend <130/80 mm Hg if albuminuria is present in patients with chronic kidney disease"	Expert opinion and ACCORD[2]
Department of Veterans Affairs and the Department of Defense (VA/DoD)[6]	<140/85	ACCORD,[2] UKPDS,[18] HOT[19]

ACCORD=Action to Control Cardiovascular Risk in Diabetes; SBP=systolic blood pressure; UKPDS=UK Prospective Diabetes Study; HOT=Hypertension Optimal Treatment; VA=Veterans Affairs

Methods

Topic Selection and Scope Development

This review included studies relevant to the following Key Questions and Eligibility Criteria.

Key Questions

1. What are the benefits and harms of more intensive versus less intensive blood pressure control in people with diabetes? Do benefits and harms vary by population?
2. What are the benefits and harms of de-intensification of blood pressure control in people with diabetes? Do benefits and harms vary by population?

Eligibility Criteria

- Population: People with diabetes
- Intervention: More intensive BP management (Key Question 1) or de-intensification of BP management (Key Question 2)
- Comparator: Less intensive BP management (Key Question 1) or continued intensive BP management (Key Question 2)
- Outcomes: All-cause and cardiovascular mortality, serious cardiovascular events, serious adverse events attributed to BP medication, quality of life
- Timing: Any
- Setting: Any
- Study design: Systematic reviews and randomized controlled trials

Searching and Study Selection

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We identified three recent systematic reviews on intensity of BP management in diabetics.[4,13,14] The reviews included studies published through 2012. To identify eligible studies from 2013 onward, the research librarian conducted searches of Ovid MEDLINE®, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews through November 2016. We also hand-searched the reference list from the 2016 Agency For Healthcare Research & Quality Effective Health Care Program's Topic Brief on Treating Hypertension[15] for relevant studies. One reviewer used the above prespecified criteria to select studies using a best evidence approach that involves using the most relevant studies with the strongest methodologies.[20,21] We included good-quality systematic reviews that provided direct evidence on glycemic control in older adults and randomized controlled trials (RCTs) that were published subsequent to the reviews, or when no good-quality systematic reviews meeting inclusion criteria were available.

Data Synthesis and Quality Assessment

Data abstraction was conducted using standard, prespecified criteria based on AHRQ guidance.[22] After studies were selected for inclusion, data was abstracted into predetermined table templates. Quality assessment of systematic reviews was based on the ROBIS tool.[23] We qualitatively summarized the evidence based on the overall quality, consistency, precision, and directness of the evidence.[22]

Results

Summary of Evidence

Bibliographic database searches identified 256 potentially relevant citations since 2013. Of those, we identified no new randomized controlled trials. The following is a summary of findings from ACCORD and the discordant systematic reviews that included ACCORD.

Key Question 1. What are the benefits and harms of more intensive versus less intensive blood pressure control in people with diabetes? Do benefits and harms vary by population?

ACCORD Trial

ACCORD randomized 4733 participants with type 2 diabetes mellitus to blood pressure management with a systolic blood pressure (SBP) target of <120 mm Hg (intensive therapy) versus <140 mm Hg (standard therapy) and followed them for a mean of 4.7 years.[2] Mean SBP was 139 mm Hg at baseline; after 1 year mean SBP was 119 mm Hg in the intensive therapy group and 133 in the standard therapy group. Compared with standard therapy, ACCORD found that intensive therapy was not associated with a statistically significantly reduction in the rate of the composite outcome of fatal and nonfatal major cardiovascular events (1.87%/year vs. 2.09%/year; HR 0.88; 95% CI, 0.73 to 1.06) or all-cause mortality (1.28 %/year vs. 1.19 %/year; HR 1.07, 95% CI, 0.85 to 1.35). Although ACCORD found that intensive therapy was associated with reduced the risk of stroke, the magnitude of the reduction was small (1.5% versus 2.6%; absolute risk difference 1.1%; NNT=91). More intensive BP lowering was associated with increased risk of serious (e.g., those that are life-threatening, cause permanent disability, or necessitate hospitalization, including hypotension, syncope, bradycardia or arrhythmia, hyperkalemia, angioedema, renal failure) adverse events (3.3% versus 1.3%; absolute risk increase of 2%; NNH=50).[2,5] ACCORD's main limitations are (1) open-label design, (2) a lower than expected rate of cardiovascular events, and (3) restriction of inclusion to persons 40 to 80 years of age.

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Recent Systematic Reviews

Table 2 summarizes the characteristics of three recent systematic reviews that included ACCORD and addressed effects of more intensive BP lowering in diabetics.[4,13,14] The reviews varied in inclusion criteria, outcomes evaluated, and statistical analysis methods. The 2016 review by Xie et al. was restricted to trials that directly compared more versus less intensive BP targets.[4] The BP target comparisons evaluated in the trials varied. As described earlier, ACCORD compared an SBP target of <120 mm Hg versus <140 mm Hg; other trials compared targets of <150/85 versus <180/105 or focused on DBP targets (e.g., <75 vs. <90 mm Hg).

The other reviews[13,14] did not directly assess benefits of more intensive versus less intensive BP targets. Rather, they assessed intensive BP lowering strategies based on analyses of effectiveness of antihypertensive treatment in persons with lower baseline BP and the effectiveness of antihypertensive therapy that achieves lower BPs. In addition to trials that compared different blood pressure targets, the reviews also included trials of antihypertensive therapy versus placebo and trials that compared different antihypertensive regimens. For assessing effectiveness of antihypertensive therapy in persons with lower baseline BP, the reviews stratified trials according to whether mean baseline SBP was less than or greater than 140 mm Hg. For assessing effectiveness of antihypertensive therapy based on achieved BPs, the reviews stratified trials according to whether mean achieved SBP was less than or greater than 130 mm Hg.

A 2015 review by Emdin et al.[13] utilized a statistical analysis in which results were standardized for every 10 mm Hg reduction in systolic BP. Because this type of analysis is based in part on how well patients responded to treatment, it may be less informative for the purpose of understanding effectiveness of different antihypertensive strategies than estimates based on nonstandardized analyses (i.e., not standardized according to degree of BP lowering). Therefore, we focused on the findings of nonstandardized analyses from this review.

A 2016 review by Brunstrom et al.[14] included additional unpublished data from 12 studies (N=8916) that were obtained through contact with authors, pharmaceutical companies, or other authorities, in addition to published studies.[14] However, the impact of the additional unpublished data appeared to be minimal. For example, for the outcome of stroke, the review included unpublished data from two trials[24,25] with an additional 499 patients, or only 3% of the overall meta-analysis sample.

Table 2. Characteristics of three recent systematic reviews

Author Year	Eligibility Criteria	Total Trials, N patients	Search Sources, Time Frame	Inclusion of Unpublished Evidence?	Outcomes	Statistical Analysis; Control for Confounding
Brunstrom 2016[14]	RCTs with N ≥ 100; ≥ 12 months that compared antihypertensive agents to one another or placebo or compared different BP targets	49 trials, N=73,738	CENTRAL, MEDLINE, Embase, BIOSIS during February 2013	Yes	(1) All-cause mortality; (2) CV and non-CV mortality; (3) MI; (4) stroke; (5) heart failure; (6) end stage renal disease, (7) amputation, (8) blindness; (9) adverse events; (10) quality of life	Relative Risks calculated individually, then pooled; random effects model; no control for confounding

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Author Year	Eligibility Criteria	Total Trials, N patients	Search Sources, Time Frame	Inclusion of Unpublished Evidence?	Outcomes	Statistical Analysis; Control for Confounding
Emdin 2015[13]	RCTs with > 1000 patient-years that compared antihypertensive agents to one another or placebo or compared different BP targets	40 trials, N=100,354	MEDLINE 1/1/66-10/28/14	No	(1) All-cause mortality; (2) CV events (MI, sudden cardiac death, revascularization, fatal and nonfatal stroke, fatal and nonfatal HF); (3) major CHD events (fatal and nonfatal MI, sudden cardiac death, with silent MI excluded); (4) stroke (fatal and nonfatal); (5) heart failure (new diagnosis and hospitalizations)	Standardized (log of summary statistic – RR or HR – and standard error of the log was multiplied by 10-mm Hg/SBP reduction) and nonstandardized analyses (relative risk); fixed effects; no control for confounding
Xie 2016[4]	RCTs with ≥ 6m follow-up that compared different BP targets	5 trials, N=6960	MEDLINE, Embase, Cochrane for inception to 11/3/15	No	Major cardiovascular events combined: MI, stroke, heart failure or CV death	Relative Risks calculated individually, then pooled; random effects model; no control for confounding

CHD=coronary heart disease; CV=cardiovascular; MI=myocardial infarction; RCT=randomized controlled trial

Table 3 summarizes the main findings of the three systematic reviews. There is consistent evidence from two reviews of no effects of intensive BP management on mortality.[13,14] Findings were somewhat inconsistent for specific cardiovascular outcomes. The review (Xie et al) that was restricted to trials that compared more intensive versus less intensive BP targets found more intensive therapy associated with decreased risk of major cardiovascular events (RR 0.83, 95% CI 0.71 to 0.96). [4] However, findings are difficult to interpret since the blood pressure targets varied and included comparisons of high targets not currently recommended (e.g., <150/85 versus <180/105). The Emdin et al. review found modest effects of antihypertensive therapy in trials of persons with mean SBP <140 mm Hg on major cardiovascular events (RR 0.92, 95% CI 0.85 to 0.99), though the effects of antihypertensive therapy in trials in which mean achieved SBP was <130 mg Hg was not statistically significant (RR 0.95, 95% CI 0.85 to 1.06).[13] The Brunstrom et al. review[14] found antihypertensive therapy associated with a 15% increased risk of cardiovascular mortality in trials in which baseline SBP was less than 140 mm Hg. Antihypertensive therapy was also associated with increased risk of cardiovascular mortality in trials in which attained SBP was <130 mm Hg, although the effect was not statistically significant. Two systematic reviews[13,14] found antihypertensive therapy associated with decreased risk of stroke in trials

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that achieved SBP <130 mm Hg (RR 0.65 and 0.72). However, in trials in which baseline SBP was less than 140 mm Hg, antihypertensive therapy was not associated with decreased risk of stroke.

None of the reviews evaluated effects of more intensive BP lowering on adverse effects or quality of life. Although one review[14] prespecified these outcomes, it found that data were reported too poorly to perform data extraction or analysis. No systematic review evaluated effects of more versus less intensive BP lowering in subgroups defined by demographic or clinical characteristics.

Table 3. Main findings for intense BP lowering from three recent systematic reviews, relative risks (95% CI)

Outcome	Emdin 2015[13]	Xie 2016[4]	Brunstrom 2016[14]
All-Cause Mortality	**No effects:** Trials with Mean Baseline SBP < 140: 0.96 (0.90, 1.04); 14 trials, N=26,559 Trials with Mean Achieved SBP < 130: 1.03 (0.86, 1.24); 4 trials, N=10,645	NR1	**No Effects:** Trials with Mean Baseline SBP < 140: 1.05 (0.95, 1.16); 14 trials, N=24,350 Trials with Mean Attained SBP < 130: 1.10 (0.91, 1.33); 9 trials, N=11,050
Cardiovascular Mortality	NR	NR	**Mixed Effects:** ↑ risk in trials with Mean Baseline < 140: 1.15 (1.00, 1.32); 10 trials, N=22,439 No effect in trials with Attained Mean BP < 130: 1.26 (0.89, 1.77); 7 trials, N=10,587
Major Cardiovascular Events	**Mixed effects:** ↓ risk in trials with Mean Baseline SBP < 140: 0.92 (0.85, 0.99); 9 trials, N=23,270 No effect in trials with Mean Achieved SBP < 130: 0.95 (0.85, 1.06); 3 trials, N=9,660	↓ risk for intense vs. standard: 0.83 (0.71-0.96); 5 trials, N=6960	NR
Stroke	**Mixed effects** No effect in trials with Mean Baseline SBP < 140: 0.98 (0.82, 1.19); 5 trials, N=17,127 ↓ risk in trials with Mean Achieved SBP < 130: 0.70 (0.55, 0.91); 3 trials, N=6,319	NR	**Mixed effects** No effect in trials with Mean Baseline < 140: 0.81 (0.53, 1.22); 8 trials, N=17,911 ↓ risk in trials with Mean Attained BP < 130: 0.65 (0.42, 0.99); 6 trials, N=7,103

* Standardized per 10 mm Hg lowering of SBP

BP=blood pressure; NR=not reported; SBP=systolic blood pressure

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Key Question 2. What are the benefits and harms of de-intensification of blood pressure control in people with diabetes? Do benefits and harms vary by population?

No study evaluated effects of de-intensification of BP management in people with DM who have blood pressures below target thresholds (e.g., <140/90 or <140/85).

Discussion

ACCORD provides the most direct evidence on the benefits and harms of more intensive versus less intensive blood pressure targets in people with diabetes, based on targets most applicable to current practice guidelines.[2] It found that an SBP target of less than 120 mm Hg did not statistically significantly reduce the rate of the composite outcome of fatal and nonfatal major cardiovascular events. While there was some potential benefit in stroke reduction, the trade-off was an increased risk of serious adverse events. A systematic review of more intensive versus less intensive BP targets that included ACCORD found more intensive targets associated with decreased risk of major cardiovascular events, but findings are difficult to interpret since the blood pressure targets really varied from trial to trial.[4] Two other reviews[13,14] that evaluated the effectiveness of antihypertensive treatment trials in persons with lower mean baseline BP and those that achieved lower BPs found that achieving SBP <130 mm Hg was associated with decreased risk of stroke, but no clear effects on major cardiovascular events or cardiovascular mortality. Neither ACCORD nor the systematic reviews evaluated effects of more versus less intensive BP lowering on quality of life, or how effects of more intensive BP management varied in subgroups. There is no direct evidence on effects of de-intensification of BP management in people with DM.

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Statin Combination Therapy Versus Monotherapy in Adults at Risk of Cardiovascular Disease: Rapid Evidence Synthesis

This report was prepared by the Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University, under Contract No. VA268-16-Q-0140, in support of an HSR&D research study focused on Identifying, Measuring, and Facilitating Opportunities for De-Intensification of Medical Services.

KEY MESSAGES

Why is this important?

- Statin monotherapy is effective at reducing risk of cardiovascular events and mortality for primary and secondary prevention. The addition of fibrates or niacin to statin therapy may further lower lipid levels and result in additional reductions in risk of cardiovascular outcomes, which may be particularly relevant for persons at high cardiovascular risk or who cannot achieve adequate lipid lowering with a statin alone.
- This rapid evidence review summarizes the evidence on benefits and harms of combination therapy with a statin plus a fibrate or niacin versus a statin alone, and on de-intensification of combination therapy to statin monotherapy.

What is the evidence on potential benefits and harms from statin combination therapy with a fibrate or niacin versus statin monotherapy in adults at risk of cardiovascular disease?

- Five trials of statin combination therapy with a fibrate (three trials) or niacin (two trials) found no significant reductions in all-cause mortality or cardiovascular outcomes with combination therapy versus statin monotherapy.
- Statin and fibrate combination therapy was associated with increased risk of renal events versus statin monotherapy, though evidence was imprecise and limited to two trials.
- Statin and niacin combination therapy was associated with an increased risk of new-onset diabetes versus statin monotherapy, and a non-significant increase in risk of ischemic stroke (three trials).

What is the evidence on benefits and harms of de-intensification of statin combination therapy with a fibrate or niacin?

- No trial evaluated benefits and harms of de-intensification of statin combination therapy.

What are the implications of our findings?

- Statin combination therapy with a fibrate or niacin was not associated with reduced risk of mortality or cardiovascular outcomes versus statin monotherapy, but was associated with increased risk of adverse events including renal dysfunction (fibrates) and incident diabetes (niacin).

Background

Statin therapy has been shown to reduce intermediate and clinical cardiovascular (CV) outcomes when used for both primary and secondary prevention of CV events, and statin therapy is considered first-line pharmacologic therapy for patients with hyperlipidemia or otherwise at higher risk for CV events.[1] Patients may still be at increased risk for CV events despite maximal statin therapy.[2] Statins are associated with increased risk of certain adverse events, including myopathies, incident diabetes (seen with high intensity statin therapy), and liver abnormalities.[3,4]

Statins used in combination with other lipid-lowering drugs may be associated with further reductions in risk of CV outcomes.[5] However, fibrate therapy and niacin are also associated with adverse events, including renal dysfunction and gastrointestinal side effects (fibrates) and flushing and

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hyperglycemia (niacin). In addition, the combination of fibrates and statins may be associated with increased risk of myopathy versus a statin alone. Further, trials of fibrate monotherapy have generally found no benefit, or even harm, on the outcome of all-cause mortality, due to an increase in non-CV mortality.[6-8] Data on the effects of niacin monotherapy for prevention of CV events are limited, but suggest potential beneficial effects for secondary prevention.[9] Therefore, there is uncertainty regarding the potential trade-offs associated with adding a fibrate or niacin to statin therapy and whether such strategies result in net benefits. Data indicate that a substantial proportion of patients on lipid-lowering therapy receive combination therapy.[10]

This rapid evidence review synthesizes the evidence on benefits and harms of statin combination therapy with fibrates or niacin, two commonly used classes of lipid-lowering therapy, versus statin monotherapy, as well as evidence on benefits and harms of de-intensification of combination therapy (to statin monotherapy) versus continued combination therapy.

Current Guidelines

Selected current practice guidelines on statin use are summarized in **Table 1**. United States guidelines from the American Heart Association and American College of Cardiology, the Department of Defense and Department of Veterans Affairs, and the National Lipid Association are consistent in recommending cautious use of statin combination therapy in carefully selected patients. The United Kingdom National Institute for Health and Care and Excellence guideline recommends against use of statin combination therapy for primary (including people with type 2 diabetes mellitus [DM]) and secondary prevention of CV mortality and morbidity.

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Table 1. Summary of current guidelines on statin monotherapy and combination therapy

Guideline	Recommendations

American College of Cardiology/American Heart Association (ACC/AHA)[11]	<u>Primary prevention population</u>
	• In adults age 40-75 years with:
	  ○ LDL-C ≥190 mg/dL: initiate high-intensity statin; non-statin therapy may be considered if at least a 50% reduction in LDL-C is not achieved
	  ○ LDL-C 70-189 and no diabetes: consider statin initiation based on 10-year CVD risk (using Pooled Equation Cohorts). If risk is ≥7.5%, initiate moderate or high-intensity statin; risk 5 to <7.5% consider initiation of moderate-intensity statin
	  ○ LDL-C 70-189 mg/dL and diabetes: initiate moderate-intensity statin; consider high-intensity statin if calculated 10-year CVD risk is ≥7.5%
	  ○ Other primary prevention populations (LDL-C ≤190 mg/dL, age <40 or >75 years, <5% 10-year CVD risk): statin initiation not routinely recommended, may be considered in some individuals
	
	<u>Secondary prevention population</u>
	  ○ Age ≤75 years and no safety concerns: initiate/continue high-intensity statin
	  ○ Age >75 years or with safety concerns: initiate/continue moderate-intensity statin
	
	<u>Primary and secondary prevention populations</u>
	• Assess adherence, response to therapy, and adverse effects within 4 to 12 weeks following statin initiation or change in therapy.
	  ○ In individuals at higher CVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less-than-anticipated therapeutic response (after reinforcement of adherence to medication and lifestyle modification), addition of non-statin cholesterol-lowering drug(s) may be considered if the CVD risk-reduction benefits outweigh the potential for adverse effects. Preference should be given to non-statin cholesterol-lowering drugs shown to reduce ASCVD events in RCTs.
	  Higher risk individuals include:
	  ▪ Individuals with clinical CVD <75 years of age
	  ▪ Individuals with baseline LDL-C ≥190 mg/dL
	  ▪ Individuals 40–75 years of age with diabetes

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Guideline	Recommendations

Department of Veterans Affairs/Department of Defense (VA/DoD)[12]	<u>Primary prevention population</u>
	• Use shared decision making about pharmacologic treatment for patients with an estimated 10-year CVD risk ≥12% that considers the known minimal harms and substantial benefits of moderate-dose therapy in this group of patients.
	• Consider a moderate-dose statin for patients with a 10-year CVD risk between 6% and 12% after a discussion of the known minimal harms and benefits derived from limited evidence and an exploration of the patient's values and preferences.
	• Recommend a moderate-dose statin as the agent of choice to reduce CVD risk if the patient chooses pharmacologic therapy.
	• For patients intolerant of statins:
	  ○ Reinforce lifestyle changes.
	  ○ For patients who prefer pharmacotherapy, consider gemfibrozil or bile acid sequestrants, although we note small CVD risk reduction in limited populations.
	
	<u>Secondary prevention population</u>
	• In patients with established ASCVD, we recommend use of a moderate-dose statin after a discussion of the minimal harms and substantial benefits and an exploration of the patient's values and preferences.
	• In patients with ASCVD who are able to tolerate statins, we recommend against the routine use of non-statin lipid-lowering drugs either as monotherapy or added to statins.
	• We suggest offering a high-dose statin only in select patient populations after a discussion of the added harms and small additional benefits and an exploration of the patient's values and preferences.

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Guideline	Recommendations
National Lipid Association[13,14]	<u>Primary prevention/low- to moderate-risk population</u> • For patients at low or moderate risk of CVD, lifestyle therapy should be given a trial of at least 3 months before initiation of drug therapy. <u>Secondary prevention/high- to very-high-risk population (includes patients with diabetes and history of CVD)</u> • For patients at very high risk and selected patients at high risk (those unlikely to reach goal with lifestyle alone), drug therapy may be started concurrently with lifestyle therapy. • First-line cholesterol-lowering drug therapy, unless contraindicated, is moderate- to high-intensity statin. The statin dosage may be increased or the patient switched to a more efficacious agent, if goal levels of atherogenic cholesterol are not achieved. ○ Combination drug therapy with a statin plus a second (or third) agent that further lowers non–HDL-C and LDL-C may be considered for patients who have not attained their atherogenic cholesterol levels after the maximum tolerated statin dosage has been reached and for those who have contraindications or are intolerant to statin therapy. <u>Special population: older adults</u> • Older, primary prevention patients who are statin-eligible should undergo a patient-centered discussion with their provider about the risks and benefits of statin therapy. • If the older primary prevention patient is unable to achieve atherogenic cholesterol goals after a minimum 3–6 month trial on lifestyle modification, the provider should discuss the pros and cons of drug therapy, and, if feasible, prescribe moderate intensity statin therapy, particularly for patients with risk exceeding the high-risk threshold. • For patients age ≥65 to <80 years of age with ASCVD or diabetes mellitus, moderate- or high-intensity statin therapy should be considered after a careful consideration of the risk-benefit ratio. • For secondary prevention in patients ≥80 years of age, moderate-intensity statin therapy should be considered based upon a provider-patient discussion of the risks and benefits of such therapy, consideration of drug-drug interactions, polypharmacy, and concomitant medical conditions including frailty, cost considerations, and patient preference. • If statin intolerance is an issue, consideration should be given to the use of alternate statin regimens such as low-intensity statin therapy or non-daily moderate intensity statin therapy, low-dose statin combination therapy with ezetimibe, bile acid sequestrants, niacin, or non-statin monotherapy or their combination, with a goal of at least a 30% reduction in LDL-C.

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Guideline	Recommendations
National Institute for HealthCare and Excellence (NICE) 2014[15]	Primary prevention population • If lifestyle modification is ineffective or inappropriate, offer statin treatment after risk assessment. • Offer atorvastatin 20 mg for the primary prevention of CVD to people who have a ≥10% 10-year risk of developing CVD (including people with type 2 diabetes) using the QRISK2 assessment tool. • For people ≥85 years, consider atorvastatin 20 mg as statins may be of benefit in reducing the risk of non-fatal myocardial infarction. Secondary prevention population • Start statin treatment in people with CVD with atorvastatin 80 mg. Use a lower dose of atorvastatin in the event of potential drug interactions, high risk of adverse effects, or patient preference. Primary and secondary prevention populations • Do not offer the combination of a bile acid sequestrant, fibrate, nicotinic acid or omega-3 fatty acid compound with a statin for primary or secondary prevention of CVD.

ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; RCT = randomized controlled trial

Methods

Topic Selection and Scope Development

This review includes studies relevant to the following Key Questions and Eligibility Criteria.

Key Questions

1. What are the benefits and harms of using statins in combination with a fibrate or niacin versus statin monotherapy in adults at increased risk of cardiovascular morbidity or mortality?
2. What are the benefits and harms of de-intensification of statin combination therapy versus continued combination therapy in adults at increased risk of cardiovascular morbidity or mortality?

Eligibility Criteria

- Population: Adults with dyslipidemia or other CVD risk factors (including type 2 diabetes) or a history of CVD (i.e., primary and secondary prevention)
- Intervention: Statin combination therapy
    - statin and fibrate
    - statin and niacin
- Comparator: Statin monotherapy
    - atorvastatin
    - fluvastatin
    - lovastatin
    - pitavastatin
    - pravastatin
    - rosuvastatin
    - simvastatin
- Outcomes: All-cause and CV mortality, serious CV events, serious adverse events attributed to lipid-lowering medications

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- Timing: Any
- Setting: Any
- Study design: High-quality systematic reviews and randomized controlled trials

Searching and Study Selection

The research librarian conducted searches of Ovid MEDLINE®, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews through March 2017. We used a best evidence approach when reviewing abstracts and selecting studies for inclusions that involves using the most relevant studies with the strongest methodologies.[16,17] We included good-quality systematic reviews that provided direct evidence on combination statin therapy versus statin monotherapy. We included randomized controlled trials (RCTs) that were published subsequent to included systematic reviews, or when no good-quality systematic reviews meeting inclusion criteria were available.

Data Synthesis and Quality Assessment

Data abstraction was conducted using standard, pre-specified criteria based on Agency for Healthcare Research and Quality guidance.[18] After studies were selected for inclusion, data was abstracted into predetermined table templates. Quality assessment of systematic reviews was based on the ROBIS tool.[19] We qualitatively summarized the evidence based on the overall quality, consistency, precision, and directness of the evidence.[18]

Results

Key Question 1. What are the benefits and harms of using statins in combination with a fibrate or niacin versus statin monotherapy in adults at increased risk of cardiovascular morbidity or mortality?

Three recently published systematic reviews assessed the effect of statin combination therapy versus monotherapy on CV morbidity and mortality; all found evidence to be very limited.[2,20,21] Across the systematic reviews, one to two trials reported clinical outcomes for statin and fibrate versus statin monotherapy, and two to three trials reported clinical outcomes for statin and niacin versus statin monotherapy. Due to the small number of trials and differences between reviews in terms of included studies, we focused on summarizing the findings from the individual studies (see below). Five trials comparing a statin plus fibrates (2 trials[22,23] or niacin (3 trials[24-26] with statin monotherapy (**Table 2** and **4**).

Statin and Fibrate Versus Statin Monotherapy

Two trials of statin and fibrate combination therapy versus statin monotherapy reported clinical outcomes: the ACCORD (n=5,518)[22] and FIRST (n=662)[23] trials (**Table 2**). The populations in both trials were primarily men in their 60s. ACCORD exclusively enrolled people with DM. The FIRST trial enrolled patients with dyslipidemia and increased carotid intima-media thickness; half of study participants had DM at baseline. The studies included a mix of primary and secondary prevention patients; about a third of the ACCORD population and about a quarter of the FIRST population had a history of CVD at the time of study enrollment.

Neither trial found a significant benefit with statin combination therapy versus monotherapy for all-cause mortality or for a composite outcome that included CV mortality, non-fatal myocardial infarction (MI), and non-fatal stroke. Pooled risk estimates for all-cause mortality (RR 0.77, 95% CI 0.33 to 1.81; I^2=25%) and the composite outcome (RR 0.84, 95% CI 0.81 to 1.09; I^2=0%) were also not significant (**Figures 1** and **2**). All estimates were imprecise and dominated by ACCORD, which enrolled nearly 10 times as many subjects as FIRST. The ACCORD trial also found no significant difference between

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combination and monotherapy in risk of individual components of the composite outcomes, including non-fatal MI (RR 0.93, 95% CI 0.76 to 1.13) and non-fatal stroke (RR 1.17, 95% CI 0.77 to 1.78; **Appendix Table A**).

Table 2. Randomized controlled trials of statin-fibrate combination therapy versus statin monotherapy

Author Year n Study Duration	**Interventions A vs. B**	**Patient Characteristics A vs. B**	**Results A vs. B**
ACCORD 2010[22] n=5,518 5 years	A. Simvastatin mean dose 22 mg/day + fenofibrate 54 or 160 mg/day* (n=2,765) B. Simvastatin 22 mg/day + placebo (n=2,753)	Mean age 62 vs. 62 years 31% vs. 31% female 69% vs. 68% white; 14% vs. 16% Black; 8% vs. 7% Hispanic History of DM 100% vs. 100% History of CVD 37% vs. 37%	All-cause mortality: 8% (203/2765) vs. 8% (221/2753); RR 0.91, 95% CI 0.76 to 1.10 CV mortality, non-fatal MI or non-fatal stroke: 11% (291/2765) vs. 11% (310/2753); RR 0.93, 95% CI 0.80 to 1.09
FIRST 2014[23] n=662 2 years	A. Atorvastatin mean dose 21 mg/day + fenofibric acid 135 mg/day (n=337) B. Atorvastatin mean dose 21 mg/day + placebo (n=339)	Mean age 61 vs. 61 years 32% vs. 32% female 89% vs. 86% white; other races not reported History of DM 50% vs. 50% History of MI 10% vs. 10%; coronary artery disease 19% vs. 26%	All-cause mortality: 0.3% (1/337) vs. 1% (4/339); RR 0.25, 95% CI 0.03 to 2.24 CV mortality, non-fatal MI or non-fatal stroke: 2% (6/337) vs. 2% (6/339); RR 1.01, 95% CI 0.33 to 3.09

CV = cardiovascular, CVD = cardiovascular disease, DM = type 2 diabetes mellitus, MI = myocardial infarction
*Fenofibrate dose depended on baseline estimated glomerular filtration rate: 30 to <50 mL/min/1.73m^2 (54 mg dose) or ≥50 (160 mg dose).

Figure 1. All-cause mortality in randomized controlled trials of statin-fibrate combination therapy versus statin monotherapy

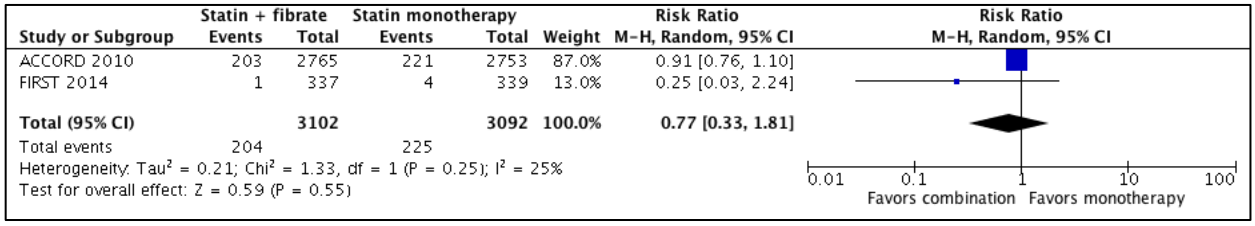
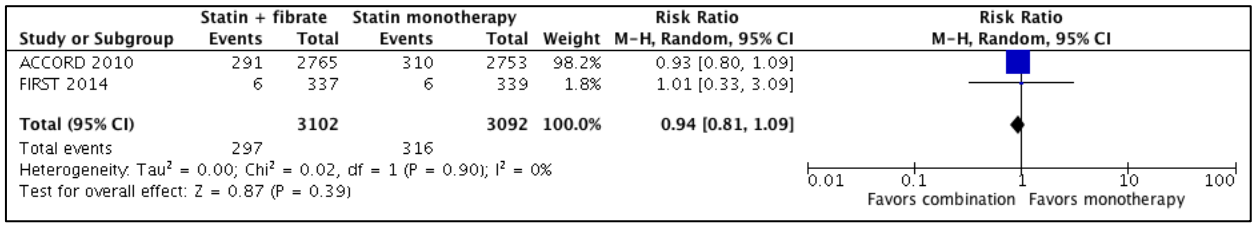


Figure 2. Cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke in randomized controlled trials of statin-fibrate combination therapy versus statin monotherapy



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The trials found few differences between combination therapy and monotherapy in risk of adverse events (**Appendix Table A**). Fenofibrate use can be associated with increased risk of renal adverse events.[27,28] In ACCORD, withdrawals due to decreased estimated glomerular filtration rate were infrequent but significantly more likely with combination therapy (2% versus 1%; RR 2.20, 95% CI 1.43 to 3.38); there was no difference in the proportion of patients requiring hemodialysis or developing end-stage renal disease.[22] In the FIRST trial, there was a higher incidence of broadly defined renal events (7% versus 0.9%; RR 7.38, 95% CI 2.23 to 24) and renal failure (3% versus 0.3%; RR 9.05, 95% CI 1.15 to 71) in the combination therapy group, but these estimates were imprecise and absolute event rates were relatively low in both combination and monotherapy groups.

Special Populations

For primary prevention, there was no difference between statin and fibrate combination therapy versus statin monotherapy in risk of all-cause mortality (RR 1.01, 95% CI 0.78 to 1.31; I^2=0%), based on pooled estimates from ACCORD and FIRST.[21] For secondary prevention, the estimate favored combination therapy, but was very imprecise and statistically non-significant (RR 0.74, 95% CI 0.26 to 2.12; I^2=22%).[21-23] For the composite outcome of CV mortality, non-fatal MI or non-fatal stroke, risk was similar for primary (ACCORD and FIRST pooled estimate; RR 0.99, 95% CI 0.78 to 2.26; I^2=0%)[21] and secondary (ACCORD only; RR 0.88, 95% CI 0.69 to 1.10)[22] prevention.

ACCORD authors conducted a number of other pre-specified subgroup analyses of the study's composite outcome. Statin combination therapy was associated with increased risk in women (RR 1.36, 95% CI 0.98 to 1.09) and decreased risk in men (RR 0.84, 95% CI 0.71 to 1.00; p for interaction=0.01). Combination therapy was more effective in those with high triglycerides and low HDL-C (RR 0.71, 95% CI 0.52 to 0.97) compared with all other lipid categories, though the interaction was not statistically significant. There was no significant interaction between effects of combination therapy and age, baseline HbA1c, or individual lipid parameters (**Table 3**). Recently published 10-year follow-up from ACCORD reported continued excess risk in women (RR 1.30, 95% CI 1.01 to 1.68 versus men RR 0.84, 95% CI 0.73 to 0.96; p for interaction=0.003); combination therapy remained more effective in the subgroup of people with high triglycerides and low HDL-C (RR 0.73, 95% CI 0.56 to 0.95 versus all others RR 0.99, 95% CI 0.86 to 1.13; p for interaction=0.05).[29]

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Table 3. Risk of cardiovascular mortality, non-fatal myocardial infarction, or non-fatal stroke in ACCORD subgroups[22]

Subgroup	Incidence; RR	p for interaction
Sex		
Male	11% (214/1914) vs. 13% (254/1910); RR 0.84, 95% CI 0.71 to 1.00	0.01
Female	9% (77/851) vs. 7% (56/843); RR 1.36, 95% CI 0.98 to 1.09	
Age		
<65 years	8% (149/1838) vs. 10% (173/1822); RR 0.85, 95% CI 0.69 to 1.05	0.25
≥65 years	15% (142/927) vs. 15% (137/931); RR 1.04, 95% CI 0.84 to 1.29	
HbA1c		
≤8.0%	9% (115/1324) vs. 11% (141/1335); RR 0.82, 95% CI 0.65 to 1.04	0.20
≥8.1%	12% (175/1435) vs. 12% (169/1415); RR 1.02, 95% CI 0.84 to 1.24	
LDL-C		
≤84 mg/dl	9% (88/938) vs. 12% (109/891); RR 0.77, 95% CI 0.59 to 1.00	0.12
85-111 mg/dl	10% (92/934) vs. 11% (103/922); RR 0.88, 95% CI 0.68 to 1.15	
≥112 mg/dl	12% (109/877) vs. 11% (98/927); RR 1.18, 95% CI 0.91 to 1.52	
Triglycerides		
≤128 mg/dL	9% (80/891) vs. 11% (103/939); RR 0.82, 95% CI 0.62 to 1.08	0.64
129-203 mg/dL	11% (97/924) vs. 10% (90/913); RR 1.06, 95% CI 0.81 to 1.40	
≥204 mg/dL	11% (104/934) vs. 13% (114/888); RR 0.87, 95% CI 0.68 to 1.11	
HDL-C		
≤34 mg/dL	12% (118/964) vs. 16% (141/906); RR 0.79, 95% CI 0.63 to 0.99	0.24
35-40 mg/dL	10% (87/860) vs. 9% (82/866); RR 1.07, 95% CI 0.80 to 1.42	
≥41 mg/dL	9% (84/925) vs. 9% (87/968); RR 1.01, 95% CI 0.76 to 1.34	
Triglycerides + HDL-C		
Triglycerides ≥204 + HDL-C ≤34 mg/dL	12% (60/485) vs. 17% (79/456); RR 0.71, 95% CI 0.52 to 0.97	0.06
All others	10% (229/2264) vs. 10% (231/2284); RR 1.00, 95% CI 0.84 to 1.19	

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol

Statin and Niacin Combination Therapy Versus Statin Monotherapy

Three trials compared statin and niacin combination therapy with statin monotherapy (**Table 4**).[24-26] As with the statin and fibrate trials, most enrolled patients were men in their 60s with a history of CVD and/or DM. The statin in all trials was exclusively or primarily simvastatin (dose 20-80 mg/day) and the dose of niacin ranged from 500 to 2000 mg/day. The largest trial (HPS2-THIRVE; n=25,673, compared with sample sizes of 3,414 and 167 in the other trials)[25] included laropiprant in the combination therapy arm. Laropipant does not have lipid-lowering effects but reduces facial flushing due to niacin. This combination, never approved for use in the United States, has since been withdrawn from the market worldwide by the manufacturer due to lack of efficacy and increased risk of serious adverse events.[30]

The trials found no effects of statin and niacin combination therapy on risk of all-cause mortality, composite CV outcomes (**Table 4**), or individual CV outcomes relative to statin monotherapy (**Appendix Table A**). Based on pooled estimates, combination therapy was associated with a slightly increased risk of all-cause mortality (2 trials; RR 1.10, 95% CI 1.00 to 1.20; I^2=0%; **Figure 3**) and no difference in risk of composite CV outcomes (3 trials; RR 1.03, 95% CI 0.84 to 1.27; **Figure 4**), though statistical heterogeneity was present (I^2=74%). Results from the largest trial (HPS2-THRIVE) were very similar to the pooled estimates.

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Table 4. Randomized controlled trials of statin and niacin combination therapy versus statin monotherapy

Author, Year n Study Duration	Interventions A vs. B	Patient Characteristics A vs. B	Results A vs. B
AIM-HIGH 2011[24] n=3,414 3 years*	A. Simvastatin 40 to 80 mg/day + niacin 1500 to 2000 mg/day (n=1,718) B. Simvastatin 40 to 80 mg/day + low-dose (50mg) niacin placebo (n=1,696)	Mean age 64 vs. 64 years 15% vs. 15% female 92% vs. 93% white; 4% vs. 3% Black; 2% vs. 2% multi-racial; ≤1% vs. ≤1% other race/ethnicity History of DM 34% vs. 34% History of CVD 100% vs. 100% Statin use at baseline 93% vs. 94%	All-cause mortality: 6% (96/1718) vs. 5% (82/1696); RR 1.16, 95% CI 0.87 to 1.54 CHD mortality, non-fatal MI, ischemic stroke, hospitalization for acute coronary syndrome, or symptom-driven coronary or cerebral revascularization: 16% (282/1718) vs. 16% (274/1969); RR 1.02, 95% CI 0.98 to 1.90 Ischemic stroke*: 2% (27/1718) vs. 1% (15/1696); RR 1.78, 95% CI 0.95 to 3.33
ARBITER-2 2004[26] n=167 1 year	A. Statin (primarily simvastatin ≥20 mg/day) + niacin 500 mg/day titrated to 1000 mg/day after 30 days (n=87) B. Statin (primarily simvastatin ≥20 mg/day) + placebo (n=80)	Mean age 67 vs. 68 years 10% vs. 7% female Race not reported History of DM 28% vs. 28% History of CHD 100% vs. 100%; MI 47% vs. 53%	Sudden cardiac death, hospitalization for an acute coronary syndrome, or arterial revascularization: 3% (3/87) vs. 9% (7/80); RR 2.76, 95% CI 0.29 to 26
HPS2-THRIVE 2014[25] n=25,673 4 years	A. Simvastatin 40 mg/day + niacin 2000 mg/day + laropiprant 40 mg/day (n=12,838) B. Simvastatin 40 mg/day + placebo (n=12,835)	Mean age 65 vs. 65 years 17% vs. 17% female Race not reported; 57% vs. 57% of participants resided in Europe, 43% vs. 43% resided in China History of DM 32% vs. 33% History of MI 68% vs. 68%; coronary heart disease 65% vs. 66%	All-cause mortality 6% (798/12838) vs. 6% (732/12835); RR 1.09, 95% CI 0.99 to 1.90 Coronary death, non-fatal MI, stroke, coronary or non-coronary revascularization: 13% (1696/12838) vs. 14% (1758/12835); RR 0.96, 95% CI 0.91 to 1.03

CHD = coronary heart disease; CVD = cardiovascular disease; DM = type 2 diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction
*Planned duration was 5 years; AIM-HIGH was stopped early due to observed lack of efficacy and unexpected excess incidence of ischemic stroke.

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Figure 3. All-cause mortality in randomized controlled trials of statin and fibrate combination therapy versus statin monotherapy

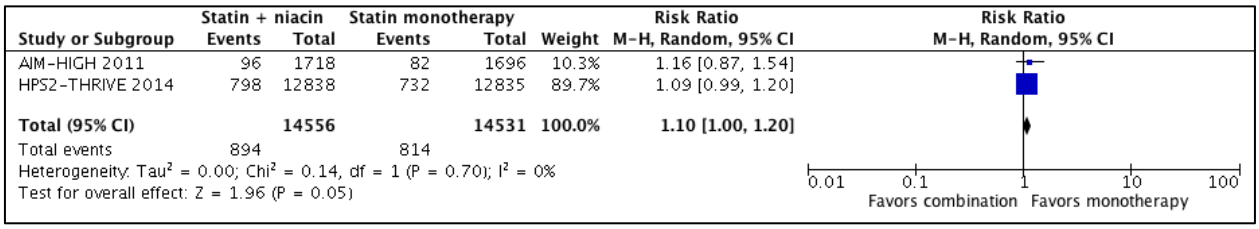
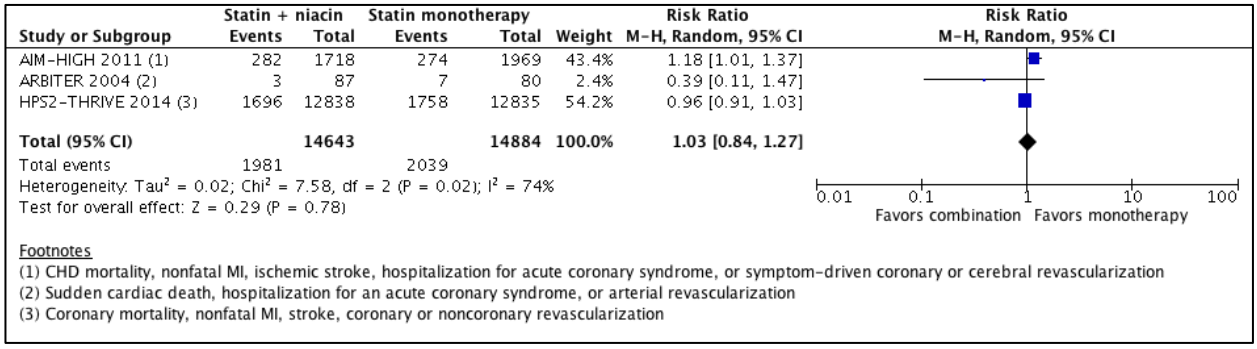


Figure 4. Composite cardiovascular outcomes in randomized controlled trials of statin and fibrate combination therapy versus statin monotherapy



Combination therapy was associated with a non-significant increased risk of ischemic stroke in AIM-HIGH (RR 1.78, 95% CI 0.98 to 1.90; **Table 4**), leading to early stoppage of the trial after 3 years (of 4 planned years) of follow-up.[24] Serious adverse events occurred frequently in both combination and monotherapy arms of HPS2-THRIVE (56% vs. 53%), but were slightly more likely with combination therapy (RR 1.06, 95% CI 1.03 to 1.08).[25] Combination therapy was associated with increased incidence of withdrawals due to adverse events in AIM-HIGH (25% vs. 20%; RR 1.26, 95% CI 1.11 to 1.43), but there was no difference between groups in the small (n=167) ARBITER-2 trial (2% vs. 8%; RR 0.31, 95% CI 0.06 to 1.48).[26] A separate meta-analysis examined the risk of new onset diabetes in trials of niacin and included evidence from AIM-HIGH, ARBITER 2 and HPS2-THRIVE.[31] All three trials found combination therapy associated with increased incidence of new onset diabetes (RR 1.64, 95% CI 1.13 to 2.38, RR 1.53, 95% CI 0.38 to 6.14 and RR 1.31, RR 1.15 to 1.49). The meta-analysis, which included additional trials of niacin without background statin therapy, found niacin associated with increased risk of diabetes 1.34 (10 trials; 95% CI 1.21 to 1.49; I^2=0%).[31]

Special Populations

All three trials of statin and niacin combination therapy versus statin monotherapy enrolled secondary prevention populations (**Table 4**). AIM-HIGH conducted subgroups analyses assessing the effect of age (<65 versus ≥65 years), gender, history of diabetes, and prior MI on the primary CV composite outcome; no significant interactions on these factors were reported.[24] HPS2-THRIVE also conducted numerous pre-specified subgroup analyses; there were no significant interactions between use of combination therapy and sex or age (**Table 5**).[25]

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Table 5. Risk of coronary death, non-fatal myocardial infarction, stroke, or revascularization in HPS2-THRIVE subgroups[25]

Subgroup	Incidence; RR	p for interaction
Sex		
Male	13% (1397/10614) vs. 14% (1484/10615); RR 0.94, 95% CI 0.88 to 1.01	0.07
Female	13% (299/2224) vs. 12% (273/2220); RR 1.09, 95% CI 0.94 to 1.27	
Age		
<65 years	11% (740/6470) vs. 12% (786/6462); RR 0.94, 95% CI 0.86 to 1.03	0.98
≥65 to <70 years	14% (392/2814) vs. 13% (367/2810); RR 1.07, 95% CI 0.93 to 1.22	
≥70 years	16% (564/3554) vs. 17% (605/3563); RR 0.93, 95% CI 0.84 to 1.04	

Key Question 2. What are the benefits and harms of de-intensification of statin combination therapy versus continued combination therapy in adults at increased risk of cardiovascular morbidity or mortality?

We identified no trial that directly evaluated benefits and harms of de-intensification of statin combination therapy.

Discussion

Table 6 summarizes the benefits and harms of statin plus fibrate or niacin combination therapy versus monotherapy and the effects of de-intensification of statin combination therapy. Combination therapy was not associated with a significant reduction in risk of all-cause mortality or CV outcomes versus statin monotherapy based on five trials (two trials of fibrates and three trials of niacin), though estimates for statin and fibrate combination therapy were imprecise. Statin and niacin combination therapy was associated with increased risk of mortality versus statin monotherapy. Although a number of other trials have evaluated statin combination therapy with fibrates or niacin, they were short-term trials that were not designed to assess clinical outcomes, and they were excluded from this rapid evidence synthesis.[32,33] Our findings are consistent with recent systematic reviews on the effect of statin combination therapy versus monotherapy.[2,21]

There were no clear differences between statin and fibrate combination therapy versus statin monotherapy in risk of most adverse events, although combination therapy was associated with increased risk of renal dysfunction.[22,23] Statin and niacin combination therapy was associated with higher risk of serious adverse events, withdrawals due to adverse events, and new onset diabetes versus statin monotherapy.[24-26] It was also associated with a non-significant trend towards increased risk of ischemic stroke.[24]

Evidence on benefits and harms of combination therapy in special populations, including elderly and frail patients and women, is limited. The ACCORD trial[22] found benefit of combination fibrate therapy in men but not women (p for interaction=0.01), a finding that was not replicated in other studies of fibrates[34] or niacin combination therapy.[25] Patients with dyslipidemia (i.e., those with high triglycerides and low HDL cholesterol) using fibrate combination therapy had greater reduction in risk of cardiovascular events than those without dyslipidemia, but the interaction between groups was not significant (p for interaction=0.06).[22] The trials did not demonstrate any significant interaction between combination therapy and age or other factors.

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Table 6. Summary of benefits and harms of statin combination therapy with a fibrate or niacin versus statin monotherapy and de-intensification of statin combination therapy to statin monotherapy

Action	Benefits	Harms
Combination therapy vs. statin monotherapy	• No clear benefit of combination therapy vs. statin monotherapy for all-cause mortality, composite cardiovascular outcomes or individual cardiovascular outcomes, based 5 RCTs with 1- to 5-year follow-up.	• Limited and imprecise evidence suggests an increased risk of renal events with statin and fibrate combination therapy vs. statin monotherapy, based on 2 RCTs • Increased risk of serious adverse events (1 RCT), including new-onset diabetes (3 RCTs) and non-significant increased risk of ischemic stroke (1 RCT) with statin and niacin combination therapy vs. statin monotherapy
De-intensification to statin monotherapy versus continued combination therapy	• No direct evidence	• No direct evidence

RCT=randomized controlled trial

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Appendix

Table A. Additional outcomes in randomized controlled trials of statin combination therapy versus statin monotherapy

Author Year n Study Duration	Interventions A vs. B	Results A vs. B
Statin + fibrate vs. monotherapy		
ACCORD 2010[22] n=5,518 5 years	A. Simvastatin mean dose 22 mg/day + fenofibrate 54 or 160 mg/day* (n=2,765) B. Simvastatin 22 mg/day + placebo (n=2,753)	CV mortality: 4% (99/2765) vs. 4% (114/2753); RR 0.86, 95% CI 0.66 to 1.13 Non-fatal CV event: 7% (192/2765) vs. 7% (196/2753); RR 0.98, 95% CI 0.81 to 1.18 Fatal stroke: 0.1% (4/2765) vs. 0.3% (8/2765); RR 0.50, 95% CI 0.15 to 1.65 Non-fatal stroke: 2% (47/2765) vs. 2% (40/2753); RR 1.17, 95% CI 0.77 to 1.78 Fatal MI: 0.4% (12/2765) vs. 0.5% (14/2765); RR 0.85, 95% CI 0.40 to 1.84 Non-fatal MI: 6% (173/2765) vs. 7% (186/2753); RR 0.93, 95% CI 0.76 to 1.13 Myopathy, myositis or rhabdomyolysis: 0.1% (4/2765) vs. 0.1% (3/2753); RR 1.33, 95% CI 0.30 to 5.93 Withdrawals due to decreased eGFR: 2% (66/2765) vs. 1% (30/2753); RR 2.20, 95% CI 1.43 to 3.38 Hemodialysis or end-stage renal disease: 3% (75/2765) vs. 3% (77/2753); RR 0.97, 95% CI 0.71 to 1.33 Hepatitis: 0.1% (3/2765) vs. 0% (0/2753); RR 6.97, 95% CI 0.36 to 135
FIRST 2014[23] n=662 2 years	A. Atorvastatin mean dose 21 mg/day + fenofibric acid 135 mg/day (n=337) B. Atorvastatin mean dose 21 mg/day + placebo (n=339)	Withdrawals due to adverse events: 14% (47/337) vs. 7% (22/339); RR 2.15, 95% CI 1.33 to 2.48 Serious adverse events: 17% (58/337) vs. 20% (66/339); RR 0.88, 95% CI 0.64 to 1.22 Renal adverse events: 7% (22/337) vs. 1% (3/339); RR 7.38, 95% CI 2.23 to 24 Renal impairment: 2% (7/337) vs. 0.6% (2/339); RR 3.52, 95% CI 0.74 to 17 Renal failure: 3% (9/337) vs. 0.3% (1/339); RR 9.05, 95% CI 1.15 to 71 Hepatic adverse events: 3% (9/337) vs. 2% (6/339); RR 1.51, 95% CI 0.54 to 4.19
Statin + niacin vs. monotherapy		
AIM-HIGH 2011[24] n=3,414 3 years*	A. Simvastatin 40 to 80 mg/day + niacin 1500 to 2000 mg/day (n=1,718) B. Simvastatin 40 to 80 mg/day + low-dose (50mg) niacin placebo (n=1,696)	CV mortality: 3% (45/1718) vs. 2% (38/1696); RR 1.17, 95% CI 0.76 to 1.79 CHD mortality: 1% (20/1718) vs. 2% (26/1696); RR 0.76, 95% CI 0.43 to 1.36 Non-fatal MI: 5% (92/1718) vs. 5% (80/1696); RR 1.14, 95% CI 0.85 to 1.90 Withdrawals due to adverse events: 25% (435/1718) vs. 20% (341/1696); RR 1.26, 95% CI 1.11 to 1.43
ARBITER 2004[26] n=167 1 year	A. Statin (primarily simvastatin ≥20 mg/day) + niacin 500 mg/day titrated to 1000 mg/day after 30 days (n=87) B. Statin (primarily simvastatin ≥20 mg/day) + placebo (n=80)	CV mortality: 1% (1/87) vs. 3% (2/80); RR 0.46, 95% CI 0.04 to 4.97 Stroke: 0% (0/87) vs. 1% (1/80); RR 0.31, 95% CI 0.01 to 7.42 Withdrawals due to adverse events: 2% (2/87) vs. 8% (6/80); RR 0.31, 95% CI 0.06 to 1.48
HPS2-THRIVE 2014[25] n=25,673 4 years	A. Simvastatin 40 mg/day + niacin 2000 mg/day + laropiprant 40 mg/day (n=12,838) B. Simvastatin 40 mg/day + placebo (n=12,835)	Coronary mortality: 5% (668/12838) vs. 5% (694/12835); RR 0.96, 95% CI 0.87 to 1.07 Non-fatal MI: 3% (402/12838) vs. 3% (431/12835); RR 0.93, 95% CI 0.82 to 1.07 Stroke: 4% (498/12838) vs. 4% (499/12835); RR 1.00, 95% CI 0.98 to 1.90 Cancer: 5% (622/12838) vs. 5% (609/12835); RR 1.02, 95% CI 0.92 to 1.14 Serious adverse events: 56% (7137/12835) vs. 53% (6762/12838); RR 1.06, 95% CI 1.03 to 1.08

CHD = coronary heart disease; CVD = cardiovascular disease; MI = myocardial infarction

*Planned duration was 5 years; AIM-HIGH was stopped early due to observed lack of efficacy and unexpected excess incidence of ischemic stroke.

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De-intensification Dual Antiplatelet Therapy (DAPT): Rapid Evidence Synthesis

This report was prepared by the Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University, under Contract No. VA268-16-Q-0140, in support of an HSR&D research study focused on Identifying, Measuring, and Facilitating Opportunities for De-Intensification of Medical Services.

KEY MESSAGES

Why is this important?

- Dual antiplatelet therapy (DAPT) can decrease ischemic risk versus single antiplatelet therapy but is associated with increased bleeding risk.
- The American College of Cardiology and the American Heart Association do not recommend DAPT in people with stable ischemic heart disease (SIHD) without stent implantation and no history of acute coronary syndrome (ACS) or myocardial infarction (MI).
- Despite guideline recommendations, DAPT is still used in some patients with SIHD.
- This rapid evidence synthesis summarizes the evidence of the benefits and harms of DAPT in SIHD patients compared with single antiplatelet therapy, and de-intensification of DAPT.

What is the evidence on benefits versus harms of DAPT in SIHD patients?

- Two trials evaluated DAPT versus aspirin in persons with SIHD or who were at high cardiovascular risk without a clear indication for DAPT.
    - The CHARISMA trial found no difference between DAPT versus aspirin in risk of all-cause mortality, cardiovascular (CV) mortality, myocardial infarction, or the primary CV composite outcome (MI, stroke, or death); DAPT was associated with a slight (not statistically significant) increase in risk of severe bleeding and an increased risk of moderate bleeding.
    - The PEGASUS-TIMI 54 trial found no difference between DAPT versus aspirin in risk of all-cause mortality or cardiovascular mortality. DAPT was associated with decreased risk of the primary composite outcome of CV death, MI, or stroke, but these effects were offset by a similar increase in the risk of severe bleeding.

What is the evidence on de-intensification?

- No study evaluated effects of de-intensification of DAPT in persons with SIHD.

What are the implications of our findings?

- DAPT does not reduce risk of mortality or CV mortality in persons with SIHD; any beneficial effects on cardiovascular outcomes are offset by increases in bleeding.

Background

Over 2,200 Americans die of cardiovascular (CV) disease each day.[1] For patients with acute coronary syndrome (ACS) and following stent implantation, treatment with dual antiplatelet therapy (DAPT) is standard therapy to reduce risk of thrombus, despite increased risk of bleeding.[2] By contrast, among patients with stable ischemic heart disease (SIHD), guidelines from the American College of Cardiology and the American Heart Association recommend against use of DAPT.[3]

Despite the guidelines, DAPT still appears to be used in some patients with SIHD. One study found that about 3% of asymptomatic patients with CV risk factors are prescribed DAPT.[4] The purpose of this rapid evidence review is to synthesize the evidence on benefits and harms of use of DAPT and de-intensification of DAPT among patients with SIHD.

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Current Guidelines

The most recent (2016) guideline from the American College of Cardiology and the American Heart Association on use of DAPT in patients with SIHD is summarized in **Table 1**.[3] The guideline does not recommend DAPT in patients with SIHD without prior stent implantation and no history of recent ACS or myocardial infarction (MI); SIHD includes patients with a history of ACS >1 year prior who have remained free of recurrent ACS.

Table 1. Summary of guidelines on the use of DAPT in stable patients

Guideline	Recommendation
American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines[3]	DAPT is not recommended in patients with SIHD without prior stent implantation and no history of ACS or MI. Decisions about treatment with and duration of DAPT in patients with SIHD with a history of MI or coronary stent implantation require a thoughtful assessment of the benefit/risk ratio, integration of study data, and consideration of patient preference.

ACS = acute coronary syndrome, DAPT = dual antiplatelet therapy, MI = myocardial infarction, SIHD = stable ischemic heart disease

Methods

Topic Selection and Scope Development

This review included studies relevant to the following questions and eligibility criteria to assess the benefits and harms of continuing or de-intensifying DAPT.

Key Questions

1. What are the benefits and harms of DAPT versus single antiplatelet therapy treatment in patients with SIHD?
    a. What are the benefits and harms of de-intensification of DAPT versus continued DAPT in patients with SIHD?

Eligibility Criteria

- Population: Adults with stable ischemic heart disease without prior history of ACS and stent implantation.
- Intervention: Dual antiplatelet therapy
- Comparator: Single antiplatelet therapy
- Outcomes: All-cause and CV mortality, serious CV events, MI, stroke, bleeding risk, ischemic events, and serious adverse events attributed to treatment with DAPT
- Timing: Any
- Setting: Any
- Study design: systematic reviews and randomized controlled trials

Searching and Study Selection

The research librarian conducted searches of Ovid MEDLINE®, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews through November 2016. More recent studies were also identified by hand searched references. We used a best evidence approach when reviewing abstracts and selecting studies for inclusion that involved using the most relevant studies with the strongest methodologies.[5,6] We included good-quality systematic reviews that provided

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direct evidence on dual antiplatelet therapy. Randomized controlled trials were included if no good-quality systematic reviews meeting inclusion criteria were available.

Data Synthesis and Quality Assessment

Data abstraction and rating of the strength of the evidence was conducted using standard, prespecified criteria based on Agency for Healthcare Research and Quality (AHRQ) guidance.[7] After studies were selected for inclusion, data was abstracted into predetermined table templates. Quality assessment of systematic reviews was based on the ROBIS tool.[8] Ratings were completed by one reviewer with a second reviewer checking discrepancies if needed. We qualitatively summarized the evidence based on the overall quality, consistency, precision, and directness of the evidence.[7] Outcomes were all-cause mortality, CV mortality, MI, CV events, stroke, and bleeding when reported compared to the benefits of continuing DAPT.

Results

Summary of Evidence

Database searches resulted in 1,402 potentially relevant citations. Over 28 systematic reviews from 2013 to 2016 and a recent summary of reviews were evaluated. The literature searches did not identify newer high-quality randomized controlled trials of the benefits of DAPT versus single antiplatelet therapy in stable patients than the two good randomized controlled trials used in the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines for the duration of DAPT in patients with SIHD.[2,9]

Key Question 1. What are the benefits and harms of DAPT versus single antiplatelet therapy treatment in patients with SIHD?

Evidence from Systematic Reviews

Although a number of systematic reviews are available on DAPT versus single antiplatelet therapy, none focused on benefits and harms in persons with SIHD.

Evidence from Randomized Controlled Trials

Two trials (CHARISMA[10] and PEGASUS-TIMI 54) evaluated DAPT versus single antiplatelet therapy in patients with SIHD.[11] **Tables 2 and 3** describe characteristics of the trials and patients.

Table 2. Randomized controlled trial characteristics

Author, Year Study Name	Countries	Intervention Characteristics	Patient Characteristics	Primary outcomes
Bhatt, 2006[10] CHARISMA Trial	Multicenter 32 countries*	DAPT clopidogrel plus low-dose aspirin (n=1,659) Placebo plus low-dose aspirin	n=15,603 patients with established atherosclerosis or high risk of atherosclerotic diseases Median Age: 64 years (range 39 to 93) Female: 29% Race: 80% white Hypertension: 73%	**Primary efficacy end point** First occurrence of myocardial infarction, stroke, death from CV causes **Secondary efficacy end point** Hospitalization for unstable angina, transient ischemic attack, or revascularization **Primary safety end point**

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		(n=1,625)	Prior MI: 34% Prior percutaneous coronary intervention: 22% Prior coronary artery bypass graft:19%	Severe bleeding, fatal bleeding, moderate bleeding, primary intracranial hemorrhage
Bonaca, 2015[11] PEGASUS-TIMI 54 Trial	Multicenter 31 countries*	DAPT ticagrelor 90 mg (n=7,050) DAPT Ticagrelor 60 mg (n=7045) Low-dose aspirin (n=7,067)	n=21,162 patients with SIHD 1 to 3 years after MI and additional high-risk features Mean Age: 65 years Female: 24% Race: 86% white Hypertension: 77% Prior MI: 16% Prior percutaneous coronary intervention: 83%	**Primary efficacy end point** Composite of MI, CV death, or stroke **Secondary efficacy end point** Cardiovascular death, death from any cause **Primary safety end point** Transient ischemic attack, major bleeding

CV = cardiovascular; DAPT = dual antiplatelet therapy; MI = myocardial infarction; SIHD = stable ischemic heart disease.
*The full list of countries is indicated in Appendix A.

Table 3. Patient characteristics and risk factors in CHARISMA and PEGASUS-TIMI 54 trials

Study Name n Study Duration	Mean Age	Age ≥65 (male) or ≥ 70 (female)	History of Prior Cardiovascular Event	Diabetes	Current Smoker	Prior Myocardial Infarction
CHARISMA[10] n=15,603 2 years, 9 months	68 years	Not reported	35%	42%	20%	34.2 vs. 34.9%
PEGASUS-TIMI 54[11] n=21,162 2 years, 4 months	65 years	51%	32%	32%	16.5%	16.2 vs. 16.6 vs. 16.8%

* Mean age calculated from reported median and range

CHARISMA Trial

The CHARISMA trial randomized 15,603 people with multiple atherothrombotic risk factors, documented coronary disease, documented cerebrovascular disease, or documented peripheral arterial disease to clopidogrel plus aspirin versus aspirin alone; the trial followed patients for 2 years and 9 months.[10] Patients who were judged to have established indications for DAPT, such as recent ACS or recent revascularization, were excluded from the trial. Overall, DAPT was not associated with reduced risk of all-cause mortality, CV mortality, or the primary composite CV outcome (MI, stroke, or CV death). However, DAPT was associated with reduced risk of the secondary composite CV outcome (adding hospitalizations for unstable angina, transient ischemic attack, and revascularization to the primary outcome) (16.7% vs. 17.9%, RR 0.92, 95% CI 0.86 to 0.995) (**Table 4**). DAPT was associated with an increased risk of moderate bleeding (2.1% vs. 1.3%, RR 1.62, 95% CI 1.27 to 2.08); effects on risk of

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severe bleeding were not statistically significant (1.7% vs. 1.3%, RR 1.25, 95% CI 0.97 to 1.61). Benefits of DAPT on the primary outcome were larger and risk of bleeding lower in patients who were symptomatic compared to those who were asymptomatic, but the interaction term for this analysis was only marginally significant. Results for the efficacy end points and safety end points are in **Table 4.**

Table 4. Clinical outcomes of the CHARISMA study of clopidogrel plus aspirin versus aspirin monotherapy

Outcome	DAPT (Clopidogrel Plus Aspirin) N (%)	Placebo Plus Aspirin N (%)	Relative Risk (95% CI)	p-Value
Efficacy end points				
Primary efficacy end point*	534 (6.8)	573 (7.3)	0.93 (0.83–1.05)	p=0.22
All-cause mortality	371 (4.8%)	374 (4.8%)	0.99 (0.86–1.14)	p=0.90
Cardiovascular mortality	238 (3.1%)	229 (2.9%)	1.04 (0.87–1.25)	p=0.68
Myocardial infarction (nonfatal)	146 (1.9%)	155 (2.0%)	0.94 (0.75–1.18)	p=0.59
Cardiovascular events*	866 (11.1%)	957 (12.3%)	0.90 (0.82–0.98)	p=0.02
Stroke (fatal)	150 (1.9%)	189 (2.4%)	0.79 (0.64–0.98)	p=0.03
Ischemic events (stroke nonfatal)	132 (1.7%)	163 (2.1%)	0.81 (0.64–1.02)	p=0.07
Secondary efficacy endpoint†	1301 (16.7%)	1395 (17.9%)	0.92 (0.86–0.995)	p=0.04
Hospitalization for angina, TIA, or revascularization	866 (11.1%)	957 (12.3%)	0.90 (0.82–0.98)	p=0.02
Safety end points				
Fatal bleeding	26 (0.3%)	17 (0.2%)	1.53 (0.83–2.82)	p=0.17
Severe bleeding	130 (1.7%)	104 (1.3%)	1.25 (0.97–1.61)	p=0.09
Moderate bleeding	164 (2.1%)	101 (1.3%)	1.62 (1.27–2.08)	p<0.001
Primary intracranial hemorrhage	26 (0.3%)	27 (0.3%)	0.96 (0.56–1.65)	p=0.89

DAPT = dual-antiplatelet therapy; TIA = transient ischemic attack

* Composite efficacy endpoint; first occurrence of myocardial infarction, stroke, or death from cardiovascular causes.

† Secondary efficacy end point; first occurrence of myocardial infarction, stroke, death from cardiovascular causes, or hospitalization for unstable angina, a transient ischemic attack, or a revascularization procedure.

PEGASUS-TIMI 54 Trial

The PEGASUS-TIMI 54 trial[11] randomized 21,162 people who had a MI 1 to 3 years prior to the study to ticagrelor plus aspirin versus aspirin alone, and followed patients for 2 years and 4 months. Patients were ineligible if DAPT use was already planned. DAPT was not associated with decreased risk of all-cause or CV mortality (**Table 5**). Although DAPT was associated with decreased risk of composite CV events (for the primary outcome of CV death, MI, or stroke 7.8% vs. 9.0%, HR 0.81 to 0.84, depending on ticagrelor dose), this was offset by a similar increase in risk of severe bleeding (2.3 to 2.6% for DAPT vs. 1.1% for aspirin alone). Outcomes are shown in **Table 5.**

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Table 5. Clinical outcomes of the PEGASUS-TIMI 54 study of ticagrelor versus aspirin monotherapy

Outcome	DAPT (Ticagrelor 90 mg) N (%)	DAPT (Ticagrelor 60 mg) N (%)	Aspirin N (%)	Ticagrelor 90 mg vs. Aspirin Hazard Ratio (95% CI)	p-Value	Ticagrelor 60 mg vs. Aspirin Hazard Ratio (95% CI)	p-Value
Efficacy end points							
All-Cause mortality	326 (5.15%)	289 (4.69%)	326 (5.16%)	1.00 (0.86-1.16)	p=0.99	0.89 (0.76-1.04)	p=0.14
Cardiovascular mortality	182 (2.94%)	174 (2.86%)	210 (3.39%)	0.87 (0.71-1.06)	p=0.15	0.83 (0.68-1.01)	p=0.07
Myocardial infarction	275 (4.40%)	285 (4.53%)	338 (5.25%)	0.81 (0.69-0.95)	p=0.01	0.84 (0.72-0.98)	p=0.03
Cardiovascular death, myocardial infarction, or stroke	493 (7.85%)	487 (7.77%)	578 (9.04%)	0.85 (0.75-0.96)	p=0.008	0.84 (0.74-0.95)	p=0.004
Death from coronary heart disease, myocardial infarction, or stroke	438 (6.99%)	445 (7.09%)	535 (8.33%)	0.82 (0.72-0.93)	p=0.002	0.83 (0.73-0.94)	p=0.003
Cardiovascular death or myocardial infarction	424 (6.79%)	422 (6.77%)	497 (7.81%)	0.85 (0.75-0.97)	p=0.01	0.85 (0.74-0.96)	p=0.01
Death from coronary heart disease or myocardial infarction	350 (5.59%)	360 (5.75%)	429 (6.68%)	0.81 (0.71-0.94)	p=0.004	0.84 (0.73-0.96)	p=0.01
Stroke	100 (1.61%)	91 (1.47%)	122 (1.94%)	0.82 (0.63-1.07)	p=0.14	0.75 (0.57-0.98)	p=0.03
Ischemic stroke	88 (1.41%)	78 (1.28%)	103 (1.65%)	0.85 (0.64-1.14)	p=0.28	0.76 (0.56-1.02)	p=0.06
Safety end points							
Severe bleeding (TIMI major bleeding)	127 (2.60%)	115 (2.30%)	54 (1.06%)	2.69 (1.96-3.70)	p≤0.001	2.32 (1.68-3.21)	p≤0.001
Fatal bleeding	32 (0.63%)	33 (0.71%)	30 (0.60%)	1.22 (0.74-2.01)	p=0.43	1.20 (0.73-1.97)	p=0.47

DAPT = dual antiplatelet therapy; TIM I=Thrombolysis in Myocardial Infarction

* Composite efficacy endpoints; myocardial infarction, cardiovascular death, or stroke.

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Key Question 1a. What are the benefits and harms of de-intensification of DAPT versus continued DAPT in patients with SIHD?

No study evaluated effects of de-intensification of DAPT in patients with SIHD versus continued DAPT.

Discussion

A summary of the benefits and harms of continuing DAPT versus single antiplatelet therapy is shown in **Table 6**. Two good-quality trials, the CHARISMA Trial and PEGASUS-TIMI 54 Trial, evaluated DAPT versus aspirin alone in patients with SIHD or at high CV risk and no clear indication for DAPT. In both trials, DAPT had no effect on all-cause or CV mortality. Although PEGASUS-TIMI 54 found DAPT associated with reduced risk of the primary composite CV outcome, this was offset by a similar increase in risk of severe bleeding. The ACC/AHA does not recommend DAPT for patients with SIHD without prior stent implantation.[3]

Table 6. Summary of benefits and harms of DAPT

Action	Benefits	Harms or Adverse Events
DAPT vs. single antiplatelet therapy	• Reduced risk of composite CV outcomes in one trial; no effect on primary composite CV outcome in another trial • No effects on all-cause or CV mortality	• Increased risk of moderate or severe bleeding
De-intensification of DAPT vs. continued DAPT	• No evidence	• No evidence

CV = cardiovascular; DAPT = dual antiplatelet therapy

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Appendix A. Characteristics of randomized controlled trials of DAPT and summary of findings

Author, Year	Countries Included		Interventions	Patient characteristics	Outcomes
Bhatt, 2006[10]	Argentina Australia Austria Belgium Brazil Canada Chile Czech Republic Denmark Finland France Germany Greece Hong Kong Hungary Italy	Malaysia Mexico Netherlands Norway Poland Portugal Russian Federation Singapore South Africa Spain Sweden Switzerland Taiwan Turkey United Kingdom United States	DAPT (clopidogrel plus low-dose aspirin) (n=1659) Placebo plus low-dose aspirin (n=1625)	n=15,603 Patients Median Age: 64 years (range 39 to 93) Female: 29% Race: 80% Hypertension: 73% Prior myocardial infarction: 34% Prior percutaneous coronary intervention: 22% Prior coronary artery bypass graft:19%	**Primary efficacy end point** All-cause mortality Cardiovascular mortality Myocardial infarction Cardiovascular events* Stroke Ischemic events **Secondary efficacy endpoint** Hospitalization for angina Transient ischemic attack Revascularization **Safety end points** Fatal bleeding Severe bleeding Moderate bleeding
Bonaca, 2015[11]	Argentina Australia Belgium Brazil Bulgaria Canada Chile China Colombia Czech Republic France Germany Hungary Italy Japan	Netherlands Norway Peru Philippines Poland Korea Romania Russian Federation Slovakia South Africa Spain Sweden Turkey Ukraine United Kingdom United States	DAPT (ticagrelor 90 mg) (n=7050) DAPT (ticagrelor 60 mg) (n=7045) Low-dose aspirin (n=7067)	n=21,162 Patients Mean Age: 65 years Female: 24% Race: 86% white Hypertension: 77% Prior myocardial infarction: 16% Prior percutaneous coronary intervention: 83%	All-cause mortality Cardiovascular mortality Myocardial infarction Cardiovascular events: Cardiovascular death, Myocardial infarction, or stroke Death from coronary heart disease, myocardial infarction, or stroke Cardiovascular death or myocardial infarction Death from coronary heart disease or Myocardial infarction Stroke Ischemic stroke Severe bleeding (TIMI* major bleeding) Fatal bleeding

DAPT = dual antiplatelet therapy; TIMI = Thrombolysis in Myocardial Infarction

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Echocardiography as Routine Follow-up for Asymptomatic Mild Native Valve Disease in Adults with No Change in Signs or Symptoms: Rapid Evidence Synthesis

This report was prepared by the Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University, under Contract No. VA268-16-Q-0140, in support of an HSR&D research study focused on Identifying, Measuring, and Facilitating Opportunities for De-Intensification of Medical Services.

KEY MESSAGES

Why is this important?

- Asymptomatic mild aortic stenosis (AS) or mitral regurgitation (MR) may progress to more severe disease. The benefits and harms of echocardiographic surveillance of persons with asymptomatic mild AS or MR is uncertain.

What is the evidence on benefits versus harms of routine surveillance with echocardiography for asymptomatic mild AS or MR in adults with no change in signs or symptoms?

- No study directly evaluated benefit or harms of surveillance with echocardiography in persons with asymptomatic mild AS or MR.
- Natural history studies indicate that mild AS and MR progress to more severe valvular disease over time, though there is individual variability in the rate of progression; no study reported the proportion of patients who progress to severe AS or MR without developing symptoms.
- The effectiveness of surgical or other interventions among persons with asymptomatic AS or MR, even when severe, is uncertain.
- Harms may include the potential for unnecessary and potentially harmful tests and treatments as a result of surveillance, due to over diagnosis, overtreatment, or incidental echocardiographic findings.

What is the evidence on de-intensification?

- No study evaluated benefits and harms of de-intensification of surveillance echocardiography for mild asymptomatic AS or MR.

What are the implications of our findings?

- There is no direct evidence on potential benefits or harms of echocardiographic surveillance in patients with asymptomatic mild AS or MR, or of de-intensification of surveillance. Although mild AS and MR progress to more severe disease over time and severe valvular disease is associated with poorer clinical outcomes, it is unclear how many patients progress to severe AS or MR without developing symptoms. Research is needed to clarify effects of interventions in persons with asymptomatic severe AS or MR.

Background

Valvular heart disease is relatively common, with an estimated overall prevalence in the United States of 2.5%.[1] Although specific estimates vary, aortic stenosis (AS) and mitral regurgitation (MR) account for the great majority of native heart valve disease.[1-3] The overall prevalence of valve disease increases considerably with age, from an estimated 0.7% in people 18 to 44 years of age to 13.2% in those 75 years of age or older.[1,3-5] Most of these studies, however, were either limited to moderate and/or severe valve disease[1,2] or incompletely reported on mild disease.[3] In smaller studies that included mild valve disease, mild disease constituted more than half of all valve disease (AS: 52% to 74%;[4,6] MR: 67% to 90%[6,7]).

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AS and MR are progressive diseases that can result in the eventual worsening of a patient's hemodynamic status, with heart failure and possible symptoms that include exertional dyspnea, decreased exercise tolerance, palpitations, angina, and syncope.[8-10] For mild or moderate asymptomatic valve disease, no intervention is usually indicated.[8,11] For symptomatic severe disease, surgical repair or replacement of the affected valve is usually recommended.[8,11] Although management of asymptomatic severe disease is controversial, current recommendations support valve repair or replacement for certain subgroups of patients with asymptomatic AS or MR (e.g., left ventricular dysfunction).[8,11]

Current Guidelines

Some guidelines recommend routine surveillance with echocardiography for asymptomatic mild AS or MR with no change in signs or symptoms (**Table 1**)[8,12] in order to determine when mild AS or MR progresses to more severe disease. The rationale for these recommendations is that it is not possible to predict the rate of progression for individual patients, progression to more advanced stages may occur without the development of symptoms, prognosis is worse in persons with advanced valve disease, and earlier interventions (i.e., before the development of symptoms) may result in better outcomes.[8]

Guidelines from the American College of Cardiology (ACC) and the American Heart Association (AHA)[8] recommend routine surveillance of asymptomatic mild AS or MR with a transthoracic echocardiogram (TTE) every 3 to 5 years. The recommendations are rated Class I (benefits > risks; procedure is deemed to be useful) and are based on a Level of Evidence of "C" (expert opinion, case studies, or standard of care).

Guidelines from the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS), published in 2012, recommend routine echocardiographic surveillance for asymptomatic severe AS and for asymptomatic moderate or severe MR, but make no specific recommendations regarding echocardiography for routine surveillance of asymptomatic mild AS or MR.[11]

In 2011, the American College of Cardiology Foundation (ACCF) and the American Society of Echocardiography (ASE) led the publication of updated appropriate use criteria (AUC) for 202 different indications, including four indications related to routine screening for asymptomatic mild AS or MR (**Table 1)**[12] with the then-current 2008 ACC/AHA guidelines as a reference.[13] Surveillance of asymptomatic mild AS with transthoracic echocardiogram (TTE) at ≥3 year intervals was rated as appropriate (Class I; Level of Evidence B), but surveillance of asymptomatic mild MR with TTE was rated as being of uncertain appropriateness (Class III; Level of Evidence: C); more frequent surveillance for either condition was rated as inappropriate.[13]

Table 1. Summary of current guidelines and recommendations

Issuing Organization	Summary of Guidelines or Recommendations
American College of Cardiology/American Heart Association[8]	**AS:** • **Surveillance with TTE every 3–5 years** for asymptomatic mild AS (V_{max} 2.0–2.9 m/s), with normal left ventricular function and normal stroke volume **MR:** • **Surveillance with TTE every 3–5 years** for asymptomatic mild MR, with normal left ventricular function
European Society of Cardiology/European Association for Cardio-Thoracic Surgery[11]	**AS:** • **No specific guidance** regarding routine surveillance with echocardiography for asymptomatic mild AS **MR:** • **No specific guidance** regarding routine surveillance with echocardiography for

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	asymptomatic mild MR
ACCF/ASE/AHA/ASNC/ HFSA/HRS/SCAI/SCCM /SCCT/SCMR[12]	**AS:** • Routine surveillance with TTE for mild valvular stenosis without a change in clinical status or cardiac exam: ○ **< every 3 years: Inappropriate (AUS = 3)** ○ **≥ every 3 years: Appropriate (AUS = 7)** **MR:** • Routine surveillance with TTE for mild valvular regurgitation without a change in clinical status or cardiac exam: ○ **< every 3 years: Inappropriate (AUS = 2)** ○ **≥ every 3 years: Uncertain (AUS = 4)**

AATS = American Association for Thoracic Surgery; ACCF = American College of Cardiology Foundation; AHA = American Heart Association; AS = aortic stenosis; ASE = American Society of Echocardiography; ASNC = American Society of Nuclear Cardiology; AUS = appropriate use score; HFSA = Heart Failure Society of America; HRS = Heart Rhythm Society; MR = mitral regurgitation; SCA = Society of Cardiovascular Anesthesiologists; SCAI = Society for Cardiovascular Angiography and Interventions; SCCM = Society of Critical Care Medicine; SCCT = Society of Cardiovascular Computed Tomography; SCMR = Society for Cardiovascular Magnetic Resonance; STS = Society of Thoracic Surgeons; TTE = transthoracic echocardiogram; V_{max}: maximum aortic jet velocity

We found no published information on the proportion of patients with asymptomatic mild AS or MR who receive routine surveillance with echocardiography. However, a study in a large urban hospital in the UK found that nearly 90% of 50 echocardiograms performed for routine surveillance of asymptomatic mild AS did not adhere to the ACC/AHA recommendation of once every 3 to 5 years; almost all were performed earlier than recommended.[14] Two other studies found that inappropriate routine (yearly) surveillance of asymptomatic mild valve disease in patients with no change in clinical status accounted for approximately 3.9% of all TTEs conducted for any reason,[15] and for between 7% and 16% of TTEs ordered for any inappropriate indication.[16]

Methods

Topic Selection and Scope Development:

We sought studies addressing the following key questions.

Key Questions

1. Does the use of echocardiography for routine surveillance of asymptomatic mild native valve disease (aortic stenosis or primary mitral regurgitation) in adults with no change in signs or symptoms improve clinical outcomes compared with no routine surveillance using echocardiography?
    a) Does the comparative effectiveness of surveillance with echocardiography differ according to the frequency of surveillance?
    b) What are the potential adverse effects of routine screening with echocardiography compared with no routine surveillance with echocardiography?
    c) Does the risk of potential adverse effects differ according to the frequency of surveillance?
2. Does de-intensification of routine echocardiographic surveillance (i.e., discontinuation or decreased frequency) of asymptomatic mild native valve disease in adults with no change in signs or symptoms improve or adversely affect clinical outcomes?

Eligibility Criteria

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- Population: Adults (male or female) with asymptomatic mild native valve disease (aortic stenosis or primary mitral regurgitation) and no change in signs or symptoms
- Intervention: Echocardiography as routine follow-up
- Comparator: No echocardiography as routine follow-up
- Outcomes: All-cause mortality, cardiovascular mortality, valve repair or replacement, onset of signs or symptoms related to valve disease
- Timing: Any
- Setting: Any
- Study design: Systematic reviews and randomized controlled trials

Searching and Study Selection

The research librarian conducted searches of Ovid MEDLINE®, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews through November 2016. We used a best evidence approach when reviewing abstracts and selecting studies for inclusion that involves using the most relevant studies with the strongest methodologies.[17,18] Our strategy was to include good-quality systematic reviews that provided direct evidence on the use of echocardiography for routine surveillance of patients with asymptomatic mild AS or MR and no change in clinical signs or symptoms. Randomized controlled trials (RCTs) were included if no good-quality systematic reviews meeting inclusion criteria were available. In addition, we reviewed studies cited in reference lists of guidelines and other relevant articles.

In the absence of evidence directly addressing the key questions, we looked for additional evidence that might inform decisions about performing surveillance echocardiography in this population: (1) studies on the natural progression of asymptomatic mild AS or MR, and (2) studies on clinical outcomes associated with earlier treatment for asymptomatic AS or MR compared with later treatment after the severity has worsened and/or symptoms have developed. For these latter two supplemental questions, we supplemented the electronic database searches described above with an additional scan of the literature.

Results

Database searches resulted in 2019 potentially relevant citations, of which 93 were identified as systematic reviews and 264 were identified as RCTs. After screening abstracts, we reviewed the full text of 24 systematic reviews, 13 RCTs, and 6 cohort studies. In addition, we reviewed the full text of 23 papers from reference lists, including all of those cited in the three guidelines in support of their recommendations.

Key Question 1. Effectiveness and potential adverse effects of echocardiography for routine surveillance of asymptomatic mild aortic stenosis or mitral regurgitation

- No study addressed the key question of the effectiveness of echocardiography for routine surveillance of adults with asymptomatic mild native valve disease and no change in signs or symptoms, compared with no routine surveillance with echocardiography.
- No study addressed the question of comparative effectiveness according to different frequencies of surveillance.
- No study addressed the questions of potential adverse effects of routine screening with echocardiography.

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Key Question 2. De-intensification of echocardiography for routine surveillance of asymptomatic mild aortic stenosis or mitral regurgitation

- No study addressed the key question of the effectiveness or potential adverse effects of de-intensification of routine surveillance with echocardiography for adults with asymptomatic mild native valve disease and no change in signs or symptoms.

Progression of Asymptomatic Mild Aortic Stenosis or Mitral Regurgitation

Aortic Stenosis

The severity of aortic stenosis is generally graded using echocardiographic measurements of the maximum aortic jet velocity (V_{max}), the mean transaortic pressure gradient (ΔP_{mean}), and the aortic valve area (AVA).[19] The 2014 ACC/AHA guidelines presented data from various studies on hemodynamic progression, clinical outcomes, and incidence of sudden death in adults with AS (Data Supplements 2, 5, and 6).[8] Of these, two studies reported progression separately among patients with mild AS.[20,21] We found four additional studies on progression of mild AS, three of which were published since the 2014 ACC/AHA guidelines.[22-25] One study explicitly excluded patients with symptoms caused by AS,[20] and another excluded patients with New York Heart Association (NYHA) Class III or Class IV functional symptoms of congestive heart failure.[23] The other four studies either did not specify symptom status,[22,24,25] or included a mix of symptomatic and asymptomatic patients.[21]

Two studies reported the proportion of patients with initially mild AS (not necessarily asymptomatic) that progressed to either moderate or severe AS (**Table 2**).[22,24] One of these studies assessed the percentage of patients with mild AS that had progressed to either moderate or severe AS at three follow-up times: 1 year (6.0%); 2 years (13.7%); and 5 years (30.9%).[22] In the other study, 11.5% of patients with initially mild AS had progressed to severe AS at a mean follow-up of 2.9 years.[24]

Four studies reported on hemodynamic progression of mild AS (**Table 2**). Two studies reported increases in V_{max} that ranged from 0.14 m/s/yr to 0.32 m/s/yr;[21,23] two studies reported increases in ΔP_{mean} that ranged from 2.0 mmHg/yr to 4.0 mmHg/yr;[23,24] and one study reported AVA that decreased by 0.09 cm^2/yr.[23] None of the studies described the proportion of patients with initially asymptomatic mild AS that progressed to more severe disease without developing symptoms.

The studies varied in the populations studied, mean baseline AS severity, and methods. Only one study reported on medical comorbidities among patients with mild AS. In that study, a high proportion of patients had other cardiac conditions in addition to AS, including other types of valvular disease.[22] Two studies excluded patients with a variety of severe medical comorbidities.[23,24]

Table 2. Hemodynamic progression of mild aortic stenosis

Author, Year	Population (mild)	Baseline AS Severity	Follow-up	Increase in Severity (per year)	Progression to Moderate or Severe
Ersboll, 2015[22]	N = 982 Age (median) = 72y Female = 53.5% Asymptomatic: NR	ΔP_{mean} = 14 mmHg (range: 11–18)	1 year 2 years 5 years	NR	1 year: 59/982 (6.0%) 2 years: 134/982 (13.7%) 5 years: 303/982 (30.9%)
Jassal, 2011[23]	N = 37 Age (mean) = 56yrs ± 13 Female = NR for mild	V_{max} = 2.8 m/s ± 0.1 AVA = 1.9 cm^2 ± 0.7 ΔP_{mean} = 17.0 mmHg ± 2.0	3.5 years (mean)	V_{max}: + 0.14 m/s/year AVA: - 0.09 cm^2/year	NR

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	(45%, overall) Asymptomatic: Excluded NYHA Class III or IV CHF symptoms			ΔP_{mean}: + 4.0 mmHg/year	
Nguyen, 2015[24]	N = 104 Age = NR for mild (74yrs ± 9, overall) Female = NR for mild (25%, overall) Asymptomatic: NR	ΔP_{mean} < 25.0 mmHg	2.9 years (mean)	ΔP_{mean}: + 2 ± 3 mmHg/year	12/104 (11.5%)
Roger, 1990[21]	N = 24 Age (mean) = 71yrs ± 11 Female = 25% Asymptomatic: 33%	V_{max} = 2.4 to 2.9 m/s	2.1 years (mean)	V_{max}: + 0.32 ± .38 m/s/year	NR

ΔP_{mean} = mean transaortic pressure gradient; AVA = aortic valve area; CHF = congestive heart failure; NYHA = New York Heart Association; NR = not reported; V_{max} = maximum aortic jet velocity

Three studies reported on clinical outcomes in patients with mild AS (**Table 3**). One study, conducted in patients who were asymptomatic at baseline found 84% of patients with initially mild AS were alive and had not undergone aortic valve surgery at 2 years (mortality not reported separately).[20] Two other studies that assessed all-cause mortality as a separate outcome found 17% to 33% of those with initially mild AS had died at a mean follow-up time of 2.1 to 2.3 years.[21,25] One of those studies also found 4% of patients with initially mild AS had died of cardiac causes.[21] The studies found that 5% to 17% of patients with mild AS had aortic valve surgery/replacement.[21,25] Findings of these studies are difficult to interpret because none included a matched comparison group of patients without AS.

Table 3. Clinical progression and outcomes in adults with mild aortic stenosis

Author, Year	Population (mild)	Baseline Mild AS Severity	Follow-up	Outcomes (with Moderate and Severe for comparison)
Otto, 1997[20]	N = NR for mild (N = 123, overall) Age = NR for mild (63 yrs ± 16, overall) Female = NR for mild (30.1%, overall) Asymptomatic: 100%	V_{max} < 3.0 m/s	2.5 years (mean)	Definitions: Mild AS: V_{max} < 3.0 m/s Moderate AS: V_{max} 3.0 - 4.0 m/s Severe AS: V_{max} > 4.0 m/s <u>Death (all cause) or aortic valve surgery</u>: Event-free survival at 2 years: **Mild AS**: 84% ± 16% Moderate AS: 66% ± 13% Severe AS: 21% ± 18%
Roger, 1990[21]	N = 24 Age (mean) = 71 yrs ± 11 Female = 25% Asymptomatic: 33%	V_{max} = 2.4 to 2.9 m/s	2.1 years (mean)	Definitions: Mild AS: V_{max} 2.4 - 2.9 m/s Moderate AS: V_{max} 3.0 - 3.4 m/s Moderate/Severe AS: V_{max} > 3.5 m/s

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				Death (all cause): **Mild AS**: 4/24 (17%) Moderate AS: 3/24 (13%) Moderate/Severe AS: 4/27 (4%) Cardiac death: **Mild AS**: 1/24 (4%) Moderate AS: 2/24 (8%) Moderate/Severe AS: 1/27 (4%) Aortic valve surgery: **Mild AS**: 4/24 (17%) Moderate AS: 6/24 (25%) Moderate/Severe AS: 13/27 (48%)
Romero, 2014[25]	N = 594 Age (mean) = 74y ± 11 Female = 54% Asymptomatic: NR	AVA = 1.7 cm^2 ± 0.2 ΔP_{mean} = 12.0 mmHg ± 4.0	2.3 years (mean)	Definitions: Mild AS: AVA 1.5-2.0 cm^2 and ΔP_{mean} < 25mmHg Moderate AS: AVA 1.0-1.5 cm^2 and ΔP_{mean} 25-40 mmHg Severe AS: AVA < 1.0 cm^2 and ΔP_{mean} > 40mmHg Death (all cause): **Mild AS**: 195/594 (33%) Moderate AS: 1086/2958 (46%) Severe AS: 254/500 (51%) Aortic valve replacement: **Mild AS**: 31/594 (5%) Moderate AS: 125/2958 (5%) Severe AS: 189/500 (38%)

ΔP_{mean} = mean transaortic pressure gradient; AVA = aortic valve area; V_{max} = maximum aortic jet velocity; NR = not reported

Mitral Regurgitation

Grading the severity of mitral regurgitation includes echocardiographic measurement of regurgitant volume (R Vol), regurgitant fraction (RF), and effective regurgitant orifice area (EROA).[10,26] The 2008 ACC/AHA guidelines[13] cite one study of progression of MR, but this study did not report specifically on MR of mild severity.[10] We found two studies on progression and clinical outcomes among patients with mild MR[27,28] (**Table 4**). One study included only patients who were asymptomatic at baseline,[27] and the other study did not specify symptom status.[28]

Neither of the studies reported on changes in hemodynamic measures. One study found that 26% of patients with initially mild MR experienced an increase in severity of one or more MR grades over a mean follow-up of 8.6 years.[28] However, the study did not describe the proportion of patients that progressed to more severe disease without developing symptoms. The other study assessed overall survival rates at 5 years, and found 91% survival among patients with initially mild MR, compared with an expected survival of 86% for the overall population.[27] Among patients with initially mild MR, the rate

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of death from cardiac causes was 3% and the rate of cardiac events (death from cardiac causes, congestive heart failure, or new atrial fibrillation) was 15% at 5 years of follow-up.[27]

Table 4. Progression and outcomes in adults with mild mitral regurgitation

Author, Year	Population (mild)	Baseline Mild MR Severity	Follow-up (years)	Progression/Outcomes (with Moderate and Severe for comparison)
Suri, 2010[28]	N = 121 Age (mean) = 52 yrs ± 19 Female = 66% Asymptomatic: NR	NR	8.6 (mean)	Definitions: NR Increase of at least one MR grade: **Mild MR**: 31/121 (26%) Mild/Moderate MR: 13/23 (57%) Moderate MR: 21/36 (58%) Moderate/Severe MR: 14/24 (58%)
Enriquez-Sarano, 2005[27]	N = 129 Age (mean) = 64 yrs ± 14 Female = 69% Asymptomatic: 100% Patients under medical management as determined by their individual physicians	EROA = 11 cm^2 ± 5 R Vol = 21 ml/beat ± 10	5.0	Definitions: Mild MR: EROA < 0.20 cm^2 Moderate MR: EROA 0.20 - 0.39 cm^2 Severe MR: EROA ≥ 0.40 cm^2 Overall five-year survival: **Mild MR**: 91% ± 3% Moderate MR: 66% ± 6% Severe MR: 58% ± 9% Five-year survival rates versus expected survival rates in overall population: **Mild MR**: 91% ± 3% vs. 86%, p=0.12 Moderate MR: 66% ± 6% vs. 84%, p=0.04 Severe MR: 58% ± 9% vs. 78%, p=0.03 Death from cardiac causes: **Mild MR**: 3% ± 2% Moderate MR: 20% ± 6% Severe MR: 36% ± 9% Cardiac events: **Mild MR**: 15% ± 4% Moderate MR: 40% ± 7% Severe MR: 62% ± 8%

EROA = effective regurgitant orifice area; NR = not reported; R Vol: regurgitant volume

Early Intervention

Experts disagree about the possible benefits versus risks of early intervention (particularly valve repair or replacement) for severe AS or severe MR in the absence of symptoms.[11,29-36] Current recommendations for valve repair or replacement for certain select subgroups of patients with asymptomatic severe or moderate AS or MR (e.g., left ventricular dysfunction, pulmonary hypertension, new onset atrial fibrillation) are lower grade recommendations and/or based on lower levels of evidence.[8,11] Guidelines on management of valvular heart disease cite two observational studies (one of

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AS[34] and one of MR[33]) of early surgery for asymptomatic severe valvular disease versus conventional (non-surgical) management (which included possible surgery if symptoms developed). In each study, the decision for surgery or conventional treatment was at the discretion of the attending physician. Studies used registry data and utilized propensity methods to match patients.

Patients in the study of AS had very severe disease, with worse markers of AS severity in the surgery (n=102) versus conventional management (n=95) group.[34] Surgery was associated with better 6-year cardiac mortality-free survival than conventional treatment (100% vs. 76%; $p < 0.001$), with no operative mortality; findings were similar in a subgroup of 57 propensity score-matched pairs.

In the MR study, the surgery group (n = 161) had worse markers of mitral valve severity and flail leaflet than the conventional treatment group (n=286).[33] Surgery was associated with a lower 7-year cardiac mortality rate than conventional treatment (0% vs. 5%; $p = 0.008$), and better 7-year event-free survival for the composite outcome of operative mortality, cardiac death, repeat mitral valve surgery, and hospitalization for congestive heart failure (99% vs. 85%; $p < 0.001$); findings were similar in a subgroup of 127 propensity-score matched pairs.

A subsequent analysis expanded on the prior study by adding data from a second registry and evaluating results through 12 years.[37] Results were similar to the original analysis. Surgery for asymptomatic severe MR was associated with a lower 12-year cardiac mortality rate versus the conventional treatment group (1% vs. 5%; $p = 0.016$), and a lower 12-year event rate for the composite outcome (5% vs. 18%; $p < 0.001$); findings were similar in a subgroup of 207 propensity-score matched pairs.

Discussion

We found no evidence on the effectiveness of echocardiography for routine surveillance of adults with asymptomatic mild native valve disease and no change in signs or symptoms. We also found no evidence on the comparative effectiveness of different frequencies of echocardiographic surveillance, or on potential adverse effects of echocardiographic surveillance. Nor did we find any evidence on the potential benefits or harms of de-intensification of routine surveillance with echocardiography.

Although interventions are generally not indicated unless AS or MR is severe and/or symptomatic, some current guidelines recommend routine surveillance with echocardiography for asymptomatic mild AS or MR with no change in signs or symptoms.[8,12] These recommendations are based on low level, indirect evidence, including: the higher morbidity and mortality associated with more advanced valve disease, the potential benefit of intervening with severe disease before symptoms develop, and limited evidence on the rate of progression of asymptomatic mild valve disease. The rationale for these recommendations is that it is not possible to predict the rate of progression for individual patients, and progression to more advanced stages may occur without the development of symptoms.

We found only two studies of AS[22,24] and one study of MR[28] that reported on the proportion of patients with initially mild valve disease that progressed to either moderate or severe disease. For mild AS, one study reported progression rates to either moderate or severe AS of 6.0% at 1 year, 13.7% at 2 years, and 30.9% at 5 years;[22] the other study reported a progression rate to severe AS of 11.5% at a mean of 2.9 years.[24] For mild MR, one study reported that 26% of patients with initially mild MR progressed in severity by one or more MR grades over a mean follow-up of 8.6 years.[28]

In addition, two studies of AS reported both baseline mean values of hemodynamic parameters and estimates of the rates of progression of those parameters,[21,23] which allowed us to calculate estimates of the time of progression to severe AS based on standard classification criteria. In one study,[23] the estimated time for progression to severe AS varied depending on the hemodynamic parameter: 5.75 years (based on ΔP_{mean}); 8.5 years (based on V_{max}); and 10.0 years (based on AVA). In the other study,[21] the estimated time for progression to severe AS was 5.0 years (based on V_{max}).

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Accurate and reliable information about the natural progression of asymptomatic mild AS and MR would be useful for making decisions on if and how often echocardiographic surveillance should occur. Understanding which factors (e.g., valve calcification, coronary artery disease) predict the rate of progression and outcomes of asymptomatic AS or MR could allow for targeted surveillance of those individuals at highest risk of rapidly developing asymptomatic severe disease or adverse clinical outcomes. However, the studies in this review that reported on progression of mild AS or MR had limitations. Most of the studies had small numbers of patients with disease of mild severity. Most studies did not distinguish symptomatic patients from asymptomatic patients. While both studies of MR had follow-up times of at least 5 years (the upper limit of the recommended surveillance frequency), only one study of AS had follow-up of at least 5 years. Most studies reported baseline severity as a categorical range of one or more hemodynamic parameters, not as the actual mean values, which limits the ability to make comparisons between the studies. The studies differed in their inclusion and exclusion of various factors and medical conditions that might affect progression and/or outcomes; few studies reported these factors for patients with mild disease; and no study stratified or adjusted the estimates of outcomes for the possible confounding effects of such factors. This limits the accuracy of any inferences about progression or outcomes attributable specifically to mild AS or MR.

Current guidelines note that for patients with asymptomatic severe AS or MR the effectiveness of surgical intervention is controversial and uncertain in most cases.[11] Studies comparing early intervention with conventional management are lacking, and for the majority of patients with asymptomatic severe valve disease the relative potential benefits versus harms of early surgery while asymptomatic are unclear. The overall incidence of sudden death in patients with asymptomatic severe AS is approximately 1% per year, but overall surgical mortality for isolated aortic valve replacement is approximately 1% to 3% for patients younger than 70 years of age and 5% to 15% for older patients.[31] More and better evidence is needed to reliably predict (based on hemodynamic parameters and other factors) which subgroups of patients are at higher risk for adverse cardiac outcomes and/or to identify those patients at lower risk of surgical complications.

We identified three studies that directly compared early surgical intervention with conventional treatment for patients with asymptomatic severe valve disease.[33,34,37] These observational studies have limitations, including the lack of randomized assignment and residual confounding by indication.[29,30,38] Stronger evidence from well-designed RCTs is needed to determine the potential effectiveness of early surgery while asymptomatic versus delaying surgery until symptoms develop, and which subgroups of patients are most likely to benefit.[30,38]

None of the natural history studies specifically described the proportion of patients with initially asymptomatic mild AS or MR that progressed to more severe disease without developing symptoms. This is relevant because the development of symptoms would ordinarily precipitate further evaluation, likely including echocardiography. Therefore, patients whose mild disease progresses to severe disease without symptoms are the subgroup of most relevance for surveillance.

Possible benefits and harms of continuing or discontinuing/de-intensifying routine echocardiographic surveillance of asymptomatic mild valve disease are summarized in **Table 5**.

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Table 5. Summary of possible benefits and harms of continuing or discontinuing/de-intensifying routine echocardiographic surveillance of asymptomatic mild valve disease

Action	Benefits	Harms
Continuing routine surveillance with echocardiography	• No direct evidence • Potential to identify the minority of patients who progress to more severe disease and remain asymptomatic within the recommended surveillance frequency • Potential to more closely follow such patients for conditions that might warrant intervention while asymptomatic according to guidelines	• No direct evidence • May be an inefficient use of resources to identify relatively few individuals, given the variation in progression and that most patients remain event-free for many years • Effectiveness of identifying and intervening early for patients who do progress to asymptomatic moderate or severe disease is uncertain • Potential harms of unnecessary tests or interventions as a result of surveillance
Discontinuing or de-intensifying routine surveillance with echocardiography	• No direct evidence	• No direct evidence

Conclusion

We found no direct evidence on benefits or harms of routine surveillance with echocardiography for asymptomatic mild aortic stenosis or mitral regurgitation. Nor did we find any evidence on the potential benefits or harms of de-intensification of routine surveillance with echocardiography. Current recommendations for routine surveillance of asymptomatic mild AS or MR every 3 to 5 years are based on indirect and limited evidence on the rate of progression of asymptomatic mild valve disease, the higher morbidity and mortality associated with more advanced valve disease, and the potential for earlier interventions in persons who develop asymptomatic severe valve disease to result in better outcomes. However, no study has reported rates of progression from initially asymptomatic mild AS or MR to more severe disease without developing symptoms. Furthermore, even for severe AS or MR, the effectiveness of interventions while asymptomatic remains uncertain in most cases. Potential harms of echocardiographic surveillance include unnecessary tests and treatments as a result of over-diagnosis, overtreatment, and incidental echocardiographic findings.

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DEPARTMENT OF VETERANS AFFAIRS
CENTER FOR CLINICAL MANAGEMENT RESEARCH

De-intensification of routine medical services

Expert Panel #2

Meeting 1: November 15, 2017
Meeting 2: December 13, 2017

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Background Information and Instructions

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Summary of Expert Panel Tasks

1. Review the attached booklet, answer the questions for each measure, and return answers to project staff prior to Meeting #1

Goal:	Have panel members become familiar with the proposed de-intensification measures, including the available evidence, for discussion during Meeting #1
Due Date:	**November 6, 2017**
Type:	Independent work
Instructions:	1. Review the attached booklet 2. Answer questions related to each measure directly into the booklet [see data entry fields] 3. Return your pdf, with answers to the questions, to Mandi.klamerus@va.gov by the above due date 4. Confirm your ThinkTank link works in preparation for meeting #1 (https://vha.thinktank.net/login.html?sessionID=86). (Session ID: 86; Passkey: 1234)) Contact Mandi if you cannot access the session.

2. Participate in Virtual Group Meeting #1

Goal:	Introduce panel members, outline the goals of the project, review the proposed measures, and collect suggestions for measure improvement
Meeting Date:	**November 15, 2017 (12:30pm – 4:00pm Eastern)**
Type:	Virtual group meeting, using ThinkTank software + teleconference • ThinkTank access: https://vha.thinktank.net/login.html?sessionID=86 (Session ID: 86; Passkey: 1234) • Call-in information: 800-767-1750; Access code: 58402#
Instructions:	Participate in a group discussion about the proposed measures

3. Conduct pre-rating of measures

Goal:	(Following Meeting #1, staff will make suggested revisions to the measures.) Rate the revised de-intensification measures using the following criteria: validity, improvement opportunity, and feasibility of implementation
Due Date:	**TBA**
Type:	Independent work, using ThinkTank software (Do not start until you receive instructions; these will be sent out after Meeting #1) • ThinkTank access: https://vha.thinktank.net/login.html?sessionID=86 (Session ID: 86; Passkey: 1234)
Instructions:	See pages 11-12 of the booklet for rating criteria

4. Participate in Virtual Group Meeting #2, including re-rating measures

Goal:	Discuss measures where there was clear disagreement in pre-rating and re-rate all measures using the following criteria: validity, improvement opportunity, and feasibility of implementation
Meeting Date:	**December 13, 2017 (12:30pm – 4:00pm Eastern)**
Type:	Virtual group meeting, using ThinkTank software + teleconference • ThinkTank access: https://vha.thinktank.net/login.html?sessionID=86 (Session ID: 86; Passkey: 1234) • Call-in information: 800-767-1750; Access code: 58402#
Instructions:	See pages 11-12 of the booklet for rating criteria

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Expert Panel Member Bios

Lori Bastian, MD, MPH

Dr. Bastian is Director of the VA Connecticut Health Services Research and Development Center for Pain Research, Informatics, Multimorbidities, and Education (PRIME), a VA Center of Innovation, and Professor of Medicine at Yale School of Medicine. Her research interests have focused on women's health, smoking cessation and increasing physical activity among Veterans. Dr. Bastian's more recent work has focused on the association of smoking status and pain intensity among Veterans.

Cynthia Boyd, MD, MPH

Dr. Boyd is the Professor of Medicine, Epidemiology and Health Policy and Management at Johns Hopkins University in the School of Medicine and the Bloomberg School of Public Health. Her research interests have focused on improving the health and health care of people with multiple chronic conditions. Her work has focused on innovative care models, clinical practice guidelines, methods of evidence synthesis and quality measures for people with multiple chronic conditions, including how to individualize care for people living with multiple chronic conditions that is evidence-based and person- and family-centered.

Michael Clay, MD

Dr. Clay is a primary care physician in the VA Ann Arbor Healthcare System and a Clinical Assistant Professor at the University of Michigan. His clinical interests, over the past 15 years, have focused on integrating mental health care and substance use disorder treatment into primary care clinics. He is the Opioid Safety Initiative lead at the Ann Arbor VA as well as the Deputy Associate Chief of Staff for Education.

Walid Gellad, MD, MPH

Dr. Gellad is an Associate Professor of Medicine and Health Policy at the University of Pittsburgh, where he directs the Center for Pharmaceutical Policy and Prescribing. He is also a health services researcher and primary care clinician with the Center for Health Equity Research and Promotion at the Pittsburgh VA Medical Center. His research interests are in the study of medication use, prescribing, and pharmaceutical policy within VA and the private sector.

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Russell Harris, MD, MPH

Dr. Harris is Emeritus Professor at the University of North Carolina, Chapel Hill. He helped start and directed the UNC MD-MPH Program between 2000 and 2014. He has worked with the US Preventive Services Task Force since 1997, as a co-author of systematic reviews, as a member, as a co-author of methods papers, and as a consultant. He led 4 multi-year community based studies to improve preventive care in community primary care practice. He has been especially interested in the issue of screening, including balancing potential benefits and harms in rational decision making about screening. He has written and spoken about overuse and overdiagnosis in medical care. He is author or co-author of over 100 articles, commentaries, or book chapters on multiple topics relevant to medical care.

Nicki Hastings, MD

Dr. Hastings is the Director of the Durham Center for Health Services Research and Development in Primary Care, a VA Center of Innovation, and an Associate Professor of Medicine, and Senior Fellow in the Center for the Study of Aging and Human Development at Duke University School of Medicine. Her research interests have focused on understanding risk factors for hospital and emergency department use and improving care transitions for older and medically complex Veterans. Dr. Hastings' current work focuses on implementing and evaluating evidence-based clinical programs to optimize function and independence in vulnerable Veterans.

Sei Lee, MD

Dr. Lee is the Senior Physician Scholar for the San Francisco VA Quality Scholars fellowship and an Associate Professor in the UCSF Division of Geriatrics. His research has focused on 1) individualizing prevention in older adults to maximize benefits and minimize harms, 2) geriatric diabetes, and 3) automated prediction using EMR data.

Deb Levine, MD

Dr. Levine is a general internist and Associate Professor of Internal Medicine at the University of Michigan. Her research interests include the prevention and care of stroke and cognitive decline, with a focus on vascular risk factors, treatment adherence, and health disparities. Dr. Levine's current work is focusing on understanding decision making for cardiovascular therapies in older adults with mild cognitive impairment.

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Carmen Lewis, MD, MPH

Dr. Lewis is the Vice Division Head of Strategy and Innovation and Clinical Director for the University of Colorado School of Medicine's Division of Internal Medicine. Dr. Lewis' research focuses on translating evidence based medicine into clinical care, the use of appropriate preventative services and development and implementation of decision aids. Relevant to this proposal, she has demonstrated an increase in appropriate care for colorectal care among elderly patients using a patient decision aid.

Amy Linsky, MD, MSc

Dr. Linsky is a clinician-investigator at the Center for Healthcare Organization and Implementation Research (CHOIR) and in the Section of General Internal Medicine at VA Boston Healthcare System. She is an Assistant Professor at Boston University School of Medicine. She is a practicing internist in Primary Care. Dr. Linsky's research interests focus on improving the quality of medication use, with a specific interest in deprescribing to reduce overmedication in an attempt to improve safe and appropriate prescribing.

Kari Nelson, MD, MSHS

Dr. Nelson is a general internist and health services researcher at the VA Puget Sound Health Care System (VAPSHCS). She is an Associate Professor in the School of Medicine, Adjunct Associate Professor in Health Services at the University of Washington and core investigator at the Seattle Health Services Research & Development (HSR&D) Center of Innovation (COIN). Dr. Nelson is the associate director for the VHA's evaluation of the patient centered medical home, the Patient Aligned Care Team (PACT) initiative. Her primary research interest is in improving disease self-management for disadvantaged populations, focusing on peer support interventions.

Donna Zulman, MD, MS

Dr. Zulman is an assistant professor in the Division of Primary Care and Population Health at Stanford University, and an investigator at the Center for Innovation to Implementation (Ci2i) in the VA Palo Alto Health Care System. Her research focuses on improving health care delivery for patients with multiple chronic conditions and complex medical and social needs, implementing and evaluating programs for high-need patients, and optimizing health-related technology to personalize care and improve outcomes for high-risk patients. Dr. Zulman is currently supported by a VA Health Services Research & Development Career Development Award.

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Why is de-intensification important?

There is an increasing consensus that overtreatment and overtesting exposes some patients to services they may not need or prefer or that may even harm them; the Choosing Wisely campaign is the most obvious manifestation of this consensus. However, the majority of recommendations, from Choosing Wisely and others, focus on reducing overuse by avoiding one-time diagnostic procedures or treatment at the beginning of a discrete episode of care. They do not focus on stopping or scaling back the intensity or frequency of medical interventions that are currently part of a patient's ongoing management. We believe that *de-intensification of routine medical services* is the next frontier for improving care quality.

De-intensification: Decreasing the intensity or frequency of medical interventions that are currently part of a patient's routine ongoing management (e.g., not acute care, not an initial work-up, not pre-operative care).

What are the goals of this project?

The current research project, funded by the Department of Veterans Affairs, will identify and validate clinical indications and measures for de-intensification and will develop multi-component strategies to disseminate and implement de-intensification measures.

The specific goal of this national, expert panel is to review and validate indications for de-intensification of routine medical services focusing on too frequent cancer and other screenings, inappropriate medication use in older adults, and other forms of overtreatment (e.g., opioids, estrogen, testosterone).

How were the indications for de-intensification identified and the proposed de-intensification measures developed for review by the expert panel?

The following steps map to one or more of the sections described under each measure. (Hover your mouse over 'Step' to see which sections.)

Step 1: environmental scan

Project staff reviewed current, high-quality recommendations and measures to identify those that were primary-care related, routine-based, and de-intensification focused. The list was enhanced by seeking nominations from our Advisory Council and their constituents.

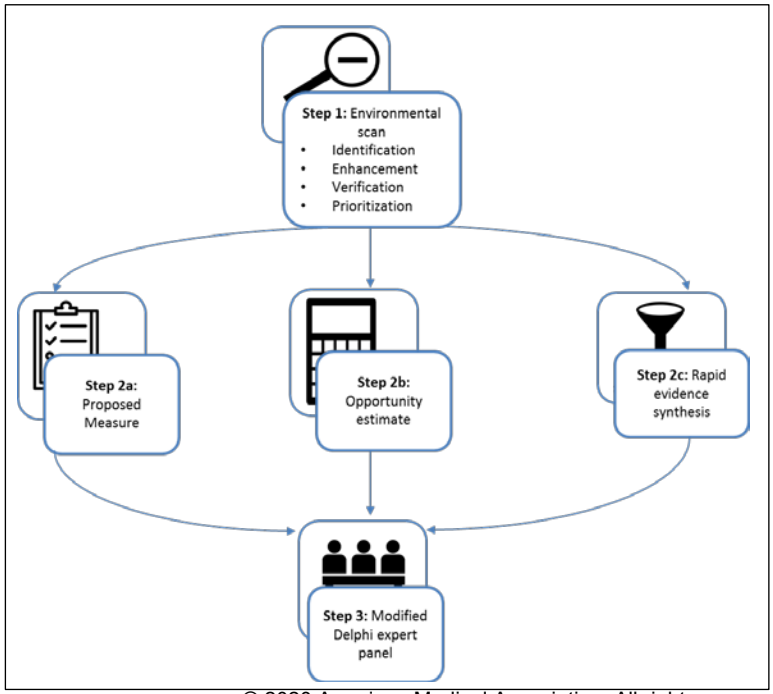

Figure 1: Steps to prepare for the expert panel

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Figure 2 provides details of Step 1's verification and prioritization process.

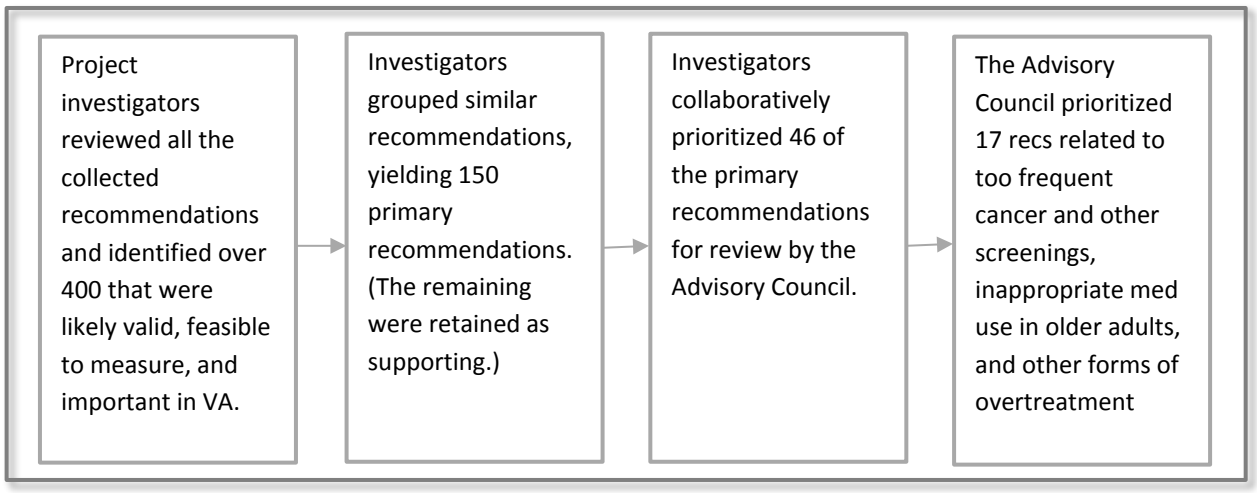


Figure 2: Environmental scan process: verification and prioritization

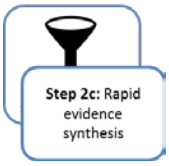
Step 2a: Proposed measure

Recommendations often do not include all the required components of a typical *measure* (e.g., denominator, numerator, exclusions); therefore, a proposed de-intensification measure was drafted by the principal investigators of the project. The draft included a population of interest (denominator) and de-intensification action (numerator). You will have an opportunity to share your viewpoint on each measure. Framing the recommendation as a measure allows us to be specific about the population and the intended action

Step 2b: Opportunity estimate

An opportunity estimate is a high-level prevalence estimate of potential opportunities for de-intensification. An estimate, for VA, has been included in the booklet for each of the proposed de-intensification measures. All opportunity estimates included active VA patients only (active is defined as having at least 1 visit in the year prior to the study year (any type) and at least 2 primary care visits during the combined period of the study year and year prior) and examined recent data (2013-2016). Note: Estimates for outside VA are not included, unless available from the literature.

Step 2c: Rapid evidence synthesis



A rapid evidence synthesis (RES) is a streamlined approach to synthesizing evidence in a timely manner to answer specific questions about a clinical problem. A RES was conducted by the Pacific Northwest Evidence-based Practice Center (EPC) in Portland, Oregon.

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De-intensification recommendations were selected for RES if they met any of the following criteria:

1. No related guideline or recent evidence synthesis/review currently existed; or
2. There appeared to be some disagreement in the primary/supporting recommendations or guidelines; or
3. Uncertainty or questions remained even with an existing guideline (e.g., some anecdotal evidence that providers weren't following the recommendation or didn't believe the recommendation).

Step 3: Modified Delphi expert panel

Two modified Delphi expert panels will be convened. The first panel was held earlier this year and focused on diabetes and cardiovascular disease. The second panel, which you are a part of, focuses on too frequent cancer and other screenings, inappropriate medication use in older adults, and other forms of overtreatment. The panel will use a modified Delphi process to prioritize the proposed measures of de-intensification.

As a member of the panel, you will rate each measure twice— after staff have revised the measures based on the discussion during virtual Meeting #1 and then again during virtual Meeting #2.
See page 5 for dates of all required tasks, including pre-rating and re-rating.

What criteria will the expert panel use to prioritize the proposed measures?

The expert panel is tasked with rating each presented de-intensification measures based on validity, improvement opportunity, and feasibility of implementation.

Ratings will be completed using the following 9-point scale, using validity as an exemplar:

Rating	Meaning
1-3	The measure is not a valid criterion for evaluating quality
4-6	The measure is an uncertain or equivocal criterion for evaluating quality.
7-9	The measure is clearly a valid criterion for evaluating quality

On the next page (page 12) is a description of each criterion and components of the measure to consider during the rating process. When evaluating a measure, we ask you to utilize any presented information in this booklet, as well as your professional knowledge, to help assess the validity and improvement opportunity. There is no information presented to help you assess feasibility of implementation; this will require you to reflect on your prior experiences and knowledge of the topic.

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Rating Criteria	When should a measure receive a high rating?	Other Considerations	Related sections in the booklet
1. Validity	A measure is rated highly on validity if it is based on high quality scientific evidence that suggests that performance on the measure is likely to improve patient outcomes and is consistent with high quality care. A quality measure is considered valid if one or more of the following are true: 1. Evidence exists that de-intensification is likely to improve patient outcomes 2. Evidence exists that intense testing/treatment could cause harm in some patients 3. There is absence of evidence of benefit of continued/repeated intense treatment or testing 4. De-intensification is consistent with high quality care; providers who have higher rates of de-intensification would be considered higher quality providers	The source of the evidence should be clearly defined and reputable, such as a systematic review, clinical guideline, or high quality studies; and the evidence should be of high quality, quantity, and consistency. There should be specific links between the clinical recommendation in the evidence and the performance measure. The measure should have a numerator with a clearly defined, specific clinical action or clinical service that is supported by evidence. If a time period of the clinical action is specified (e.g., annual, not more often than 5 years) it should be supported by the evidence whenever possible and balance the possibility of underuse and overuse. The denominator should clearly define the eligible patient population and contain appropriate exclusions to make the eligible population specific to the action defined in the numerator.	• Proposed measure • Recommendation and supporting recommendations • Rapid evidence synthesis summary • Evidence base (if no RES was completed)
2. Improvement opportunity	A measure is rated highly on improvement opportunity if: 1. It is likely to affect a large number of patients or have a significant impact on a smaller number of patients 2. The current rate of de-intensification is low or likely to be low	The numerator should include a clinically significant population, and the denominator should not have unnecessary exclusions (which could minimize the potential scope and/or impact of the measure). *Please consider opportunities in VA (data presented) and outside VA when you are rating	• Potential opportunity for improvement
3. Feasibility of implementation	A measure is rated highly on feasibility of implementation if: 1. De-intensification of this treatment/testing is under the control of the health professional or health organization	It is possible to imagine an intervention (e.g., clinical decision support, detailing, patient education or empowerment, pay for performance, etc.) that could promote de-intensification ***Do not consider feasibility of measurement**	None, please use your knowledge in this area in order to evaluate whether this measure would be feasible to implement

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What happens after the expert panel?

Following the two virtual expert panel meetings, project staff will determine what data source(s) (e.g., automated data, manual medical record abstraction, other) will be required for each measure that was rated highly. The measure specification (i.e., numerator, denominator, exclusions) will be refined and the measure will be generated. Then, the prevalence of de-intensification in VA will be assessed. The reliability of the measure, variation in de-intensification rates across sites, and predictors of de-intensification will also be examined.

In addition, project staff will be conducting collaborative decision-making sessions with patients and providers in order to identify gaps in understanding and potential barriers to deploying de-intensification measures and recommendations. Findings from all the work in this project, including from the expert panel, will be synthesized into practical intervention strategies.

What should you do next?

On the following pages [14-82] you will find the proposed de-intensification measures and information pertaining to the measures, including any rapid evidence synthesis reports [pages 83-172]. (*Note: If you choose to print the documents, we recommend that you only print pages 14-82.*) At this time, we are asking you to review all of the provided information and answer the questions that follow each measure. (Example: Do you agree that the topic/measure is valid and that there is an opportunity for improvement? [Click here to enter text]) Please just type your answers directly into the fields provided. Then, save the pdf and e-mail it to Mandi.Klamerus@va.gov by **November 6th**. The information you provide will help guide the discussion during Meeting #1.

We thank you for your participation on the panel and look forward to discussing the proposed de-intensification measures with you over the next few weeks!

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Measures related to Screening

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Measure 1 – De-intensification of Vitamin D screening

Proposed de-intensification measure

Action: Don't perform 25-OH-Vitamin D testing

Population: All patients

Population exclusions: Patients with a diagnosis of chronic kidney disease, osteomalacia, osteoporosis, active rickets, malabsorption, inflammatory bowel disease, obesity, or Crohn's disease. Patients with a history of bariatric surgery or with >30 days of prednisone use (in the study year) also excluded.

Existing recommendation that motivated the proposed de-intensification measure

Choosing Wisely – De-intensification Vitamin D screening: "Don't perform population based screening for 25-OH-Vitamin D deficiency."

- Source: Choosing Wisely
- Steward: American Society of Clinical Pathology
- Last Update: February 21, 2013

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

Potential opportunity for improvement

In VA (estimate)

- [FY2015] 683,802 Vitamin D tests were conducted on patients unlikely to benefit* from Vitamin D testing

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*Patients who may benefit from testing include patients with: Chronic Kidney Disease, Osteomalacia, Osteoporosis, Active Rickets, Malabsorption, Inflammatory Bowel Disease, Crohn's Disease, or Obesity; these patients were excluded from the above estimate. Additionally, patients with a prior history of bariatric surgery and patients on prednisone for >30 days during the study year were excluded.

Outside VA

The following is extracted from: Colla CH, et al. Payer Type and Low-Value Care: Comparing Choosing Wisely Services across Commercial and Medicare Populations. Health Serv Res. 2017 Feb 19.

- [2011] Using Medicare administrative claims data for fee-for-service low-risk beneficiaries enrolled in Medicare Parts A and B:
  - The mean prevalence of low-risk patients who received at least one nonindicated vitamin D screening test = 12.8% (20,400,000/159,400,000)

- [2011] Using commercial insurance claims data obtained from the Health Care Cost Institute (representative of Aetna, Humana, and United Healthcare):
  - The mean prevalence of low-risk patients who received at least one nonindicated vitamin D screening test = 8.1% (20,700,000/255,600,000)

Evidence-Base

Rationale

The following information is extracted directly and verbatim from Choosing Wisely.

Vitamin D deficiency is common in many populations, particularly in patients at higher latitudes, during winter months and in those with limited sun exposure. Over the counter Vitamin D supplements and increased summer sun exposure are sufficient for most otherwise healthy patients. Laboratory testing is appropriate in higher risk patients when results will be used to institute more aggressive therapy (e.g., osteoporosis, chronic kidney disease, malabsorption, some infections, obese individuals).

The U.S. Preventive Services Task Force recommendation follows:

- The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults. (Evidence Grade I)

The Endocrine Society recommendation follows:

- Does not recommend population screening for vitamin D deficiency in individuals who are not at risk. Recommends screening for vitamin D deficiency in individuals at risk for deficiency. (Strength of Recommendation: Strong; Quality of Evidence: High)

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- There is no evidence demonstrating benefits of screening for vitamin D deficiency at a population level. Such evidence would require demonstration of the feasibility and cost-effectiveness of such a screening strategy, as well as benefits in terms of important health outcomes. In the absence of this evidence, it is premature to recommend screening at large at this time.

Citations provided for the evidence

Bilinski KL, Boyages SC. The rising cost of vitamin D testing in Australia: time to establish guidelines for testing. *Med J Aust*. 2012;197(2):90.

Holick MF, Binkely NC, Bischoll-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2011;96(7):1911-1930.

LeFevre ML; U.S. Preventive Services Task Force. Screening for vitamin D deficiency in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2015;162(2):133-140.

Lu CM. Pathology consultation on vitamin D testing: Clinical indications for 25(OH) vitamin D measurement [Letter to the editor]. *Am J Clin Pathol*. 2012;137(5):831-832.

Sattar N, Welsh P, Panarelli M, et al. Increasing requests for vitamin D measurement: Costly, confusing, and without credibility. *Lancet*. 2012;379(9811):95-96.

Additional supporting recommendations

Source	Recommendations
U.S. Preventive Services Task Force	1. The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults.
The Endocrine Society	1. We recommend screening for vitamin D deficiency in individuals at risk for deficiency. We do not recommend population screening for vitamin D deficiency in individuals who are not at risk. 2. We recommend using the serum circulating 25-hydroxyvitamin D [25(OH)D] level, measured by a reliable assay, to evaluate vitamin D status in patients who are at risk for vitamin D deficiency. We recommend against using the serum 1,25-dihydroxyvitamin D [1,25(OH)2D] assay for this purpose and are in favor of using it only in monitoring certain conditions, such as acquired and inherited disorders of vitamin D and phosphate metabolism.

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Choosing Wisely. American Association of Clinical Endocrinologists and the Endocrine Society	1. Don’t routinely measure 1,25-dihydroxy vitamin D unless the patient has hypercalcemia or decreased kidney function.

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Measure 2 – De-intensification of DEXA screening

Proposed de-intensification measure 1

Action: Don't screen for osteoporosis using Dual-energy X-ray Absorptiometry (DXA/DEXA) screening

Population: Women younger than 65 with no risk factors* and Men under 70 with no risk factors*

**Risk factors include: Osteopenia, Primary hyperparathyroidism, Osteoporosis, Hypercalcemia, or Malabsorption. Patients on prednisone for >30 days during the study year, on androgen deprivation therapy, or who had a Glomerular Filtration Rate (GFR) < 30 were also excluded.*

Proposed de-intensification measure 2

Action: Don't repeat DEXA screening within 2 years of the previous scan

Population: Patients who have had a DEXA scan

Existing recommendations that motivated the proposed de-intensification measure

Choosing Wisely – De-intensification of DEXA screening 1: "Don't use dual-energy x-ray absorptiometry (DEXA) screening for osteoporosis in women younger than 65 or men younger than 70 with no risk factors."

- Source: Choosing Wisely
- Steward: American Academy of Family Physicians
- Last Update: April 4, 2012

Choosing Wisely – De-intensification of DEXA screening 2: "Don't routinely repeat DXA scans more often than once every two years."

- Source: Choosing Wisely
- Steward: American Academy of Rheumatology
- Last Update: February 21, 2013

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

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2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

Potential opportunity for improvement

In VA (estimate)

- [FY2014-2015] 71,160 women younger than 65 and men younger than 70, without a known risk factor*, received a DEXA scan

  *Risk factors include: Osteopenia, Primary hyperparathyroidism, Osteoporosis, Hypercalcemia, Malabsorption. Additionally, patients on prednisone for >30 days during the study year, patients on androgen deprivation therapy, and patients who had a GFR< 30 were excluded.

- [FY2014-2015] 5% (7,057/133,746) of all patients who had a DEXA scan had more than one in a two-year period

Outside VA

The following is extracted from: Colla CH, et al. Payer Type and Low-Value Care: Comparing Choosing Wisely Services across Commercial and Medicare Populations. Health Serv Res. 2017 Feb 19.

- [2011] Using Medicare administrative claims data for fee-for-service low-risk beneficiaries enrolled in Medicare Parts A and B:
  - The mean prevalence of a nonindicated dual-energy X-ray absorptiometry (DXA) test performed within 23 months of a previous DXA test = 8.5% (12,200,000/143,000,000)
- [2011] Using commercial insurance claims data obtained from the Health Care Cost Institute (representative of Aetna, Humana, and United Healthcare):
  - The mean prevalence of a nonindicated dual-energy X-ray absorptiometry (DXA) test performed within 23 months of a previous DXA test = 7.5% (600,000/8,000,000)

Rapid evidence synthesis summary (Review the entire rapid evidence synthesis report.)

Why is this important?

- Osteoporosis affects more than 10 million older adults in the United States and is associated with reduced quality of life, chronic pain, loss of independence, hospitalization, and mortality.
- Screening using dual-energy x-ray absorptiometry (DXA) can identify those at risk of osteoporotic fracture, and multiple pharmacologic and non-pharmacologic interventions have been shown to reduce fracture risk in older patients with low bone mass. However, screening

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also involves opportunity costs, exposure to ionizing radiation, and the downstream harms of subsequent intervention, which will vary by treatment.

- The U.S. Preventive Services Task Force recommends screening in women older than 65 years of age and in women younger than 65 at increased risk of fracture and found insufficient evidence to support recommendations on screening in men. The USPSTF and guidance from the Choosing Wisely campaign recommend screening no more frequently than once every 2 years.[1] However, some data suggest that clinicians screen more frequently or in populations in whom screening is not recommended.

What are the benefits and harms of osteoporosis screening in women younger than 65 years of age or men younger than 70 years of age not at increased risk for osteoporosis?

- Convincing evidence supports the utility of DXA screening to estimate fracture risk, and the harms of treatment for osteoporosis are outweighed by the benefits.
- Based on the number needed to screen, the USPSTF selected the 10-year fracture risk of a 65-year-old white woman (9.3%) as determined by a risk screening instrument such as FRAX® as the threshold for screening.
- The Choosing Wisely campaign of the American College of Family Physicians largely adopted the USPSTF recommendations but also recommended DXA screening of men aged 70 years or older and men aged 50–69 years with risk factors, based on an assumption of similar risk and effectiveness in these groups.

What are the benefits and harms of osteoporosis screening more frequently than once every 2 years?

- The USPSTF suggests not screening more frequently than once every 2 years and the Choosing Wisely recommendation of the American College of Rheumatology states, “Don’t routinely repeat DEXA scans more often than once every two years.” No studies have directly compared the benefits and harms of different screening intervals; however, the USPSTF recommendation notes that due to limitations in the precision of testing, a minimum of 2 years may be needed to reliably measure a change in bone mineral density.

What are the benefits and harms of de-intensification of osteoporosis screening?

- No study evaluated benefits and harms of de-intensification of osteoporosis screening.

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Additional supporting recommendations

Source	Recommendations
U.S. Preventive Services Task Force	1. The USPSTF recommends screening for osteoporosis in women aged 65 years and older and in younger women whose fracture risk is equal to or greater than that of a 65-year-old white woman who has no additional risk factors. [B recommendation] 2. The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for osteoporosis in men. [I recommendation] 3. Screening should not be performed more than once every 2 years. [ungraded]

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Measure 3 – De-intensification of cervical cancer screening

Proposed de-intensification measure 1

Action: Do not perform cervical cancer screening (cervical cytology or Human Papilloma Virus (HPV) testing)

Population: Women under 21 years, over 65 years and at low risk*, or with a history of total hysterectomy for benign disease

**Low risk is defined as no history of cervical changes and either 3 negative pap test results in a row or 2 negative co-test results in a row within the past 10 years, with the most recent test performed within the past 5 years*

Population exclusions: patients with a prior history of exposure to diethylstilbestrol before birth, diagnosis of HIV, a weakened immune system, high-grade precancerous lesion, or cervical cancer

Proposed de-intensification measure 2

Action: Do not perform cervical cancer screening more often than every 3 years with cytology OR every 5 years with HPV + cervical cytology

Population: Women who are 30-65 years old

Population exclusions: patients with a prior history of exposure to diethylstilbestrol before birth, diagnosis of HIV, a weakened immune system, high-grade precancerous lesion, or cervical cancer (including total hysterectomy with a history of high-grade precancerous lesion or cervical cancer)

Existing recommendation that motivated the proposed de-intensification measure

USPSTF Recommendation – De-intensification of cervical cancer screening:

1. The USPSTF recommends screening for cervical cancer in women age 21 to 65 years with cytology (Pap smear) every 3 years or, for women age 30 to 65 years who want to lengthen the screening interval, screening with a combination of cytology and human papillomavirus (HPV) testing every 5 years. (Grade A)
2. The USPSTF recommends against screening for cervical cancer with HPV testing, alone or in combination with cytology, in women younger than age 30 years. (Grade D)
3. The USPSTF recommends against screening for cervical cancer in women younger than age 21 years. (Grade D)
4. The USPSTF recommends against screening for cervical cancer in women older than age 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer. (Grade D)
5. The USPSTF recommends against screening for cervical cancer in women who have had a hysterectomy with removal of the cervix and who do not have a history of a high-grade

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precancerous lesion (cervical intraepithelial neoplasia [CIN] grade 2 or 3) or cervical cancer. (Grade D)

- Source and Steward: U.S. Preventive Services Task Force (USPSTF)
- Last Update: March 15, 2012
- Level of Evidence: See above for evidence grades.

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

Potential opportunity for improvement

In VA (estimate)

- [FY2013-2015] 16% (10,503/67,037) of women under 21, over 65, or with a hysterectomy had at least one PAP smear or HPV test

*Patients with exposure to diethylstilbestrol before birth, diagnosis of HIV/AIDS, diagnosis of cervical cancer, or diagnosis of immune deficiency were excluded from the estimate

- [FY2013-2015] 14% (43,964/316,908) of women between the ages of 30-65 had more than 1 pap smear or HPV test in the three-year study period

*Patients with exposure to diethylstilbestrol before birth, diagnosis of HIV/AIDS, diagnosis of cervical cancer, or diagnosis of immune deficiency were excluded from the estimate

Outside VA

The following is extracted from: Colla CH, et al. Payer Type and Low-Value Care: Comparing Choosing Wisely Services across Commercial and Medicare Populations. Health Serv Res. 2017 Feb 19.

- [2011] Using Medicare administrative claims data for fee-for-service female beneficiaries enrolled in Medicare Parts A and B:

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- The mean prevalence of female patients (over age 65) who received at least one nonindicated screening test for cervical cancer = 8.3% (14,300,000/172,300,000
- [2011] Using commercial insurance claims data obtained from the Health Care Cost Institute (representative of Aetna, Humana, and United Healthcare) for adult women:
  - The mean prevalence of female patients (over age 65) who received at least one nonindicated screening test for cervical cancer = 9.1% (1,500,000/16,500,000)

Rapid evidence synthesis summary (Review the entire rapid evidence synthesis report.)

Why is this important?

- Various factors can affect the relative benefits and harms of cervical cancer screening in different subgroups and at different intervals. Therefore, understanding these relative benefits and risks is important for appropriate screening.

What are the benefits and harms of screening for cervical cancer?

(1) Versus no screening in women younger than 21 years of age?

Benefits: No benefit in life-years, cancer cases, cytological abnormalities detected, or cervical cancer deaths

Harms: Increased false-positive test results, colposcopies, cervical biopsies, pain, bleeding, discharge, and adverse outcomes in future pregnancies

(2) Annually in average-risk women aged 30 to 65 years versus less frequently?

Benefits: Slightly fewer cancer cases and cervical cancer deaths

Harms: Increased false-positive test results, colposcopies, cervical biopsies, pain, bleeding, discharge, and adverse outcomes in future pregnancies

(3) Versus no screening in low-risk women aged 65 years or older?

Benefits: Slightly fewer cancer cases and cervical cancer deaths

Harms: Increased false-positive test results, colposcopies, cervical biopsies, pain, bleeding, discharge

(4) Versus no screening in women who have had a total hysterectomy for benign disease?

Benefits: No benefit in detection of cytological abnormalities or vaginal cancer

Harms: Possible invasive procedures and treatment due to positive test results

What are the benefits and harms of de-intensification of cervical cancer screening?

- No study evaluated benefits and harms of de-intensification of cervical cancer screening (discontinuation of screening in women younger than 21 or older than 65 years of age or in women who have had a total hysterectomy, or decreasing from annual to less frequent screening in women 30 to 65 years of age).

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What are the implications of our findings?

- Current guideline recommendations are in agreement that the harms outweigh the benefits of screening for cervical cancer: (1) before age 21; (2) more frequently than every 3 to 5 years; (3) after age 65; and (4) after total hysterectomy for benign disease.

Additional supporting recommendations

Source	Recommendations
American College of Physicians (ACP)	1. Women younger than age 21 years at average risk: No screening 2. Women aged 21 to 29 years: Screen with cytology alone every 3 years 3. Women aged 30 to 65 years: Screen average-risk women once every 3 years with cytology (without HPV testing); Do not screen average-risk women with cytology more often than once every 3 years; May use combination of cytology and HPV testing once every 5 years for women who prefer screening less often than every 3 years 4. Women older than 65 years at average risk and with adequate negative prior screening*: Stop screening 5. Women at average risk after hysterectomy with removal of the cervix: No screening
American College of Obstetrics and Gynecology (ACOG)	1. Women younger than age 21 years: Screening should begin at 21 years of age, regardless of sexual behaviors and risk factors 2. Women aged 21 to 29 years: Screen with cytology alone every 3 years 3. Women aged 30 to 65 years: Co-testing with cervical cytology and HPV testing every 5 years, or Cytology alone every 3 years (alternative) 4. Women older than 65 years with adequate negative results* and no history of CIN2+: No screening 5. Women after hysterectomy with removal of the cervix who have no history of CIN2+: No screening
American Cancer Society/American Society for Colposcopy and Cervical Pathology/American Society for Clinical Pathology (ACS/ASCCP/ASCP	1. Women younger than age 21 years: No screening 2. Women aged 21 to 29 years: Screen with cytology alone every 3 years 3. Women aged 30 to 65 years: HPV and cytology “co-testing” every 5 years (preferred), or Cytology alone every 3 years (acceptable) 4. Women older than 65 years with evidence of adequate negative prior screening* and no history of CIN2+ within the last 20 years: No screening

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	5. Women after hysterectomy with removal of the cervix who have no history of CIN2+: No screening
American College of Preventive Medicine (ACPM)	1. Women older than 65 years that are at low risk for cervical cancer and have had negative results from adequate prior screenings*: Don't perform screening 2. Women who have had a total hysterectomy for benign disease and do not have a history of cervical cancer or high-grade cervical lesions: Don't perform screening
American Academy of Family Physicians (AAFP)	1. All recommendations identical to those of the USPSTF

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Measure 4 – De-intensification of breast cancer screening

Proposed de-intensification measure

Action: Do not do screening mammography

Population: Average-risk* women younger than 40, 75 years or older, or with a life expectancy less than 10 years

**Average-risk is defined as those without a personal history of breast cancer, a suspected or confirmed genetic mutation known to increase risk of breast cancer [e.g., BRCA], or a history of previous radiotherapy to the chest at a young age*

Existing recommendation that motivated the proposed de-intensification measure

ACP Guideline Recommendation – De-intensification of breast cancer screening: "Clinicians should not screen average-risk women younger than 40 years or aged 75 years or older for breast cancer or screen women of any age with a life expectancy less than 10 years."

- Source and Steward: American College of Physicians (ACP)
- Last Update: May 19, 2015

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

Potential opportunity for improvement

In VA (estimate)

- [FY2015] 1.6% (2,190/132,846) of women under 40, 75 or older, or with a life expectancy of 10 years or less had one or more mammograms in the study year

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**Patients with a diagnosis of breast cancer or a diagnosis of genetic susceptibility to breast cancer were excluded*

Outside VA

The following is extracted from: Kapp JM, et al. Are mammography recommendations in women younger than 40 related to increased risk? Breast Cancer Res Treat. 2010;119(2):485-490.

- [2005] Of 2,703 women ages 30-39 who completed the National Health Interview Survey and reported at least one visit with a doctor or other health professional in the past 12 months:
  - 19% reported receiving a physician recommendation for mammography
  - 30% reported ever having a mammogram

The following is extracted from: Chang CH, et al. Screening Mammography Use Among Older Women Before And After the 2009 U.S. Preventive Services Task Force Recommendations. J Womens Health. 2016;25(10):1030-1037.

- [2010-2012] In a cohort study of 12 million Medicare fee-for-service women ages 75 and older:
  - 31.7% received a screening mammography

Evidence-Base

Rationale

*The following is extracted from the ACP's "*Screening for Cancer: Advice for High-Value Care from the American College of Physicians*."*

On the basis of RCTs and corresponding modeling studies, all groups have at one time recommended mammography screening, or discussions about screening, at least every 2 years for women aged 40 to 74 years (Smith 2015, American Academy of Physicians 2015). Reasons for not recommending more intensive strategies (such as annual screening, screening younger or older age groups, screening persons of any age with a life expectancy less than 10 years, and screening with more sensitive tests) include concerns that they would lead to few benefits but large increases in harms, such as false positive screening test results and overdiagnosis and overtreatment of lesions that would never have progressed to cause clinical problems (Welch 2014, Pace 2014, Gross 2013, Lee 2013). Screening costs would also greatly increase (O'Donoghue 2014).

The U.S. Preventive Services Task Force (2016) recommends:

- The USPSTF recommends biennial screening mammography for women aged 50 to 74 years. (Evidence Grade B)
- The decision to start screening mammography in women prior to age 50 years should be an individual one. Women who place a higher value on the potential benefit than the potential

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harms may choose to begin biennial screening between the ages of 40 and 49 years. (Evidence Grade C)

- The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening mammography in women aged 75 years or older. (Evidence Grade I)

Citations provided for the evidence

American Academy of Family Physicians. Summary of Recommendations for Clinical Preventive Services. 2017. Accessed at www.aafp.org/dam/AAFP/documents/patient_care/clinical_recommendations/cps-recommendations.pdf.

Gross CP, Long JB, Ross JS, et al. *The cost of breast cancer screening in the Medicare population.* *JAMA Intern Med*. 2013;173(3):220-226.

Lee SJ, Boscardin WJ, Stijacic-Cenzer I, et al. Time lag to benefit after screening for breast and colorectal cancer: meta-analysis of survival data from the United States, Sweden, United Kingdom, and Denmark. *BMJ*. 2013;346:e8441.

O'Donoghue C, Eklund M, Ozanne EM, et al. Aggregate cost of mammography screening in the United States: comparison of current practice and advocated guidelines. *Ann Intern Med*.2014;160(3):145.

Pace LE, Keating NL. A systematic assessment of benefits and risks to guide breast cancer screening decisions. *JAMA*. 2014;311(13):1327-1335.

Siu AL; U.S. Preventive Services Task Force. Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2016;164(4):279-296.

Smith RA, Manassaram-Baptiste D, Brooks D, et al. Cancer screening in the United States, 2015: a review of current American cancer society guidelines and current issues in cancer screening. CA Cancer J Clin. 2015;65(1):30-54.

Welch HG, Passow HJ. Quantifying the benefits and harms of screening mammography. *JAMA Intern Med*. 2014;174(3):448-454.

Additional supporting recommendations

Source	Recommendations
U.S. Preventive Services Task Force	1. The USPSTF recommends biennial screening mammography for women aged 50 to 74 years. 2. The decision to start screening mammography in women prior to age 50 years should be an individual one. Women who place a higher value

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	on the potential benefit than the potential harms may choose to begin biennial screening between the ages of 40 and 49 years. 3. The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening mammography in women aged 75 years or older.
American Cancer Society	1. Women with an average risk of breast cancer should undergo regular screening mammography starting at age 45 years. 2. Women should continue mammography as long as their overall health is good and they have a life expectancy of 10 years or longer. 3. The ACS does not recommend clinical breast examination (CBE) for breast cancer screening among average-risk women at any age. 4. Woman aged 45 to 54 years should be screened annually. 5. Women 55 years and older should transition to biennial screening or have the opportunity to continue screening annually. 6. Women should have the opportunity to begin annual screening between the ages of 40 and 44 years.
American College of Physicians	1. Clinicians should encourage biennial mammography screening in average-risk women aged 50 to 74 years. 2. Clinicians should discuss the benefits and harms of screening mammography with average-risk women aged 40 to 49 years and order biennial mammography screening if an informed woman requests it. 3. Clinicians should not screen average-risk women of any age for breast cancer with MRI or tomosynthesis.
Choosing Wisely. American Geriatrics Society	1. Don’t recommend screening for breast, colorectal, prostate or lung cancer without considering life expectancy and the risks of testing, overdiagnosis and overtreatment.
Choosing Wisely. Society for General Internal Medicine	1. Don’t recommend cancer screening in adults with life expectancy of less than 10 years.
Choosing Wisely. Society for Post-acute and Long-term Care Medicine	1. Don’t recommend screening for breast, colorectal or prostate cancer if life expectancy is estimated to be less than 10 years.

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Measure 5 – De-intensification of colorectal cancer screening (age)

Proposed de-intensification measure

Action: Do not do screening colonoscopy, screening sigmoidoscopy, fecal immunochemical test (FIT), or fecal occult blood test (FOBT)

Population: Average-risk* adults younger than 50 years, older than 75 years, or with a life expectancy less than 10 years

**Average risk is defined as: (1) no prior colectomy; (2) no history of colorectal cancer; (3) no history of colon polyps; (4) no history of inflammatory bowel disease; and (5) no family history of colorectal cancer.*

Existing recommendation that motivated the proposed de-intensification measure

ACP Guideline Recommendation – De-intensification of colorectal cancer screening**:** "Clinicians should not screen for colorectal cancer in average-risk adults younger than 50 years or older than 75 years or those with an estimated life expectancy of less than 10 years."

- Source and Steward: American College of Physicians (ACP)
- Last Update: May 19, 2015

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

Potential opportunity for improvement

In VA (estimate)

- [FY2015] 15,214 patients younger than 50 years old or with a life expectancy less than 10 years had a screening colonoscopy

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*Note: In this estimate, screening colonoscopies were identified using a method developed by Cynthia W. Ko and colleagues, Medical Care, 2014, and life expectancy was estimated using a method developed by Hyunsoon Cho and colleagues, Annals of Internal Medicine, 2013

The following is extracted from: Saini SD, et al. Developing and Testing an Electronic Measure of Screening Colonoscopy Overuse in a Large Integrated Healthcare System. J Gen Intern Med. 2016;31 Suppl1:53-60.

- [2011-2013] In a cross-sectional study using electronic data from the VA Health Care System, 23% (20,530/88,754) of screening colonoscopies met the definition of possible or probable overuse. Of these colonoscopies:
  - 8% (N=1,579) were in people age < 40 years
  - 1% (N=141) were in people age >85 years
  - 1% (N=142) were in people with a life expectancy < 6 months
  - 17% (N=3,462) were in people age 40-49
  - 9% (N=1,863) were in people age 76-85

    Note: The remaining 13,343 were in people with a screening colonoscopy less than 6 months after a negative FOBT (N=6,904) or less than 9 years after a negative colonoscopy (N=6,439)

Outside VA

The following is extracted from: Schwartz AL, et al. Measuring low-value care in Medicare. JAMA Intern Med. 2014;174(7):1067-76.

- [2009] Using claims data from Medicare beneficiaries, as well as demographic information from enrollment files and chronic conditions from the Chronic Conditions Data Warehouse:
  - 6.9% of patients ≥ 75 years old received colorectal cancer screening – using a more sensitive measure.
    - More sensitive, less specific (base definition): Colorectal cancer screening (colonoscopy, sigmoidoscopy, barium enema, or fecal occult blood testing) for patients aged >= 75 y
  - 0.8% of patients ≥ 85 years old received colorectal cancer screening – using a more specific measure.
    - Less sensitive, more specific (additional restrictions): No personal history of colon cancer; only screening (ie, no diagnostic) procedure codes; only patients aged >= 85 y

Evidence-Base

Rationale

The following information is extracted directly and verbatim from the ACP's "Screening for Cancer: Advice for High-Value Care from the American College of Physicians."

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On the basis of results from RCTS of screening (fecal occult blood test [FOBT] and sigmoidoscopy) and consistent observational studies, all organizations recommend screening persons aged 50 to 75 years with 1 of 4 strategies: high-sensitivity FOBT or fecal immunochemical test (FIT) (every year); sigmoidoscopy (every 5 years); combined high-sensitivity FOBT or FIT (every 3 years) plus sigmoidoscopy (every 5 years); or optical colonoscopy (every 10 years) (Smith 2015, American Academy of Family Physicians 2014, U.S. Preventive Services Task Force 2008, Levin 2008, Qaseem 2012, Winawer 2006). The U.S. Food and Drug Administration approved a new DNA stool test, Cologuard (Exact Sciences), for which more comparative effectiveness data are needed. More intensive screening strategies, such as starting at a younger age, continuing to an older age, screening more frequently than recommended, or screening with tests not yet recommended, would be of lower value because benefits would increase only slightly while costs and harms would increase greatly, including complications due to more colonoscopies, overdiagnosis, and overtreatment (Qaseem 2012, Lansdorp-Vogelaar 2011, Warren 2009, Knudsen 2010).

The U.S. Preventive Services Task Force recommends:

- Screening for colorectal cancer starting at age 50 years and continuing until age 75 years. (Grade A)
- The decision to screen for colorectal cancer in adults aged 76 to 85 years should be an individual one, taking into account the patient's overall health and prior screening history. (Grade C)
    - Adults in this age group who have never been screened for colorectal cancer are more likely to benefit.
    - Screening would be most appropriate among adults who:
        - are healthy enough to undergo treatment if colorectal cancer is detected and
        - do not have comorbid conditions that would significantly limit their life expectancy.

Citations provided for the evidence

American Academy of Family Physicians. Summary of Recommendations for Clinical Preventive Services. 2015.

Knudsen AB, Lansdorp-Vogelaar I, Rutter CM, et al. Cost-effectiveness of computed tomographic colonography screening for colorectal cancer in the Medicare population. *J Natl Cancer Inst*. 2010;102(16):1238-1252.

Lansdorp-Vogelaar I, Knudsen AB, Brenner H. Cost-effectiveness of colorectal cancer screening. *Epidemiol Rev*. 2011;33:88-100.

Levin B, Lieberman DA, McFarland B, et al. American Cancer Society Colorectal Cancer Advisory Group. Screening and surveillance for the early detection of colorectal cancer and adenomatous

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polyps, 2008: a joint guideline from the American Cancer Society, the U.S. Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology*. 2008;134(5):1570-1595.

Qaseem A, Denberg TD, Hopkins RH Jr, et al. Clinical Guidelines Committee of the American College of Physicians. Screening for colorectal cancer: a guidance statement from the American College of Physicians. *Ann Intern Med*. 2012;156(5):378-386.

Smith RA, Manassaram-Baptiste D, Brooks D, et al. Cancer screening in the United States, 2015: a review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin*. 2015;65(1):30-54.

U.S. Preventive Services Task Force. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2008;149(9):627-637.

US Preventive Services Task Force., Bibbins-Domingo K, Grossman DC, et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2016;315(23):2564-75.

Warren JL, Klabunde CN, Mariotto AB, et al. Adverse events after outpatient colonoscopy in the Medicare population. *Ann Intern Med*. 2009;150(12):849-857.

Winawer SJ, Zauber AG, Fletcher RH, et al. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the U.S. Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. *CA Cancer J Clin*. 2006;56(3):143-159; quiz 184-185.

Additional supporting recommendations

Source	Recommendations
U.S. Preventive Services Task Force	1. The USPSTF recommends screening for colorectal cancer starting at age 50 years and continuing until age 75 years. 2. The decision to screen for colorectal cancer in adults aged 76 to 85 years should be an individual one, taking into account the patient's overall health and prior screening history.
American College of Physicians	1. ACP recommends that clinicians screen for colorectal cancer in average-risk adults starting at the age of 50 years and in high-risk adults starting at the age of 40 years or 10 years younger than the age at which the youngest affected relative was diagnosed with colorectal cancer. 2. ACP recommends that clinicians stop screening for colorectal cancer in adults over the age of 75 years or in adults with a life expectancy of less than 10 years.

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Choosing Wisely. American College of Surgeons	1. Avoid colorectal cancer screening tests on asymptomatic patients with a life expectancy of less than 10 years and no family or personal history of colorectal neoplasia.
Choosing Wisely. Society for General Internal Medicine	1. Don’t recommend cancer screening in adults with life expectancy of less than 10 years.
Choosing Wisely. Society for Post-acute and Long-term Care Medicine	1. Don’t recommend screening for breast, colorectal or prostate cancer if life expectancy is estimated to be less than 10 years.
Choosing Wisely. American Geriatrics Society	1. Don’t recommend screening for breast, colorectal, prostate or lung cancer without considering life expectancy and the risks of testing, overdiagnosis and overtreatment.

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Measure 6 – De-intensification of colorectal cancer screening (frequency)

Proposed de-intensification measure

Action: Don't screen more than every 10 years with colonoscopy, every 5 years with sigmoidoscopy, or yearly with FOBT/FIT

Population: Patients with average-risk* of colorectal cancer

**Average risk is defined as: (1) no prior colectomy; (2) no history of colorectal cancer; (3) no history of colon polyps; (4) no history of inflammatory bowel disease; and (5) no family history of colorectal cancer.*

Existing recommendation that motivated the proposed de-intensification measure

ACP Guideline Recommendation – De-intensification of colorectal cancer screening**:** "Clinicians should encourage colorectal cancer screening [in persons aged 50-75 years] by 1 of 4 strategies: high-sensitivity FOBT or FIT (every year); sigmoidoscopy (every 5 years); combined high-sensitivity FOBT or FIT (every 3 years) plus sigmoidoscopy (every 5 years); or optical colonoscopy (every 10 years) in average-risk adults aged 50 to 75 years."

- Source and Steward: American College of Physicians (ACP)
- Last Update: May 19, 2015

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

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Potential opportunity for improvement

In VA (estimate)

The following is extracted from: Saini SD, et al. Developing and Testing an Electronic Measure of Screening Colonoscopy Overuse in a Large Integrated Healthcare System. J Gen Intern Med. 2016;31 Suppl1:53-60.

- [2011-2013] In a cross-sectional study using electronic data from the VA Health Care System, 23% (20,530/88,754) of screening colonoscopies met the definition of possible or probable overuse. Of these colonoscopies:
  - 34% (6,904) were in patients who received a colonoscopy less than 6 months after a negative FOBT
  - 31% (6,439) were in patients who received a colonoscopy less than 9 years after a negative colonoscopy

Outside VA

The following is extracted from: Wilt TJ, et al.; High Value Care Task Force of the American College of Physicians. Screening for cancer: advice for high-value care from the American College of Physicians. Ann Intern Med. 2015;162(10):718-725.

- "Inappropriate colorectal cancer screening is also common":
  - Sixty percent of adults had colonoscopies more frequently than guidelines recommend (Walter 2009, Korenstein 2012, Sheffield 2013).
  - Among persons having an FOBT screening test, 8% had a negative result less than 1 year before (Partin 2012).

Evidence-Base

Rationale

*The following information is extracted directly and verbatim from the ACP's "*Screening for Cancer: Advice for High-Value Care from the American College of Physicians*."*

On the basis of results from RCTS of screening (fecal occult blood test [FOBT] and sigmoidoscopy) and consistent observational studies, all organizations recommend screening persons aged 50 to 75 years with 1 of 4 strategies: high-sensitivity FOBT or fecal immunochemical test (FIT) (every year); sigmoidoscopy (every 5 years); combined high-sensitivity FOBT or FIT (every 3 years) plus sigmoidoscopy (every 5 years); or optical colonoscopy (every 10 years) (Smith 2015, American Academy of Family Physicians 2014, U.S. Preventive Services Task Force 2008, Levin 2008, Qaseem 2012, Winawer 2006). The U.S. Food and Drug Administration approved a new DNA stool test, Cologuard (Exact Sciences), for which more comparative effectiveness data are needed. More intensive screening strategies, such as starting at a younger age, continuing to an older age, screening more frequently than recommended, or screening with tests not yet recommended, would be of lower value because benefits would increase only slightly while costs and harms would increase greatly, including complications due to more colonoscopies, overdiagnosis, and overtreatment (Qaseem 2012, Lansdorp-Vogelaar 2011, Warren 2009, Knudsen 2010).

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The U.S. Preventive Services Task Force recommends:

Screening Method	Frequency	Evidence of Efficacy	Other Considerations
Stool-Based Tests			
gFOBT	Every year	RCTs with mortality end points: High-sensitivity versions (eg, Hemoccult SENSA) have superior test performance characteristics than older tests (eg, Hemoccult II)	Does not require bowel preparation, anesthesia, or transportation to and from the screening examination (test is performed at home)
FIT	Every year	Test characteristic studies: Improved accuracy compared with gFOBT Can be done with a single specimen	Does not require bowel preparation, anesthesia, or transportation to and from the screening examination (test is performed at home)
FIT-DNA	Every 1 or 3 y	Test characteristic studies: Specificity is lower than for FIT, resulting in more false-positive results, more diagnostic colonoscopies, and more associated adverse events per screening test Improved sensitivity compared with FIT per single screening test	There is insufficient evidence about appropriate longitudinal follow-up of abnormal findings after a negative diagnostic colonoscopy; may potentially lead to overly intensive surveillance due to provider and patient concerns over the genetic component of the test
Direct Visualization Tests			
Colonoscopy	Every 10 y	Prospective cohort study with mortality end point	Requires less frequent screening. Screening and diagnostic followup of positive results can be performed during the same examination.
CT colonography	Every 5 y	Test characteristic studies	There is insufficient evidence about the potential harms of associated extracolonic findings, which are common
Flexible sigmoidoscopy	Every 5 y	RCTs with mortality end points: Modeling suggests it provides less benefit than when combined with FIT or compared with other strategies	Test availability has declined in the United States
Flexible sigmoidoscopy with FIT	Flexible sigmoidoscopy every 10 y plus FIT every year	RCT with mortality end point (subgroup analysis)	Test availability has declined in the United States Potentially attractive option for patients who want endoscopic screening but want to limit exposure to colonoscopy

Abbreviations: FIT=fecal immunochemical test; FIT-DNA=multitargeted stool DNA test; gFOBT=guaiac-based fecal occult blood test; RCT=randomized clinical trial

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From USPSTF Final Recommendation Statement: Screening Intervals - Evidence from RCTs demonstrates that annual or biennial screening with gFOBT as well as 1-time and every 3- to 5-year flexible sigmoidoscopy reduces colorectal cancer deaths. The CISNET models found that several screening strategies were estimated to yield comparable life-years gained (ie, life-years gained with the noncolonoscopy strategies were within 90% of those gained with the colonoscopy strategy) among adults aged 50 to 75 years and an efficient balance of benefits and harms. These screening strategies include 1) annual screening with FIT, 2) screening every 10 years with flexible sigmoidoscopy and annual screening with FIT, 3) screening every 10 years with colonoscopy, and 4) screening every 5 years with CT colonography. The findings for CT colonography depend on the proxy measure used for the burden of screening (number of lifetime colonoscopies or lifetime cathartic bowel preparations). Two of the 3 CISNET models found that FIT-DNA screening every 3 years (as recommended by the manufacturer) was estimated to yield life-years gained less than 90% of the colonoscopy screening strategy (84% and 87%, respectively). Another way to conceptualize these findings is to note that CISNET modeling found that FIT-DNA screening every 3 years was estimated to provide about the same amount of benefit as screening with flexible sigmoidoscopy alone every 5 years.

Citations provided for the evidence

American Academy of Family Physicians. Summary of Recommendations for Clinical Preventive Services. 2015.

Knudsen AB, Lansdorp-Vogelaar I, Rutter CM, et al. Cost-effectiveness of computed tomographic colonography screening for colorectal cancer in the Medicare population. *J Natl Cancer Inst*. 2010;102(16):1238-1252.

Lansdorp-Vogelaar I, Knudsen AB, Brenner H. Cost-effectiveness of colorectal cancer screening. *Epidemiol Rev*.2011;33:88-100.

Levin B, Lieberman DA, McFarland B, et al. American Cancer Society Colorectal Cancer Advisory Group. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the U.S. Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology*.2008;134(5):1570-1595.

Qaseem A, Denberg TD, Hopkins RH Jr, et al. Clinical Guidelines Committee of the American College of Physicians. Screening for colorectal cancer: a guidance statement from the American College of Physicians. *Ann Intern Med*. 2012;156(5):378-386.

Smith RA, Manassaram-Baptiste D, Brooks D, et al. Cancer screening in the United States, 2015: a review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin*. 2015;65(1):30-54.

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U.S. Preventive Services Task Force. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2008;149(8):627-637.

US Preventive Services Task Force., Bibbins-Domingo K, Grossman DC, et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2016 Jun 21;315(23):2564-2575.

Warren JL, Klabunde CN, Mariotto AB, et al. Adverse events after outpatient colonoscopy in the Medicare population. *Ann Intern Med*. 2009;150(12):849-857.

Winawer SJ, Zauber AG, Fletcher RH, et al. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the U.S. Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. *CA Cancer J Clin*. 2006;56(3):143-159; quiz 184-5.

Additional supporting recommendations

Source	Recommendations
American College of Physicians	1. For adults <50 or >74 in the absence of abnormal results do not repeat: colonoscopy more frequently than every 10yr; or flexible sigmoidoscopy more frequently than every 5yr. 2. Do not perform fecal testing [for colorectal cancer] with 10yr screening colonoscopies; or more frequently than yearly in those receiving 5yr screening sigmoidoscopies.
U.S. Preventive Services Task Force	1. When screening for colorectal cancer using colonoscopy, screening should be performed every 10 years.
U.S. Multi-Society Task Force (AGA/ACG/ASGE/ACP)	1. Colonoscopy should be repeated at 10 years after a baseline exam shows no polyps.
Choosing Wisely. American Gastroenterological Association	1. Do not repeat colorectal cancer screening (by any method) in average risk-individuals for 10 years after a high-quality colonoscopy is negative.
American Cancer Society	1. If colonoscopy is used to screen for colon cancer, it should be performed every 10 years beginning at age 50.
American Gastroenterological Association	1. Percentage of patients aged 50 years and older receiving a screening colonoscopy without biopsy or polypectomy who had a recommended follow-up interval of at least 10 years for repeat colonoscopy documented in their report. [NQF Measure]

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Measure 7 – De-intensification of PSA-based screening

Proposed de-intensification measure

Action: Don't screen for prostate cancer using prostate specific antigen (PSA)

Population: Men younger than 55, older than 69, or with a life expectancy of less than 10 years

Existing recommendations that motivated the proposed de-intensification measure

ACP Guideline Recommendation – De-intensification of PSA-based screening: "ACP recommends that clinicians should not screen for prostate cancer using the prostate-specific antigen test in average-risk men under the age of 50 years, men over the age of 69 years, or men with a life expectancy of less than 10 years."

- Source and Steward: American College of Physicians (ACP)
- Last Update: May 19, 2015

See all additional supporting recommendations.

(Note: The USPSTF [2017] recommends that screening not be done in men younger than 55; therefore, we used 55 instead of 50 for the proposed measure)

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

Potential opportunity for improvement

In VA (estimate)

- [FY2015] 1,653,843 patients, who were not previously diagnosed with prostate cancer and who did not have a PSA>5 in the previous year, had a PSA test
    - Under 55: 277,969 (16.8%)
    - 55-69: 944,389 (57.1%)

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- Older than 69: 431,485 (26.1%)

Outside VA

The following is extracted from: Schwartz AL, et al. Measuring low-value care in Medicare. JAMA Intern Med. 2014;174(7):1067-1076.

- [2009] Using claims data from Medicare beneficiaries, as well as demographic information from enrollment files and chronic conditions from the Chronic Conditions Data Warehouse:
  - 8.3% of patients older than 75 received PSA screening– using a more sensitive measure
    - More sensitive, less specific (base definition): PSA test for patients aged >=75y
  - 2.7% of patients older than 75 received PSA screening– using a more specific measure
    - Less sensitive, more specific (additional restrictions): No history of prostate cancer; only screening (ie, not diagnostic) procedure codes

Rapid evidence synthesis summary (Review the entire rapid evidence synthesis report.)

Why is this important?

- Prostate cancer is the third most commonly diagnosed cancer in the United States, and an estimated 20 million men undergo prostate cancer screening annually in the United States.
- Prostate specific antigen-based screening can lead to overdiagnosis and overtreatment, as a significant proportion of cancers detected by PSA screening are indolent and likely to remain asymptomatic during the course of a man's lifetime.
- In April 2017, the U.S. Preventive Services Task Force released updated draft recommendations on prostate cancer screening in asymptomatic men.

What are the benefits and harms of routine screening for prostate cancer with prostate-specific antigen (PSA) testing?

Screening benefits:

- Increased prostate cancer detection.
- One large screening trial found no effect on prostate cancer-specific mortality and another found screening associated with decreased risk of prostate cancer-specific mortality.
- No effect on all-cause mortality.

Screening harms:

- False-positive screening tests are common (10-45%) leading to biopsy.
- Biopsy associated with harms, including pain, bleeding, and infections
- Screening can lead to overdiagnosis (estimated up to 50%) and overtreatment.
- Prostatectomy increased risk of urinary incontinence and sexual dysfunction; radiation therapy associated with bowel dysfunction

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What are the benefits and harms of not conducting PSA-based prostate cancer screening?

- Reduction in the number biopsies and diagnosed low-grade prostate cancer cases.
- Greater proportion of high-grade and metastatic cancers diagnoses, with potentially (as yet unproven) increased mortality.

What are the implications of our findings?

- PSA-based screening can potentially reduce risk of prostate cancer mortality (based on one study), but screening benefits may not be apparent for 12 years or more and does not decrease overall mortality.
- The benefits of PSA screening must be weighed against high false positive rates and the risk of overdiagnosis leading to overtreatment.

Additional supporting recommendations

Source	Recommendations
U.S. Preventive Services Task Force (2017)	1. The USPSTF recommends that clinicians inform men ages 55 to 69 years about the potential benefits and harms of PSA-based screening for prostate cancer (C recommendation). Additional considerations: Recommends individualized decision-making about screening for prostate cancer after discussion with a clinician, so that each man has an opportunity to understand the potential benefits and harms of screening and to incorporate his values and preferences into his decision. No separate recommendations regarding screening in Black men and men with a family history of prostate cancer, due to insufficient evidence. 2. The USPSTF recommends against PSA-based screening for prostate cancer in men age 70 years and older (D recommendation).
American College of Physicians	1. ACP recommends that clinicians inform men between the age of 50 and 69 years about the limited potential benefits and substantial harms of screening for prostate cancer. ACP recommends that clinicians base the decision to use PSA-based screening on the risk for prostate cancer, a discussion of the benefits and harms of screening, the patient's general health and life expectancy and patient preferences. 2. ACP recommends that clinicians should not screen for prostate cancer using the PSA test in patients who do not express a clear preference for screening. 3. ACP recommends that clinicians should not screen for prostate cancer using the PSA test in average-risk men under age 50 years, men over age 69 years, or men with a life expectancy of less than 10 to 15 years.

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American Urological Association	1. The AUA panel does not recommend routine screening in men between ages 40 and 54 years. For men age 40 to 54 years at higher risk (e.g., positive family history, African-American), decisions regarding prostate cancer screening should be individualized. 2. The AUA panel recommends shared decision-making for men age 55 to 69 years that are considering PSA screening and proceeding based on a man's values and preferences. For those men who choose to undergo screening, a routine screening interval of 2 years or more may be preferred over annual screening. 3. The AUA panel does not recommend routine screening in men over age 70 years or in any many with a 10 to 15 year life expectancy.
Choosing Wisely. American College of Preventive Medicine (ACPM)	1. Don't routinely perform PSA-based screening for prostate cancer. Men should only consent to being screened for prostate cancer after they clearly understand the associated benefits and risks. 2. Decision aids may be effective ways to engage men in a conversation about the risks and benefits of prostate cancer screening.
Choosing Wisely. American Academy of Family Physicians	1. Don't routinely screen for prostate cancer using a prostate-specific antigen test or digital rectal exam.
Choosing Wisely. American Society of Clinical Oncology	1. Don't perform PSA testing for prostate cancer screening in men with no symptoms of the disease when they are expected to live less than 10 years.
Choosing Wisely. American Geriatrics Society	1. Don't recommend screening for breast, colorectal, prostate or lung cancer without considering life expectancy and the risks of testing, overdiagnosis and overtreatment.
American Cancer Society	1. Asymptomatic men who have less than a 10-year life expectancy based on age and health status should not be offered prostate cancer screening. 2. Prostate cancer screening should not occur without an informed decision-making process.

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Measure 8 – De-intensification of lung cancer screening

Proposed de-intensification measure 1

Action: Don't perform a screening computerized tomography (CT) for lung cancer

Population: Patients at low risk* for lung cancer

**Low risk is defined as: Patients younger than 55, with fewer than 30 pack year history, or who quit smoking more than 15 years ago*

Proposed de-intensification measure 2

Action: Don't perform a screening CT for lung cancer

Population: Patients who would receive little benefit** from lung cancer screening

***Little benefit is defined as: Patients older than 80, with a life expectancy less than 10 years, or with severe comorbidities that would preclude potentially curative treatment*

Existing recommendation that motivated the proposed de-intensification measure

Choosing Wisely – De-intensification of lung cancer screening: "Don't perform computer tomography (CT) screening for lung cancer among patients at low risk for lung cancer."

- Source: Choosing Wisely
- Steward: American College of Chest Physicians (ACP) and American Thoracic Society
- Last Update: October 27, 2013

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

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Potential opportunity for improvement
In VA (estimate)
1. [FY2015] 17% (1,959/11,489) of patients with a CT scan for lung cancer screening had no ICD9 or Health Factor code indicating a history of smoking.

Notes: 1. In order to determine smoking status, we looked for an ICD-9 code for tobacco use disorder [305.1] or mention of smoking in the health factors data (an open text field in the VA data) in FY13-15. It is likely that some of the patients we categorized as *having no history of smoking* are actually former smokers (e.g., just without a ICD-9 code for tobacco use disorder in the 3 year timeframe we examined) and thus potentially eligible for screening. Additionally, the health factors data field is not used consistently across facilities and the text that is entered is frequently ambiguous (e.g., "current non-user," "date last smoked"), making it challenging to determine smoking status using that method as well. 2. In order to determine whether the CT scan was done for lung cancer screening purposes, we looked for a CPT code for Computed Tomography-thorax [71250] with a study reason (open text field) suggesting lung cancer screening. Unfortunately, there is no standard text used in the study reason field across facilities for lung cancer screening. This makes it challenging to determine which of the CT scans were done specifically for lung cancer screening purposes.

Outside VA
The following is extracted from: Huo J, et al. Use of CT and Chest Radiography for Lung Cancer Screening Before and After Publication of Screening Guidelines: Intended and Unintended Uptake. JAMA Intern Med. 2017;177(3):439-441.

- [2015] Using data from the National Health Interview Survey Cancer Control Module, in people age 55-74 years:
    - 1.5% (75/5062) who never-smoked received a CT scan for lung cancer screening (LCS)
    - 3.8% (121/3186) low-risk smokers received a CT scan for LCS
        - Low risk was defined as current or former smokers who had less than 30 pack-years of smoking history or quit more than 15 years ago
- In people younger than 55 years:
    - 1% (78/7510) received a CT scan for LCS (32/78 who never smoked)
- In people older than 74 years:
    - 2.7% (91/3397) received a CT scan for LCS (36/91 who never smoked)

Evidence-Base

Rationale
The following information is extracted directly and verbatim from Choosing Wisely.

Low dose chest CT screening for lung cancer has the potential to reduce lung cancer death in patients at high risk (i.e., individuals aged 55-74 with at least a 30-pack year history of tobacco use, who are either still smoking or quit within the past 15 years). However, CT screening for lung cancer also has the potential to cause a number of adverse effects (e.g., radiation exposure, high false positive rate, harms related to downstream evaluation of pulmonary nodules, overdiagnosis of indolent tumors).

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Thus, screening should be reserved for patients at high risk of lung cancer and should not be offered to individuals at low risk of lung cancer.

The U.S. Preventive Services Task Force recommends:

- The USPSTF recommends annual screening for lung cancer with low-dose computed tomography (LDCT) in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery. (Evidence Grade B)

Citations provided for the evidence

Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365(5):395–409.

Bach PB, Mirkin JN, Oliver TK, et al. Benefits and harms of CT screening for lung cancer: a systematic review. *JAMA*. 2012;307(22):2418–2429.

Humphrey LL, Deffebach M, Pappas M, et al. Screening for lung cancer with low-dose computed tomography: a systematic review to update the U.S. Preventive Services Task Force recommendation. *Ann Intern Med*. 2013;159(6):411–420.

Moyer VA; U.S. Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;160(5):330-338.

Veronesi G, Maisonneuve P, Bellomi M, et al. Estimating overdiagnosis in low-dose computed tomography screening for lung cancer: a cohort study. *Ann Intern Med*. 2012;157(11):776–784.

Additional supporting recommendations

Source	Recommendations
U.S. Preventive Services Task Force	1. The USPSTF recommends annual screening for lung cancer with low-dose computed tomography in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.
American Association for Thoracic Surgery	1. American Association for Thoracic Surgery guidelines call for annual lung cancer screening with low-dose computed tomography screening to start at age 55 years for smokers and former smokers with a 30 pack-year history of smoking, with annual screening continuing through age 79 years. 2. AATS recommends that annual low-dose computer tomography lung

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	cancer screening should be offered starting at age 50 years for those with a 20 pack-year smoking history if there is additional cumulative risk of developing lung cancer of ≥ 5% over the following 5 years. 3. Do not offer or perform annual LDCT screening for lung cancer in at-risk adults between ages 55-79 years for whom adequate treatment cannot be offered because of comorbidity or functional status, regardless of age (e.g., COPD FEV1<70%, environmental/occupational exposures, history of prior cancer/radiation therapy, genetic/family history)
American Cancer Society, American College of Chest Physicians, American Society of Clinical Oncology, National Comp Cancer Network	1. For individuals who have accumulated fewer than 30 pack-years of smoking, are either younger than 55 or older than 74, or who quit smoking more than 15 years ago, as well as for individuals with severe comorbidities that would preclude potentially curative treatment and/or limit life expectancy, guideline group suggests that CT screening should not be performed. 2. For smokers and former smokers who are age 55 to 74 and who have smoked for 30 pack-years or more and either continue to smoke or have quit within the past 15 years, we suggest that annual screening with low-dose CT (LDCT) should be offered over both annual screening with CXR or no screening, but only in settings that can deliver the comprehensive care provided to National Lung Screening Trial participants. 3. Clinicians with access to high-volume, high-quality lung cancer screening and treatment centers should initiate a discussion about screening with apparently healthy patients aged 55 years to 74 years who have at least a 30–pack-year smoking history and who currently smoke or have quit within the past 15 years and for those who value the opportunity to be screened to reduce their risk of dying. Annual screening with LDCT should be offered over both annual screening with chest radiograph or no screening until the age of 74 years.
Choosing Wisely. American Geriatrics Society	1. Don’t recommend screening for breast, colorectal, prostate or lung cancer without considering life expectancy and the risks of testing, overdiagnosis and overtreatment.

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Measures related to Opioid Prescribing

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Measure 9 – De-intensification of opioids

Proposed de-intensification measure

Action: Stop or decrease the opioid dose

Population: Patients on ≥90 morphine milligram equivalents/day

Existing recommendation that motivated the proposed de-intensification measure

CDC Guideline Recommendation - De-intensification of opioids: "When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day."

- Source and Steward: Centers for Disease Control and Prevention (CDC)
- Last Update: March 18, 2016
- Evidence: Type 3 (observational studies, or randomized clinical trials with notable limitations)

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

    a. Should there be a third action (e.g. stop, decrease, or document justification for ≥90mg day).

3. Do you agree with the population, including exclusions?

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Potential opportunity for improvement

In VA (estimate)

- [FY2014] 9.1% (13,034/142,591) of patients with chronic opioid use, defined as contiguous opioid coverage during the baseline period [Jan-June 2014], were prescribed an average dose ≥ 90 mg/day.

The following is extracted from: Lin LA, Bohnert AS, Kerns RD, Clay MA, Ganoczy D, Ilgen MA. Impact of the Opioid Safety Initiative on opioid-related prescribing in veterans. Pain. 2017; 158(5): 833-839.

- [FY2014] In a retrospective system-wide interrupted time series analysis, using outpatient-prescription medication data from the VHA's Pharmacy Benefits management service, of patients who filled an outpatient prescription for opioids (N=514,883):
  - 46,780 patients received a daily dosage of opioids >100MEQ
  - 15,121 patients received a daily dosage of opioids >200MEQ

Note: Only the first estimate above examined chronic users.

Outside VA

The following is extracted from: U.S Department of Health and Human Services; Office of Inspector General. Opioids in Medicare Part D: Concerns about Extreme Use and Questionable Prescribing*. HHS OIG Data Brief OEI-02-17-00250. 2016:1-16.*

- [2016] A total of 501,008 beneficiaries received high amounts of opioids through Medicare Part D in 2016. This does not include beneficiaries who had cancer or were in hospice care. Each of the 501,008 beneficiaries received an average morphine equivalent dose (MED) of greater than 120 mg a day for at least 3 months.

Rapid evidence synthesis summary (Review the entire rapid evidence synthesis report.)

Why is this important?

- Prescribing and use of opioids for chronic pain has increased substantially.
- In addition to increased rates of prescribing, data also indicate that opioids are being prescribed at higher doses.
- Opioids are associated with serious harms, including overdose deaths and opioid use disorder; higher doses may be associated with increased risk.
- In 2015, the rate of high-dose (>=90 mg morphine equivalents (MME/day) opioid prescribing was 6.7 per 100 persons.
- De-intensification of high-dose opioid therapy could prevent harms associated with opioids.

What are the benefits of prescribing higher versus lower doses of opioids?

- One randomized trial found no difference between more liberal dose escalation of opioids versus maintenance of current doses, but differences in opioid doses between groups were relatively small.
- A meta-regression found no clear association between higher doses of opioids and improved pain or function.

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What are the harms of prescribing higher versus lower doses of opioids?

- A systematic review consistently found an association between higher doses of opioids and increased risk of overdose deaths or overdose events.
- Additional studies published since the systematic review also found a dose-dependent risk between higher doses of opioids and increased risk of overdose deaths or overdose events.

What are the benefits and harms of de-intensification of opioid doses in persons prescribed high-dose opioid therapy?

- A systematic review found very low quality evidence that several types of interventions are effective for lowering or tapering opioids, and may improve pain, function, and quality of life; studies were not designed to assess effects on serious harms such as overdose.
- Rapid tapering and discontinuation of opioids can result in withdrawal symptoms.

What are the implications of our findings?

- The CDC recommends that clinicians reassess benefits and harms when prescribing doses of >=50 mg MME/day and avoid doses >=90 MME/day.
- Tapering of opioids should be gradual to reduce the rate and severity of withdrawal symptoms.

Additional supporting recommendations

Source	Recommendations
VA/DoD	1. If prescribing opioids, we recommend prescribing the lowest dose of opioids as indicated by patient-specific risks and benefits. Note: There is no absolutely safe dose of opioids. 2. We recommend against opioid doses over 90 MME/day for treating chronic pain. 3. Recommend tapering to reduced dose or to discontinuation of long-term opioid therapy when risks of long-term opioid therapy outweigh benefits. Note: Abrupt discontinuation should be avoided unless required for immediate safety concerns.

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Measure 10 – De-intensification of opioids and benzodiazepines

Proposed de-intensification measure

Action: Stop or decrease the dose of at least one of the two medications

Population: All patients, 18 years and older, who are on both opioids and benzodiazepines

Existing recommendation that motivated the proposed de-intensification measure

CDC Guideline Recommendation – De-intensification of opioids and benzodiazepines: "Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible."

- Source and Steward: Centers for Disease Control and Prevention (CDC)
- Last Update: March 18, 2016
- Evidence: Type 3 (observational studies, or randomized clinical trials with notable limitations)

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

Potential opportunity for improvement

In VA (estimate)

- [3/1/2014 to 2/28/2015] 126,788 patients were on an opioid and benzodiazepine concurrently (defined as having at least 30 simultaneous days of opioid and benzo use)
    - 18,517 (14.6%) were still on both agents 6 months later

The following is extracted from: Lin LA, et al. Impact of the Opioid Safety Initiative on opioid-related prescribing in veterans. Pain. 2017; 158(5): 833-839.

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- [Sept 2014] In a retrospective system-wide interrupted time series analysis, using outpatient-prescription medication data from the VHA's Pharmacy Benefits management service, 514,883 patients filled an outpatient prescription for opioids
    - 89,564 (17.4%) patients also received a benzodiazepine prescription

Note: Only the first estimate above examined chronic users.

Outside VA

The following is extracted from: Sun EC, et al. Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis. BMJ. 2017; 356: j760.

- [2013] Using administrative health claims data provided by Marketscan (of patients enrolled in private insurance plans through a participating employer, health plan, or government organization) in a retrospective analysis:
    - 17% (14,415/85,617) of opioid users were also taking a benzodiazepine

Rapid evidence synthesis summary (Review the entire rapid evidence synthesis report.)

Why is this important?

- Prescribing and use of opioids for chronic pain has increased substantially.
- Opioids are associated with serious harms, including overdose deaths and opioid use disorder.
- Benzodiazepines are commonly prescribed in persons using opioids, but can potentiate the respiratory depressant effect of opioids, increasing the risk of overdose, and are also associated with risk of abuse and dependence.
- De-intensification of medications in persons co-prescribed opioids and benzodiazepines could prevent harms associated with this combination.
- Studies found that the proportion of patients prescribed an opioid who are also prescribed a benzodiazepine ranges from 17% to 80%.

What are the benefits of co-prescribing of opioids and benzodiazepines?

- No study evaluated the incremental benefits of opioids in combination with benzodiazepines versus either of these medications alone.

What are the harms of co-prescribing of opioids and benzodiazepines?

- Studies found that 50% to 60% of opioid overdoses also involve concurrent use of benzodiazepines.
- A large study of administrative claims data found opioids + benzodiazepines associated with increased risk of an emergency room visit or inpatient admission versus opioid use alone (adjusted OR 2.14, 95% CI 2.05 to 2.24).

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- A study of U.S. Veterans receiving opioids for chronic pain found current benzodiazepine use associated with increased risk of overdose deaths versus no benzodiazepines (adjusted HR 3.86, 95% CI 3.49 to 4.26).
- A study of Washington State Medicaid enrollees who received at least one opioid prescription found use of benzodiazepines associated with increased risk of opioid-related death versus no benzodiazepines (adjusted HR 7.5, 95% CI 5.5-10.0).

What are the benefits and harms of de-intensification of benzodiazepines use in persons prescribed opioids?

- No study evaluated benefits and harms of de-intensification of benzodiazepines in persons prescribed opioids.
- Rapid tapering and discontinuation of benzodiazepines can result in withdrawal symptoms, which may be serious.
- One study estimated that discontinuation of benzodiazepines in persons prescribed opioids could reduce opioid-related emergency department visits and inpatient admissions by 15%.

What are the implications of our findings?

- The CDC recommends that concurrent use of opioids and benzodiazepines be avoided whenever possible.
- Benzodiazepine tapering should be gradual, as stopping abruptly can result in serious withdrawal.
- In 2016, the FDA announced that it requires black box warnings on risks of concurrent use of opioids and benzodiazepines.

Additional supporting recommendations

Source	Recommendations
VA	1. Recommend against the concurrent use of benzodiazepines and opioids.

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Measures related to Medication Use in Older Adults

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Measure 11 – De-intensification of benzodiazepines

Proposed de-intensification measure

Action: Stop or decrease dose of benzodiazepines or other sedative-hypnotics

Population: Patients older than 65

Existing recommendation that motivated the proposed de-intensification measure

Choosing Wisely – De-intensification of benzodiazepines: "Don't use benzodiazepines or other sedative-hypnotics in older adults as first choice for insomnia, agitation or delirium."

- Source: Choosing Wisely
- Steward: American Geriatrics Society (AGS)
- Last Update: April 23, 2015

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

    a. Should documented failure of first line (non-BZP) treatments be an exclusion?

Potential opportunity for improvement

In VA (estimate)

- [FY2015] In patients 65 years and older:
    - 6.1% (179,243/2,958,651) were prescribed a benzodiazepine

- [FY2015] In patients 65 years and older with dementia:
    - 9.9% (5,108/51,647) were prescribed a benzodiazepine

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Outside VA

The following is extracted from: Maust DT, et al. National Trends in Antidepressant, Benzodiazepine, and Other Sedative-Hypnotic Treatment of Older Adults in Psychiatric and Primary Care. J Clin Psychiatry. 2017; 78(4): e363-e371.

- [2010-2012] Using data from the National Ambulatory Medical Care Survey:
  - Of patients 65 years or older who were seen by a primary care provider (N=9,547):
    - 8.7% were prescribed a benzodiazepine. Of these patients:
      - 22.1% were diagnosed with insomnia
      - 14.9% were diagnosed with dementia
      - 6.9% had no mental health or pain diagnosis
    - 4.7% were prescribed another sedative-hypnotic. Of these patients:
      - 40.2% were diagnosed with insomnia
      - 2.3% were diagnosed with dementia
      - 4.3% had no mental health or pain diagnosis

Rapid evidence synthesis summary (Review the entire rapid evidence synthesis report.)

Why is this important?

- Insomnia, agitation, and delirium are common in older adults and can be associated with decreased quality of life. Although benzodiazepines and sedative hypnotics have been a mainstay of treatment of these conditions, the American Geriatrics Society Beers Criteria for Potentially Inappropriate Medical Use in Older Adults and the Choosing Wisely campaign recommended against their use due to concerns of serious risks such as fractures and mortality. Discontinuing benzodiazepines and sedative hypnotics can be a challenge due to physical dependence and withdrawal. This rapid evidence synthesis summarizes the evidence on risk of mortality and fractures for benzodiazepines and sedative hypnotics versus nonuse in older adults and effects of their discontinuation.

What is the association between benzodiazepines and sedative hypnotics and risk of mortality when used in older adults for insomnia, agitation, and delirium?

- Benzodiazepine and sedative hypnotic use is consistently associated with increased risk of mortality (HR range 3.32 to 5.32) in studies of adults (mean age 50s) with long-term follow-up, although an association was not observed in studies restricted to older adults (HR range, 1.01 to 1.06; RR 0.68).

What is the association between benzodiazepines and sedative hypnotics and risk of fractures when used in older adults for insomnia, agitation, and delirium?

- Benzodiazepines and zolpidem are associated with increased risk of fractures in older persons when prescribed for various indications; zolpidem is associated with increased risk of fracture when prescribed specifically for insomnia.

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What are the benefits and harms of discontinuing benzodiazepines and sedative hypnotics versus continuing them in older people with insomnia, agitation and delirium?

- Empirical evidence on the relapse, withdrawal, and health care utilization effects of discontinuing benzodiazepines and sedative hypnotics is too limited to draw conclusions specific to older adults with insomnia, agitation, or delirium.

What are the implications of our findings?

- Benzodiazepines and sedative hypnotics are associated with risk of fracture in older persons. Evidence on the association between benzodiazepines and sedative hypnotics and increased risk of mortality is somewhat mixed and has been primarily observed in populations not restricted to older persons. Alternative treatments and approaches for management of insomnia, agitation, and delirium in older persons are available and may provide a superior balance of benefits to harms

Additional supporting recommendations

Source	Recommendations
American Geriatrics Society Beers Criteria	1. In patients older than 65, avoid use of benzodiazepines: (short- and intermediate-acting) Alprazolam, Estazolam, Lorazepam, Oxazepam, Temazepam, Triazolam; (long-acting) Clorazepate, Chlordiazepoxide (alone or in combination with amitriptyline or clidinium), Clonazepam, Diazepam, Flurazepam, Quazepam. 2. Avoid use of nonbenzodiazepine benzodiazepine receptor agonist hypnotics (Eszopiclone, Zolpidem, Zaleplon). 3. In patients older than 65 with dementia or cognitive impairment, avoid use of benzodiazepines. 4. In patients with a history of falls or fractures, avoid benzodiazepines (nonbenzodiazepine benzodiazepine receptor agonist hypnotics, Eszopiclone, Zaleplon, Zolpidem) unless safer alternatives are not available.
Choosing Wisely. American Academy of Sleep Medicine	1. In patients older than 65, avoid use of hypnotics as primary therapy for chronic insomnia in adults; instead offer cognitive-behavioral therapy, and reserve medication for adjunctive treatment when necessary adjunctive treatment when necessary.

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Measure 12 – De-intensification of antipsychotics

Proposed de-intensification measure 1

Action: Stop or decrease dose of antipsychotics

Population: Patients older than 65 with dementia

Population exclusions: Patients with schizophrenia, bipolar disorder, major depression, or using antipsychotics (short-term) as antiemetics during chemotherapy

Proposed de-intensification measure 2

Action: Stop or decrease dose of antipsychotics

Population: Patients older than 65

Population exclusions: Patients with schizophrenia, bipolar disorder, major depression, or using antipsychotics (short-term) as antiemetics during chemotherapy

Existing recommendation that motivated the proposed de-intensification measure

Choosing Wisely Recommendation – De-intensification of antipsychotic medications: "Don't use antipsychotics as the first choice to treat behavioral and psychological symptoms of dementia."

- Source: Choosing Wisely
- Steward: American Geriatrics Society (AGS)
- Last Update: April 23, 2015

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

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a. Should short term use and/or documented failure of first line therapy be added to the exclusions?

Potential opportunity for improvement

In VA (estimate)

- [FY2015] In patients 65 years and older:
  - 1.3% (28,669/2,275,669) were prescribed an antipsychotic for >30 days
  - 0.5% (22,214/2,275,669) were prescribed an antipsychotic for >90 days

- [FY15] In patients 65 years and older with dementia:
  - 10.8% (6,869/63,331) were prescribed an antipsychotic for >30 days
  - 7.9% (5,025/63,331) were prescribed an antipsychotic for >90 days

**The above estimates exclude patients with schizophrenia, bipolar disease, and/or major depression; several antipsychotics have FDA approval as add-ons for major depression, so we included that as an exclusion.*

Outside VA

The following is extracted from: Colla CH et al. Choosing wisely: prevalence and correlates of low-value health care services in the United States. J Gen Intern Med. 2015; 30(2): 221-8.

- [2011] Using Medicare administrative claims data for fee-for-service beneficiaries older than 65 with dementia and without a severe mental illness diagnosis:
  - 31.0% (Affected population = 1 million) received antipsychotics

Evidence-base

Rationale

The following information is extracted directly and verbatim from The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients with Dementia.

Estimates suggest that 5%–10% of individuals over age 65 and 30%–40% of individuals over age 85 in the United States have dementia. In addition to cognitive impairments, individuals with dementia often come to clinical attention because of symptoms of a behavioral disturbance (e.g., irritability, agitation, aggression) or psychosis. Treatment of psychotic symptoms and agitation in individuals with dementia has often involved use of antipsychotic medications. In recent years, the risks associated with use of these agents in the older adult population have become apparent.

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Benefits

In clinical trials, the benefits of antipsychotic medications are at best small (Corbett et al. 2014; Kales et al. 2015; see "Review of Supporting Research Evidence" in Appendix A of the APA 2016 guideline) whether assessed through placebo controlled trials, head-to-head comparison trials, or discontinuation trials. Effect sizes of second generation antipsychotics (SGAs) range from nonsignificant to small depending on symptom domain (agitation, psychosis, and overall behavioral/psychological symptoms) and agent (see "Review of Supporting Research Evidence" in Appendix A of the APA guideline). First-generation antipsychotics (FGAs) are deemed not different from SGAs in the management of agitation and overall behavioral/psychological symptoms, but the strength of the evidence for the comparisons is low, and haloperidol is the predominant agent that has been studied.

Harms

The strength of evidence for harms of antipsychotic agents ranges from insufficient to high depending on the specific adverse effect; however, on the whole, there is consistent evidence that antipsychotics are associated with clinically significant adverse effects, including mortality (see section "Review of Supporting Research Evidence" in Appendix A). Harms data are rarely a primary outcome of randomized trials, and there is a paucity of randomized head-to-head comparisons of antipsychotic medications using equivalent doses of drug. In addition, the absolute number of serious adverse events in randomized trials is typically small, and this confounds statistical analysis. For SGAs as a group, meta-analysis of the data from randomized placebo-controlled trials indicates that there is a statistically significant increase in mortality relative to placebo (Schneider et al. 2005).

In terms of decisions about doses of antipsychotic medications, there is strong evidence that SGAs are associated with clinically significant dose-related adverse effects (Maust et al. 2015; see section "Review of Supporting Research Evidence" in Appendix A). Thus, if medications are begun at a low dose and increased gradually depending on clinical response, adverse effects may be minimized. On the other hand, it is possible that harms to the patient or others may occur if the response to treatment is delayed by underdosing of medication, particularly in emergency situations**.**

The American Psychiatric Association recommends: (*Strength of supporting evidence: A=High; B=Moderate; C=Low)*

- That nonemergency antipsychotic medication should only be used for the treatment of agitation or psychosis in patients with dementia when symptoms are severe, are dangerous, and/or cause significant distress to the patient. (1B)
- Reviewing the clinical response to nonpharmacological interventions prior to nonemergency use of an antipsychotic medication to treat agitation or psychosis in patients with dementia. (1C)
- That before nonemergency treatment with an antipsychotic is initiated in patients with dementia, the potential risks and benefits from antipsychotic medication be assessed by the clinician and discussed with the patient (if clinically feasible) as well as with the patient's

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surrogate decision maker (if relevant) with input from family or others involved with the patient. (1C)

- That if a risk/benefit assessment favors the use of an antipsychotic for behavioral/psychological symptoms in patients with dementia, treatment should be initiated at a low dose to be titrated up to the minimum effective dose as tolerated. (1B)
- That if a patient with dementia experiences a clinically significant side effect of antipsychotic treatment, the potential risks and benefits of antipsychotic medication should be reviewed by the clinician to determine if tapering and discontinuing of the medication is indicated. (1C)
- That in patients with dementia with agitation or psychosis, if there is no clinically significant response after a 4-week trial of an adequate dose of an antipsychotic drug, the medication should be tapered and withdrawn. (1B)
- That in a patient who has shown a positive response to treatment, decision making about possible tapering of antipsychotic medication should be accompanied by a discussion with the patient (if clinically feasible) as well as with the patient's surrogate decision maker (if relevant) with input from family or others involved with the patient. The aim of such a discussion is to elicit their preferences and concerns and to review the initial goals, observed benefits and side effects of antipsychotic treatment, and potential risks of continued exposure to antipsychotics, as well as past experience with antipsychotic medication trials and tapering attempts. (1C)
- That in patients with dementia who show adequate response of behavioral/psychological symptoms to treatment with an antipsychotic drug, an attempt to taper and withdraw the drug should be made within 4 months of initiation, unless the patient experienced a recurrence of symptoms with prior attempts at tapering of antipsychotic medication. (1C)
- That in patients with dementia whose antipsychotic medication is being tapered, assessment of symptoms should occur at least monthly during the taper and for at least 4 months after medication discontinuation to identify signs of recurrence and trigger a reassessment of the benefits and risks of antipsychotic treatment. (1C)

Citations provided for the evidence

Corbett A, Burns A, Ballard C. Don't use antipsychotics routinely to treat agitation and aggression in people with dementia. *BMJ*. 2014;349;g6420.

Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. *BMJ*. 2015;350:h369.

Maust DT, Kim HM, Seyfried LS, et al. Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. *JAMA Psychiatry*. 2015;72(5):438-445.

Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA*. 2005;294(15):1934-1943.

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Additional supporting recommendations

Source	Recommendations
Choosing Wisely and AMDA. The Society for Post-Acute and Long-Term Care Medicine	1. Don't prescribe antipsychotic medications for behavioral and psychological symptoms of dementia (BPSD) in individuals with dementia without an assessment for an underlying cause of the behavior.
Choosing Wisely. American Psychiatric Association	1. Don't routinely prescribe antipsychotics as first choice to treat behavioral and psychological symptoms of dementia. 2. Don't routinely prescribe antipsychotic medications as a first-line intervention for insomnia in adults.
American Geriatrics Society Beers Criteria	1. Avoid use of first-generation (conventional) and second-generation (atypical) antipsychotics, except for schizophrenia, bipolar disorder, or in short-term use as antiemetics during chemotherapy. 2. In patients with Parkinson disease, avoid use of all antipsychotics (except aripiprazole, quetiapine, clozapine). 3. In patients with a history of falls or fractures, avoid antipsychotics unless safer alternatives are not available.
Pharmacy Quality Alliance	1. The percentage of individuals 65 years of age and older with dementia who are receiving an antipsychotic medication without evidence of a psychotic disorder or related condition [NQF Measure].
Food and Drug Administration	1. Several atypical antipsychotics have been approved by the Food and Drug Administration as add-ons to treat depression that hasn't responded to antidepressants or other treatments.

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Measure 13 – De-intensification of anticholinergics

Proposed de-intensification measure

Action: Stop or decrease dose of anticholinergics

Population: Patients older than 65 with dementia or cognitive impairment

Existing recommendation that motivated the proposed de-intensification measure

AGS Beers Criteria Recommendation – De-intensification of anticholinergics (to view this specific recommendation in the guideline, see page 12, table 3 in the PDF):

"In patients older than 65 with dementia or cognitive impairment, avoid use of: Anticholinergics (Brompheniramine, Carbinoxamine, Chlorpheniramine, Clemastine, Cyproheptadine, Dexbrompheniramine, Dexchlorpheniramine, Dimenhydrinate, Diphenhydramine [oral], Doxylamine, Hydroxyzine, Meclizine, Triprolidine)."

- Source and Steward: American Geriatrics Society (AGS) Beers Criteria
- Last Update: October 8, 2015
- Quality of Evidence**:** Moderate (Evidence is sufficient to determine risks of adverse outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes limits the strength of evidence)
- Strength of Recommendation: Strong (Benefits clearly outweigh harms, adverse events, and risks, or harms, adverse events, and risks clearly outweigh benefits)

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

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Potential opportunity for improvement

In VA (estimate)

- [FY2015] 15.2% (11,162/73,382) of patients older than 65, with a diagnosis of dementia, were prescribed an anticholinergic agent.

Outside VA

The following is extracted from: Kachru N et al. Potentially inappropriate anticholinergic medication use in older adults with dementia. J Am Pharm Assoc. 2015; 55(6): 603-12.

- [2010] In a retrospective, cross-sectional study of adults 65 years and older with dementia from the Medical Expenditure Panel Survey data:
    - 26.95% (1,002,000/3,780,000) were prescribed potentially inappropriate anticholinergic medications.

Rapid evidence synthesis summary (Review the entire rapid evidence synthesis report.)

Why is this important?

- The American Geriatrics Society Beers Criteria for Potentially Inappropriate Medical Use in Older Adults strongly recommends avoiding use of anticholinergic drugs in older adults with dementia or cognitive impairment because of the potential for adverse effects on cognition.
- Nearly a quarter of older adults with dementia currently receive at least one anticholinergic medication.

What is the association between anticholinergics and risk of cognitive impairment when used in older adults?

- The Beers Criteria cite three systematic reviews and five observational studies regarding the use of anticholinergics. The systematic reviews describe a dearth of evidence related to the adverse effects of anticholinergics, although the observational studies suggest a dose-response relationship of anticholinergics with increased risk of hospitalization for cognitive dysfunction or greater cognitive impairment.
- A subsequent systematic review found anticholinergics associated with increased risk of cognitive impairment (3 studies, OR 1.45; 95% CI 1.16-1.73; I^2=0%).

What are the benefits and harms of discontinuing anticholinergics in older people?

- Another recent systematic review reported conflicting results on effects of discontinuation of anticholinergics on cognitive function, with two observational studies reporting improved cognitive performance after discontinuation and two trials reporting no differences.

What are the implications of our findings?

- Anticholinergic drugs are associated with increased risk of cognitive impairment in older persons, although evidence for this association is somewhat weak.

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- Evidence on effects of anticholinergic de-intensification or discontinuation is inconsistent, with some cohort studies finding improvement in cognitive function upon discontinuation of anticholinergics.

Additional supporting recommendations

Source	Recommendations
American Geriatrics Society Beers Criteria	1. In men older than 65 with lower urinary tract symptoms and/or benign prostatic hyperplasia, avoid use of strongly anticholinergic drugs (except antimuscarinics for urinary incontinence). 2. In patients older than 65, avoid use of anticholinergic drugs with other anticholinergic drugs; minimize the number of anticholinergic drugs prescribed.

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Measure 14 – De-intensification of skeletal muscle relaxants

Proposed de-intensification measure

Action: Stop or decrease the dose of skeletal muscle relaxants

Population: Patients older than 65

Existing recommendation that motivated the proposed de-intensification measure

AGS Beers Criteria Recommendation – De-intensification of skeletal muscle relaxants (to view this specific recommendation in the guideline, see page 10, table 2 in the PDF):
"In patients older than 65, avoid use of skeletal muscle relaxants (Carisoprodol, Chlorzoxazone, Cyclobenzaprine, Metaxalone, Methocarbamol, Orphenadrine)."

- Source and Steward: American Geriatrics Society (AGS) Beers Criteria
- Last Update: October 8, 2015
- Quality of Evidence: Moderate (Evidence is sufficient to determine risks of adverse outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes limits the strength of evidence)
- Strength of Recommendation: Strong (Benefits clearly outweigh harms, adverse events, and risks, or harms, adverse events, and risks clearly outweigh benefits)

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

Potential opportunity for improvement

In VA (estimate)

1. [FY15] 5.6% (154,615/2,768,500) of patients older than 65 were prescribed a skeletal muscle relaxant

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Outside VA

1. Davidoff AJ, Miller GE, Sarpong EM, Yang E, Brandt N, Fick DM. Prevalence of potentially inappropriate medication use in older adults using the 2012 Beers criteria. J Am Geriatr Soc. 2015; 63(3): 486-500.
    - [2009-2010] In a sample of community-dwelling adults aged 65 and older (N = 18,475) from the Medical Expenditure Panel Survey data:
        - 3.3% received a potentially inappropriate skeletal muscle relaxant prescription.

Rapid evidence synthesis summary (Review the entire rapid evidence synthesis report.)

Why is this important?

- The American Geriatrics Society Beers Criteria for Potentially Inappropriate Medical Use in Older Adults strongly recommends avoiding use of skeletal muscle relaxants in older adults because of their potential for anticholinergic adverse effects, sedation, and increased risk of injury.
- Approximately 15% of the 2 million people who use skeletal muscle relaxants annually are older adults, suggesting a potential target for de-intensification.

What is the association between skeletal muscle relaxants and risk of injury and mortality when used in older adults?

- In two studies cited by the Beers Criteria, skeletal muscle relaxants (primarily cyclobenzaprine and methocarbamol) were associated with increased risk of injuries (OR range, 1.32 to 1.35) in older adults (mean age 75 years) when prescribed for various indications.
- Skeletal muscle relaxants are associated with increased risk of emergency department care for falls and fractures within 1 year of new use in older veterans when they are prescribed specifically for chronic pain or for various indications (OR range, 1.81 to 2.20). New use was associated with increased risk of hospitalization for falls and fractures in older veterans when prescribed for various indications.
- Studies have not shown an association between new use of skeletal muscle relaxants in older adults and increased risk of mortality.

What are the benefits and harms of discontinuing skeletal muscle relaxants versus continuing them in older adults?

- We found no studies evaluating the effects of discontinuing skeletal muscle relaxants in older adults.

What are the implications of our findings?

- Skeletal muscle relaxants are associated with increased risk of injury in older adults.
- Alternative pharmacological and nonpharmacological treatments and approaches for management of muscular conditions and spasticity are available and may provide a superior balance of benefits to harms.

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Additional supporting recommendations

Source	Recommendations
	None

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Measure 15 – De-intensification of antidepressants

Proposed de-intensification measure

Action: Stop or decrease dose of single or combined antidepressants (tricyclics and paroxetine)

Population: Patients older than 65

Existing recommendation that motivated the proposed de-intensification measure

AGS Beers Criteria Recommendation - De-intensification of antidepressants (to view this specific recommendation in the guideline, see page 7, table 2 in the PDF):

"In patients older than 65, avoid use of single or combined antidepressants (Amitriptyline, Amoxapine, Clomipramine, Desipramine, Doxepin (>6 mg/d), Imipramine, Nortriptyline, Paroxetine, Protriptyline, Trimipramine)"

- Source and Steward: American Geriatrics Society Beers Criteria (AGS)
- Last Update: October 8, 2015
- Quality of Evidence: High (Evidence includes consistent results from well- designed, well-conducted studies in representative populations that directly assess effects on health outcomes)
- Strength of Recommendation: Strong (Benefits clearly outweigh harms, adverse events, and risks, or harms, adverse events, and risks clearly outweigh benefits)

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

   Choosing Wisely, NICE do-not-do list, USPSTF, ACP, AGS, AAFP, VA, NQF, and other relevant

2. Do you agree with the description of the action?

   Information derived during Step 1 can be found in the following booklet section(s):

3. Do you agree with the population, including exclusions?

   Information derived during Step 2a can be found in the following booklet section(s):

Potential opportunity for improvement

In VA (estimate)

- [FY2015] 3.6% (99,157/2,764,344) of patients older than 65 were prescribed one of the

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following antidepressants: Amitriptyline, Amoxapine, Clomipramine, Desipramine, Doxepin (>6 mg/d), Imipramine, Nortriptyline, Paroxetine, Protriptyline, Trimipramine

Outside VA

The following is extracted from: Maust DT, et al. National Trends in Antidepressant, Benzodiazepine, and Other Sedative-Hypnotic Treatment of Older Adults in Psychiatric and Primary Care. J Clin Psychiatry. 2017; 78(4): e363-e371.

- [2010-2012] Using data from the National Ambulatory Medical Care Survey:
  - Of patients 65 years or older who were seen by a primary care provider (N=9,547):
    - 12.3% were prescribed an antidepressant. Of these patients:
      - 13.1% were prescribed a TCA/MAOI (TCA: amitriptyline, amoxapine, clomipramine, desipramine, doxepin (>6 mg/d), imipramine, nortriptyline, protriptyline, trimipramine; MAOI: isocarboxazid, pargyline, phenelzine, selegiline, tranylcypromine)

Rapid evidence synthesis summary (Review the entire rapid evidence synthesis report.)

Why is this important?

- The proportion of older adults using antidepressant medications has risen dramatically over the past 25 years, as have hospital admissions for antidepressant-related adverse events.
- The American Geriatrics Society Beers Criteria for Potentially Inappropriate Medical Use in Older Adults strongly recommends against the use of tricyclic antidepressants and the selective serotonin reuptake inhibitor paroxetine due to anticholinergic adverse effects, sedation, and increased risk of orthostatic hypotension.

What is the association between use of tricyclic antidepressants or paroxetine in older adults with depression and risk of mortality, falls, or anticholinergic side effects?

- In a large cohort study cited by the Beers Criteria, both tricyclic antidepressants (TCAs) (adjusted HR 1.16; 95% CI 1.10 to 1.22) and paroxetine (adjusted HR 1.24; 95% 1.14 to 1.35 were associated with increased risk of mortality versus nonuse. A more recent study, not limited to older adults, found excess mortality with TCA use, but not with paroxetine.
- Results from the cohort study and two other systematic reviews were consistent in finding an increased risk of falls and fracture with TCAs and paroxetine.
- Evidence on an association between use of TCAs and paroxetine and anticholinergic effects such as sedation or cognitive dysfunction is limited. Anticholinergic adverse effects such as sedation, dry mouth, and urinary retention are commonly observed in research studies and in clinical practice.

What are the benefits and harms of discontinuing tricyclic antidepressants or paroxetine versus continuing them in older people?

- There is limited evidence about the risks and benefits of discontinuation. One study showed that selective serotonin reuptake inhibitor (SSRI) discontinuation (including

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paroxetine) may increase risk of depressive symptoms in people with dementia, with no change in risk of mortality or falls.
- We found no direct evidence on the effect of TCA discontinuation in older adults.

What are the implications of our findings?

- Evidence shows TCA and paroxetine use increases risk of falls and fracture and may increase mortality risk; anticholinergic side effects are commonly reported in clinical practice.
- Alternative antidepressants that are associated with fewer anticholinergic adverse effects are available for use in older adults.

Additional supporting recommendations

Source	Recommendations
American Psychiatric Association	1. SSRIs, SNRIs, and other antidepressants should be considered over MAOIs or TCAs MAOI = monoamine oxidase inhibitors; SNRI = serotonin and norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant

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Measures related to Testosterone or Estrogen/Progestin Prescribing

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Measure 16 – De-intensification of testosterone therapy

Proposed de-intensification measure 1

Action: Stop testosterone therapy

Population: Men with erectile dysfunction (ED) who have normal testosterone levels prior to testosterone initiation

Proposed de-intensification measure 2

Action: Stop testosterone and recheck testosterone levels within 3 months

Population: Men with ED on testosterone

Existing recommendation that motivated the proposed de-intensification measure

Choosing Wisely – De-intensification of testosterone therapy: "Don't prescribe testosterone to men with erectile dysfunction who have normal testosterone levels."

- Source: Choosing Wisely
- Steward: The American Urological Association
- Last Update: May 26, 2017

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

Information derived during Step 2b can be found in the following booklet section(s):

2. Do you agree with the description of the action?

Information derived during Step 2c can be found in the following booklet section(s):

3. Do you agree with the population, including exclusions?

Potential opportunity for improvement

In VA (estimate)

- [FY2015] Of patients prescribed testosterone:
  - 25% (19,360/77,033) had a diagnosis of ED

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- [FY2015] Of patients receiving a new testosterone prescription (i.e., initiated testosterone therapy):
    - 40% (4,558/11,411) had 1 or more tests for testosterone level in the previous year

- [FY2015] Of patients prescribed testosterone and having testing:
    - 85% (3,890/4,558) had at least one measurement of low testosterone (<300 ng/dL or <3 ng/mL)

The following is extracted from: Jasuja GK, et al. Ascertainment of Testosterone Prescribing Practices in the VA. Med Care. 2015; 53(9): 746-52.

- [FY2009-2012] In a cross-sectional study of all outpatient clinics within Veterans Affairs:
    - 1.7% (N=111,631) of men received a new testosterone prescription (i.e., initiated testosterone therapy) in the 4-year study period. Of these men:
        - Only 3.1% had:
            - 2 or more low (total or free) testosterone levels in the morning AND
            - LH and/or FSH level measured AND
            - No contraindications to testosterone therapy
        - 16.5% did not have their testosterone level checked at all

The following is extracted from: Jasuja GK, et al. Patterns of testosterone prescription overuse. Curr Opin Endocrinol Diabetes Obes. 2017; 24(3): 240-245.

- [2016] Systematic review summarizing the recent trends in testosterone prescribing and appropriateness of prescribing guidelines
    - 1.5% (69,645/4,523,139) of male patients receiving outpatient medications at the VA were prescribed testosterone

Outside VA

The following is extracted from: Jasuja GK, et al. Patterns of testosterone prescription overuse. Curr Opin Endocrinol Diabetes Obes. 2017; 24(3): 240-245.

- [2011] Systematic review summarizing the recent trends in testosterone prescribing and appropriateness of prescribing guidelines. In U.S.:
    - Of patients initiating testosterone:
        - 40% did not have a baseline testosterone test
        - 50% had documentation of only 1 test
        - Therefore, only 10% had two or more tests before starting
    - 73.2% of newly tested testosterone users had normal testosterone levels (implying that most of the testing was for screening rather than workup of symptoms)
    - 9% of cases with normal or high testosterone levels received testosterone treatment

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Rapid evidence synthesis summary (Review the entire rapid evidence synthesis report.)

Why is this important?

- Erectile dysfunction (ED) can be associated with lower satisfaction in relationships, lower self-esteem, and poorer quality of life.
- Testosterone deficiency is associated with ED. However, the benefits and harms of treatment with testosterone for ED in men with normal serum testosterone levels are uncertain.

What are the benefits and harms of treatment with testosterone for erectile dysfunction in men with a normal serum testosterone level?

- Benefits: No clear benefit for improving erectile function.
- Harms: Potential harms include polycythemia, venous thromboembolism, myocardial infarction, stroke, edema, hepatotoxicity, sleep apnea, prostate enlargement, and promotion of prostate cancer.

What are the benefits and harms of de-intensification of testosterone treatment for erectile dysfunction in men with normal serum testosterone levels?

- No study evaluated the benefits or harms of de-intensification of testosterone treatment for erectile dysfunction in men with normal serum testosterone levels**.**

What are the implications of our findings?

- There is no clear evidence that testosterone therapy improves erectile function in men with ED and normal testosterone levels. Testosterone therapy is associated with many potential adverse effects.

Additional supporting recommendations

Source	Recommendations
American Geriatrics Society Beers Criteria	1. In patients older than 65, avoid use of androgens: Methyltestosterone, Testosterone unless indicated for confirmed hypogonadism with clinical symptoms.
Choosing Wisely. American Association of Clinical Endocrinologists and the Endocrine Society	1. Don’t prescribe testosterone therapy unless there is biochemical evidence of testosterone deficiency.

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Measure 17 – De-intensification of estrogen and progestin

Proposed de-intensification measure

Action: Stop estrogen or combined estrogen/progestin therapy

Population: Women on hormonal therapy who are over age 60 or more than 10 years after menopause

Existing recommendation that motivated the proposed de-intensification measure

USPSTF Recommendation– De-intensification of estrogen and progestin: "The USPSTF recommends against the use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women."

- Source and Steward: U.S. Preventive Services Task Force (USPSTF)
- Last Update: January 1, 2013
- Level of Evidence: Grade D (The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.)

See all additional supporting recommendations.

Questions to consider

Please consider the following questions and enter your thoughts in the fields.

1. Do you agree that the topic/measure is valid and that there is an opportunity for improvement?

2. Do you agree with the description of the action?

3. Do you agree with the population, including exclusions?

    a. Should there be an exclusion for women on intravaginal therapy?

Potential opportunity for improvement

In VA (estimate)

- [FY2015] 1.8% (1,863/103,137) of female patients, 60 years and older, were prescribed combined estrogen and progestin

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Outside VA

The following is extracted from: Jirón M, et al. Trends in Prevalence and Determinants of Potentially Inappropriate Prescribing in the US 2007 – 2012. J Am Geriatr Soc. 2016 ;64(4): 788-797.

- [2007-2012] In a retrospective cohort study of a random national sample of fee-for-service Medicare beneficiaries:
  - 2.6% of patients were prescribed an estrogen with or without progestins. This was the third most common medication potentially inappropriately prescribed.

The following is extracted from: Davidoff AJ, et al. Prevalence of potentially inappropriate medication use in older adults using the 2012 Beers criteria. J Am Geriatr Soc. 2015; 63(3): 486-500.

- [2009-2010] In a sample of community-dwelling adults aged 65 and older (N = 18,475) from the Medical Expenditure Panel Survey data:
  - 3.2% received a potentially inappropriate prescription for estrogen with or without progestin.

Rapid evidence synthesis summary (Review the entire rapid evidence synthesis report.)

Why is this important?

- Menopause, which occurs when the ovaries cease production of estrogen, typically occurs at age 51; nearly 40 million U.S. women are past the average age of menopause.
- Menopause is associated with symptoms such as hot flashes, mood changes, and weight gain, and with increased risk of conditions such as cardiovascular disease and osteoporosis.
- Hormone replacement therapy (HRT) with estrogen and progestin (estrogen only in women without a uterus) can be used to treat symptoms of menopause and potentially decrease risk of associated conditions.
- The prevalence of HRT has declined in the United States from 44% in 1998–1994 to 4.7% in 2010.
- The U.S. Preventive Services Task Force updated draft statement recommends against the use of HRT for the prevention of chronic conditions in postmenopausal women (D recommendation). The recommendations and related evidence review do not address HRT to treat menopausal symptoms.
- Discontinuation of HRT is postmenopausal women is a potential target for de-intensification.

What are the benefits and harms of hormone replacement therapy for prevention of chronic conditions in postmenopausal women?

- HRT is associated with decreased risk of colorectal cancer (33 fewer cases per 10,000 women over 5.6 years [95% CI, 8 to 52 fewer]), diabetes (77 fewer cases per 10,000 women over 5.6 years [95% CI, 21 to 206 fewer]), and fractures (222 fewer cases per 10,000 women over 5.0 years [95% CI, 67 to 354 fewer]) versus placebo.

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- HRT is associated with increased risk of invasive breast cancer (52 more cases per 10,000 women over 5.6 years [95% CI, 6 to 107 more]), coronary heart disease (41 more cases per 10,000 women over 5.1 years [95% CI, 0 to 93 more]), probable dementia (88 more cases per 10,000 women over 4 years [95% CI, 15 to 213 more]), gallbladder disease (259 more cases per 10,000 women over 5.6 years [95% CI, 167 to 366 more]), stroke (53 more cases per 10,000 women over 5.6 years [95% CI, 12 to 104 more]), urinary incontinence (876 more cases per 10,000 women over 1 year [95% CI, 606 to 1,168 more]), and venous thromboembolism (120 more cases per 10,000 women over 5.6 years [95% CI, 68 to 185 more]) versus placebo.
- There is no demonstrated protective effect of HRT on risk of coronary heart disease or cognitive impairment.
- Limited evidence indicates that estrogen alone is associated with lower risk of myocardial infarction in younger (ages 50 to 59 years) women, but did not decrease risk of total coronary heart disease events. Estrogen alone was associated with increased risk of colorectal cancer in older (ages 70 to 79 years) women.
- Subgroup analyses of results from one trial provide conflicting findings on the timing of HRT initiation after menopause and association with benefits and harms.

What are the benefits and harms of de-intensification of postmenopausal hormone therapy used to prevent chronic conditions?

- No evidence was found.

What are the implications of our findings?

- The USPSTF concluded that potential benefits of postmenopausal HRT are outweighed by potential harms.
- Discontinuation of postmenopausal HRT is a potential target for de-intensification efforts.

Additional supporting recommendations

Source	Recommendations
U.S. Preventive Services Task Force	1. The USPSTF recommends against the use of estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy.
American Geriatrics Society Beers Criteria	1. In women older than 65 with urinary incontinence, avoid use of: Estrogen oral and transdermal (excludes intravaginal estrogen) 2. In patients older than 65, avoid use of estrogens (with or without progestins) with administration by oral and topical patch; or administration by vaginal cream or tablets [acceptable to use low-dose intravaginal estrogen for management of dyspareunia, lower urinary tract infections, and other vaginal symptoms].

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American College of Physicians	1. Recommends against using menopausal estrogen therapy or menopausal estrogen plus progestogen therapy or raloxifene for the treatment of osteoporosis in women. (Grade: strong recommendation; moderate-quality evidence).

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Rapid Evidence Synthesis Reports

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DXA Screening: Rapid Evidence Summary

This report was prepared by the Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University, under Contract No. VA268-16-Q-0140, in support of an HSR&D research study focused on Identifying, Measuring, and Facilitating Opportunities for De-Intensification of Medical Services.

KEY MESSAGES

Why is this important?

- Osteoporosis affects more than 10 million older adults in the United States and is associated with reduced quality of life, chronic pain, loss of independence, hospitalization, and mortality.
- Screening using dual-energy x-ray absorptiometry (DXA) can identify those at risk of osteoporotic fracture, and multiple pharmacologic and non-pharmacologic interventions have been shown to reduce fracture risk in older patients with low bone mass. However, screening also involves opportunity costs, exposure to ionizing radiation, and the downstream harms of subsequent intervention, which will vary by treatment.
- The U.S. Preventive Services Task Force recommends screening in women older than 65 years of age and in women younger than 65 at increased risk of fracture and found insufficient evidence to support recommendations on screening in men. The USPSTF and guidance from the Choosing Wisely campaign recommend screening no more frequently than once every 2 years.[1] However, some data suggest that clinicians screen more frequently or in populations in whom screening is not recommended.

What are the benefits and harms of osteoporosis screening in women younger than 65 years of age or men younger than 70 years of age not at increased risk for osteoporosis?

- Convincing evidence supports the utility of DXA screening to estimate fracture risk, and the harms of treatment for osteoporosis are outweighed by the benefits.
- Based on the number needed to screen, the USPSTF selected the 10-year fracture risk of a 65-year-old white woman (9.3%) as determined by a risk screening instrument such as FRAX® as the threshold for screening.
- The Choosing Wisely campaign of the American College of Family Physicians largely adopted the USPSTF recommendations but also recommended DXA screening of men aged 70 years or older and men aged 50–69 years with risk factors, based on an assumption of similar risk and effectiveness in these groups.

What are the benefits and harms of osteoporosis screening more frequently than once every 2 years?

- The USPSTF suggests not screening more frequently than once every 2 years and the Choosing Wisely recommendation of the American College of Rheumatology states, "Don't routinely repeat DEXA scans more often than once every two years." No studies have directly compared the benefits and harms of different screening intervals; however, the USPSTF recommendation notes that due to limitations in the precision of testing, a minimum of 2 years may be needed to reliably measure a change in bone mineral density.

What are the benefits and harms of de-intensification of osteoporosis screening?

- No study evaluated benefits and harms of de-intensification of osteoporosis screening.

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Background

Osteoporosis, a condition characterized by low bone mineral density (BMD) resulting in increased fracture risk, is estimated to affect more than 10 million adults older than 50 years in the United States; more than 43 million have low bone mass but not so low as to meet criteria for osteoporosis (osteopenia).[2] Osteoporosis is more common in women than men and in White persons than other ethnic groups, and prevalence increases with age. Half of women with osteoporosis will have an osteoporosis-related fracture in their lifetime.[3] In addition, osteoporosis and fractures are associated with reduced quality of life, disability and loss of independence, chronic pain, and increased mortality.

Screening using dual-energy x-ray absorptiometry (DXA or DEXA) of the hip and lumbar spine can identity those at high risk of osteoporotic fractures, and multiple effective treatments exist to reduce the risk of fracture in women, including bisphosphonates, parathyroid hormones, raloxifene, and estrogen. The U.S. Preventive Services Task Force (USPSTF) recommends screening in women aged 65 years or older and in women younger than 65 who are at increased risk of fracture. The USPSTF found insufficient evidence to support recommendations on screening in men. The USPSTF and guidance from the Choosing Wisely campaign recommend screening no more frequently than once every 2 years.[1] However, some data suggest that clinicians screen more frequently or in populations in whom screening is not recommended.[4-6] An update to the USPSTF osteoporotic fractures screening topic is in progress.[7]

This report summarizes recommendations from the USPSTF and Choosing Wisely on osteoporosis screening, focusing on aspects relevant to de-intensification of screening in populations in whom it is not currently recommended and de-intensification of screening frequency.

Current Guidelines

Several current clinical practice guidelines on screening for osteoporosis are summarized in **Table 1**. The USPSTF recommends screening women ≥65 years and women younger than 65 years at increased risk of fracture (Grade B recommendation).[1] The recommendations were based on the higher prevalence of osteoporosis in women meeting these criteria and evidence on effectiveness of treatments. For men, the USPSTF found insufficient evidence to recommend for or against DXA screening, due to the lower prevalence of osteoporosis in men and limited evidence on effectiveness of treatments in men (Grade I recommendation). The USPSTF does not recommend screening more frequently than once every 2 years, based on the imprecision of BMD testing and the estimated duration required to reliably measure a change in BMD, as well as limited evidence that subsequent BMD measurements do not improve the predictive utility for fractures compared to the initial measurement. Although American Association of Family Physicians[8] and American College of Rheumatology[9] Choosing Wisely guidance recommends consideration of screening in men over 70 years of age, no guideline recommends screening men younger than 70 years of age without risk factors.

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Table 1. Summary of current guidelines on osteoporosis screening

Organization	Recommendation
U.S. Preventive Services Task Force[1]	Screen women aged ≥65 years without previous fractures or risk factors, as well as women younger than 65 years whose fracture risk exceeds that of a 65-year-old white woman with no additional risk factors (corresponding to a 10-year fracture risk of 9.3%) **[B recommendation]** There is insufficient evidence to recommend for or against screening in men. **[I recommendation]** Screening should not be performed more than once every 2 years. **[ungraded]**
American Academy of Family Physicians (Choosing Wisely)[8]	Do not use dual-energy x-ray absorptiometry (DEXA) screening for osteoporosis in women younger than 65 or men younger than 70 with no risk factors. Screen women aged ≥65 years; have a clinical conversation about screening for men ≥70 years, as well as for men aged 50-69 years and women aged <65 years with risk factors for bone loss (previous fracture, rheumatoid arthritis, having a parent with a hip fracture, smoking, heavy drinking, low body weight, very low vitamin D levels, or use of corticosteroids for ≥3 months).
American College of Rheumatology (Choosing Wisely)[9]	Do not routinely repeat DEXA scans more often than once every two years. Screen women ≥65 years and post-menopausal women <65 years with risk factors; screen men aged ≥70 years and men aged 50-69 years with risk factors.
National Osteoporosis Foundation[10]	Screen women aged ≥65 years and post-menopausal women aged <65 years with risk factors; screen men aged ≥70 years and men aged 50-69 years with risk factors.
American College of Physicians[11]	Clinician assessment of older men for osteoporosis risk factors and DEXA screening of men who are candidates for osteoporosis drug therapy.

Methods

Topic Selection and Scope Development

Key Questions

We reviewed evidence relevant to the following Key Questions.

Key Question 1: What are the benefits and harms of osteoporosis screening in women younger than 65 years of age or men younger than 70 years of age not at increased risk for osteoporosis?

Key Question 2: What are the benefits and harms of osteoporosis screening more frequently than once every 2 years?

Key Question 3: What are the benefits and harms of de-intensification of osteoporosis screening?

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Eligibility Criteria

- Population: Asymptomatic adults without previous low-trauma fractures, endocrinopathies, or steroid use
- Intervention: Dual-energy x-ray absorptiometry; de-intensification of screening
- Comparators: No screening or another risk assessment/testing method; more intensive screening
- Outcomes: Test characteristics, fracture risk prediction, harms

Searching and Study Selection

We focused on the recommendations and evidence presented in the USPSTF 2011 recommendation on screening and treatment of osteoporosis,[1] as well as the Choosing Wisely recommendations related to DXA screening from the American College of Rheumatology and the American Academy of Family Physicians pertaining to potential de-intensification of screening in women younger than 65 years of age, men younger than 70 years of age, and persons undergoing screening more frequently than once every 2 years.[8,9] In addition to these guidelines, we searched Ovid MEDLINE® (through June 2017) and hand-searched reference lists of relevant studies for new evidence pertinent to osteoporosis screening in the United States.

Results

Key Question 1. What are the benefits and harms of osteoporosis screening in women younger than 65 years of age or men younger than 70 years of age not at increased risk for osteoporosis?

The USPSTF recommendations are based on a 2010 evidence review on the benefits and harms of screening and treatment for osteoporosis.[12] While no controlled studies evaluated the effects of screening for osteoporosis versus no screening on fractures or fracture-related morbidity and mortality, the USPTF found convincing evidence to support the predictive utility of DXA screening to identify those at risk of osteoporotic fractures and to support the effectiveness of pharmacologic treatments in reducing fracture risk in women. The USPSTF concluded that the benefits of common osteoporosis treatments (bisphosphonates and estrogen or selective estrogen receptor modulators) for women outweigh the harms. The USPSTF found insufficient evidence to determine benefits of treatment for osteoporosis in men, due to lack of evidence.

The USPSTF estimated a number needed to screen of 278 to prevent one clinical fracture in "average-risk" women 55 to 59 years of age, 187 in women 60 to 64 years of age, 103 in women 65 to 69 years of age, 61 in women 70 to 74 years of age, and 43 in women 75 to 79 years of age. As individual fracture risk among women varies, the USPSTF selected the 10-year fracture risk of a 65-year old white woman (9.3%) as determined by a risk screening instrument such as FRAX® as the threshold for screening. The rationale for this cut-off was based on the precipitous drop in the number needed to screen between women aged 65 to 69 years and women aged 70-74 years.

The Choosing Wisely recommendation of the American Academy of Family Physicians regarding DXA screening ("Don't use DEXA screening for osteoporosis in women younger than 65 or men younger than 70 with no risk factors"[8]) is consistent with that of the USPSTF for women, but adopts the recommendation of the National Osteoporosis Foundation for men (i.e.,

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DXA screening of men aged ≥70 years and men aged 50-69 years with risk factors). These recommendations were not based on additional evidence, but based on the assumption that treatments for osteoporosis are similarly effective in women and men and the age at which osteoporosis risk in men is similar to a 65 year old woman.

Key Question 2. What are the benefits and harms of osteoporosis screening more frequently than once every 2 years?

The USPSTF suggests not screening more frequently than once every 2 years and the Choosing Wisely recommendation of the American College of Rheumatology states, "Don't routinely repeat DXA scans more often than once every two years."[9] No studies have directly compared the benefits and harms of different screening intervals. However, the USPSTF recommendation notes that due to limitations in the precision of testing, a minimum of 2 years may be needed to reliably measure a change in BMD. A prospective study of over 4,000 women found that neither repeated BMD measurement nor change in BMD after 8 years was more predictive of subsequent fracture risk compared with the original measurement, indicating that long rescreening intervals may be necessary to improve fracture risk prediction. Other potential harms are that more frequent screening could expose patients to unnecessary radiation (albeit small amounts) and potentially unnecessary changes in medication management, but these outcomes were not evaluated in the USPSTF review.

Key Question 3. What are the benefits and harms of de-intensification of osteoporosis screening?

No study evaluated benefits and harms of de-intensification of osteoporosis screening (defined as discontinuation of screening in women and men in whom it is not currently recommended, or decreased frequency of screening in persons undergoing screening more frequently than once every 2 years).

Conclusions

The USPSTF Force recommends DXA screening for women aged 65 years or older and for younger women with a 10-year fracture risk of ≥9.3%, with an estimated number needed to screen to prevent one clinical fracture of 103. Based on Choosing Wisely guidance from the American Academy of Family Physicians and the American College of Rheumatology, men ≥70 years of age or younger than 65 with increased risk of fracture may also be considered for osteoporosis screening, based on similar prevalence of osteoporosis and assuming similar benefits of treatment as in women. Screening in younger women and men with no risk factors is substantially less efficient, given the marked decrease in osteoporosis prevalence and estimated benefits, supporting de-intensification of screening in these populations. De-intensification of screening more frequently than once every 2 years is supported by the imprecision of BMD measurements (requiring longer intervals to detect true changes) and some evidence suggesting that substantially longer intervals may be required to improve fracture prediction, and might reduce risks related to exposure to frequent testing.

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Screening for Cervical Cancer: Rapid Evidence Summary

This report was prepared by the Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University, under Contract No. VA268-16-Q-0140, in support of an HSR&D research study focused on Identifying, Measuring, and Facilitating Opportunities for De-Intensification of Medical Services.

KEY MESSAGES

Why is this important?

- Various factors can affect the relative benefits and harms of cervical cancer screening in different subgroups and at different intervals. Therefore, understanding these relative benefits and risks is important for appropriate screening.

What are the benefits and harms of screening for cervical cancer?

(5) Versus no screening in women younger than 21 years of age?

Benefits: No benefit in life-years, cancer cases, cytological abnormalities detected, or cervical cancer deaths

Harms: Increased false-positive test results, colposcopies, cervical biopsies, pain, bleeding, discharge, and adverse outcomes in future pregnancies

(6) Annually in average-risk women aged 30 to 65 years versus less frequently?

Benefits: Slightly fewer cancer cases and cervical cancer deaths

Harms: Increased false-positive test results, colposcopies, cervical biopsies, pain, bleeding, discharge, and adverse outcomes in future pregnancies

(7) Versus no screening in low-risk women aged 65 years or older?

Benefits: Slightly fewer cancer cases and cervical cancer deaths

Harms: Increased false-positive test results, colposcopies, cervical biopsies, pain, bleeding, discharge

(8) Versus no screening in women who have had a total hysterectomy for benign disease?

Benefits: No benefit in detection of cytological abnormalities or vaginal cancer

Harms: Possible invasive procedures and treatment due to positive test results

What are the benefits and harms of de-intensification of cervical cancer screening?

- No study evaluated benefits and harms of de-intensification of cervical cancer screening (discontinuation of screening in women younger than 21 or older than 65 years of age or in women who have had a total hysterectomy, or decreasing from annual to less frequent screening in women 30 to 65 years of age).

What are the implications of our findings?

- Current guideline recommendations are in agreement that the harms outweigh the benefits of screening for cervical cancer: (1) before age 21; (2) more frequently than every 3 to 5 years; (3) after age 65; and (4) after total hysterectomy for benign disease.

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Background

Since its introduction in the middle of the 20th century, cervical cancer screening has proven to be extremely effective in reducing mortality from cervical cancer, previously the most frequent cause of cancer deaths among women.[1] Between 1975 and 2004, the age-adjusted incidence of and mortality from cervical cancer in the United States decreased by more than 50% and has remained stable through 2014.[2] In 2017, an estimated 12,820 incident cases of cervical cancer and 4,210 cervical cancer deaths will occur in the United States.[3] Historically, cervical cancer screening has been via cervical cytological testing (Papanicolaou [Pap] testing). Persistent cervical infection with certain human papillomavirus (HPV) genotypes is necessary for the development of cervical cancer and "pre-cancerous" cervical intraepithelial neoplasia grade 3 (CIN3);[4] testing for the presence of HPV (in conjunction with cervical cytology) is now an option for screening.

Various factors can affect the balance of benefits and harms of cervical cancer screening for different age groups and screening intervals, including: the age-group prevalence of HPV, the incidence of cervical cancer, screening test characteristics, spontaneous clearance of HPV infection and/or regression of cytologic abnormalities, and adverse consequences due to false-positive test results and invasive procedures. Therefore, to clarify the appropriate age at which to begin screening, the appropriate age at which to end screening, and the optimal screening interval, the U.S. Preventive Services Task Force (USPSTF) commissioned a systematic review and decision analysis to assess relative benefits and risks of various screening strategies and to inform its 2012 recommendations.[5,6] Recommendations from the USPSTF and others recommend against cervical cancer screening in women younger than 21 years of age, low-risk women older than 65 years of age, and women who have had a hysterectomy for benign disease, and recommend screening at 3 or 5 year intervals among women 21 to 65 years of age. However, some reports indicate that screening is being conducted in women in whom it is not recommended, suggesting potential targets for de-intensification. One study found that approximately 60% of women have been screened for cervical cancer by age 21 years;[7] and another found that 53% of women 75 to 79 years of age and 38% of women older than 80 years of age have been recently screened for cervical cancer,[8] though these studies were based on practices prior to the 2012 USPSTF recommendation. Data are limited on changes in cervical cancer screening practices since the publication of the 2012 USPSTF recommendations.[9]

This rapid review summarizes those USPSTF recommendations and those of other guideline groups, as well as the results of a literature scan for more recent evidence relevant to four questions related to appropriate cervical cancer screening (screening in women younger than 21 years of age, screening in women 65 years of age and older, screening in women who have had a total hysterectomy for benign disease, and frequency of screening in women 30 to 65 years of age).

Current Guidelines

Selected current practice guidelines on the ages at which to begin and end cervical cancer screening, screening intervals, and screening for women after total hysterectomy are summarized in Table 1. The USPSTF commissioned a systematic evidence review and a decision analysis modeling study to inform its 2012 recommendations.[6] A consortium of the American Cancer

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Society, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology (ACS/ASCCP/ASCP) also conducted a systematic evidence review for their 2012 recommendations.[10] The recommendations of various other guideline groups are based on one or both of these reviews/recommendations.[9,11-13]

Women younger than 21 years of age: Each guideline group recommends against screening for cervical cancer in women younger than age 21, regardless of the age of onset of sexual activity or other risk factors.

Women aged 30 to 65 years: For women between the ages of 30 and 65 years, each guideline supports the use of either cytology every 3 years *or* HPV co-testing (cytology + HPV testing together) every 5 years. The guidelines differ slightly in the preference they place on these two options. The ACS/ ASCCP/ASCP and the American College of Obstetrics and Gynecology (ACOG) recommend co-testing with HPV and cytology every 5 years as the preferred method, with cytology alone every 3 years as an acceptable alternative. In contrast, the USPSTF, American College of Physicians (ACP), and American Academy of Family Physicians (AAFP) each recommend HPV co-testing every 5 years as an alternative option for women who prefer screening less often than every 3 years with cytology alone. Each guideline notes that screening more frequently than every 3 years with cytology or every 5 years with HPV testing confers little added benefit with large increases in harms.[6,9,10,14] Three guideline groups explicitly recommend against annual screening.[9,10,14]

Women aged 65 and older: All guidelines also agree in recommending against cervical cancer screening for women older than 65 years who have had "adequate" prior negative screening and are not otherwise at high risk. All guidelines use the ACS/ASCCP/ASCP definition of adequate prior screening as 3 consecutive negative cervical cytology results or 2 consecutive negative "co-test" (cytology and HPV testing) results within 10 years before cessation of screening, with the most recent test performed within the past 5 years. For women older than 65 years with a history of CIN2, CIN3, or adenocarcinoma in situ, routine screening should continue for at least 20 years after spontaneous regression or appropriate management of the lesion(s), even if this extends screening past age 65. The recommendations do not address women aged 65 or older who may be at higher risk, such as those exposed to in utero diethylstilbestrol, those infected with HIV, or those who are otherwise immunocompromised.

Women who have had a total hysterectomy for benign disease: All guidelines agree in recommending against continued cervical cancer screening in women who have had a hysterectomy with removal of the cervix and with no history of CIN2, CIN3, or cervical cancer.

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Table 1. Summary of current guidelines on cervical cancer screening

Guideline group	Recommendations
U.S. Preventive Services Task Force (USPSTF), 2012[6]	• Women younger than age 21 years: o Do Not Screen (Grade D recommendation; moderate certainty) • Women aged 21 to 29 years: o Screen with cytology alone every 3 years (Grade A recommendation; high certainty) • Women aged 30 to 65 years: o Screen with cytology every 3 years; or co-testing (cytology/HPV testing) every 5 years for women who prefer screening less often than every 3 years (Grade A recommendation; high certainty) • Women older than 65 years who have had adequate prior screening* and are not high risk: o Do Not Screen (Grade D recommendation; moderate certainty) • Women after hysterectomy with removal of the cervix with no history of high-grade pre-cancer or cervical cancer: o Do Not Screen (Grade D recommendation; high certainty)
American Cancer Society/American Society for Colposcopy and Cervical Pathology/American Society for Clinical Pathology (ACS/ASCCP/ASCP), 2012[10]	• Women younger than age 21 years: o No screening • Women aged 21 to 29 years: o Screen with cytology alone every 3 years • Women aged 30 to 65 years: o HPV and cytology “co-testing” every 5 years (preferred), or o Cytology alone every 3 years (acceptable) • Women older than 65 years with evidence of adequate negative prior screening* and no history of CIN2+ within the last 20 years: o No screening • Women after hysterectomy with removal of the cervix who have no history of CIN2+: □ No screening
American College of Physicians (ACP), 2015[9]	• Women younger than age 21 years at average risk: o No screening • Women aged 21 to 29 years: o Screen with cytology alone every 3 years • Women aged 30 to 65 years: o Screen average-risk women once every 3 years with cytology (without HPV testing) o Do not screen average-risk women with cytology more often than once every 3 years o May use combination of cytology and HPV testing once every 5 years for women who prefer screening less often than every 3 years • Women older than 65 years at average risk and with adequate negative prior screening*: o Stop screening • Women at average risk after hysterectomy with removal of the cervix: □ No screening
American College of Obstetrics and Gynecology (ACOG), 2012[14]	• Women younger than age 21 years: o Screening should begin at 21 years of age, regardless of sexual behaviors and risk factors • Women aged 21 to 29 years: o Screen with cytology alone every 3 years • Women aged 30 to 65 years: o Co-testing with cervical cytology and HPV testing every 5 years, or o Cytology alone every 3 years (alternative) • Women older than 65 years with adequate negative results* and no history of CIN2+: o No screening • Women after hysterectomy with removal of the cervix who have no history of CIN2+: □ No screening

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Guideline group	Recommendations

American College of Preventive Medicine (ACPM), 2016[12]	• Women older than 65 years that are at low risk for cervical cancer and have had negative results from adequate prior screenings*:
	  Don't perform screening
	• Women who have had a total hysterectomy for benign disease and do not have a history of cervical cancer or high-grade cervical lesions:
	  Don't perform screening

American Academy of Family Physicians (AAFP), 2012[13]	• All recommendations identical to those of the USPSTF, above.

*Adequate prior screening is defined as 3 consecutive negative cervical cytology results or 2 consecutive negative "co-test" (cytology and HPV testing) results within 10 years before cessation of screening, with the most recent test performed within the past 5 years. Women aged > 65 years with a history of CIN2, CIN3, or adenocarcinoma in situ should continue routine screening for at least 20 years after spontaneous regression or appropriate management of the lesion(s).
HPV = human papillomavirus; CIN = cervical intraepithelial neoplasia

Key Questions

This rapid review addresses the following five key questions:

Key Question 1: What are the relative benefits and harms of screening for cervical cancer versus no screening ***in women younger than 21 years of age?***

Key Question 2: What are the relative benefits and harms of screening for cervical cancer ***annually versus less frequently in average-risk women aged 30 to 65 years?***

Key Question 3: What are the relative benefits and harms of screening for cervical cancer versus no screening ***in low-risk women aged 65 years or older***?

Key Question 4: What are the relative benefits and harms of screening for cervical cancer versus no screening ***in women who have had a total hysterectomy for benign disease?***

Key Question 5: What are the benefits and harms of de-intensification of screening for cervical cancer (discontinuation of screening in women younger than 21 or older than 65 years of age or in women who have had a total hysterectomy, or decreasing from annual to less frequent screening in women 30 to 65 years of age)?

Methods and Rationale

We reviewed and summarized the 2012 USPSTF systematic review[15] and concurrent decision analysis.[5,16] The decision analysis was used to help clarify the age at which to begin and end screening and the optimal interval for screening.[6] This modeling study was used to complement the systematic review because of limited or absent evidence that directly addressed questions of ages at which to begin and end screening and optimal frequency.[6] They did not update the

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previously reviewed direct evidence on screening after a total hysterectomy for benign disease because the recommendation to discontinue screening in that circumstance is clearly supported.[17]

We also conducted a targeted search of the literature for recent relevant evidence. Our research librarian conducted a search of Ovid MEDLINE® from 2010 through April 25, 2017. This search resulted in 352 potentially relevant citations. After screening abstracts, we reviewed the full text of 10 publications. None of the reviewed papers directly addressed any of the five key questions. The USPSTF is currently updating their recommendations for cervical cancer screening.

Results

Key Question 1: What are the relative benefits and harms of screening for cervical cancer versus no screening ***in women younger than 21 years of age?***

The USPSTF recommendation against screening in women younger than 21 years of age is based on a number of factors. Invasive cervical cancer is rare in women younger than 20 years of age. Although infection with HPV and cytologic abnormalities are common in this age group, CIN 3 is rare.[6,15] Furthermore, infection with HPV and cytological abnormalities (CIN1 and CIN2) are highly likely to regress in young women,[17] and the average time for high-grade pre-cancerous lesions to progress to cervical cancer is estimated to be 10 years.[18] The highest percentage of false-positive test results also occurs in women younger than 21 years of age. Hence, many women in this age group who are screened will have colposcopy and biopsies and will be treated for lesions with a high likelihood of regression.[9] Potential harms are related directly to screening (psychological distress related to positive test results), to evaluation of positive results with colposcopy and biopsy (pain, bleeding, and/or discharge), and to treatments for neoplastic lesions (pain, bleeding, discharge, and/or adverse outcomes in future pregnancies, such as preterm delivery).[6]

Results of the USPSTF decision analysis found screening beginning at age 21 years at an interval of every 3 years to be associated with the best balance of benefits versus harms.[6,16] Screening every 3 years with cytology results in a similar number of life-years compared with screening annually (69,213 vs. 69,247, per 1000 women), but with fewer false-positive tests and half as many colposcopies.[6,16] In contrast, the USPSTF decision analysis found that beginning screening earlier than age 21 years (compared with age 18 years or age 15 years in the models) is associated with no improvement in cervical cancer deaths (1.55 vs. 1.54 vs. 1.54, per 1000 women, respectively), no improvement in cancer cases detected (8.50 vs. 8.45 vs. 8.45, per 1000 women), and no improvement in CIN2/CIN3 detected (80.21 vs. 80.53 vs. 80.55, per 1000 women); with some increase in colposcopies performed (758 vs. 767 vs. 777, per 1000 women) and increase in false positive tests (350 vs. 359 vs. 368, per 1000 women) compared with screening starting at age 21 years.[16]

The USPSTF and other guideline groups conclude that for women younger than age 21 years, regardless of sexual history, there is moderate certainty that the harms of screening outweigh the benefits.

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Key Question 2: What are the relative benefits and harms of screening for cervical cancer ***annually versus less frequently in average-risk women aged 30 to 65 years?***

The USPSTF recommends screening every 3 to 5 years in women 30 to 65 years of age. While the prevalence of infection with high-risk HPV genotypes decreases across the lifespan— from a high of approximately 35% in the teenage years to approximately 6% in women aged 50 to 65 years—the incidence of CIN3 or worse peaks in women aged 25 to 29 and the incidence of cervical cancer peaks among women in their 40s.[15] In general, screening at more frequent intervals results in fewer cancer cases and fewer cancer deaths; but it also results in more false-positive test results, more colposcopies and more biopsies, with the associated potential harms. The USPSTF decision analysis was designed to determine the optimal screening interval by examining the relative balance of these benefits and harms for different screening strategies at various intervals.

Compared with screening every 3 years, the decision analysis found more frequent screening with cytology alone (at 2 or 1 year intervals) to be associated with slightly fewer life-time cervical cancer cases (8.50 vs. 5.80 vs. 2.50, per 1000 women; for 3-yrs, 2-yrs, and 1-yr, respectively) and fewer cancer deaths (1.55 vs. 0.92 vs. 0.32, per 1000 women).[16] However, more frequent screening was also associated with a substantially increased number of false-positive test results (350 vs. 727 vs. 951, per 1000 women) and colposcopies (758 vs. 1488 vs. 1931, per 1000 women).[16]

In a comparison between two strategies: (1) screening with cytology alone every 3 years (beginning at age 21 years); and (2) screening with co-testing (cytology alone every 3 years beginning at age 21 years, followed with cytology and HPV testing every 5 years beginning at age 30 years), the results of the decision analysis showed little difference in life-time cancer cases (8.50 vs. 7.44, per 1000 women, respectively) or cancer deaths (1.55 vs. 1.35, per 1000 women); with modestly fewer false-positive test results (350 vs. 255, per 1000 women) and fewer colposcopies (758 vs. 757, per 1000 women) when using co-testing.[16]

The USPSTF and other guideline groups conclude that screening more frequently than every 3 years with cytology or every 5 years with cytology/HPV co-testing confers little additional benefit with large increases in harms and, therefore, is not recommended.

Key Question 3: What are the relative benefits and harms of screening for cervical cancer versus no screening ***in low-risk women aged 65 years or older***?

The USPSTF recommends against cervical cancer screening in low-risk women 65 years of age or older. The incidence and prevalence of CIN and high-risk HPV infection decrease with age and are lowest in women older than 65 years of age.[15] Furthermore, the incidence of cervical cancer peaks among women in their 40s,[15] and cervical cancer in older women is no more aggressive than in younger women.[6] The decision analysis study modeled the expected benefits and harms of continued screening beyond age 65 years in women who had been screened every 3 years to age 65. Models were constructed for screening ending at various ages in 5-year intervals, from age 70 to age 90.

The USPSTF concluded that screening beyond age 65 confers no substantial benefit but increases harms due to false-positive results and increased numbers of colposcopies and cervical

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biopsies.[6,16] For example, compared with ending screening at age 65, screening at 3-year intervals until age 70 or age 80 results in slightly fewer life-time cervical cancer cases (11 vs. 10.3 vs. 8.8, per 1000 women; for ages 65, 70 and 80, respectively) and fewer cancer deaths (2.5 vs. 2.03 vs. 1.65, per 1000 women).[16] However, screening beyond age 65 also results in a substantial increased number of false-positive test results (273 vs. 300 vs. 334, per 1000 women; for ages 65, 70 and 80, respectively) and colposcopies (590 vs. 649 vs. 723, per 1000 women).[16] Importantly, these results apply only to women who have had prior screening until age 65. For women older than 65 who have had no previous screening, the models indicate that screening every 2 to 5 years and ending at age 70 represents the best balance between benefits and harms.[6,16]

The USPSTF and other guideline groups conclude that women older than 65 years of age with an adequate prior screening history should not be screened for cervical cancer. Adequate prior screening is defined as 3 consecutive negative cervical cytology results or 2 consecutive negative "co-test" (cytology and HPV testing) results within 10 years before cessation of screening, with the most recent test performed within the past 5 years.[10]

Key Question 4: What are the relative benefits and harms of screening for cervical cancer versus no screening ***in women who have had a total hysterectomy for benign disease?***

Women who have had a hysterectomy with removal of the cervix, with no history of high-grade CIN or cervical cancer, are not at risk for cervical cancer.[6] In their guideline, the USPSTF cites two large studies that documented the very low risk for cytological abnormalities in women after having a hysterectomy.[6,19,20] A study of approximately 9610 Pap smears in 5682 women who had a hysterectomy with removal of the cervix for benign disease found 104 abnormal results among 79 women. Of these, only 6 smears (0.1% of total smears) in 6 women found a high-grade squamous intraepithelial lesion and only 2 smears (< 0.1% of total smears) in 1 woman found squamous-cell carcinoma.[19] The positive predictive value of Pap testing for detecting vaginal cancer was 0 percent (95% CI: 0% to 33%). The mean time from hysterectomy to abnormal Pat smear was 19 years.[19] A cross-sectional study of Pap tests in women who had had a hysterectomy, found only 1 case of cytologic dysplasia was identified (0.18 per 1000 women screened).[20] Neither study indicated whether or not detection of these abnormalities improved clinical outcomes. The USPSTF concludes that the harms of screening after total hysterectomy for benign disease outweigh the benefits.

The USPSTF and other guideline groups agree in recommending that cervical cancer screening should not be performed in women who have had a hysterectomy for benign disease and no history of CIN2 or greater in the past 20 years.

Key Question 5: What are the benefits and harms of de-intensification of screening for cervical cancer **(**discontinuation of screening in women younger than 21 or older than 65 years of age or in women who have had a total hysterectomy, or decreasing from annual to less frequent screening in women 30 to 65 years of age)?

No study directly assessed the benefits or harms of any type of de-intensification of screening for cervical cancer.

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Summary

Table 2 summarizes the benefits and harms of cervical cancer screening: (1) beginning before age 21; (2) annually in women between the ages of 30 and 65 years; (3) after the age of 65 years; and (4) in women after total hysterectomy for benign disease. No study directly evaluated benefits and harms of de-intensification of screening.

Table 2. Summary of benefits and harms of cervical cancer screening

Action	Benefits	Harms
(1) Screening vs. no screening **before age 21**	• No benefit in life-years, cancer cases, cytological abnormalities detected, or cervical cancer deaths	• Increased false-positive test results, colposcopies, cervical biopsies, pain, bleeding, discharge, and adverse outcomes in future pregnancies
(2) Screening **annually vs. less frequently between ages 30 and 65**	• Slightly fewer cancer cases and cervical cancer deaths	• Increased false-positive test results, colposcopies, cervical biopsies, pain, bleeding, discharge, and adverse outcomes in future pregnancies
(3) Screening vs. no screening **after age 65**	• Slightly fewer cancer cases and cervical cancer deaths	• Increased false-positive test results, colposcopies, cervical biopsies, pain, bleeding, and discharge
(4) Screening vs. no screening in women **after total hysterectomy for benign disease**	• No benefit in detection of cytological abnormalities or vaginal cancer	• Possible invasive procedures and treatment due to positive test results
(5) De-intensification of screening	• No direct evidence	• No direct evidence

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Prostate-Specific Antigen-Based Screening for Prostate Cancer

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KEY MESSAGES

Why is this important?

- Prostate cancer is the third most commonly diagnosed cancer in the United States, and an estimated 20 million men undergo prostate cancer screening annually in the United States.
- Prostate specific antigen-based screening can lead to overdiagnosis and overtreatment, as a significant proportion of cancers detected by PSA screening are indolent and likely to remain asymptomatic to during the course of a man's lifetime.
- In April 2017, the U.S. Preventive Services Task Force released updated draft recommendations on prostate cancer screening in asymptomatic men.

What are the benefits and harms of routine screening for prostate cancer with prostate-specific antigen (PSA) testing?

Screening benefits:

- Increased prostate cancer detection.
- One large screening trial found no effect on prostate cancer-specific mortality and another found screening associated with decreased risk of prostate cancer-specific mortality.
- No effect on all-cause mortality.

Screening harms:

- False-positive screening tests are common (10-45%) leading to biopsy.
- Biopsy associated with harms, including pain, bleeding, and infections
- Screening can lead to overdiagnosis (estimated up to 50%) and overtreatment.
    - Prostatectomy increased risk of urinary incontinence and sexual dysfunction; radiation therapy associated with bowel dysfunction

What are the benefits and harms of not conducting PSA-based prostate cancer screening?

- Reduction in the number biopsies and diagnosed low-grade prostate cancer cases.
- Greater proportion of high-grade and metastatic cancers diagnoses, with potentially (as yet unproven) increased mortality.

What are the implications of our findings?

- PSA-based screening can potentially reduce risk of prostate cancer mortality (based on one study), but screening benefits may not be apparent for 12 years or more and does not decrease overall mortality.
- The benefits of PSA screening must be weighed against high false positive rates and the risk of overdiagnosis leading to overtreatment.

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Background

Prostate cancer is the third most commonly diagnosed cancer in the United States. An estimated 20 million men undergo prostate cancer screening annually in the United States. Beginning in the early 1990s, use of the prostate-specific antigen (PSA) test as a screening method led to a large increase in the number of annual prostate cancer diagnoses, although prostate cancer mortality has remained relatively stable over the past 25 years. PSA-based screening can lead to overdiagnosis and overtreatment, as a significant proportion of cancers detected by PSA screening are indolent and likely to remain asymptomatic to during the course of a man's lifetime. Additionally, false positive results are common with PSA-based testing, leading to unnecessary harms associated with additional testing and biopsy.[1]

Due to the uncertain balance of benefits and harms associated with PSA-based screening, in 2012 the U.S. Preventive Services Task Force (USPSTF) recommended against the use of routine PSA screening.[2] In April 2017, the USPSTF released an updated draft recommendation and evidence review on prostate cancer screening.[3,4] This rapid evidence review summarizes the most recent USPSTF evidence on benefits and harms of PSA-based screening for prostate cancer versus no screening, as well as evidence on benefits and harms of de-intensification of PSA-based prostate cancer screening.

Current Guidelines

Selected current practice guidelines on the use of PSA-based prostate cancer screening are summarized in **Table 1**. No organization recommends routine, PSA-based screening, regardless of age or risk factors (e.g., Black men, men with a family history of prostate cancer). Instead, guidelines uniformly recommend an informed, individualized decision-making process for men variably ranging in age from 40 to 70 years. PSA-based screening is not recommended in men over age 70 to 75 years or in men with life expectancy of less than 10 to 15 years, due to the time required to experience benefits of prostate cancer screening.

Table 1. Summary of current guidelines on prostate cancer screening

Guideline Group	Recommendations
USPSTF 2017*[3]	• The USPSTF recommends that clinicians inform men ages 55 to 69 years about the potential benefits and harms of PSA-based screening for prostate cancer (C recommendation). Additional considerations: o Recommends individualized decision-making about screening for prostate cancer after discussion with a clinician, so that each man has an opportunity to understand the potential benefits and harms of screening and to incorporate his values and preferences into his decision. o No separate recommendations regarding screening in Black men and men with a family history of prostate cancer, due to insufficient evidence. • The USPSTF recommends against PSA-based screening for prostate cancer in men age 70 years and older (D recommendation).
American College of Preventive Medicine (ACPM)/Choosing Wisely 2016[5]	• Don't routinely perform PSA-based screening for prostate cancer. □ Men should only consent to being screened for prostate cancer after they clearly understand the associated benefits and risks. □ Decision aids may be effective ways to engage men in a conversation about the risks and benefits of prostate cancer screening.

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Guideline Group	Recommendations

National Comprehensive Cancer Network (NCCN) 2016[6]	• The NCCN panel recommends that baseline PSA testing should be offered to healthy, well-informed (i.e., after clinician-patient discussion of the pros and cons of testing) men aged 45 to 75 years.
	  For men with PSA <1 mg/ml, retesting should occur every 2 to 4 years.
	  For men with PSA 1 to 3 ng/mL, retesting should occur every 1 to 2 years.
	• The NCCN panel recommends that PSA testing be considered only in very select patients >age 75 years. PSA testing in men unlikely to benefit from prostate cancer diagnosis based on age and/or comorbidity is discouraged.

American Urological Association (AUA) 2013[7]	• The AUA panel does not recommend routine screening in men between ages 40 and 54 years. o For men age 40 to 54 years at higher risk (e.g., positive family history, African-American), decisions regarding prostate cancer screening should be individualized. • The AUA panel recommends shared decision-making for men age 55 to 69 years that are considering PSA screening and proceeding based on a man's values and preferences. o For those men who choose to undergo screening, a routine screening interval of 2 years or more may be preferred over annual screening. • The AUA panel does not recommend routine screening in men over age 70 years or in any many with a 10 to 15 year life expectancy.
American College of Physicians (ACP) 2013[8,9]	• ACP recommends that clinicians inform men between the age of 50 and 69 years about the limited potential benefits and substantial harms of screening for prostate cancer. o ACP recommends that clinicians base the decision to use PSA-based screening on the risk for prostate cancer, a discussion of the benefits and harms of screening, the patient's general health and life expectancy and patient preferences. • ACP recommends that clinicians should not screen for prostate cancer using the PSA test in patients who do not express a clear preference for screening. • ACP recommends that clinicians should not screen for prostate cancer using the PSA test in average-risk men under age 50 years, men over age 69 years, or men with a life expectancy of less than 10 to 15 years.

*Draft recommendation, released for public comment April 2017

Methods

Topic Selection and Scope Development

Key Questions

We reviewed evidence relevant to the following Key Questions:

1. What are the benefits and harms of routine screening for prostate cancer with prostate-specific antigen (PSA) testing?
   1a. Do the benefits and harms of routine prostate cancer screening with PSA testing vary according to specific subgroups, including age, race or family history?
2. What are the benefits and harms of not conducting PSA-based prostate cancer screening?

Eligibility Criteria

- Population: Asymptomatic men age ≥40 years without previous prostate cancer diagnosis
- Intervention: PSA-based prostate cancer screening

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- Comparator: No screening
- Outcomes: Prostate cancer incidence and mortality, all-cause mortality, harms of screening

Results

In 2012, the USPSTF recommended against routine prostate cancer screening, regardless of age or presence of demographic or clinical risk factors, based on the evidence available at that time showing harms that were not outweighed by benefits.[2,10] In April, 2017, the USPSTF released an updated draft recommendation statement[3] and accompanying evidence review.[4] Results of the 2017 draft evidence review are summarized below.

Key Question 1. What are the benefits and harms of routine screening for prostate cancer with prostate-specific antigen (PSA) testing?

The USPSTF based their draft evidence review on the benefits and harms of PSA-based screening versus no screening on the results of two large, fair-quality trials: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial and the European Randomized Study of Screening for Prostate Cancer (ERSPC).[4] The two trials both had methodological limitations. In the PLCO trial, there was a high rate of contamination in the no screening group, as over 80% of participants had PSA testing at some point during the study's six-year active screening phase. Contamination was not well-reported in the ERSPC trial, but appeared to range widely from 14% to 37% in the no screening arm, depending on study site. In addition, recruitment procedures, inclusion criteria, and screening protocols varied among the ERSPC study sites, introducing potential heterogeneity; results from some sites were reported separately. In PLCO, screening was performed yearly and a PSA threshold of 4.0 ng/mL was used; in ERSPC, screening frequency varied from 2 to 4 years at most sites, and PSA thresholds varied from 2.5 to 10 ng/mL according to study site and time point.

Benefits of Screening

The effects of screening on prostate cancer incidence and mortality, and on all-cause mortality, are summarized in **Table 2**. The draft evidence review found that PSA-based screening, when compared with no screening, increased detection of prostate cancer, regardless of time point. The risk of metastatic cancer was reduced after 13 years follow up in ERSPC, an effect not observed after 7 years in the PLCO trial. Results for prostate cancer mortality were mixed. In the PLCO trial, there was no difference between screening and no screening in risk of prostate cancer mortality, but in ERSPC, screening significantly reduced the risk of prostate cancer-specific death. Neither trial showed a significant reduction in all-cause mortality with screening. In ERSPC, benefits of screening have increased with longer follow-up, accounting in part for the change in USPSTF recommendations. The ERSPC site with the longest follow up (Goteborg, Sweden) also included patients who were not enrolled in ERSPC. It found screening associated with a reduced risk of prostate cancer mortality after 18 years follow up (RR 0.58, 95% CI 0.46 to 0.72), with no difference between groups in all-cause mortality after 14 years follow up (RR 1.00, 95% CI 0.95 to 1.06).[11]

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Table 2. Benefits of prostate cancer screening versus no screening

Trial Setting n= Follow up	Prostate cancer incidence	Prostate cancer mortality	All-cause mortality
PLCO[12,13] United States n=76,683	7-year follow up 9% vs 8% RR 1.22 (95% 1.16 to 1.29); NNI 100 • Stage IV: 0.2% vs 0.2%; RR 0.92 (95% CI 0.67 to 1.27)	7-year follow up 0.13% vs 0.11% RR 1.13 (95% CI 0.75 to 1.70)	7-year follow up 10% vs 11% RR 0.98 (95% CI 0.92 to 1.03)
	13-year follow up 11% vs 10% RR 1.12 (95% CI 1.07 to 1.17); NNI 88 • Stage IV: Not reported	13-year follow up 0.41% vs 0.38% RR 1.04 (95% CI 0.87 to 1.67)	13-year follow up 24% vs 25% RR 0.98 (95% CI 0.95 to 1.00)
ERSPC (all sites)[14-17] Europe n=162,388 13 years	9-year follow up 11% vs 6% RR 1.91 (95% CI1.83 to 1.99); NNI 25 • Stage IV: Not reported	9-year follow up 0.31% vs 0.37% RR 0.85 (95% CI 0.70 to 1.03)	9-year follow up Proportions not reported RR 0.99 (95% CI 0.97–1.02)
	13-year follow up 10% vs 6% RR 1.57 (95% CI 1.51 to 1.62); NNI 29 • Stage IV: 0.3% vs 0.7%; RR 0.53 (95% CI 0.45 to 0.61)	13-year follow up 0.5% vs. 0.6% RR 0.79 (95% CI 0.69 to 0.91)	13-year follow up 21% vs 21% RR 1.00 (95% CI 0.98 to 1.02)

Abbreviations: NNI=number needed to invite to screening

Harms of Screening

Direct Harms of Screening

The 2017 USPSTF draft evidence review included evidence on direct harms of screening from the PLCO and ERSPC trials described above, and from two cohort studies (n=1,147 and 295,645) with 35 days and 5 years follow up, respectively (**Table 3**).[4] False positive PSA tests were common in both PLCO and ERSPC, but rates varied according to PSA threshold used. For example, ERSPC sites that used lower PSA thresholds (2.5 to 3.0 ng/mL) to define a positive test result had the highest false positive rates (up to 45%). Serious harms and hospitalization following biopsy were infrequent in the trials, though short-term observational evidence found that most men (89%) undergoing prostate biopsy experienced some negative post-biopsy symptoms.

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Table 3. Direct harms of prostate cancer screening

Study Country n= Follow up Study design	False positives and estimated overdiagnosis	Serious harms associated with screening or subsequent biopsy	Short-term mortality associated with screening or subsequent biopsy	Short-term mortality (screening vs control)
PLCO[12,18] United States n=76,683 13 years RCT	False positive rate (PSA >4 ng/mL + no prostate cancer diagnosis within 3 years of testing): 10% Estimated overdiagnosis: 21%	Any complication: 2% • Infection: 0.8% • Non-infectious complication: 1%	4-month follow up: 0.1% 6-month follow up: 0.2%	4-month follow up: 0.1% (6/6,295) vs 0.2% (255/139,931); RR 0.49 (95% CI 0.2 to 1.1) 6-month follow up: 0.2% (14/6,295) vs 0.3% (411/139,931) RR 0.70 (95% CI 0.4 to 1.2)
ERSPC (all sites) [14,15] Europe n=162,388 13 years RCT	False positive rate (definition varied by site, PSA range >2.5 to >4.0 ng/mL): 18% Estimated overdiagnosis: 50%	Pain: 8% Fever: 4% Hospitalization: 0.5%	12-month follow up: 0.6%	12-month follow up: 0.6% (72/11,721) vs 0.9% (330/37,235); RR 0.54 (95% CI 0.42 to 0.70)
ProBE[19] UK n=1,147 35 days Cohort	Not reported	Moderate or severe hematuria: 7% Infective/hemorrhagic symptoms: 89% Hospitalization: 1% • Sepsis: 0.6%	35-day follow up: 0%	Not reported
Walter 2013[20] United States n=295,645 5 years Cohort	Not reported	Infectious or urinary complications: 6% Hospitalization: 2%	7-day follow up: 0.12%	Not reported

Downstream Effects of Screening

A potential harm of screening is overdiagnosis, which can lead to overtreatment.[21] The USPSTF draft evidence review estimated overdiagnosis rates in the PLCO and ERSPC screening trials of 21 and 50 percent, respectively. In addition, active surveillance, a preferred treatment choice for many men with low-grade, screen-detected prostate cancer, can be associated with emotional distress and may not be acceptable to some patients.[22,23] This can lead patients to make more invasive treatment decisions, increasing the risk of treatment harms.

Benefits of Prostate Cancer Treatment

The most relevant evidence included in the USPSFT draft review on the benefits of treating screen-detected prostate cancer comes from the Prostate Testing for Cancer and Treatment (ProtecT) trial of treatment for screen-detected, primarily low-grade, prostate cancer.[24] At 10-

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year follow up, compared with active surveillance, there was no statistically significant difference in rates of prostate cancer and all-cause mortality among men randomized to radical prostatectomy (HR 0.63, 95% CI 0.21 to 1.93; and HR 0.93, 95% CI 0.65 to 1.35, respectively) or radiation therapy (HR 0.51, 95% CI 0.15 to 1.69; and HR 0.94, 95% CI 0.65 to 1.36). However, progression of prostate cancer was less likely in men randomized to prostatectomy (HR 0.39, 95% CI 0.27 to 0.54) and radiation (HR 0.39, 95% CI 0.27 to 0.55) compared with active surveillance, including risk of metastatic disease. Results from other trials and observational studies that included a mix of men with screen- and clinically-detected prostate cancer also found prostatectomy and radiation both associated with reductions in prostate cancer progression, but the long-term effect on cancer-specific and all-cause mortality in men with screen-detected cancer was less clear.

Harms of Prostate Cancer Treatment

Harms of radical prostatectomy and radiation therapy are summarized in **Table 4**. Radical prostatectomy is associated with increased risk of urinary incontinence and erectile dysfunction; some data also suggest increased risk of bowel complications. The perioperative mortality rate ranges from 0 to 0.5%. Radiation therapy is associated with increased risk of bowel complications; there was no increased risk of erectile dysfunction and evidence on risk of urinary incontinence was inconsistent. Harms varied according to treatment modality, and risk estimates varied according to study design. Evidence on harms of other treatments, including androgen deprivation therapy, cryotherapy, and high-intensity focused ultrasound was limited, with no clear differences between treatment and conservative management.

Table 4. Harms of prostate cancer treatment in RCTs and observational studies

	Treatment Versus Conservative Management			
	Urinary incontinence	**Erectile dysfunction**	**Bowel function**	**Surgical complications**
Radical prostatectomy	RCTS (3 trials): RR 2.3 (95% CI 1.8 to 2.8; I^2=0%) Cohort studies (4 studies): RR 3.7 (95% CI 2.4 to 5.7; I^2=23%)	RCTs (2 trials): RR 1.8 (95% CI 1.6 to 2.0; I^2=0%) Cohort studies (5 studies): RR 1.6 (95% CI 1.3 to 1.8; I^2=63%)	No pooled estimate; limited trial evidence suggests higher risk of fecal incontinence with prostatectomy vs. conservative management	Perioperative mortality 0.0-0.5%, based on uncontrolled observational evidence
Radiation therapy	No pooled estimate; RR 0.4 to 8.31, based on 2 RCTs and 4 cohort studies	RCT (1 trial): RR 0.9 (95% CI 0.8 to 1.1) Cohort studies (6 studies): 1.3 (95% CI 1.2 to 1.5; I^2=0%)	No pooled estimate; evidence from trials and cohort studies suggests higher risk of fecal incontinence and rectal urgency with radiation therapy vs. conservative management	

*Conservative management includes active surveillance and watchful waiting.

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Key Question 1a. Do the benefits and harms of routine prostate cancer screening with PSA testing vary according to specific subgroups, including age, race, or family history?

Benefits of Screening

Age

Both the PLCO and ERSPC trials conducted sensitivity analyses on the effect of screening according to patient age. Neither found a significant interaction in risk of prostate cancer mortality and age, although neither trial enrolled men under age 50 or over age 74 years (**Table 5**). When stratified by age, the only group that had a significant reduction in prostate cancer mortality was men aged 65 to 69 years enrolled in the ERSPC trial. In the ERSPC trial, PSA-based screening was associated with no beneficial effects in men ≥70 years of age.

Table 5. The effect of PSA-based screening on prostate cancer mortality according to age

	Subgroup	RR (95% CI)	p for interaction
Trial	***Age***		
PLCO	55 to 64 years	1.19 (0.83 to 1.72)	0.25
	65 to 74 years	1.02 (0.77 to 1.37)	
ERSPC	≤54 years	0.84 (0.28 to 2.49)	0.18
	55-59 years	0.81 (0.93 to 1.03)	
	60-64 years	0.90 (0.71 to 1.15)	
	65-69 years	0.69 (0.55 to 0.87)	
	≥70 years	1.17 (0.82 to 1.66)	

Race/Ethnicity

Black men are at increased risk of prostate cancer incidence and mortality.[25] Black men accounted for 5% of the PLCO population. Race/ethnicity in ERSPC was not reported, and neither PLCO nor ERSPC conducted separate outcome analyses according to race or ethnicity. The USPSTF surmised that prostate cancer screening may confer greater benefit in Black men relative to other racial and ethnic groups, but they found no direct evidence to support this supposition and therefore made no explicit recommendation about screening in this group.[3]

Family History

The PLCO analyzed the effect of family history of prostate cancer on prostate cancer mortality in men undergoing screening.[26] The analysis only included white men, due to limited numbers of men of other races with a family history of prostate cancer. When limited to men with a family history of prostate cancer, the hazard ratio of prostate cancer mortality was 0.49 (95% CI 0.22 to 1.00) for screening versus no screening. The risk estimate for men without a family history of prostate cancer was not reported, nor was a test for interaction between groups. As with race, the USPSTF determined that although men with a family history of prostate cancer might benefit from screening, evidence was too limited to make a recommendation about screening in this group.[3]

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Harms of Screening

Direct Harms of Screening

Age

The USPSTF draft review reported that the risk of a false positive screening test was highest in men over age 70 years (21% false positive rate) and lowest among men younger than age 55 years (4%) in the ERSPC trial. The review also reported that older men (≥75 years) were less likely to undergo biopsy in the presence of PSA test results >4.0 ng/mL than younger men, but that there was no age-based difference in risk of biopsy complications, based on evidence from the PLCO trial and a large VA cohort study.

Race/Ethnicity

In the PLCO trial, Black men were more likely than non-Black men to have infections as a result of prostate biopsy (odds ratio 7.1), but the risk estimate was imprecise (95% CI 2.7 to 18) and USPSTF review authors noted that the reason for this increased risk is unclear.

Family History

The USPSTF draft review found no evidence on differential harms of screening according to family history of prostate cancer.

Downstream Effects of Screening

Treatment Benefits

Age

Evidence on differential effects of treatment according to patient age is limited. Two trials of prostatectomy found no interaction between patient age at diagnosis and risk of progression to metastatic disease. Relative to (undefined) observation, a large database study of the effectiveness of radiation therapy found a significantly reduced risk of prostate cancer mortality in men age 75 to 80 years (HR 0.70, 95% CI 0.59 to 0.80), but not in men in the 65 to 69 or 70 to 74 year age groups.

Race/Ethnicity

The USPSTF review included one trial that found no effects of race/ethnicity on any outcome.

Family History

The USPSTF draft review found no evidence on differential effects of treatment according to family history of prostate cancer.

Treatment Harms

Age

The USPSTF review found that older men were more likely than younger men to have bothersome urinary or sexual function following treatment with prostatectomy or radiation therapy, and were more likely to have prostatectomy-related surgical complications, based on observational evidence. Risk of 30 and 90-day mortality following prostatectomy was also increased as age increased.

Race/Ethnicity

Based on observational evidence, the USPSTF review found Black men were less likely than white men to report urinary or sexual dysfunction following radiation therapy, with no difference in bowel dysfunction according race/ethnicity. When compared with White men, both Black men

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(HR 1.4, 95% CI 1.0 to 2.0) and other Non-White men (HR 1.6, 95% CI 1.1 to 2.6) were more likely to experience medical or surgical complications following prostatectomy.

Family History

The USPSTF draft review found no evidence on differential harms of treatment according to family history of prostate cancer.

2. What are the benefits and harms of not conducting PSA-based prostate cancer screening?

The USPSTF draft review did not directly assess the benefits and harms of de-intensification of PSA-based prostate cancer screening. However, estimates of the effects of screening from the PLCO, ERSPC (all sites), and the ERSPC Goteborg trials provide some contextual evidence on the potential effects of not screening. The USPSTF estimated that for every 1,000 men screened annually, 248 to 282 would have a positive screen and most of those (130 to 274) would undergo one or more biopsy. The estimated number of prostate cancer deaths averted ranged from 0 to 3, and an estimated 3 to 4 cases of metastatic prostate cancer would be averted. Conversely, 25 to 26 men would undergo invasive treatment with radical prostatectomy or radiation therapy with no observed benefit during follow up.

A recent literature review assessed the effect of the previous (2012) USPSTF recommendation on prostate cancer screening rates and outcomes.[27] Based on longitudinal, observational evidence, the review found that prostate cancer screening rates have generally declined across all age groups since 2012, continuing a trend that began prior to the 2012 USPSTF recommendation. Along with reduced screening, both the number of biopsies and prostate cancer incidence have declined. However, among all prostate cancer diagnoses, the proportion of higher stage (T3+) and metastatic cancers diagnoses increased, signaling that the decline in overall incidence is likely the result of lower stage tumors going undetected. The effect on reduced screening on mortality from prostate cancer in the population in unclear, given the limited passage of time since the 2012 recommendation.

Discussion

Table 6 summarizes the benefits and harms of prostate cancer screening, and the effects of de-intensification of prostate cancer screening. Although the ERSPC trial found that screening was associated with decreased risk of prostate cancer mortality and metastatic prostate cancer, there were no effects on all-cause mortality, and screening is associated with trade-offs due to false-positives and harms of follow-up testing and treatments, including those related to overdiagnosis and overtreatment. The USPSTF estimated that for every 1,000 men screened annually, 248 to 282 would have a positive screen and most of those (130 to 274) would undergo one or more biopsies. The estimated number of prostate cancer deaths averted ranged from 0 to 3, and an estimated 3 to 4 cases of metastatic prostate cancer would be averted. Conversely, 25 to 26 men would undergo invasive treatment with radical prostatectomy or radiation therapy with no observed benefit during follow up, additionally resulting in 2 to 8 cases of erectile dysfunction and 1 to 3 cases or urinary incontinence. Evidence on benefits of screening in men younger than 55 years is limited, and the USPSTF had not made screening recommendations in this age group.

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Evidence from the ERSPC trial showed similar risk in prostate cancer mortality in screened and unscreened men across age groups. ERSPC also found relatively modest benefits of screening until 10 years of follow up, which increased with longer follow-up. Although Black men and men with a family history of prostate cancer are at higher risk for prostate cancer, the USPSTF found insufficient evidence to make screening recommendations based on race/ethnicity or family history.

Direct evidence on the effect of de-intensification of prostate cancer screening is limited. Recent reports show a downward trend in the number of men undergoing screening and biopsy annually following the 2012 USPSTF recommendation against prostate cancer screening, but the effect of de-intensification on clinical outcomes has not yet been observed.[27,28]

Table 6. Summary of benefits and harms of PSA-based prostate cancer screening versus no screening

Action	Benefits	Harms
Screening	• Increased prostate cancer detection • One large screening trial found no effect on prostate cancer specific mortality and another found screening associated with decreased risk of prostate cancer specific mortality. • No effect on all-cause mortality.	• False-positive tests are common (10-45%) leading to biopsy. • Biopsy associated with harms including pain, bleeding, and infections • Screening can lead to overdiagnosis (estimated up to 50%) and overtreatment. o Prostatectomy increased risk of urinary incontinence and sexual dysfunction; radiation therapy associated with bowel dysfunction
No screening	• Reduction in the number of biopsies and diagnosed low-grade prostate cancer cases	• A greater proportion diagnosed high-grade and metastatic cancers, with potentially (as yet unproven) increased mortality

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High-Dose Opioid Therapy: Rapid Evidence Summary

This report was prepared by the Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University, under Contract No. VA268-16-Q-0140, in support of an HSR&D research study focused on Identifying, Measuring, and Facilitating Opportunities for De-intensification of Medical Services.

KEY MESSAGES

Why is this important?

- Prescribing and use of opioids for chronic pain has increased substantially.
- In addition to increased rates of prescribing, data also indicate that opioids are being prescribed at higher doses.
- Opioids are associated with serious harms, including overdose deaths and opioid use disorder; higher doses may be associated with increased risk.
- In 2015, the rate of high-dose (>=90 mg morphine equivalents (MME/day) opioid prescribing was 6.7 per 100 persons.
- De-intensification of high-dose opioid therapy could prevent harms associated with opioids.

What are the benefits of prescribing higher versus lower doses of opioids?

- One randomized trial found no difference between more liberal dose escalation of opioids versus maintenance of current doses, but differences in opioid doses between groups were relatively small.
- A meta-regression found no clear association between higher doses of opioids and improved pain or function.

What are the harms of prescribing higher versus lower doses of opioids?

- A systematic review consistently found an association between higher doses of opioids and increased risk of overdose deaths or overdose events.
- Additional studies published since the systematic review also found a dose-dependent risk between higher doses of opioids and increased risk of overdose deaths or overdose events.

What are the benefits and harms of de-intensification of opioid doses in persons prescribed high-dose opioid therapy?

- A systematic review found very low quality evidence that several types of interventions are effective for lowering or tapering opioids, and may improve pain, function, and quality of life; studies were not designed to assess effects on serious harms such as overdose.
- Rapid tapering and discontinuation of opioids can result in withdrawal symptoms.

What are the implications of our findings?

- The CDC recommends that clinicians reassess benefits and harms when prescribing doses of >=50 mg MME/day and avoid doses >=90 MME/day.
- Tapering of opioids should be gradual to reduce the rate and severity of withdrawal symptoms.

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Background

Chronic pain is common in the United States, and opioids have been prescribed increasingly for this condition. From 1999 to 2010, opioid prescribing in the United States quadrupled, in parallel with similar increases in opioid-related overdoses deaths and admissions for treatment of opioid use disorder.[1] In 2015, there were approximately 15,000 overdose deaths involving a prescription opioid, and an estimated 2 million people with opioid use disorder associated with prescription opioid use.[2]

For acute pain, higher doses of opioids are associated with greater analgesic effects, although the association between opioid dose and pain relief is less clear in persons with chronic pain. In addition, a property of opioids is tolerance, meaning that individuals who are continuously exposed to opioids require higher doses over time to maintain the original effects, both beneficial and harmful. For most opioids, there is no clear ceiling or maximum dose, provided there is sufficient time to develop tolerance. However, there are also potential harms associated with the use of higher doses of opioids, including risk of fatal and nonfatal overdose. Data indicate that along with increased prescribing of opioids in the United States, opioids were also prescribed at higher doses, although recent data indicate that prescribing of higher doses has started to decline. In the United States, high-dose opioid prescribing (defined as prescribing of >=90 mg morphine equivalents [MME]/day) was stable from 2006 to 2010 and declined from 11.4 per 100 persons in 2010 to 6.7 per 100 persons in 2015.[2]

Therefore, reductions in high opioid dosing could be an important target for de-intensification. In 2016, the Centers for Disease Control and Prevention (CDC) recommended that clinicians reassess benefits and harms when prescribing doses of >=50 MME/day and avoid doses >=90 MME/day.[3,4] The purpose of this report is to summarize the CDC recommendation and supporting evidence on opioid doses for chronic pain and to consider additional evidence, published since the CDC guideline, on benefits and harms of use of higher versus lower doses of opioids and on de-intensification of opioid doses.

Key Questions

This evidence summary addresses the following key questions.

Key Question 1 (KQ1): What are the benefits of prescribing higher versus lower doses of opioids?

Key Question 2 (KQ2): What are the harms of prescribing higher versus lower doses of opioids?

Key Question 3 (KQ3): What are the benefits and harms of de-intensification of opioid doses in persons prescribed high-dose opioid therapy?

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Current Guidelines

Guidelines from the CDC,[3,4] the Department of Veterans Affairs/Department of Defense,[5] and Health Canada/Canadian Institutes for Health Research[6] on opioid doses for chronic pain are summarized in **Table 1**. All recommend against doses greater than 90 MME/day.

Table 1. Summary of current guidelines on opioid prescribing

Guideline Group	Recommendations
Centers for Disease Control and Prevention, 2016[3,4]	• Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to 50 morphine milligram equivalents or more per day, and should avoid increasing dosage to 90 morphine milligram equivalents per day or carefully justify a decision to titrate dosage to 90 morphine milligram equivalents or more per day.
Department of Veterans Affairs/Department of Defense, 2017[5]	• If prescribing opioids, we recommend prescribing the lowest dose of opioids as indicated by patient-specific risks and benefits. Note: There is no absolutely safe dose of opioids. • We recommend tapering to reduced dose or to discontinuation of long-term opioid therapy when risks of long-term opioid therapy outweigh benefits. Note: Abrupt discontinuation should be avoided unless required for immediate safety concerns.
Health Canada/Canadian Institutes for Health Research, 2017[6]	• For patients with chronic noncancer pain who are beginning opioid therapy, we suggest restricting the prescribed dose to less than 50 mg morphine equivalents daily. • For patients with chronic noncancer pain who are currently using 90 mg morphine equivalents of opioids per day or more, we suggest tapering opioids to the lowest effective dose, potentially including discontinuation, rather than making no change in opioid therapy.

Methods and Rationale

We reviewed and summarized the 2016 CDC guideline recommendations[3,4] on use of opioids, and the evidence supporting the CDC recommendation. We also conducted a targeted search of the literature for additional studies. Our research librarian conducted a search of Ovid MEDLINE® from 2010 through April 25, 2017. This search resulted in 221 potentially relevant citations. Four studies addressed the key questions in this review.

Results

Key Question 1: What are the benefits of prescribing higher versus lower doses of opioids?

Evidence on the benefits of prescribing higher doses of opioids is limited. One randomized trial (cited in the CDC guideline) of VA patients with chronic pain prescribed opioids (n=135) found no difference between a more liberal dose escalation policy versus maintenance of current doses in pain severity, disability, or opioid misuse behaviors.[7] However, average doses of opioids were similar between the two groups (52 vs. 40 MME/day).

A meta-regression based on within-study comparisons conducted for the 2017 Canadian guideline found no evidence for a dose-response effect on pain (6 studies, p=0.49) or function (3 studies, p=0.22).[6] Although a systematic review of opioids for low back pain[8] (not cited by the CDC guideline) found each 1 log unit increase in morphine equivalent dose associated with 12.0

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points greater pain relief (0 to 100 scale), findings were based primarily on indirect, cross-study comparisons. One head-to-head trial[9] included in the systematic review found higher doses of opioids associated with minimally greater pain relief (<2 points on a 0 to 100 scale) than lower doses (comparisons were buprenorphine transdermal 20 or oxycodone 40 mg/day vs. buprenorphine transdermal 5 mcg/hr).

Key Question 2: What are the harms of prescribing higher versus lower doses of opioids?

The CDC guideline[3,4] cited nine studies that consistently found an association between higher opioid dose and increased risk of fatal or nonfatal opioid overdose, after adjusting for potential confounders, including comorbidities and concomitant medication use. In one study of VA patients prescribed opioids, compared with a dose of 1 to <20 MME/day, 50 to <100 MME/day was associated with an adjusted HR of 4.63 for fatal opioid overdose and >=100 MME/day associated with an adjusted HR of 7.18.[10] The overdose death rate per 100 person-months was 0.11 in persons prescribed 1 to <20 MME/day, 0.24 for 20 to <50 MME/day, 0.66 for 50 to <100 MME/day, and 1.24 for >=100 MME/day. Similarly, a study of patients in a health maintenance organization found that, compared with a dose of 1 to <20 MME/day, 50 to <100 MME/day was associated with an adjusted HR of 3.7 and a dose of >100 MME/day associated with an adjusted HR of 8.9.[11] The overdose death rate per 100,000 person-years was 160 for 1 to <20 MME/day, 260 for 20 to <50 MME/day, 677 for 50 to <100 MME/day, and 1791 for >=100 MME/day. Other studies cited in the CDC guideline also found doses >100 MME/day associated with increased risk (risk estimates ranged from 1.9 to 11.2).[3,4] A study published subsequent to the CDC guideline also found higher doses associated with increased risk of overdose death (compared to 1-19 MME/day, adjusted HR 2.3 for 50-89 mg/day and 3.8-4.9 for >20 MME/day).[12]

Key Question 3: What are the benefits and harms of de-intensification of opioid doses in persons prescribed high dose opioid therapy?

The CDC guideline[3,4] cited no study on the benefits and harms of de-intensification of therapy with opioids. A systematic review published subsequent to the CDC guideline on opioid dose reduction or discontinuation included 67 studies; the majority of studies (56/67) were observational.[13] It found very low quality evidence that several types of interventions (e.g., interdisciplinary pain programs, buprenorphine-assisted dose reduction, and behavioral interventions) may be effective to reduce or discontinue long-term opioid therapy and that pain, function, and quality of life may improve with opioid dose reduction. There was insufficient data to assess effects on overdose deaths (only one death was reported). An analysis of VA data found a dose threshold MME/day associated with a sensitivity for overdose cases of 33% and specificity of 88% and a threshold of MME/day associated with a sensitivity of 59% and specificity of 76%, indicating potential trade-offs between application of different dosing thresholds.[14]

Summary

Table 2 summarizes the benefits and harms of high-dose opioid therapy and de-intensification of concurrent therapy. Evidence indicates an association between higher opioid dose and risk of

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overdose, with no clear evidence of benefits. At >100 MME/day, the risk of overdose is 2 to 9 times higher than at doses of 1 to 20 MME/day. Limited evidence indicates that opioids can be successfully tapered, with potential positive effects on pain, function, and quality of life, although effects on overdose risk have not been adequately studied. Despite lack of evidence on benefits of high doses of opioids and evidence indicating increased risk of serious harms, use of high dose opioid therapy remains common, indicating a potential target for de-intensification.

Table 2. Summary of benefits and harms of high dose opioid therapy

Action	Benefits	Harms
(1) High dose opioid therapy	• No clear evidence of improved pain or function	• Increased risk of overdose, including overdose deaths
(2) De-intensification of high dose opioid therapy	• May improve pain, function, and quality of life • No direct evidence on decreasing overdose risk	• Abrupt discontinuation/tapering of opioids can cause withdrawal

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Opioids and Benzodiazepines: Rapid Evidence Synthesis

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KEY MESSAGES

Why is this important?

- Prescribing and use of opioids for chronic pain has increased substantially.
- Opioids are associated with serious harms, including overdose deaths and opioid use disorder.
- Benzodiazepines are commonly prescribed in persons using opioids, but can potentiate the respiratory depressant effect of opioids, increasing the risk of overdose, and are also associated with risk of abuse and dependence.
- De-intensification of medications in persons co-prescribed opioids and benzodiazepines could prevent harms associated with this combination.
- Studies found that the proportion of patients prescribed an opioid who are also prescribed a benzodiazepine ranges from 17% to 80%.

What are the benefits of co-prescribing of opioids and benzodiazepines?

- No study evaluated the incremental benefits of opioids in combination with benzodiazepines versus either of these medications alone.

What are the harms of co-prescribing of opioids and benzodiazepines?

- Studies found that 50% to 60% of opioid overdoses also involve concurrent use of benzodiazepines.
- A large study of administrative claims data found opioids + benzodiazepines associated with increased risk of an emergency room visit or inpatient admission versus opioid use alone (adjusted OR 2.14, 95% CI 2.05 to 2.24).
- A study of U.S. Veterans receiving opioids for chronic pain found current benzodiazepine use associated with increased risk of overdose deaths versus no benzodiazepines (adjusted HR 3.86, 95% CI 3.49 to 4.26).
- A study of Washington State Medicaid enrollees who received at least one opioid prescription found use of benzodiazepines associated with increased risk of opioid-related death versus no benzodiazepines (adjusted HR 7.5, 95% CI 5.5-10.0).

What are the benefits and harms of de-intensification of benzodiazepines use in persons prescribed opioids?

- No study evaluated benefits and harms of de-intensification of benzodiazepines in persons prescribed opioids.
- Rapid tapering and discontinuation of benzodiazepines can result in withdrawal symptoms, which may be serious.
- One study estimated that discontinuation of benzodiazepines in persons prescribed opioids could reduce opioid-related emergency department visits and inpatient admissions by 15%.

What are the implications of our findings?

- The CDC recommends that concurrent use of opioids and benzodiazepines be avoided whenever possible.
- Benzodiazepine tapering should be gradual, as stopping abruptly can result in serious withdrawal.
- In 2016, the FDA announced that it requires black box warnings on risks of concurrent use of opioids and benzodiazepines.

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Background

Chronic pain is common in the United States, and opioids have increasingly been prescribed for this condition. Between 1999 to 2010, opioid prescribing in the United States quadrupled, in parallel with similar increases in opioid-related overdoses deaths and admissions for treatment of opioid use disorder.[1] In 2015, there were approximately 15,000 overdose deaths involving a prescription opioid, and an estimated 2 million persons with opioid use disorder associated with prescription opioid use.[2]

Benzodiazepines are used to treat anxiety and insomnia, which are common in persons with chronic pain, as well as other conditions. Benzodiazepines are frequently prescribed in persons prescribed opioids, with estimates ranging from 17% to 80%.[3-5]

There are potential harms associated with the use of opioids and benzodiazepines. Like opioids, benzodiazepines are associated with risk of abuse and dependence. In addition, benzodiazepines can potentiate the respiratory depressant effects of opioids, increasing the risk of opioid overdose.

Therefore, de-intensification of concurrent use of opioids and benzodiazepines could be an important target for de-intensification efforts. In 2016, the Centers for Disease Control and Prevention (CDC) recommended that clinicians avoid concurrent use of opioids and benzodiazepines whenever possible.[6] Also in 2016, the FDA required prescription label black box warnings on the risks of concurrent use of opioids and benzodiazepines.[7] The purpose of this rapid evidence review is to summarize the CDC recommendation and supporting evidence, as well as additional evidence published since the CDC guideline, on benefits and harms of concurrent use of opioids and benzodiazepines, as well as on de-intensification of combined opioids and benzodiazepine therapy.

Key Questions

This rapid evidence synthesis addresses the following three key questions:

Key Question 1: What are the benefits of co-prescribing of opioids and benzodiazepines?

Key Question 2: What are the harms of co-prescribing of opioids and benzodiazepines?

Key Question 3: What are the benefits and harms of de-intensification of concurrent therapy with opioids and benzodiazepines (i.e., discontinuation of benzodiazepines or opioids) in persons prescribed opioids?

Current Guidelines

Guidelines from CDC and the Department of Veterans Affairs/Department of Defense[8] on concurrent use of opioids and benzodiazepines are summarized in **Table 1**. Both recommend against concurrent use of opioids and benzodiazepines. A recent Canadian guideline on use of opioids for chronic pain did not address concurrent use of opioids and benzodiazepines.[9]

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Table 1. Summary of current guidelines on opioids and benzodiazepines

Guideline Group	Recommendation
Centers for Disease Control and Prevention, 2016[6]	Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible
Department of Veterans Affairs/Department of Defense, 2017[8]	We recommend against the concurrent use of benzodiazepines and opioids

Methods and Rationale

We reviewed and summarized the 2016 CDC guideline recommendations on use of opioids with benzodiazepines[6] and the evidence supporting the CDC recommendation. We also conducted a targeted search of the literature for additional studies. Our research librarian conducted a search of Ovid MEDLINE from 2010 through April 25, 2017, which resulted in 37 potentially relevant citations. Altogether, four studies addressed the key questions in this review.[3-5,10]

Key Question 1: What are the benefits of co-prescribing of opioids and benzodiazepines?

No study addressed the incremental benefits of concurrent use of opioids and benzodiazepines versus either of those medications alone. However, benzodiazepines are generally not recommended for treatment of chronic pain conditions or as first line therapy for management of insomnia or anxiety, given the availability of effective and safer alternatives.

Key Question 2: What are the harms of co-prescribing of opioids and benzodiazepines?

The CDC guideline cited a case-cohort study of U.S. veterans (2,400 overdoses and 420,386 controls) who were prescribed opioids.[4] This study found that current use of benzodiazepines was associated with a nearly fourfold increase in risk of overdose death versus no use of benzodiazepines after adjustment for sex, age, race, socioeconomic status, Charlson comorbidity index, substance use disorder diagnosis, psychiatric diagnoses, cancer, and use of other drugs (adjusted HR 386, 95% CI 3.49 to 4.26).[4] The study also found a dose-response relationship between higher benzodiazepines dose and risk of overdose (vs. a dose of 0-10 mg/day, adjusted HR for >40 mg/day 3.06 [2.38 to 3.92] and for >10-20 mg/day 1.69 [95% CI 1.42 to 2.01]). There were no clear differences in risk across specific benzodiazepines or dosing pattern (regularly scheduled vs. as needed only). In this study, 27% of veterans prescribed opioids also received benzodiazepines, and about 50% of overdose deaths occurred in veterans who received both medications concurrently.

Three subsequent studies not published in the CDC guideline also found an association between concurrent use of opioids and benzodiazepines and increased risk of serious harms. A large retrospective study of privately insured patients prescribed opioids (n=315,428) found concurrent use of opioids and benzodiazepines associated with increased risk of an ED visit or inpatient admission for opioid overdose after adjustment for year, sex, age, and medical and psychiatric comorbidities versus no benzodiazepines (adjusted OR 2.14, 95% CI 2.05 to 2.24).[5] The study also found that concurrent prescribing of these two medications increased from 9% in 2001 to 17% in 2013. A study of Washington State Medicaid enrollees who were prescribed opioids found that concurrent use of benzodiazepines was associated with increased risk of opioid-related death versus no opioids, after adjusting for age, sex, race/ethnicity, area of

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residence, and Charlson score (adjusted HR 7.5, 95% CI 5.5 to 10.0).[10] The risk associated with sedative-hypnotics (primarily benzodiazepines and skeletal muscle relaxants) increased at higher opioid doses (adjusted HR 5.6, 95% CI 1.6 to 19.3 at opioid dose of 1-19 MME [milligrams of morphine equivalents]/day to adjusted HR of 20.3, 95% CI 6.4 to 64.3 at >=120 MME/day). Data for risk of benzodiazepine use alone stratified according to opioid dose were not reported. The third study, which evaluated a sample of over 2 million persons prescribed opioids in North Carolina, found opioids associated with a nearly 10-fold increase in risk of overdose deaths (7.0 versus 0.7 per 10,000 person-years), but did not adjust for potential confounders.[3] The increase in mortality risk increased at higher doses (rate difference 2.8 per 10,000 person-years for >0 to 74.9 MME/day and 45.8 per 10,000 person-years for 300 to 5,000 MME/day). In this study, about 80% of patients prescribed opioids also received benzodiazepines, and about 60% of opioid analgesic deaths also involved benzodiazepines.

A Canadian study found that approximately 60% of opioid overdose deaths also involved benzodiazepines, based on toxicology screening, but did not evaluate the association between concurrent use of these medications and risk of overdose death.[11]

Key Question 3: What are the benefits and harms of de-intensification of concurrent therapy with opioids and benzodiazepines (i.e., discontinuation of benzodiazepines or opioids) in persons prescribed opioids?

No study evaluated the benefits and harms of de-intensification of concurrent therapy with opioids and benzodiazepines. One study estimated that discontinuation of benzodiazepines in persons prescribed opioids would reduce the number of emergency department visits and inpatient admissions for opioid overdose by 15% (95% CI 14 to 16%).[5]

Summary

Table 2 summarizes the benefits and harms of concurrent therapy with opioids and benzodiazepines, and de-intensification of concurrent therapy. New evidence published since the 2016 CDC guideline supports an association between concurrent therapy with opioids and benzodiazepines and risk of serious harms. Despite lack of evidence on benefits of opioids combined with benzodiazepines and evidence indicating increased risk of serious harms, concurrent use of these medications is common, indicating a potential target for de-intensification.

Table 2. Summary of benefits and harms of opioids and benzodiazepines

Action	Benefits	Harms
(1) Concurrent use of opioids and benzodiazepines	• No evidence on benefits of concurrent therapy versus one of these medications alone	• Increased risk of overdose, including overdose deaths • Potential increase risk of dependence and abuse
(2) De-intensification of concurrent therapy	• No direct evidence on discontinuation of opioids or benzodiazepines • One study estimated that discontinuation of benzodiazepines would reduce emergency room and inpatient admissions for opioid overdose by 15%	• Abrupt discontinuation/tapering of benzodiazepines can cause severe withdrawal

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Benzodiazepines and Other Sedative Hypnotics for Older Adults with Insomnia, Agitation, or Delirium: Rapid Evidence Synthesis

This report was prepared by the Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University, under Contract No. VA268-16-Q-0140, in support of an HSR&D research study focused on Identifying, Measuring, and Facilitating Opportunities for De-Intensification of Medical Services.

KEY MESSAGES

Why is this important?

- Insomnia, agitation, and delirium are common in older adults and can be associated with decreased quality of life. Although benzodiazepines and sedative hypnotics have been a mainstay of treatment of these conditions, the American Geriatrics Society Beers Criteria for Potentially Inappropriate Medical Use in Older Adults and the Choosing Wisely campaign recommended against their use due to concerns of serious risks such as fractures and mortality. Discontinuing benzodiazepines and sedative hypnotics can be a challenge due to physical dependence and withdrawal. This rapid evidence synthesis summarizes the evidence on risk of mortality and fractures for benzodiazepines and sedative hypnotics versus nonuse in older adults and effects of their discontinuation.

What is the association between benzodiazepines and sedative hypnotics and risk of mortality when used in older adults for insomnia, agitation, and delirium?

- Benzodiazepine and sedative hypnotic use is consistently associated with increased risk of mortality (HR range 3.32 to 5.32) in studies of adults (mean age 50s) with long-term follow-up, although an association was not observed in studies restricted to older adults (HR range, 1.01 to 1.06; RR 0.68).

What is the association between benzodiazepines and sedative hypnotics and risk of fractures when used in older adults for insomnia, agitation, and delirium?

- Benzodiazepines and zolpidem are associated with increased risk of fractures in older persons when prescribed for various indications; zolpidem is associated with increased risk of fracture when prescribed specifically for insomnia.

What are the benefits and harms of discontinuing benzodiazepines and sedative hypnotics versus continuing them in older people with insomnia, agitation and delirium?

- Empirical evidence on the relapse, withdrawal, and health care utilization effects of discontinuing benzodiazepines and sedative hypnotics is too limited to draw conclusions specific to older adults with insomnia, agitation, or delirium.

What are the implications of our findings?

- Benzodiazepines and sedative hypnotics are associated with risk of fracture in older persons. Evidence on the association between benzodiazepines and sedative hypnotics and increased risk of mortality is somewhat mixed and has been primarily observed in populations not restricted to older persons. Alternative treatments and approaches for management of insomnia, agitation, and delirium in older persons are available and may provide a superior balance of benefits to harms.

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Background

Insomnia, agitation, and delirium are common in older adults and can be associated with decreased quality of life. Benzodiazepines and sedative hypnotics have been a mainstay of treatment of these conditions. However, these sedating medications are scheduled by the FDA due to their abuse potential, and they are associated with other harms; these harms include dizziness, balance difficulties, and mental impairment, which can lead to falls, bone fractures, hospitalizations, and even death.[1-5] Older adults may be more susceptible to these risks due to increased frailty, combined with age-related increased sensitivity to and decreased metabolism of drugs[6] and greater likelihood of polypharmacy-related drug-drug interaction. Due to concern that risks of benzodiazepines and sedative hypnotics may outweigh their benefits in older adults, the American Geriatrics Society Beers Criteria for Potentially Inappropriate Medical Use in Older Adults[7] and Choosing Wisely[8] recommended against using benzodiazepines and sedative hypnotics as first-line therapy for insomnia, agitation and delirium in older adults. Table 1 lists other guideline statements concerning use of benzodiazepines and sedative hypnotics in older adults, the majority of which were identified by a 2011 review by the Canadian Agency for Drugs and Technologies in Health.[9]

Current Guidelines

Table 1. Summary of insomnia guideline statements on using benzodiazepines and sedative hypnotics in the elderly[9]

Source	Guideline Statements
American College of Physicians, 2016[10]	"Evidence [from short-term randomized controlled trials] was insufficient to determine the benefits of pharmacologic therapy with benzodiazepines in the general population or in older adults. Few trials met the inclusion criteria for the evidence review, largely because many assessed short durations of treatment."
American Medical Directors Association, 2005. Sleep Disorders Clinical Practice Guideline*	"Continuous use of benzodiazepines should be discouraged in the long-term care setting because of the risk of side effects, physiological tolerance, and adverse effects on discontinuation." (ages not specified) "Adverse effects generally appear to be worse in the elderly."
National Institutes of Health, 2005. State-of-the-Science Conference Statement on manifestations and management of chronic insomnia in adults.[11]	"Adverse effects associated with these medications include, residual daytime sedation, cognitive impairment, motor incoordination, dependence, and rebound insomnia. These problems appear to be worse in the elderly."
Montgomery and Lilly, 2007. Insomnia in the elderly.[12]	In patients ≥ 65 years: "Benzodiazepines may improve sleep outcomes but are likely to cause adverse events." "Observational studies suggest an increased risk of falls, hip fractures, cognitive impairment, and car accidents." "There is little evidence regarding the clinical benefits or adverse effects of benzodiazepine usage for greater than one month."

*The American Medical Directors Association is now the Society for Post-Acute and Long-Term Care Medicine. The Society for Post-Acute and Long-Term Care Medicine retained this 2005 AMDA sleep disorders guideline. The guideline has been archived by the National Guideline Clearinghouse, but is available for purchase through the Society for Post-Acute and Long-Term Care Medicine.

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Despite these cautions, CDC data indicates that peak prescribing of benzodiazepines is still in the oldest age group (≥ 65 years).[13] Reasons for continued overuse are complex and include both patient and provider factors, including lack of readiness to discontinue treatment, fear of withdrawal, or insufficient time or confidence in managing tapering.[14-18]

To assist the Veterans Health Administration in assessing use of benzodiazepines and sedative hypnotics for insomnia, agitation, and delirium in elderly adults as a potential target for de-intensification, we performed a rapid evidence-based synthesis of evidence, focusing on risk of mortality and fractures and effects of discontinuation.

Methods

Topic Selection and Scope Development

This review included studies relevant to the following key questions and eligibility criteria.

Key Questions

Key Question 1: What is the association between use of benzodiazepines and sedative hypnotics in elderly adults with insomnia, agitation, or delirium and risk of mortality and fractures?

Key Question 2: What are the benefits and harms of discontinuing benzodiazepines and sedative hypnotics in elderly adults with insomnia, agitation, or delirium?

Eligibility Criteria

- Population: Elderly adults with insomnia, agitation, or delirium
- Intervention and Comparison:
  - Key Question 1: Use of benzodiazepines or sedative hypnotics versus non-use
  - Key Questions 2: Discontinuation versus continuation of benzodiazepines or sedative hypnotics
- Outcomes:
  - Key Question 1: Fractures and mortality
  - Key Question 2: Withdrawal and relapse
- Timing: Any
- Setting: Any
- Study design: Systematic reviews, randomized controlled trials, and concurrently-controlled cohort studies
- Other: Sample size ≥ 1000 patients

Searching and Study Selection

We identified a good-quality comparative effectiveness review conducted by the Minneapolis Evidence-based Practice Center on Management of Insomnia Disorder,[19] which included studies published through January 2015. This review served as the foundation for our review on the insomnia population. To identify additional studies for insomnia and studies in agitation and delirium, we searched MEDLINE® back to January 2012 using terms for drug names and insomnia, agitation, and delirium; searched the Agency for Healthcare Research and Quality

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(AHRQ), the Canadian Agency for Drugs and Technologies in Health (CADTH), Cochrane, and ECRI Institute systematic review organization websites; and hand-searched the Choosing Wisely reference list, the Beers Criteria Evidence Tables, and the reference lists of included studies. One reviewer used the above prespecified criteria to select studies.

Data Synthesis and Quality Assessment

One reviewer abstracted brief data on sample size, setting, and results into intext tables. We did not formally rate risk of bias of individual studies or strength of the body of evidence. For risk of bias, we primarily relied on ratings from the Minneapolis EPC review. For additional studies we qualitatively commented on the type and seriousness of methodological limitations, based on the principles outlined in the AHRQ Methods Guide.[20] We also informally considered the strength of the body of evidence through qualitative comments on directness, precision, and consistency.[21]

Results

Evidence on the serious harms of using benzodiazepines and sedative hypnotics in elderly adults is exclusively in the insomnia population. We found no studies of serious harms in elderly adults with agitation or delirium. We found no studies in Veteran populations.

Key Question 1: What is the association between use of benzodiazepines and sedative hypnotics in elderly adults with insomnia, agitation, or delirium and risk of mortality and fractures?

Insomnia

Mortality

In the Kripke et al. study cited by the Choosing Wisely campaign, benzodiazepines and sedative hypnotics use over 2.5 years was associated with increased risk of mortality (HR 3.32; 95% CI, 3.19 to 3.45) (Table 2).[4] A dose-response association was demonstrated as risk increased with increasing numbers of prescribed pills per year (0.4-18 to > 132 pills) for zolpidem (HR 3.93; 95% CI, 2.98 to 5.17 to HR 5.69; 95% CI, 4.58 to 7.07) and temazepam (HR 3.71; 95% CI, 2.55 to 5.38 to HR 6.56; 95% CI, 5.03 to 8.55).[4] However, the applicability of these findings to older adults with insomnia is unclear as the average age in the study by Kripke et al. was 54 years and the indication for treatment was not specified. Other studies of benzodiazepines and sedative hypnotics prescribed for any reason[22-24] also found associations with increased risk of mortality (HR range, 3.32 to 3.73) over follow-up periods of 1 to 8 years; mean age in these studies ranged from 46 to 55 years (Table 2). One study also found a dose-response association between benzodiazepines and sedative hypnotics and mortality, with risk increasing with increasing numbers of prescribed pills per year (≤ 30 days to ≥ 91 days) both for benzodiazepines (HR 2.78; 95% CI, 2.62 to 2.96 to HR 5.10; 95% CI, 4.67 to 5.58) and for z drugs (zaleplon, zolpidem and zopiclone; HR 2.36; 95% CI, 2.05 to 2.74 to HR 3.90; 95% CI, 3.39 to 4.47).[23] One recent, large study that used a propensity adjusted analysis found no association between benzodiazepine use over 6 months and all-cause mortality (average age 46 years).[24]

Among three studies focusing on exclusively older populations, [25-27] benzodiazepine and sedative hypnotic use was not associated with increased risk of mortality (HR range, 1.01 to

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1.06; RR 0.68) over follow-up periods of 3 to 9 years (Table 2), including one study that was restricted to persons with "at least 1 insomnia complaint".[25]

Table 2. Association between benzodiazepine and sedative hypnotic use and risk of mortality: summary of study characteristics and results

Author Year	Setting, Data Source, Mean Age, Sample Size	Adjustment for Demographics, Lifestyle, SES, Medical and Psychiatric Co-morbidities and Co-medications	Follow-up Period	Main Findings
Older persons, for insomnia				
Jaussent, 2013[25]	3 French cities Three-City Prospective Study Mean age=72.8 yrs N=6,696	All	9 yrs	No increased risk for any BSH (mainly benzodiazepines): HR 1.06 (95% CI, 0.92 to 1.23)
Older persons, for any reason				
Gisev, 2011[26]	Leppavirta, Finland National Prescription Register Mean age=74 yrs N=1845	No lifestyle or SES	9 yrs	No increased risk for any BSH: HR 1.01 (95% CI, 0.84 to 1.21)
Vinkers, 2003[27]	Leiden, the Netherlands Leiden 85-plus Prospective Study Mean age NR (≥85 yrs) N=599	No lifestyle, SES or comedications	3 yrs	No increased risk for any benzodiazepine: RR 0.68 (95% CI, 0.44-1.04)
Not restricted to older persons, for any reason				
Patorno, 2017[24]	US Commercial healthcare database Mean age=46 yrs N=2,505,976	All	6 months	No increased risk for benzodiazepines: HR 1.00 (95% CI, 0.96 to 1.04)
Palmaro, 2015[22]	UK and France Nationally representative databases Mean age=54 yrs N=454,230	All	1 yr	Increased risk for benzodiazepine users: HR 3.73 (95% CI, 3.43–4.06)
Weich, 2014[23]	UK General Practice Research Database (GPRD) Mean age=55 yrs N=104,145	No anxiety or SES	7.6 yrs	Increased risk for any BSH use: HR 3.32 (95% CI, 3.19 to 3.45)
*Kripke, 2012[4]	Rural Pennsylvania Geisinger Health System Mean age=54 yrs N=34,205	No psychiatric comorbidity, SES, or comedications	2.5 yrs	Increased risk for any BSH: HR 3.60 (95% CI, 2.92 to 4.44) to 5.32 (95% CI, 4.50 to 6.30) with increasing use (prescription of 0.4-18 to > 132 pills/yr)

BSH = benzodiazepine and sedative hypnotic; CI= confidence interval; HR = hazard ratio; SES = socioeconomic status; UK = United Kingdom; yr(s) = year(s)
* Cited by Choosing Wisely

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Fractures

Three studies cited by the Choosing Wisely campaign and/or the Beers Criteria consistently found that benzodiazepine and sedative hypnotic use within 30 to 180 days was associated with increased risk of primarily hip fractures (OR range, 1.46 to 1.95; RR range, 2.03 to 3.11) (Table 3).[2,28,29] Among these, one study of a Medicare population found an increased risk of hip fractures for use of zolpidem tartrate, eszopiclone, or zaleplon within 0 to 29 days compared to nonexposure 60 to 89 and 120 to 149 days before the fracture.[29] Risk of hip fracture was higher among new users who used zolpidem tartrate, eszopiclone, or zaleplon within 15 days (OR 2.20; 95% CI, 1.76-2.74). Strengths of this study are that it focused on older people with insomnia and extensively addressed potential confounding. Other studies cited by the Beers criteria and Choosing Wisely did not focus on or adjust for insomnia and adjusted for fewer other potential confounders.[2,28]

We identified three additional studies from Taiwan[30,31] and South Korea[32] with mixed findings (Table 3). Zolpidem was associated with increased risk of primarily femur fractures[32] and diazepam was associated with increased risk of all-site fractures.[31] However, benzodiazepines overall were not associated with increased risk of all-site fractures[31] or primarily femur fractures.[32] Zolpidem was also not associated with all-site fractures[31] or major head injury or fractures requiring hospitalization.[30]

Determination of the main reason(s) for the differences in risk of fracture is difficult due to heterogeneity in settings, adjustment for confounders, description of treatment indications, and fracture sites.

Table 3. Association between benzodiazepine and sedative hypnotic use and fracture risk: summary of study characteristics and results

Author Year	Setting, Data Source, Mean Age, Sample Size	Adjustment for Demographics, Lifestyle, SES, Medical and Psychiatric Co-morbidities and Co-medications	Follow-up Period	Main Findings
Older persons, for insomnia				
Tang 2015[31]	Taiwan's National Health Insurance Research Database Mean age NR; 41% aged 65-74 yrs, 47% aged 75-84 N=6,010	All	Use within 24 hrs	Increased risk of all-site fractures for diazepam (OR 1.49; 95% CI, 1.05 to 2.11), but not for benzodiazepines overall (OR 1.08; 95% CI, 0.97 to 1.22) or zolpidem (OR 1.13; 95% CI, 0.96-1.34)
Berry 2013[29‡]	Medicare Part A and D hip fracture claims Mean age 81 years N=927 exposure-discordant nursing home resident pairs in a case-crossover study	Not for potential fluctuations in insomnia severity	Nonbenzodiazepine exposure (zolpidem tartrate, eszopiclone, or zaleplon) 0 to 29 days before the fracture vs nonexposure 60-89 and 120-149 days before fracture	Increased risk of hip fractures for nonbenzodiazepines: OR 1.66 (95% CI, 1.45-1.90)

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Author Year	Setting, Data Source, Mean Age, Sample Size	Adjustment for Demographics, Lifestyle, SES, Medical and Psychiatric Co-morbidities and Co-medications	Follow-up Period	Main Findings
Kang 2012[32]	South Korea Health Insurance Review and Assessment Service Database Mean age NR; 20% aged 65-69 yrs; 27% aged 70-74 yrs; 27% aged 75-79 yrs N=1508	Not for comorbidities	Use within 24 hrs	Increased risk of mainly femur fractures for zolpidem use within 24 hours: OR 1.72 (95% CI, 1.37 to 2.16), but not for benzodiazepines (OR 1.00; 95% CI, 0.83 to 1.21)
Older persons, for any reason				
Lai 2014[30] Cohort with concurrent control group, subgroup analysis	Taiwan National Health Insurance Database Mean age NR (aged ≥55 yrs) N=NR	No adjustment for demographics or lifestyle; adjusted for sleep disorder	1 yr	No increased risk of major head injury or fracture requiring hospitalization for zolpidem: HR 1.57 (95% CI, 0.78-3.13
Finkle 2011[2†‡] Pre-Post Cohorts, subgroup analysis	Kaiser Permanente health plan members in Southern California Mean age NR (aged ≥65 yrs) N=89,738	No adjustment for lifestyle, SES, or insomnia	1-3 yrs before initial treatment vs 90 days after	Increased risk (RR [95% CI]) of nonvertebral fracture / hip fracture for: zolpidem (2.55 [1.78 to 3.65] / 3.11 [1.96 to 4.91]), lorazepam (1.53 [1.23 to 1.91] / 2.05 [1.58 to 2.66]), diazepam (1.97 [1.22 to 3.18] / 2.03 [1.03 to 4.00]), but not alprazolam (1.14 [0.80 to 1.64]) / 1.46 [0.91 to 2.35])
Wang 2001[28‡] Case-control	New Jersey Medicare, Medicaid, or Pharmaceutical Assistance to the Aged and Disabled program Mean age=82 years N=6,110	No adjustment for lifestyle or psychiatric comorbidity; medical comorbidity via index score only	180 days prior	Increased risk of hip fracture with zolpidem use (OR 1.95; 95% CI 1.09 to 3.51) and benzodiazepine use (OR 1.46; 95% CI 1.21 to 1.76)

BSH = benzodiazepine and sedative hypnotic; CI= confidence interval; HR = hazard ratio; NR = not reported; OR = odds ratio; SES = socioeconomic status; yr(s) = year(s)

†=cited by Choosing Wisely; ‡cited by Beers criteria

Agitation

We found no studies on serious harms in older adults using benzodiazepines or sedative hypnotics specifically to treat agitation. As benzodiazepines have the potential to be overly sedating and induce respiratory depression or hypotension, the American Association for Emergency Psychiatry Project "Best Practices in Evaluation and Treatment of Agitation" (BETA) Psychopharmacology Workgroup Consensus Statement recommends limiting their use to cases where alcohol or benzodiazepine withdrawal or CNS stimulant intoxication is suspected and avoiding them in cases where CNS depressant intoxication is suspected.[33]

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Delirium

We found no studies on serious harms in older adults using benzodiazepines or sedative hypnotics specifically to treat delirium. However, a systematic review found benzodiazepines associated with an increased risk of delirium (OR 3.0; 95% CI, 1.3-6.8) in surgical patients.[34]

Key Question 2: What are the benefits and harms of discontinuing benzodiazepines and sedative hypnotics in elderly adults with insomnia, agitation, or delirium?

Chronic benzodiazepine use results in physical dependence with withdrawal when discontinued, which can be serious and increase risk of agitation, delirium, and falls. However, empirical evidence on the benefits and harms of discontinuing benzodiazepines and sedative hypnotics in elderly adults with insomnia, agitation or delirium is very limited. Inpatient discontinuation of benzodiazepines was associated with a nonsignificant increase in agitation (40% vs 20%; P=0.06), but no withdrawal symptoms and no difference in length of stay.[35] However, this was a population admitted with behavioral disturbance and applicability to the general population of persons prescribed benzodiazepines and sedative hypnotics for agitation, insomnia, or delirium is unclear.

One small RCT (mean age 52 years) found discontinuation of zolpidem associated with no increase in risk of rebound insomnia (% of patients with worse sleep efficiency at month 1, 4, and 12: 31% vs. 32%, 30% vs. 25%, 40% vs. 30%) or clinically significant withdrawal (none reported).[36]

Discussion

Although commonly used in older adults for insomnia, agitation, and delirium, the American Geriatrics Society Beers Criteria for Potentially Inappropriate Medical Use in Older Adults[7] and the Choosing Wisely[8] campaign recommends against use of benzodiazepines and sedative hypnotics due to concerns of serious risks such as fractures and mortality. Some studies suggest that benzodiazepines and sedative hypnotics are associated with increased risk of mortality and fractures. However, findings were inconsistent, indications for treatment were usually not specified, and studies had methodological limitations, including susceptibility to confounding. Although we found no studies on serious harms in older adults using benzodiazepines or sedative hypnotics to treat delirium, some evidence indicates that benzodiazepines can cause or exacerbate delirium. Although we found no studies on serious harms in older adults using benzodiazepines or sedative hypnotics specifically to treat agitation, as benzodiazepines are known to have the potential to be overly sedating and induce respiratory depression or hypotension, expert consensus recommends limiting their use to cases where alcohol or benzodiazepine withdrawal or central nervous system (CNS) stimulant intoxication is suspected and avoiding them in cases where CNS depressant intoxication is suspected. Although chronic benzodiazepine use discontinuation can result in withdrawal, which can be serious and increase risk of agitation, delirium, and falls, evidence is too limited to draw conclusions on effects of discontinuation of these medications

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Use of Anticholinergic Drugs in Older Adults with Cognitive Impairment: Rapid Evidence Synthesis

This report was prepared by the Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University, under Contract No. VA268-16-Q-0140, in support of an HSR&D research study focused on Identifying, Measuring, and Facilitating Opportunities for De-Intensification of Medical Services.

KEY MESSAGES

Why is this important?

- The American Geriatrics Society Beers Criteria for Potentially Inappropriate Medical Use in Older Adults strongly recommends avoiding use of anticholinergic drugs in older adults with dementia or cognitive impairment because of the potential for adverse effects on cognition.
- Nearly a quarter of older adults with dementia currently receive at least one anticholinergic medication.

What is the association between anticholinergics and risk of cognitive impairment when used in older adults?

- The Beers Criteria cite three systematic reviews and five observational studies regarding the use of anticholinergics. The systematic reviews describe a dearth of evidence related to the adverse effects of anticholinergics, although the observational studies suggest a dose-response relationship of anticholinergics with increased risk of hospitalization for cognitive dysfunction or greater cognitive impairment.
- A subsequent systematic review found anticholinergics associated with increased risk of cognitive impairment (3 studies, OR 1.45; 95% CI 1.16-1.73; I^2=0%).

What are the benefits and harms of discontinuing anticholinergics in older people?

- Another recent systematic review reported conflicting results on effects of discontinuation of anticholinergics on cognitive function, with two observational studies reporting improved cognitive performance after discontinuation and two trials reporting no differences.

What are the implications of our findings?

- Anticholinergic drugs are associated with increased risk of cognitive impairment in older persons, although evidence for this association is somewhat weak.
- Evidence on effects of anticholinergic de-intensification or discontinuation is inconsistent, with some cohort studies finding improvement in cognitive function upon discontinuation of anticholinergics.

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Background

Drugs with anticholinergic properties are used for a wide variety of medical conditions in older adults, including cardiovascular disease, incontinence, asthma, allergies, depression, anxiety, sleep disorders, dementia, and Parkinson's disease.[1,2] Additionally, their use for the treatment of the extrapyramidal side effects of antipsychotic medications is increasing.[3] Use of anticholinergics is common, with more than half of the general population using at least one anticholinergic drug.[4] Nearly a quarter (23%) of elderly adults with dementia, who may be more susceptible to the cognitive harms associated with anticholinergics, receive at least one anticholinergic medication,[5] and as many as one in ten older adults in the United States use anticholinergics inappropriately.[6]

Potential harms associated with the use of anticholinergic drugs include gastrointestinal and ophthalmologic symptoms.[7] Most importantly for the elderly population, anticholinergic drugs can also cause central nervous system symptoms, including dizziness, lightheadedness, confusion, and delirium.[8]

Therefore, de-intensification of anticholinergic drugs in older adults could be an important target for de-intensification efforts. The purpose of this rapid evidence review is to assist the VA in assessing anticholinergics in older persons with dementia or cognitive impairment as a potential target for de-intensification, based on evidence on harms associated with use of anticholinergics in this population as well as evidence on benefits and harms of de-intensification of anticholinergic use.

Current Guidelines

The 2015 version of the Beers Criteria recommends against use of anticholinergics in patients older than 65 years with dementia or cognitive impairment.[9] Of note, the Beers Criteria focus on the following anticholinergic drugs: brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dexbrompheniramine, dexchlorpheniramine, dimenhydrinate, diphenhydramine, doxylamine, hydroxyzine, meclizine, promethazine, and triprolidine; however, many other drugs are associated with anticholinergic effects.

METHODS

Topic Section and Scope Development

This review included studies relevant to the following key questions and eligibility criteria.

Key Questions

Key Question 1: What is the association between use of anticholinergics in elderly adults and risk of dementia or cognitive impairment?

Key Question 2: What are the benefits and harms of discontinuing anticholinergics in elderly adults?

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Eligibility Criteria

- Population: Elderly adults with muscle spasms
- Interventions: Drugs with an anticholinergic effect (study-defined)
- Comparisons:
    - Key Question 1: Use of anticholinergics versus non-use
    - Key Questions 2: Discontinuation versus continuation of anticholinergics
- Outcomes:
    - Key Question 1: Cognitive impairment, including delirium and dementia
    - Key Question 2: Cognitive impairment, including delirium and dementia; falls and fractures; mortality; withdrawal due to adverse events; serious adverse events
- Timing: Any
- Setting: Any
- Study design: Systematic reviews, randomized controlled trials, and concurrently-controlled studies

Searching and Study Selection

We used the 2015 American Geriatrics Society Beers Criteria Evidence Tables[9] as the foundation for our search. To identify additional guidelines, reviews and studies, we searched MEDLINE® using terms for drug names and potentially inappropriate prescribing and tapering. We also searched the National Guideline Clearinghouse, Agency for Healthcare Research and Quality (AHRQ), the Canadian Agency for Drugs and Technologies in Health (CADTH), Cochrane, and ECRI Institute systematic review organization websites; reference lists of included studies and Google. One reviewer used the above prespecified criteria to select studies.

Data Synthesis and Quality Assessment

One reviewer abstracted data on sample size, setting, and results. We did not formally rate risk of bias of individual studies or strength of the body of evidence. Instead, we qualitatively commented on the type and seriousness of methodological limitations, based on the principles outlined in the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[10] We also informally considered the strength of the body of evidence, based on directness, precision, and consistency.[11]

Results

Key Question 1: What is the association between use of anticholinergics in elderly adults and risk of dementia or cognitive impairment?

The Beers Criteria recommendation regarding the use of anticholinergic drugs was based on evidence from three systematic reviews[2,12,13] and five observational studies[14-18] (**Table 1**). One systematic review[12] evaluated studies of risk scales for anticholinergic drugs and reported questionable validity of the scales, with large variations in the criteria used to determine anticholinergic activity. A review on the effect of increasing anticholinergic load on cognitive function and delirium reported insufficient evidence for a non-reversible effect of anticholinergic

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burden on cognition outcomes, based on 46 short-term or cross-sectional studies.[13] The third systematic review assessed the efficacy of hydroxyzine on symptoms of generalized anxiety disorder, but the review provided no data on specific adverse events, including memory impairment.[2]

Three observational studies cited in the Beers Criteria support a dose-response relationship between anticholinergic drug use and cognitive impairment.[16-18] A large (n=36,015) claims database study reported increasing risk of hospitalization for confusion, dementia, or delirium with increasing number of anticholinergic drugs (vs. no anticholinergics: IRR 1.17, 95% CI 0.99-1.39 for 1 drug; IRR 2.58, 95% CI 1.91-3.48 for 2 drugs; and IRR 3.87, 95% CI 1.83-8.21 for 3 drugs).[17] A small (n=278) prospective cohort study found that anticholinergic risk score, number of anticholinergic medications, and increasing number of anticholinergic medications were associated with delirium severity, and that use of any anticholinergic medication was associated with presence of dementia and with Delirium Index score.[16] Another small (n=249) study that conducted retrospective and prospective analyses of an American outpatient sample reported that the Anticholinergic Risk Score (ARS), which is based on the number of anticholinergic drugs and the degree of their anticholinergic effects, was associated with anticholinergic adverse events in retrospective (RR 1.5, 95% CI 1.3-3.8) and prospective (RR 2.1, 95% CI 1.5-2.9) analyses.[18]

Two additional observational studies were cited in the Beers Criteria.[14,15] A small (n=426) hospital cohort study reported that use of diphenhydramine as a sleep aid in older adults (vs. non-use) was associated with anticholinergic adverse events, including cognitive decline (RR 1.7, 95% CI 1.3-2.3), inattention (RR 3.0, 95% CI 1.5-5.9), disorganized speech (RR 5.5, 95% CI 1.0-29.8), altered level of consciousness (RR 3.1, 95% CI 1.6-6.1), and behavioral disturbances (RR 5.6, 95% CI 1.0-19.9).[14] A moderately large (n=1,558) observational study of histamine-2 receptor antagonist use versus non-use in a community setting found continuous use associated with cognitive impairment (OR 2.42, 95% CI 1.17-5.04).[15]

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Table 1. Studies supporting the Beers Criteria regarding anticholinergic drugs

Author, Year Study Design	Data Source, Sample Size	Purpose	Included Drugs	Findings	Comment
Duran, 2013[12] Systematic Review	7 included studies (3 cross-sectional and 4 cohorts) Total n=2,517	Assessment of anticholinergic drug risk scales	Studies assessed 22-117 different anticholinergic drugs	Validity of identifying drugs with anticholinergic activity is questionable, with large variation in criteria	Assesses risk scales, not drugs
Fox, 2014[13] Systematic Review	46 included studies (38 cohorts, 6 trials, and 2 case-controls) Total n=60,944	Assessment of the effect of increasing anticholinergic load on cognitive function, delirium, physical function, and mortality	Not reported in the Beers Criteria evidence table	Little, if any, evidence of a non-reversible effect of increased anticholinergic burden on cognition outcomes; 5 studies did not show negative effects	Studies were cross-sectional or had short follow-up
Guaiana, 2010[2] Systematic Review	5 included studies (all trials) Total n=NR	Efficacy of hydroxyzine vs. placebo or active control on symptoms of generalized anxiety disorder	Hydroxyzine	Hydroxyzine superior to placebo and comparable to active controls, based on few small studies, many of which had methodologic problems	Little relevant data
Kalisch, 2014[17] Retrospective Cohort	Australian Department of Veterans' Affairs administrative claims database N=36,015	Effect of anticholinergics on risk of hospitalization for confusion, dementia, or delirium	13 included drugs (Loperamide, disopyramide, baclofen, carbamazepine, prochlorperazine, amantadine, haloperidol, ziprasidone, quetiapine, risperidone, paroxetine, and cyproheptadine)	Adjusted IRR per 10 years (vs. 0 drugs) 1 drug: 1.17 (0.99-1.39) 2 drugs: 2.58 (1.91-3.48) 3 drugs: 3.87 (1.83-8.21)	Risk of hospitalization for confusion or dementia increases with increasing number of anticholinergic drugs
Agostini, 2001[14] Prospective Cohort	United States hospital inpatients N=426	Rate of diphenhydramine use among elderly hospitalized patients and adverse events	Diphenhydramine	RR, exposed vs. unexposed Cognitive decline: 1.7 (1.3-2.3) Inattention: 3.0 (1.5-5.9) Disorganized speech: 5.5 (1.0-29.8) Altered level of consciousness: 3.1 (1.6-6.1) Behavioral disturbance: 5.6 (1.0-19.9)	Use of diphenhydramine as a sleep aid in older adults associated with anticholinergic adverse events
Han, 2001[16] Prospective Cohort	Canadian hospital N=278	Longitudinal association of anticholinergics and severity of delirium symptoms	Not reported in the Beers Criteria evidence table	Anticholinergic score (not defined), number of anticholinergic medications, and increasing number of anticholinergic medications are associated with delirium severity; use of any anticholinergic medication associated with presence of dementia and with Delirium Index score	Use of and increasing number of anticholinergic drugs associated with delirium in elderly patients

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Rudolph, 2008[18] Prospective and Retrospective Cohort	United States outpatient clinics N=249	Predictive utility of Anticholinergic Risk Score (ARS)* for adverse events	Not reported in the Beers Criteria evidence table	Retrospective: ARS associated with anticholinergic adverse events (RR 1.5, 95% CI 1.3-3.8) Prospective: ARS associated with anticholinergic adverse events (RR 2.1, 95% CI 1.5-2.9)	Evidence of a dose-response relationship
Boustani, 2007[15] Case-control, Prospective Cohort, and Cross-sectional Analyses	United States community setting N=1,558	Association of histamine-2 receptor antagonists and incident cognitive impairment	Not reported in the Beers Criteria evidence table	No use vs. intermittent use vs. continuous use Cognitive impairment: 17% vs. 19% vs. 34%; p=0.03; continuous use vs. no use, OR 2.42 (1.17-5.04)	Cognitively-intact Blacks older than 65 years who used histamine-2 receptor antagonists continuously were at greatest risk of cognitive impairment

*Risk based on number of drugs and degree of anticholinergic effect

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Subsequent to the publication of the Beers Criteria, a systematic review of 18 studies evaluated the association of drugs with anticholinergic effects with cognitive impairment in older adults[19] (**Table 2**). This review used multiple criteria to determine anticholinergic drugs (as a whole drug class, when defined; using a scoring system for anticholinergic effect [ARS]; and using a pre-defined validated list of anticholinergic drugs) and included three studies that assessed the association of anticholinergic drugs with cognitive impairment. While only one of the three studies reported a significant risk of cognitive impairment with anticholinergics, the other studies were small and the pooled estimate suggested an increased risk of cognitive impairment, with an OR of 1.45 (95% CI 1.16-1.73; I^2=0%).

Table 2. New evidence supporting the Beers Criteria regarding anticholinergic drugs

Author Year Study Design	Data Source, Sample Size	Purpose	Included drugs	Findings	Comment
Ruxton, 2015[19] Systematic Review	18 included studies (2 trials, 10 prospective cohorts, 4 retrospective cohorts, and 2 case-control studies) Total n=124,286	Association of anticholinergic drugs with cognitive impairment, falls, and all-cause mortality in older adults	Drug classes defined as anticholinergics, anticholinergics as defined by a scoring system, or use of anticholinergics included in a validated list	Exposure to anticholinergic drugs associated with cognitive impairment based on 3 studies (OR 1.45, 95% CI 1.16-1.73; I^2=0%)	Few studies (3) contributed to cognitive impairment findings

Key Question 2: What are the benefits and harms of discontinuing anticholinergics in older adults?

One systematic review assessed effects of anticholinergic discontinuation on cognitive impairment in older adults[20] (**Table 3**). This review included four studies (2 trials and 2 prospective cohort studies), which differed in population, drugs, discontinuation interventions, and outcome assessment methods and timing. The two trials (n=64 and n=15) were both conducted among nursing home residents and reported no improvement in cognition following discontinuation of anticholinergic drugs. The 2 cohort studies were also small (n=9 and n=21) and were shorter in duration (2-3 weeks vs. 4-8 weeks in the trials) and reported significant improvements in cognition in patients with Parkinson's disease or schizophrenia, respectively.

Table 3. Evidence regarding discontinuation of anticholinergic drugs

Author Year Study Design	Data Source, Sample Size	Purpose	Included drugs	Findings	Comment
Salahudeen, 2014[20] Systematic Review	4 included studies (2 trials and 2 prospective cohorts) Total n=109	The effect of discontinuation of anticholinergic drugs on cognitive outcomes	Any study-defined anticholinergic except for inhaled medications	Benefit of discontinuation on cognitive outcomes seen in cohort studies but not trials	Few studies (4) with very small sample sizes and heterogeneous populations, interventions, outcomes, and timing

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Discussion

While anticholinergic drugs are commonly used in older adults, the American Geriatrics Society Beers Criteria for Potentially Inappropriate Medical Use in Older Adults[9] recommends against use of anticholinergics in older adults with dementia or cognitive impairment due to concerns about risks to cognition. The recommendation was based on three systematic reviews and five observational studies, which provided some evidence of a dose-response relationship between anticholinergic drug use and cognitive impairment. A subsequent systematic review found anticholinergics associated with increased risk of cognitive impairment, based on three studies. Another recent systematic review identified four studies (2 trials and 2 cohorts) evaluating the impact of discontinuation of anticholinergic drugs on cognitive outcomes. Improvements in cognitive performance were noted in the observational studies, but not in the trials.

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Skeletal Muscle Relaxants for Older Adults: Rapid Evidence Synthesis

This report was prepared by the Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University, under Contract No. VA268-16-Q-0140, in support of an HSR&D research study focused on Identifying, Measuring, and Facilitating Opportunities for De-Intensification of Medical Services.

KEY MESSAGES

Why is this important?

- The American Geriatrics Society Beers Criteria for Potentially Inappropriate Medical Use in Older Adults strongly recommends avoiding use of skeletal muscle relaxants in older adults because of their potential for anticholinergic adverse effects, sedation, and increased risk of injury.
- Approximately 15% of the 2 million people who use skeletal muscle relaxants annually are older adults, suggesting a potential target for de-intensification.

What is the association between skeletal muscle relaxants and risk of injury and mortality when used in older adults?

- In two studies cited by the Beers Criteria, skeletal muscle relaxants (primarily cyclobenzaprine and methocarbamol) were associated with increased risk of injuries (OR range, 1.32 to 1.35) in older adults (mean age 75 years) when prescribed for various indications.
- Skeletal muscle relaxants are associated with increased risk of emergency department care for falls and fractures within 1 year of new use in older veterans when they are prescribed specifically for chronic pain or for various indications (OR range, 1.81 to 2.20). New use was associated with increased risk of hospitalization for falls and fractures in older veterans when prescribed for various indications.
- Studies have not shown an association between new use of skeletal muscle relaxants in older adults and increased risk of mortality.

What are the benefits and harms of discontinuing skeletal muscle relaxants versus continuing them in older adults?

- We found no studies evaluating the effects of discontinuing skeletal muscle relaxants in older adults.

What are the implications of our findings?

- Skeletal muscle relaxants are associated with increased risk of injury in older adults.
- Alternative pharmacological and nonpharmacological treatments and approaches for management of muscular conditions and spasticity are available and may provide a superior balance of benefits to harms.

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Background

Skeletal muscle relaxants are a heterogeneous group of medications approved by the U.S. Food and Drug Administration (FDA) for treatment of musculoskeletal conditions or spasticity due to neurological disorders. However, for common musculoskeletal conditions such as low back pain, guidelines generally do not recommend skeletal muscle relaxants as first-line medication therapy due to limited benefits and potential harms.[1] Common adverse effects of skeletal muscle relaxants include confusion, sedation, and orthostatic hypotension, all of which can increase risk of accidents and injuries. Age-related changes in drug metabolism, increased frailty, and greater likelihood of polypharmacy-related drug interactions may increase the risks of skeletal muscle relaxants in older adults.[2] In addition, carisoprodol is metabolized to meprobamate, a medication associated with physical dependence and abuse and classified by the FDA as a schedule IV drug under the Controlled Substances Act.

Among the 2 million people who use skeletal muscle relaxants annually, approximately 15% are older adults, suggesting a potential target for de-intensification efforts.[3] To assist the Veterans Health Administration in assessing use of skeletal muscle relaxants in older adults as a potential target for de-intensification, we performed a rapid evidence-based synthesis of evidence, focusing on risk of injury and mortality and effects of discontinuation in older adults.

Guidelines on Skeletal Muscle Relaxants in Older Adults

In the 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults[4] the American Geriatrics Society strongly recommends avoiding use of skeletal muscle relaxants in older adults. Note that the Beers Criteria focus on use of skeletal muscle relaxants approved for treatment of musculoskeletal conditions (specifically carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, and orphenadrine) and not on skeletal muscle relaxants approved for treatment of spasticity due to neurological conditions (e.g., baclofen, dantrolene, or tizanidine). Guidelines from other organizations also consistently consider skeletal muscle relaxant use in older adults to be potentially harmful and recommend limiting or avoiding their use (**Table 1**).

Table 1. Summary of guideline statements on using skeletal muscle relaxants in older adults

Source	Guideline Statement
American Geriatric Society Foundation for Health in Aging, 2012[5]	AVOID muscle relaxants in older adults. Reasons: They can leave you feeling groggy and confused, increase your risk of falls, and cause constipation, dry mouth, and problems urinating. Plus, there is little evidence that they work well.
American Geriatrics Society Beers Criteria for Potentially Inappropriate Medical Use in Older Adults, 2015 [4]	Most muscle relaxants poorly tolerated by older adults because some have anticholinergic adverse effects, sedation, increased risk of fractures; effectiveness at dosages tolerated by older adults questionable
Institute for Clinical Systems Improvement, 2016[6]	Work Group Recommendation: Sedative hypnotics including benzodiazepines and carisoprodol should be rarely used and if so for short-term (<1 week) treatment of muscle spasms related to acute pain. Use of non-sedative hypnotic muscle relaxants are of low benefit, but if used, limit to less than four weeks. Do not use carisoprodol for pain. Muscle relaxants are central nervous system (CNS) depressants and cause additive sedation and other adverse effects, especially in combination with opioids…and specifically in the geriatric population.

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Methods

Topic Selection and Scope Development

This review included studies relevant to the following key questions and eligibility criteria.

Key Questions

Key Question 1: What is the association between use of skeletal muscle relaxants in older adults with muscle spasms and risk of mortality and serious injury?

Key Question 2: What are the benefits and harms of discontinuing skeletal muscle relaxants in older adults with muscle spasms?

Eligibility Criteria

- Population: Older adults (>65 years of age)
- Interventions: Skeletal muscle relaxants approved for treatment of musculoskeletal conditions and addressed in the Beers criteria: carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, orphenadrine (benzodiazepines are evaluated in a separate report)
- Comparison:
    - Key Question 1: Use of skeletal muscle relaxants versus non-use
    - Key Questions 2: Discontinuation versus continuation of skeletal muscle relaxants
- Outcomes:
    - Key Question 1: Serious injury and mortality
    - Key Question 2: Withdrawal and relapse
- Timing: Any
- Setting: Any
- Study design: Systematic reviews, randomized controlled trials, and concurrently-controlled studies

Searching and Study Selection

We used the 2015 American Geriatrics Society Beers Criteria Evidence Tables as the foundation for our search.[4] To identify additional guidelines, reviews and studies, we searched MEDLINE® back to January 2010 using terms for drug names and potentially inappropriate prescribing and tapering. We also searched the National Guideline Clearinghouse, Agency for Healthcare Research and Quality, the Canadian Agency for Drugs and Technologies in Health, Cochrane, and ECRI Institute systematic review organization websites, reference lists of included studies, and Google. One reviewer used the above prespecified criteria to select studies.

Data Synthesis and Quality Assessment

One reviewer abstracted data on sample size, setting, and results. We did not formally rate risk of bias of individual studies or strength of the body of evidence. Instead, we qualitatively commented on the type and seriousness of methodological limitations, based on the principles

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outlined in the AHRQ *Methods Guide*.[7] We also considered the strength of the body of evidence based on directness, precision, and consistency.[8]

Results

Key Question 1: What is the association between use of skeletal muscle relaxants in older adults with muscle spasms and risk of mortality and serious injury?

We identified five studies related to Key Question 1 (**Table 2**).

In two cohort studies cited by the Beers Criteria,[4] skeletal muscle relaxants (primarily cyclobenzaprine and methocarbamol) were associated with increased risk of injuries (OR range, 1.32 to 1.35).[2,9] The mean age of individuals in these studies was 75 years. Skeletal muscle relaxant type, dose, and duration of use were not described. Neither study was conducted in a VA population. Results were adjusted for confounding medications in both studies[2,9] and additionally for demographics, socioeconomic status, and some medical and psychiatric co-morbidities in the larger Southern California study.[2]

Two subsequent studies in nationwide VA cohorts prescribed skeletal muscle relaxants for any reason[10] or specifically for chronic pain[11] also found skeletal muscle relaxants associated with increased risk of emergency department care for falls and fractures within 1 year of new use (OR range, 1.81 to 2.20). Skeletal muscle relaxants were also associated with increased risk of hospital care for falls of fractures within 1 year of new use when prescribed for any reason in one VA study (OR 1.46; 95% CI, 1.001 to 2.12),[10] but not in a study of Veterans prescribed skeletal muscle relaxants for chronic pain (OR 1.10; 95% CI, 0.77 to 1.58).[11] In both studies, skeletal muscle relaxant prescriptions were consistently associated with slightly *decreased* risk of mortality (OR range, 0.80 to 0.87); the pathophysiological mechanism for this association is unclear and could be due to confounding by indication (e.g., prescribing of skeletal muscle relaxants to patients who are more functional or active).

Skeletal muscle relaxant use was associated with increased fracture risk (OR 1.40; 95% CI, 1.15–1.72) in an earlier nationwide case-control study of the Medicare Advantage population.[12] But, as the “skeletal muscle relaxant” category in this study included the bladder selective muscarinic antagonist, oxybutynin, and this drug had the highest frequency of use, the applicability of these findings to the six skeletal muscle relaxants of interest in this report is limited.

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Table 2. Skeletal muscle relaxants in older adults: risks of serious injury and mortality

Author, Year Study Design	Data Source Sample Size Mean Age	Adjustment for Demographics, Lifestyle, Socioeconomic Status, Medical and Psychiatric Co-morbidities and Co-medications	Drugs Indication for Prescription Dose	Follow-up Period	Injuries	Mortality
Golden, 2010[12] Case control	Humana's National Medicare Advantage N=8164 cases Mean age=80 years	No lifestyle or socioeconomic status	Primarily cyclobenzaprine, but skeletal muscle relaxant category also included oxybutynin Indication and dose not reported	Not reported	Fractures: OR 1.40 (95% CI, 1.15 to 1.72)	Not reported
*Billups, 2011[9] Retrospective Cohort	Kaiser Permanente Colorado N=11,875 Mean age=75.5 years	Only for confounding medications	Primarily cyclobenzaprine and methocarbamol Indication and dose not reported	60 days before vs. after	Injuries (e.g., fracture, contusion, laceration, injury NOS, fall): OR 1.35 (95% CI, 1.01 to 1.81)	Not reported
*Spence, 2013[2] Case control	Kaiser Permanente Southern CA N=27974 cases, 104303 controls Mean age=75 years	Not lifestyle or arthritis	Primarily cyclobenzaprine and methocarbamol Indication and dose not reported	Not reported	Injuries (non-vertebral fractures, soft tissue injuries, fall-related hospital admissions): OR 1.32 (95% CI, 1.16 to 1.50)	Not reported
Alvarez, 2015[10] Retrospective cohort	128 VA hospitals N=55,566 Aged 65-74=58% Aged 75-84=37%	Not lifestyle, function	Drug type, indication, and dose not reported	Within 1 year of new use	ED falls and fractures: OR 2.20 (95% CI, 1.84 to 2.63) Hospitalization falls and fractures: OR 1.46 (95% CI, 1.001 to 2.12)	OR 0.87 (95% CI, 0.81 to 0.94)
Makris, 2015[11] Retrospective cohort	150 VA hospitals N=6,932 Aged 65-74=44% Aged 75-84=46%	Not lifestyle, function	SMR type and dose not reported Prescription for chronic pain	Within 1 year of new use	ED falls and fractures: OR 1.81 (95% CI, 1.57-2.09); Hospitalizations falls and fractures: OR 1.10 (95% CI, 0.77 to 1.58)	OR 0.80 (95% CI, 0.74 to 0.86)

*Cited in the Beers Criteria

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Key Question 2: What are the benefits and harms of discontinuing skeletal muscle relaxants in older adults with muscle spasms?

We did not identify any study that evaluated the effects of discontinuation of skeletal muscle relaxants in older adults.

Discussion

Although commonly used in older adults, the American Geriatrics Society Beers Criteria for Potentially Inappropriate Medical Use in Older Adults[4] recommends against use of skeletal muscle relaxants approved by the FDA for treatment of musculoskeletal conditions, due to concerns about risk of injury. Studies found that such skeletal muscle relaxants are consistently associated with increased risk of injuries, falls, and fractures in older adults, including VA populations, although skeletal muscle relaxants were not associated with increased risk of mortality. We found no studies evaluating the effects of discontinuing skeletal muscle relaxants in older adults. However, carisoprodol is a schedule IV medication associated with physical dependence and withdrawal symptoms. Given the risk of harms and availability of other pharmacological and nonpharmacological treatments for musculoskeletal conditions with a more favorable benefit to harm profile, discontinuation of skeletal muscle relaxants in older adults may represent a potential target for de-intensification efforts.

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Inappropriate Antidepressant Use in Older Adults: Rapid Evidence Synthesis

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KEY MESSAGES

Why is this important?

- The proportion of older adults using antidepressant medications has risen dramatically over the past 25 years, as have hospital admissions for antidepressant-related adverse events.
- The American Geriatrics Society Beers Criteria for Potentially Inappropriate Medical Use in Older Adults strongly recommends against the use of tricyclic antidepressants and the selective serotonin reuptake inhibitor paroxetine due to anticholinergic adverse effects, sedation, and increased risk of orthostatic hypotension.

What is the association between use of tricyclic antidepressants or paroxetine in older adults with depression and risk of mortality, falls, or anticholinergic side effects?

- In a large cohort study cited by the Beers Criteria, both tricyclic antidepressants (TCAs) (adjusted HR 1.16; 95% CI 1.10 to 1.22) and paroxetine (adjusted HR 1.24; 95% 1.14 to 1.35 were associated with increased risk of mortality versus nonuse. A more recent study, not limited to older adults, found excess mortality with TCA use, but not with paroxetine.
- Results from the cohort study and two other systematic reviews were consistent in finding an increased risk of falls and fracture with TCAs and paroxetine.
- Evidence on an association between use of TCAs and paroxetine and anticholinergic effects such as sedation or cognitive dysfunction is limited. Anticholinergic adverse effects such as sedation, dry mouth, and urinary retention are commonly observed in research studies and in clinical practice.

What are the benefits and harms of discontinuing tricyclic antidepressants or paroxetine versus continuing them in older people?

- There is limited evidence about the risks and benefits of discontinuation. One study showed that selective serotonin reuptake inhibitor (SSRI) discontinuation (including paroxetine) may increase risk of depressive symptoms in people with dementia, with no change in risk of mortality or falls.
- We found no direct evidence on the effect of TCA discontinuation in older adults.

What are the implications of our findings?

- Evidence shows TCA and paroxetine use increases risk of falls and fracture and may increase mortality risk; anticholinergic side effects are commonly reported in clinical practice.
- Alternative antidepressants that are associated with fewer anticholinergic adverse effects are available for use in older adults.

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Background

Depression in adults over age 65 is common and is associated with significant burden of disease, including increased risk of death that worsens with advancing age.[1-3] The proportion of older adults using antidepressant medications has risen from about 3% to 25% over the past 25 years.[4] Hospital admissions for antidepressant-related adverse events have risen even more dramatically in this age group, up nearly 65% during the 10-year period from 2001 to 2011.[5] Multiple drug classes are used to treat depression, including selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), norepinephrine and dopamine reuptake inhibitors (NDRIs), and tricyclic antidepressants (TCAs), among others. SSRIs are the most commonly prescribed antidepressant in the United States, but over 10% of antidepressant prescriptions are for TCAs.[6-8] Over two-thirds of antidepressants prescribed to older adults in the United States are for treatment of depression, but antidepressants are also prescribed in patients with anxiety, insomnia, dementia, or pain.[8] Nearly 10% of antidepressants are prescribed to patients with no mental health or pain indication.

Antidepressants have similar efficacy in older adults with depression across drug classes, although adverse events associated with each class varies.[9,10] For example, TCAs are associated with anticholinergic adverse events, sedation, orthostatic hypotension, and increased risk of cardiac events, while SSRI use can lead to nausea, insomnia, tremors, sexual dysfunction, and weight gain. More serious harms associated with SSRIs include risk of suicide/suicidal ideation, arrhythmia, gastrointestinal bleeding, and falls. The risk of negative effects associated with antidepressants increases with polypharmacy.[11]

Despite recommendations to avoid TCAs and paroxetine in older adults, they still appear to be commonly used. A large United Kingdom study found that 32% of antidepressant prescriptions for older adults with a new episode of depression were for TCAs, with amitryptiline the third most commonly prescribed antidepressant and paroxetine the fifth most commonly prescribed antidepressant.[12] There is also evidence that antidepressants in general are over-prescribed in older adults.[6,13,14] For example, a study of Veterans Affairs Community Living Center residents (n=3,692) showed that antidepressants were prescribed to 42% of people without depression, of whom only 4% (48/1,190) had an FDA-approved indication for antidepressant use (indicating overuse).[6]

To assist the Veterans Health Administration in assessing use of TCA's and paroxetine in older adults as a potential target for de-intensification, we performed a rapid evidence-based synthesis of evidence on harms of these drugs and on effects of discontinuation.

Current Guidelines

Current treatment recommendations on the use of antidepressants are summarized in **Table 1**. The American Geriatric Society (Beers Criteria) recommends against use of TCAs in older adults, due to risk of anticholinergic adverse effects, sedation, and increased risk of orthostatic hypotension (which can lead to other adverse events, such as falls).[15] The Beers Criteria also recommend against the use of paroxetine, an older SSRI, due to risk of anticholinergic effects (anticholinergic effects of paroxetine are more pronounced than with other SSRIs). Other organizations vary in their recommendations regarding TCAs; none are focused specifically on older adults. For example, the American Psychiatric Association recommends other drug classes

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over TCA use due to increased risk of orthostatic hypotension and anticholinergic effects, while the Anxiety and Depression Association of American recommends avoiding TCA use, also due to anticholinergic effects. In addition to the guidelines listed in **Table 1**, the American College of Physicians has issued recommendations on the use of second-generation antidepressants (SSRIs, SNRIs, and selective serotonin norepinephrine reuptake inhibitors [SSNRIs]) but made no recommendation on the use of first-generation antidepressants (TCAs and monoamine oxidase inhibitors [MAOIs]) due to their less favorable safety profile.[16]

Table 1. Current recommendations on the use of antidepressants

Organization	Recommendation
American Geriatric Society[15]	• Avoid use of TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin (in doses >6 mg/d), imipramine, nortriptyline, protriptyline, trimipramine) and paroxetine (an SSRI). Strength of recommendation: strong; high-quality evidence
American Psychiatric Association[17]	• SSRIs, SNRIs, and other antidepressants should be considered over MAOIs or TCAs.
Anxiety and Depression Association of America[18]	• SSRIs, TCAs, and MAOIs are evidence-based; the side effect profile of SSRIs is likely preferable; fluoxetine is less ideal due to its long half-life (if medication changes are needed), as is paroxetine due to anticholinergic characteristics and notable drug-drug interactions.
Kaiser Permanente Care Management Institute[19]	• Any class of antidepressant (SSRI, TCA, SNRI, NRI, or dopamine agonist) is recommended for first-line treatment of major depressive disorder. Strong recommendation • Given the equivalence of therapeutic effect, clinicians may base the choice of antidepressant on patient's prior response, patient and clinician preference, potential side effects, and cost. Weak recommendation

MAOI = monoamine oxidase inhibitors; NRI = norepinephrine reuptake inhibitor; SNRI = serotonin and norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant

Methods

Topic Selection and Scope Development

This review included studies relevant to the following key questions and eligibility criteria.

Key Questions

Key Question 1: What is the association between use of tricyclic antidepressants or paroxetine in older adults with depression and risk of mortality, falls, or anticholinergic side effects?

Key Question 2: What are the benefits and harms of discontinuing tricyclic antidepressants or paroxetine in older adults with depression?

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Eligibility Criteria

- Population: Adults age ≥65 years with depression
- Intervention: Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin [doses>6 mg/d], imipramine, nortriptyline, protriptyline, primipramine) or paroxetine
- Comparator:
    - Key Question 1: TCA or paroxetine use versus nonuse
    - Key Question 2: Discontinuation versus continuation of TCA or paroxetine
- Outcomes: Mortality, falls and/or fractures, serious anticholinergic side effects (i.e., leading to hospitalization)
- Timing: Any
- Setting: Any
- Study design: Systematic reviews, randomized controlled trials, and large, controlled cohort studies

Study Selection

We included studies on antidepressant use cited by the 2015 American Geriatrics Society Beers Criteria.[15] We searched Ovid MEDLINE®, the Cochrane Database of Systematic Reviews and Embase® for relevant studies published subsequent to the Beers Criteria. In addition to MEDLINE, we also searched the National Guideline Clearinghouse and the websites of professional organizations to identify other guidelines on the use of antidepressants in older adults. One reviewer used the eligibility criteria described above to select studies.

Results

Key Question 1. What is the association between use of tricyclic antidepressants or paroxetine in older adults with depression and risk of mortality, falls, or anticholinergic side effects?

Mortality

The Beers Criteria[15] cites a large (n=60,746), 2011 cohort study[12,20] conducted in the United Kingdom on harms associated with TCAs and paroxetine. That study found use of TCAs and paroxetine both associated with increased mortality risk relative to nonuse (**Table 2**). The same study found that risk of mortality was both dose-dependent (higher doses=increased risk) and highest in the first 28 days of antidepressant use and in the first 28 days following drug withdrawal. A more recent, large database study of antidepressant exposures over a 15-year period found TCAs associated with a higher rate of death per 10,000 exposures (40.7, 95% CI 35.9 to 46.0), but paroxetine was not associated with increased rate of death (1.4, 95% CI 0.5 to 3.4; **Table 2**).[21] In the latter study, detailed patient demographics were not reported and the data analysis was not limited to patients over age 65 years, which could account for the somewhat discordant findings for paroxetine.

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Table 2. Antidepressant use and risk of mortality in older adults

Author Year	Sample Size Study Design Setting/Data source Population	Main Findings
*Coupland 2011[12,20]	n=60,746 Cohort study 570 UK general practices Mean age 75 years (SD 7.6) 67% female Depression severity: 70% mild; 26% moderate; 5% severe	Use vs. no antidepressant use – TCAs: aHR 1.16 (1.10 to 1.22) Paroxetine: aHR 1.24 (1.14 to 1.35)
Nelson 2017[21]	n=64,103 adjusted TCA exposures; n=34,720 adjusted paroxetine exposures Cohort study/ National Poison Data System Patient demographics not reported; analysis not limited by age	Mortality Index per 10,000 exposures (deaths/number of exposures x 10,000) – TCAs: 40.7 (95% CI 35.9 to 46.0) Paroxetine: 1.4 (95% CI 0.5 to 3.4)

*Included in American Geriatrics Society Beers Criteria evidence review

Falls

The Beers Criteria recommends against the use of TCAs and paroxetine, in part, due to the increased risk of orthostatic hypotension. Orthostatic hypotension in the elderly can increase the risk of falls, which in turn can lead to associated morbidity (including fracture) and mortality.[22,23] The large Coupland study cited by the Beers Criteria found use of TCAs and paroxetine associated with increased risk of falls (aHR 1.30, 95% CI 1.23 to 1.38; and 1.45, 95% CI 1.25 to 1.60) and fractures (aHR 1.26, 95% CI 1.16 to 1.37; and 1.46, 95% CI 1.20 to 1.70) compared with nonuse.[12,20] These results were consistent with two other systematic reviews that both found TCA and SSRI use associated with increased risk of falls,[24,25] particularly in the first two weeks of use (TCAs: OR 4.76, 95% CI 3.06 to 7.41; SSRIs [including paroxetine]: OR 6.30, 95% CI 2.65 to 14.97).[25]

Anticholinergic Effects

The Beers Criteria recommended against use of TCAs and paroxetine due to the anticholinergic effects of antidepressants. Immediate anticholinergic effects of antidepressant use (such as sedation) could potentially increase the risk of falls, and longer-term antidepressant use can increase the risk of cognitive dysfunction. A large French database study cited in the Beers Criteria recommendation found paroxetine use increased risk of memory disorders (OR 3.3, 95% CI 2.0 to 5.4) but found no such association with TCA use.[26] The study's authors speculated this may be more due to limited use of TCAs and lack of reporting when harms associated with TCA use do occur, rather than a true reflection of incidence. A narrative review cited in the Beers recommendation found significant negative effects on vigilance and attention with TCA use, with inconsistent effects on memory,[27] and the Coupland study found no association between risk of traffic accidents (a potential consequence of cognitive dysfunction) and TCAs (aHR 1.06, 95% CI 0.86 to 1.29) or paroxetine (aHR 0.90, 95% CI 0.50 to 1.60).[12,20] Anticholinergic adverse effects of TCAs such as sedation, dry mouth, and urinary retention are commonly observed in research studies and clinical practice.

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Key Question 2. What are the benefits and harms of discontinuing tricyclic antidepressants or paroxetine in older adults with depression?

Direct evidence on the effects of discontinuing antidepressant use is limited. One randomized controlled trial that compared discontinuing versus continuing use of one of four SSRIs (including paroxetine) in nursing home patients with dementia with no depressive disorder (n=128) found no difference in risk of death, somatic disease, or hospital admission (OR 1.04, 95% CI 0.34 to 3.14) or in the number of falls per day (0.01 versus 0.01, p=0.27) after 25 weeks intervention.[28] The same study found increased depression in the group that discontinued treatment, based on Cornell Scale total score (6.03 to 4.42, p=0.45) with no difference in other neuropsychiatric outcome measures. We identified no studies on effects of de-intensification of TCAs.

Discussion

Antidepressant use, and associated adverse effects, has risen dramatically in the past 25 years. Although there are numerous drugs from a variety of classes available to clinicians, and despite a strong Beers Criteria recommendation against their use, older adults are frequently prescribed TCAs and/or paroxetine. There is evidence that use of these antidepressants increases the risk of falls and fracture in this population, particularly in the first two weeks of use and may increase risk of mortality; anticholinergic adverse effects such as sedation, dry mouth, and urinary retention are common. Direct evidence on de-intensification of TCAs or paroxetine is very limited, and any adverse effects of de-intensification (e.g., worsening of depression) could be ameliorated by switching to an alternative antidepressant. Given the association between TCAs and paroxetine with adverse effects in older adults and the availability of effective alternatives that are safer and better tolerated, use of TCAs and paroxetine represent a potential target for de-intensification.

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Testosterone for Erectile Dysfunction in Men with Normal Serum Testosterone Levels: Rapid Evidence Synthesis

This report was prepared by the Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University, under Contract No. VA268-16-Q-0140, in support of an HSR&D research study focused on Identifying, Measuring, and Facilitating Opportunities for De-Intensification of Medical Services.

KEY MESSAGES

Why is this important?

- Erectile dysfunction (ED) can be associated with lower satisfaction in relationships, lower self-esteem, and poorer quality of life.
- Testosterone deficiency is associated with ED. However, the benefits and harms of treatment with testosterone for ED in men with *normal* serum testosterone levels are uncertain.

What are the benefits and harms of treatment with testosterone for erectile dysfunction in men with a normal serum testosterone level?

- Benefits: No clear benefit for improving erectile function.
- Harms: Potential harms include polycythemia, venous thromboembolism, myocardial infarction, stroke, edema, hepatotoxicity, sleep apnea, prostate enlargement, and promotion of prostate cancer.

What are the benefits and harms of de-intensification of testosterone treatment for erectile dysfunction in men with normal serum testosterone levels?

- No study evaluated the benefits or harms of de-intensification of testosterone treatment for erectile dysfunction in men with normal serum testosterone levels.

What are the implications of our findings?

- There is no clear evidence that testosterone therapy improves erectile function in men with ED and normal testosterone levels. Testosterone therapy is associated with many potential adverse effects.

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Background

Erectile dysfunction (ED) is defined as the consistent inability to achieve or maintain a penile erection adequate for satisfactory sexual intercourse.[1] For many men, ED is associated with poorer satisfaction in maintaining intimate relationships, poor self-esteem, and lowered quality of life.[2-4] Estimates of the prevalence of ED vary according to the age of the men included and the method used to define and measure ED. A study using data from the 2001-2002 National Health and Nutrition Examination Survey (NHANES) found an overall prevalence of 18.4% in men aged 20 years and older, with ED defined as self-report of being sometimes able or never able to keep an erection adequate for satisfactory intercourse.[5] The prevalence of ED increased with age from 6.5% in men aged 20 to 29 years to 77.5% in men aged 75 years and older.[5] A population-based epidemiologic survey found that approximately 21% of men reported mild/moderate, moderate, or severe ED, using the five-item International Index of Erectile Function (IIEF-5); with approximately 47% of men reporting any symptom of ED.[6]

Testosterone deficiency is a condition associated with ED, but is not present in most men with ED. A systematic review found that the prevalence of low serum testosterone levels (commonly defined as total serum level < 300 ng/dL [10.41 nmol/L]) among men with ED ranged from 14% to 36%.[7] In addition, low testosterone levels are common in men without ED. One study found the prevalence of low testosterone levels to be 35% in men with ED and 23% in men without ED.[8]

Oral phosphodiesterase-5 (PDE-5) inhibitors are a recommended first-line treatment for ED.[7,9-11] However, treatment with testosterone has not been clearly shown to improve erectile function, even in men with low serum testosterone levels. The results of trials of testosterone therapy for improving erectile function are inconsistent, with most showing testosterone to be no more effective than placebo, although testosterone therapy may improve libido.[7,12-15] The use of testosterone for other purported benefits (e.g., depression, muscle strength, insulin resistance, visceral fat, quality of life) remains controversial.[16-20] In addition, the safety of testosterone therapy is not clearly established, with conflicting and generally low-quality evidence on possible harms. Some recent trials and meta-analyses report increased risk of adverse events associated with testosterone use—particularly cardiovascular events—while others have found no increased risk.[21-26]

Despite the uncertainty regarding potential benefits and harms of testosterone therapy, even for men with low testosterone levels, use of testosterone therapy has steadily increased.[27,28] A study of more than 10 million men, aged 40 or older, with employment-based commercial health insurance, found the prevalence of testosterone replacement therapy increased steadily from 0.81% in 2001 to 2.91% in 2011, with the highest proportions among men aged 60 to 69 years (3.75%) and 50 to 59 years (3.26%).[27] Of those treated, only 50.6% had a diagnosis of hypogonadism and 31.9% had a diagnosis of erectile dysfunction.[27] Another study of more than 400,000 men, with commercial and/or Medicare insurance and who initiated testosterone therapy between 2000 and 2011, found only 39.9% of those started on testosterone had a diagnosis of hypogonadism or low serum testosterone.[28]

Therefore, reductions in use of testosterone in men with ED and normal serum testosterone levels could be an important target for de-intensification efforts. The purpose of this rapid

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evidence review is to summarize recent recommendations and supporting evidence on use of testosterone for ED in men with normal testosterone levels, and the effects of de-intensification of testosterone therapy in this population.

Current Guidelines

The American Urological Association (AUA) issued a recommendation against the use of testosterone therapy for erectile dysfunction in men with normal serum testosterone levels.[10,29] Two additional guidelines from the American College of Physicians (ACP)[9] and the Endocrine Society[13] include recommendations specific to men with hypogonadism and/or based on evidence solely from men with hypogonadism, but do not directly address use of testosterone in men with normal testosterone levels. The guidelines are summarized in **Table 1**. The AUA guideline recommends against use of testosterone in men with normal serum testosterone levels, the ACP guideline found insufficient evidence to recommend for or against testosterone therapy for ED regardless of testosterone level, and the Endocrine Society guideline recommends testosterone therapy for men with ED and low testosterone levels, with very low quality evidence.

Table 1. Summary of current guidelines on testosterone treatment for erectile dysfunction

Guideline group	Recommendations
American Urological Association, 2011[29]	• Testosterone therapy is not indicated for the treatment of erectile dysfunction in the patient with a normal serum testosterone level
American College of Physicians (ACP), 2009[9]	• Does not recommend for or against hormonal treatment in the management of patients with erectile dysfunction (regardless of testosterone level)* (Grade: insufficient evidence to determine net benefits and harms)
Endocrine Society, 2010[13]	• We suggest that clinicians offer testosterone therapy to men with erectile dysfunction (ED) who have low testosterone levels after evaluation of underlying causes of ED and consideration of established therapies for ED† (Very low quality evidence)

* Does not specify baseline testosterone status (i.e., normal or low); all evidence from studies of men with hypogonadism

† Recommendation is specific to men with low testosterone levels

Methods

Topic Selection and Scope Development

Key Questions

We reviewed evidence relevant to the following Key Questions:

Key Question 1: What are the benefits and harms of treatment with testosterone for erectile dysfunction in men with a normal serum testosterone level?

Key Question 2: What are the benefits and harms of de-intensification of testosterone treatment for erectile dysfunction in men with normal serum testosterone levels?

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Eligibility Criteria

- Population: Men with erectile dysfunction and a normal serum testosterone level
- Intervention: Treatment with testosterone (oral, intramuscular, gel, cream, or patch)
- Comparator: No treatment or placebo
- Outcomes: Successful sexual intercourse or improvement in erections

Searching and Study Selection

We conducted a targeted search of the literature for evidence relevant to testosterone treatment for ED in men with normal serum testosterone levels. Our research librarian conducted searches of Ovid MEDLINE® from 1996 through June 2017. This resulted in 368 potentially relevant citations. After screening abstracts, we reviewed the full text of 8 systematic reviews and 4 randomized controlled trials (RCTs). Two systematic reviews included trials of testosterone therapy that measured change in erectile function in men with normal serum testosterone levels.[14,30] One review[30] was of high quality and one[14] was of medium quality.[31] Two of the RCTs were already included in these systematic reviews and the other two RCTs did not evaluate men with normal testosterone levels. We hand-searched reference lists of relevant studies, including those cited in the three guidelines in support of their recommendations, and found no additional studies.

Results

Key Question 1: What are the benefits and harms of treatment with testosterone for erectile dysfunction in men with a normal serum testosterone level?

Benefits

The AUA guideline[11] included a double-blind, cross-over trial of men with normal serum testosterone levels and either low sexual interest (n = 10) or erectile dysfunction (n = 10) who received Intramuscular (IM) testosterone and IM placebo.[32] Erectile function was not significantly changed in either group.

Two systematic reviews included a total of eleven unique RCTs of testosterone therapy for ED in men with normal or low-normal testosterone levels.[14,30] Both reviews included the trial cited in the AUA guideline.[32] Trial sample sizes ranged from 8 to 108 subjects, with all but 2 trials enrolling fewer than 40 subjects. Mean baseline serum testosterone levels varied between the studies. The studies used a variety of doses and forms of testosterone therapy, and a variety of definitions and measures of erectile function.

One systematic review found no statistically significant difference in standardized effect size of testosterone treatment compared with placebo for over-all erectile function (0.19; 95% CI: -0.19 to 0.58; 4 trials) or sexual-related erectile function (0.22; 95% CI -0.17 to 0.61; 4 trials).[30] The other review found a slight improvement in erectile function among men treated with testosterone, with a combined effect size of 0.34 (95% CI 0.03 to 0.65; 6 trials).[14] However, five of the six trials included in this meta-analysis found no statistically significant difference in erectile function (range: 0.00 to 0.40); and, importantly, subjects in the single study that found a significant difference (1.47; 95% CI 0.45 to 2.49) were using sildenafil in addition to testosterone as part of the study protocol.[33]

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Two other guidelines were based on trials conducted in men with ED and low testosterone/hypogonadism. The ACP guideline was based on a systematic review of 8 RCTs (7 low quality, 1 fair quality) that found insufficient evidence to determine if testosterone therapy was more effective than placebo in improving either successful sexual intercourse or improvement of erections.[7] The Endocrine Society guideline was based on a systematic review and meta-analysis of four trials in men with low testosterone levels that found no significant improvement in self-reported erectile function with testosterone therapy (effect size, 0.80; 95% CI -0.10 to 1.60; $I^2 = 86\%$).[13]

Harms

Various adverse effects of testosterone therapy have been reported, including polycythemia, venous thromboembolism, myocardial infarction, stroke, edema, hepatotoxicity, sleep apnea, prostate enlargement, and increased serum prostate specific antigen.[34]

Evidence on some potential harms associated with testosterone therapy, such as cardiovascular events, is inconsistent.[21-26] One recent systematic review found an increase in serious cardiovascular events associated with testosterone therapy (OR 1.61; 95% CI 1.01 to 2.56; 23 trials),[26] while another recent review found no significant association with myocardial infarction (OR 0.87; 95% CI 0.39 to 1.93; 17 trials), stroke (OR 2.17; 95% CI 0.63 to 7.75; 9 trials), or all-cause death (OR 0.88; 95% CI 0.55 to 1.41; 21 trials).[21] This inconsistency may be due to characteristics and quality of the included studies, differences in the choice of outcomes examined, and different analytic approaches.[21] Another systematic review found testosterone therapy associated with a higher risk of elevated hematocrit (> 50%) compared with placebo (OR 3.69; 95% CI: 1.82 to 7.51; 19 trials).[23] The same review found testosterone therapy associated with an increased rate of all prostate adverse events combined (OR 1.78; 95% CI 1.07 to 2.95; 19 trials); however, the rates for each individual event were not statistically significant increased: prostate cancers (OR 1.09; 95% CI 0.48 to 2.49); prostate biopsies (OR 1.87; 95% CI 0.84 to 4.15); increased prostate-specific antigen (OR 1.19; 95% CI 0.67 to 2.09); and increased International Prostate Symptom Score (OR 1.08; 95% CI 0.46 to 2.52).[23]

Key Question 2: What are the benefits and harms of de-intensification of testosterone treatment for erectile dysfunction in men with normal serum testosterone levels?

No study directly assessed the benefits or harms of any type of de-intensification of testosterone treatment for erectile dysfunction in men with normal serum testosterone levels.

Summary

Table 2 summarizes the benefits and harms of testosterone treatment for erectile dysfunction in men with normal serum testosterone levels. Evidence shows no clear benefit of testosterone treatment for improving erectile function in men with ED and a normal serum testosterone level. Furthermore, the evidence does not clearly support the use of testosterone therapy for ED even in men with *low* serum testosterone levels. Testosterone therapy may be associated with a variety of adverse effects. We found no evidence directly assessing de-intensification of testosterone treatment for erectile dysfunction in men with normal serum testosterone levels. Widespread and increasing use of testosterone, the lack of demonstrated benefit for testosterone therapy in men

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with ED and normal testosterone levels, and potential for harms, suggest use of testosterone therapy in this population as a potential target for de-intensification.

Table 2. Summary of benefits and harms of testosterone treatment for erectile dysfunction in men with normal serum testosterone levels

Action	Benefits	Harms
(1) Testosterone therapy for erectile dysfunction in men with normal testosterone levels	• No clear improvement in erectile function	• Possible harms include: polycythemia, venous thromboembolism, myocardial infarction, stroke, edema, hepatotoxicity, sleep apnea, prostate enlargement, and increased prostate specific antigen
(2) De-intensification of testosterone therapy for erectile dysfunction in men with normal testosterone levels	• No direct evidence	• No direct evidence

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Estrogen and Progestin in Postmenopausal Women: Rapid Evidence Synthesis

This report was prepared by the Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University, under Contract No. VA268-16-Q-0140, in support of an HSR&D research study focused on Identifying, Measuring, and Facilitating Opportunities for De-Intensification of Medical Services.

KEY MESSAGES

Why is this important?

- Menopause, which occurs when the ovaries cease production of estrogen, typically occurs at age 51; nearly 40 million U.S. women are past the average age of menopause.
- Menopause is associated with symptoms such as hot flashes, mood changes, and weight gain, and with increased risk of conditions such as cardiovascular disease and osteoporosis.
- Hormone replacement therapy (HRT) with estrogen and progestin (estrogen only in women without a uterus) can be used to treat symptoms of menopause and potentially decrease risk of associated conditions.
- The prevalence of HRT has declined in the United States from 44% in 1998–1994 to 4.7% in 2010.
- The U.S. Preventive Services Task Force updated draft statement recommends against the use of HRT for the prevention of chronic conditions in postmenopausal women (D recommendation). The recommendations and related evidence review do not address HRT to treat menopausal symptoms.
- Discontinuation of HRT is postmenopausal women is a potential target for de-intensification.

What are the benefits and harms of hormone replacement therapy for prevention of chronic conditions in postmenopausal women?

- HRT is associated with decreased risk of colorectal cancer (33 fewer cases per 10,000 women over 5.6 years [95% CI, 8 to 52 fewer]), diabetes (77 fewer cases per 10,000 women over 5.6 years [95% CI, 21 to 206 fewer]), and fractures (222 fewer cases per 10,000 women over 5.0 years [95% CI, 67 to 354 fewer]) versus placebo.
- HRT is associated with increased risk of invasive breast cancer (52 more cases per 10,000 women over 5.6 years [95% CI, 6 to 107 more]), coronary heart disease (41 more cases per 10,000 women over 5.1 years [95% CI, 0 to 93 more]), probable dementia (88 more cases per 10,000 women over 4 years [95% CI, 15 to 213 more]), gallbladder disease (259 more cases per 10,000 women over 5.6 years [95% CI, 167 to 366 more]), stroke (53 more cases per 10,000 women over 5.6 years [95% CI, 12 to 104 more]), urinary incontinence (876 more cases per 10,000 women over 1 year [95% CI, 606 to 1,168 more]), and venous thromboembolism (120 more cases per 10,000 women over 5.6 years [95% CI, 68 to 185 more]) versus placebo.
- There is no demonstrated protective effect of HRT on risk of coronary heart disease or cognitive impairment.
- Limited evidence indicates that estrogen alone is associated with lower risk of myocardial infarction in younger (ages 50 to 59 years) women, but did not decrease risk of total coronary heart disease events. Estrogen alone was associated with increased risk of colorectal cancer in older (ages 70 to 79 years) women.
- Subgroup analyses of results from one trial provide conflicting findings on the timing of HRT initiation after menopause and association with benefits and harms.

What are the benefits and harms of de-intensification of postmenopausal hormone therapy used to prevent chronic conditions?

- No evidence was found.

What are the implications of our findings?

- The USPSTF concluded that potential benefits of postmenopausal HRT are outweighed by potential harms.
- Discontinuation of postmenopausal HRT is a potential target for de-intensification efforts.

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Background

Menopause occurs when the ovaries cease production of estrogen. Women experience menopause at an average age of 51 years.[1] The U.S. Census Bureau predicts that the number of U.S. women older than 51 will exceed 50 million by 2020.[2] Menopause is associated with symptoms such as hot flashes, mood changes, and weight gain. Menopause is also associated with increased risk of conditions such as cardiovascular disease, osteoporosis, urinary incontinence, sexual dysfunction, and weight gain. Hormone replacement therapy (HRT) with estrogen and progesterone (estrogen only in women without a uterus) can reduce symptoms of menopause, and could potentially reduce the risk of conditions associated with menopause. Following the publication of results from the Women's Health Initiative in 2002, use of postmenopausal HRT has declined in the United States. The U.S. Preventive Services Task Force indicates that The prevalence of HRT was estimated at 44% between 1988 and 1994[3] and declined to 4.7% in 2010.[4]

The U.S. Preventive Services Task Force (USPSTF) 2012 Recommendation Statement, Menopausal Hormone Therapy: Preventive Medication,[5] and the recently updated 2017 Draft Recommendation Statement, Menopausal Hormone Therapy: Primary Prevention of Chronic Conditions,[6] recommend against the use of hormone replacement therapy for prevention of chronic conditions in postmenopausal women (D Recommendation). This rapid evidence review summarizes the findings of the systematic review[7] conducted for the USPSTF and the USPSTF recommendation on benefits and harms of hormone replacement therapy for the purpose of preventing chronic conditions associated with menopause. The USPSTF review and recommendations do not address HRT for treatment of menopausal symptoms.

Current Guidelines

Like the 2012 USPSTF recommendations,[5] the 2017 draft statement[6] recommends against the use of estrogen and progestin for the prevention of chronic conditions in postmenopausal women. Recommendations from other groups (**Table 1**) are generally concordant with the USPSTF recommendations, except that the American Association of Clinical Endocrinologists recommends that HRT can be discussed as an option for prevention of osteoporosis using an individualized shared decision-making approach.

Table 1. Summary of current guidelines on estrogen and progestin in postmenopausal women

Guideline Group	Recommendations
U.S. Preventive Services Task Force[8]	• The USPSTF recommends against the use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women. The 2017 draft recommendation statement[6] is the same as the USPSTF 2012 recommendation (Grade D recommendation).[5]
Canadian Task Force on Preventive Health Care, 2004[9]	• Recommends against the use of estrogen only and estrogen plus progestin therapy for the primary prevention of chronic diseases in menopausal women (Grade D recommendation).
American Association of Clinical Endocrinologists, 2011[10]	• Recommends against the use of menopausal hormone therapy for primary or secondary prevention of cardiovascular disease (Grade D; Best Evidence Level 1). • Recommends that menopausal hormone therapy should be used for the prevention and treatment of osteoporosis within the context of the overall benefit-versus-risk analysis of each patient. (Grade A; Best Evidence Level 1). • Hormone therapy for the prevention or treatment (or both) of dementia is not recommended (Grade D; Best Evidence Level 1).

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Guideline Group	Recommendations
American Heart Association, 2011[11]	• Recommends against the use of hormone therapy for primary and secondary prevention of cardiovascular disease in women (Class III, Level of Evidence A).
American Academy of Family Physicians, 2012[12]	• Recommends against the use of estrogen plus progestin for the prevention of chronic conditions in postmenopausal women (Grade: D recommendation). • The American Academy of Family Physicians recommends against the use of estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy (Grade: D recommendation).
American Congress of Obstetricians and Gynecologists, 2013–2014[13]	• Recommends against the use of menopausal hormone therapy for primary and secondary prevention of coronary heart disease because of insufficient evidence for benefit. The guidelines also note the following consideration: o Recent evidence suggests that women in early menopause who are in good cardiovascular health and are at low risk of adverse cardiovascular outcomes should be considered candidates for the use of estrogen therapy or conjugated equine estrogen plus a progestin for relief of menopausal symptoms.
American College of Physicians, 2015[14]	• Recommends against using menopausal estrogen therapy or menopausal estrogen plus progestogen therapy or raloxifene for the treatment of osteoporosis in women. (Grade: strong recommendation; moderate-quality evidence)

Methods

Topic Selection and Scope Development

Key Questions

Key Question 1: What are the benefits and harms of postmenopausal hormone therapy when used to prevent chronic conditions?

Key Question 2: What are the benefits and harms of discontinuing postmenopausal hormone therapy used to prevent chronic conditions?

Eligibility Criteria

- Population: Healthy postmenopausal women
- Intervention: Hormone therapy with estrogen alone or estrogen and progestin combined
- Comparator: Placebo-controlled trials and studies with inactive treatments
- Outcomes: Prevention of chronic conditions
- Timing: One year or more of hormone therapy
- Setting: Primary care or primary care-like settings
- Study design: Randomized controlled trials

Searching and Study Selection

The USPSTF draft updated evidence review[7] was used as the basis for our literature search. The USPSTF reviewers searched MEDLINE®, the Cochrane Library, and Embase® for articles published from June 1, 2011, through August 1, 2016. We conducted an update search for additional trials in Ovid MEDLINE® on May 8, 2017. One reviewer used the eligibility criteria described above to select studies.

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Results

The USPSTF posted a draft updated systematic review on the effectiveness of menopausal hormone therapy and its adverse effects in May of 2017.[7] The review included 18 trials on the benefits and harms of hormone therapy with estrogen alone or with estrogen and progestin. The Women's Health Initiative (WHI) Estrogen-plus-Progestin randomized controlled trial[22] provided critical evidence for the systematic review. The WHI trial, conducted in 40 clinical medical centers in the United States, was a large (n=16,608) randomized trial of hormone therapy versus placebo with 11 years of follow-up. Patients were postmenopausal women 50 to 79 years of age, randomly assigned to receive estrogen plus progesterone or placebo. Clinical outcomes assessed were cardiovascular disease, cancer, and fractures.

We found no additional studies published subsequent to the USPSTF May 2017 draft report that would change the conclusions of the USPSTF draft report.

Key Question 1. What are the benefits and harms of menopausal hormone therapy when used to prevent chronic conditions?

Benefits

The USPSTF draft evidence review reported that women on estrogen plus progestin therapy experienced reduced risks (**Table 2**) for colorectal cancer (33 fewer cases per 10,000 women over 5.6 years [95% CI, 8 to 52 fewer]), diabetes (77 fewer cases per 10,000 women over 5.6 years [95% CI, 21 to 206 fewer]), and fractures (222 fewer cases per 10,000 women over 5.0 years [95% CI, 67 to 354 fewer]), compared with women taking a placebo.

Table 2. Benefits of estrogen and progestin in postmenopausal women: absolute risk reductions

Study Country Sample Size	Condition	Absolute Risk Reduction
USPSTF 2017 Draft Evidence Review[8] United States n=40,058	Colorectal cancer	RR 0.64 (95% CI 0.44 to 0.91)
	Diabetes	RR 0.84 (95% CI 0.72 to 0.97)
	Fractures	RR 0.80 (95% CI 0.68 to 0.94)

Regarding the possible protective effect of menopausal hormone therapy on coronary heart disease, the WHI and other trials did not demonstrate such an effect.[7] Similarly, the WHI Memory Study (WHIMS) did not confirm a protective effect against dementia or cognitive impairment.[15,16]

Harms

The USPTSTF systematic review found HRT associated with harms (**Table 3**), including increased risk of invasive breast cancer (52 more cases per 10,000 women over 5.6 years [95% CI, 6 to 107 more]), coronary heart disease (41 more cases per 10,000 women over 5.1 years [95% CI, 0 to 93 more]), probable dementia (88 more cases per 10,000 women over 4 years [95% CI, 15 to 213 more]), gallbladder disease (259 more cases per 10,000 women over 5.6

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years [95% CI, 167 to 366 more]), stroke (53 more cases per 10,000 women over 5.6 years [95% CI, 12 to 104 more]), urinary incontinence (876 more cases per 10,000 women over 1 year [95% CI, 606 to 1,168 more]), and venous thromboembolism (120 more cases per 10,000 women over 5.6 years [95% CI, 68 to 185 more]).

Table 3. Harms of estrogen and progestin in postmenopausal women: absolute risk increases

Study Country Sample Size	Condition	Absolute Risk Increase
USPSTF 2017 Draft Evidence Review[8] United States n=40,058	Invasive breast cancer	RR 1.27 (95% CI 1.03 to 1.56)
	Coronary heart disease	RR 1.43 (95% CI 0.76 to 2.69)
	Dementia	RR 1.97 (95% CI 1.16 to 3.33)
	Gallbladder disease	RR 1.56 (95% CI 1.36 to 1.79)
	Stroke	RR 1.39 (95% CI 1.27 to 1.52)
	Urinary incontinence	RR 1.95 (95% CI 1.54 to 2.47)
	Venous thromboembolism	RR 1.01 (95% CI 0.88 to 1.17)

Effects of Age or Timing of HRT Administration

The WHI trial provided limited evidence on estrogen alone in younger (ages 50 to 59 years) and older (70 to 79 years) women. Estrogen alone in younger women was associated with lower risk of myocardial infarction, although not total coronary heart disease events, and estrogen alone in older women was associated with higher risk of colorectal cancer. Subgroup analyses of results from the WHI trial provided conflicting findings on the timing of HRT initiation after menopause and association with benefits and harms.

Key Question 2: What are the benefits and harms of discontinuing menopausal hormone therapy used to prevent chronic conditions?

The USPSTF draft systematic review update[7] did not address de-intensification and we found no studies on effects of de-intensification of HRT on clinical outcomes

Discussion

The benefits and harms of estrogen plus progestin therapy are summarized in **Table 4**. Although HRT is associated with potential benefits, the USPSTF determined that potential benefits are outweighed by potential harms. Therefore, discontinuation of HRT in postmenopausal women represents a potential target for de-intensification efforts.

Table 4. Summary of benefits and harms of estrogen and progestin in postmenopausal women

Action	Benefits	Harms
(1) Hormone replacement therapy	• Decreased risk of colorectal cancer, diabetes, and fractures	• Increased risk of: invasive breast cancer, coronary heart disease, dementia, gallbladder disease, stroke, urinary incontinence, and venous thromboembolism
(2) De-intensification of hormone replacement therapy	• No evidence	• No evidence

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eMethods 5. Panel Process

Introductory materials for members, including rating criteria

Approximately 2 weeks prior to the first meeting, expert panel members received a packet of materials outlining the goals of the project, selection process for candidate recommendations, candidate recommendations (i.e., de-intensification action, eligible population, exclusions), evidence supporting each recommendation, opportunity estimate(s), and rating criteria. The rating criteria included validity, improvement opportunity, and feasibility of implementation, assessed using a nine-point scale with the following anchors: for *validity* ratings (1=the recommendation is definitely not based on high quality evidence, 9=the recommendation is definitely based on high quality evidence), for *improvement opportunity* ratings (1=the recommendation is definitely not likely to affect a large number of patients or have a significant impact on a smaller number of patients, 9=the recommendation is definitely likely to affect a large number of patients or have a significant impact on a smaller number of patients), and for *feasibility of implementation* ratings (1=de-intensification of the treatment or testing is definitely not under the control of the health professional or health organization, 9=de-intensification of the treatment or testing is definitely under the control of the health professional or health organization). While the packet included specific information on validity and improvement opportunity, the panelists were not provided with any information related to feasibility of implementation; they were asked to simply use their knowledge to evaluate whether the recommendation appeared to be under the control of the health professional or health organization. (A copy of the packet is available upon request.)

The panelists were instructed to review all the materials, answer several questions for each recommendation (*Do you agree the recommendation is valid and that there is an opportunity for improvement? Do you agree with the de-intensification action? Do you agree with the description of the eligible population, including exclusions?*) and return their answers to study staff prior to the first meeting. Study staff reviewed answers in preparation for the meeting.

Expert panel protocol (Meeting 1, Initial rating, Meeting 2)

At the start of meeting 1, study investigators summarized how the candidate recommendations were selected, discussed the goals for the panel, and reviewed the three rating criteria. Panelists then participated in group discussion about each of the proposed recommendations and provided

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suggestions on how a recommendation could be improved. Meeting 1 lasted three hours for panel 1 and three and one-half hours for panel 2.

Immediately following the meeting, investigators revised the recommendations based on the feedback provided by panel members. In some cases, the feedback resulted in dividing a recommendation into two or more recommendations (e.g., where panel members suggested different populations to include or exclude). Approximately 1 week after the meeting, panel members received e-mailed instructions on how to access the initial rating form in ThinkTank and were reminded to rate each of the candidate de-intensification recommendations (some of which had been revised) based on validity, improvement opportunity, and feasibility of implementation. Following the initial ratings, staff prepared and distributed summary reports to each panelist. The report included the frequency of responses and the overall median rating. Additionally, each panelist's individual report included their initial ratings so they could compare their own ratings with those of other panelists.

During the second meeting, each candidate recommendation was discussed in turn, again using the collaborative cloud-based tool. The facilitators allowed more time for discussion of a recommendation when the initial ratings did not converge tightly around the median rating. During the meeting, minor modifications were made to several recommendations based on panelists' recommendations. Once a recommendation had been fully discussed, or facilitators indicated that they needed to move on to keep within the time constraints, panelists confidentially and synchronously reassessed validity, improvement opportunity, and feasibility of implementation. Panelists were instructed that there was no requirement to reach consensus, and that they should change their ratings only if the discussion had provided new information or reasoning that caused them to revise their opinions. Panelists were not shown the results of the second rating during the meeting. The second meeting lasted three hours for panel 1 and three and one-half hours for panel 2.

Selection of expert panel members and makeup of the panel

Study staff solicited recommendations for expert panel members from study investigators, advisory council members, and other colleagues. Inclusion requirements included the following: 1) physician; 2) significant knowledge of 1 or more of our clinical content areas; and 3) excellent communication skills, collaborative skills and critical thinking abilities. Investigators (TH, EK) reviewed and prioritized all suggestions to ensure diverse representation based on geographic region, specialty and gender. Twenty-nine people were invited to participate. Based primarily on availability, fourteen

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experts were recruited for the first panel and twelve for the second panel. One expert had to drop out of panel 1 because of a scheduling conflict. Each of the panel members reported no financial conflict of interest.

Panel 1 included physicians with expertise in internal medicine, geriatric medicine, endocrinology and/or cardiology. Specific areas of interest included chronic disease management, performance measurement, and/or overtreatment. Panel 2 included physicians with expertise in internal medicine and/or geriatric medicine. Areas of interest in Panel 2 included women's health, mental health, cancer screening, prescribing practices, performance measurement, and/or overtreatment. Several panel members had experience serving on guideline committees. Panel members received a $450 gift card for their participation.

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eTable 4. Primary recommendations

The two principal investigators (EK, TH) grouped recommendations that had similar intent, assigning one as the primary recommendation and the others as supporting recommendations. Many of the primary recommendations (N=178) had one or more supporting recommendations.

ACC/AHA: **2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy (DAPT) in Patients with Coronary Artery Disease**	
1	**In Patients Treated With DAPT**: In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended.
2	**In Patients With ACS (Acute Coronary Syndrome) Treated with PCI (angioplasty)**: In patients with ACS (non-ST-elevation [NSTE-ACS]) or ST-elevation myocardial infarction [STEMI]) treated with coronary stent implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT (clopidogrel, prasugrel, or ticagrelor) for longer than 12 months may be reasonable.
3	**SIHD (stable ischemic heart disease)**: In patients with SIHD without prior history of ACS, coronary stent implantation, or recent (within 12 months) CABG (coronary artery bypass graft), treatment with DAPT is not beneficial.
ACC/AHA: **Management of Patients with Peripheral Artery Disease (Compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations)**	
4	**Antiplatelet and Antithrombotic Drugs:** In the absence of any other proven indication for warfarin, its addition to antiplatelet therapy to reduce the risk of adverse cardiovascular ischemic events in individuals with atherosclerotic lower extremity peripheral artery disease (PAD) is of no benefit and is potentially harmful due to increased risk of major bleeding.
5	**Pentoxifylline:** The clinical effectiveness of pentoxifylline as therapy for claudication is marginal and not well established.
6	**Other Proposed Medical Therapies:** Oral vasodilator prostaglandins such as beraprost and iloprost are not effective medications to improve walking distance in patients with intermittent claudication.
7	**Aortic Aneurysm Rupture:** Patients with infrarenal or juxtarenal abdominal aortic aneurysms (AAAs) measuring 4.0 to 5.4 cm in diameter should be monitored by ultrasound or computed tomographic scans every 6 to 12 months to detect expansion.
8	**Aortic Aneurysm Rupture:** In patients with AAAs smaller than 4.0 cm in diameter, monitoring by ultrasound examination every 2 to 3 years is reasonable.
ACC/AHA: **2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease**	
9	**Diagnostic Testing – Routine Follow-up (Bicuspid aortic value**): Serial evaluation of the size and morphology of the aortic sinuses and ascending aorta by echocardiography, cardiovascular magnetic resonance (CMR), or computed tomography (CT) angiography is recommended in patients with a bicuspid aortic valve and an aortic diameter greater than 4.0 cm, with the examination interval determined by the degree and rate of progression of aortic dilation and by family history. In patients with an aortic diameter greater than 4.5 cm, this evaluation should be performed annually.
10	**Medical Therapy:** Anticoagulation with a vitamin K antagonists (VKA) is reasonable for the first 3 months after bioprosthetic MVR or repair to achieve an INR of 2.5.
ACC/AHA:	

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2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease	
11	**Stress Testing and Advanced Imaging in Patients with Known SIHD Who Require Noninvasive Testing for Risk Assessment**: Pharmacological stress imaging (nuclear myocardial perfusion imaging [MPI], echocardiography, or CMR) or coronary CT angiography (CCTA) is not recommended for risk assessment in patients with SIHD who are able to exercise to an adequate workload and have an interpretable electrocardiogram (ECG).
12	**Risk Factor Modification-Diabetes Management:** Therapy with rosiglitazone should not be initiated in patients with SIHD.
13	**Additional Medical Therapy to Prevent MI (myocardial infarction) and Death-Beta-Blocker Therapy:** Beta-blocker therapy should be started and continued for 3 years in all patients with normal left ventricular (LV) function after MI or ACS.
14	**Additional Therapy to Reduce Risk of MI and Death:** Estrogen therapy is not recommended in postmenopausal women with SIHD with the intent of reducing cardiovascular risk or improving clinical outcomes.
15	**Clinical Evaluations, Echocardiography During Routine, Periodic Follow-up:** Measurement of LV function with a technology such as echocardiography or radionuclide imaging is not recommended for routine periodic reassessment of patients who have not had a change in clinical status or who are at low risk of adverse cardiovascular events.
16	**Noninvasive Testing in Known SIHD (Asymptomatic (or Stable Symptoms)):** In patients who have no new or worsening symptoms or no prior evidence of silent ischemia and are not at high risk for a recurrent cardiac event, the usefulness of annual surveillance exercise ECG testing is not well established.
ACC/AHA: **Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women - A Guideline from the American Heart Association**	
17	**Preventive drug interventions:** **β-Blockers:** β-Blockers should be used for up to 3 y in all women after MI or ACS with normal left ventricular function unless contraindicated.
ACC/AHA: **2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults**	
18	**Statin Safety:** It may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily.
19	**Addressing Insufficient Response to Statin Therapy:** In individuals who are candidates for statin treatment but are completely statin intolerant, it is reasonable to use non-statin cholesterol-lowering drugs that have been shown to reduce **Atherosclerotic Cardiovascular Disease (ASCVD)** events in RCTs (randomized control trials) if the ASCVD risk-reduction benefits outweigh the potential for adverse effects.
ACC/AHA: **2013 ACCF/AHA Guideline for the Management of Heart Failure**	
20	**Noninvasive Cardiac Imaging:** Routine repeat measurement of LV function assessment in the absence of clinical status change or treatment interventions should not be performed.
21	**Aldosterone Receptor Antagonists:** Inappropriate use of aldosterone receptor antagonists is potentially harmful because of life-threatening hyperkalemia or renal insufficiency when serum creatinine is greater than 2.5 mg/dL in men or greater than 2.0 mg/dL in women (or estimated glomerular filtration rate <30 mL/min/1.73 m2), and/or potassium greater than 5.0 mEq/L.

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22	**Anticoagulation:** Anticoagulation is not recommended in patients with chronic H**eart Failure** with reduced Ejection Fraction (HFrEF) without atrial fibrillation (AF), a prior thromboembolic event, or a cardioembolic source.
23	**Drugs of Unproven Value or That May Worsen HF (heart failure):** Drugs known to adversely affect the clinical status of patients with current or prior symptoms of HFrEF are potentially harmful and should be avoided or withdrawn whenever possible (e.g., most antiarrhythmic drugs, most calcium channel–blocking drugs [except amlodipine], NSAIDs, or thiazolidinediones).
ACC/AHA **2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation**	
24	**Prevention of Thromboembolism (Risk-Based Antithrombotic Therapy):** Following coronary revascularization (percutaneous or surgical) in patients with AF and a CHA2DS2-VASc score of 2 or greater, it may be reasonable to use clopidogrel (75 mg once daily) concurrently with oral anticoagulants but without aspirin.
25	**Antiarrhythmic Drugs to Maintain Sinus Rhythm:** Antiarrhythmic drugs for rhythm control should not be continued when AF becomes permanent, including dronedarone.
ACC/AHA: **2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the Management of Patients with Extracranial Carotid and Vertebral Artery Disease**	
26	**Duplex Ultrasonography to Evaluate Asymptomatic Patients with Known or Suspected Carotid Stenosis:** It is reasonable to repeat duplex ultrasonography annually by a qualified technologist in a certified laboratory to assess the progression or regression of disease and response to therapeutic interventions in patients with atherosclerosis who have had stenosis greater than 50% detected previously. Once stability has been established over an extended period or the patient's candidacy for further intervention has changed, longer intervals or termination of surveillance may be appropriate.
27	**Antithrombotic Therapy** **in Patients with Extracranial Carotid Atherosclerotic** **Disease Not Undergoing Revascularization:** Administration of clopidogrel in combination with aspirin is not recommended within 3 months after stroke or transient ischemic attack (TIA).
AATS: **The American Association for Thoracic Surgery (AATS) guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups**	
28	**Lung Cancer Screening:** AATS recommends that long-term lung cancer survivors who have completed 4 years of surveillance without recurrence (and who can tolerate lung cancer treatment following screening) should have annual low-dose computed tomography to detect second primary lung cancer until the age of 79.
ACS: **American Cancer Society Colorectal Cancer Survivorship Care Guidelines**	
29	**Surveillance of CRC Recurrence:** Do not perform routine blood tests for surveillance for colorectal cancer recurrence.
30	**Surveillance of CRC Recurrence:** Do not perform routine **Carotid Endarterectomy (CEA)** monitoring for colorectal cancer recurrence after 5 years.
31	**Surveillance of CRC Recurrence:** Do not perform routine CT scans for colorectal cancer recurrence after 5 years.
32	**Surveillance of CRC Recurrence:** Do not routinely use **Positron Emission Tomography (PET**)/CT to monitor for colorectal cancer recurrence.
33	**Surveillance of CRC Recurrence:** Chest/abdominal/pelvic CT should be performed every 12 months for up to 5 years after treatment.

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ACS: **American Cancer Society Prostate Cancer Survivorship Care Guidelines**	
34	**Surveillance For Prostate Cancer Recurrence:** Measure serum prostate specific antigen (PSA) level every 6 to 12 months for the first 5 years after treatment, then recheck annually thereafter.
ACS: **American Cancer Society Guideline for the Early Detection of Prostate Cancer**	
35	**Early Prostate Cancer Detection**: For men who choose to be screened for prostate cancer after considering the possible benefits and risks, screening can be conducted every 2 years for men whose PSA level is <2.5 ng/mL.
ACS: **American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline**	
36	**Surveillance for breast cancer recurrence**: It is recommended that primary care clinicians should not refer for routine screening with magnetic resonance imaging (MRI) of the breast unless the patient meets high risk criteria for increased breast cancer surveillance as per ACS guidelines.
37	**Surveillance for breast cancer recurrence:** It is recommended that primary care clinicians should not offer routine laboratory tests or imaging, except mammography if indicated, for the detection of disease recurrence in the absence of symptoms.
ACCP: **Screening for lung cancer: Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines**	
38	**Lung Cancer Screening:** In patients at risk for developing lung cancer, screening for lung cancer with chest radiograph (CXR) once or at regular intervals is not recommended.
ACCP: **Evaluation of Individuals with Pulmonary Nodules: When Is It Lung Cancer? Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines**	
39	**Solid nodules:** In the individual with a solid, indeterminate nodule that has been stable for at least 2 years, we suggest that **no** additional diagnostic evaluation need be performed.
ACP: **Screening for Prostate Cancer: A Guidance Statement from the Clinical Guidelines Committee of the American College of Physicians**	
40	**Screening for Prostate Cancer:** ACP recommends that clinicians should not screen for prostate cancer using the prostate-specific antigen test in average-risk men under the age of 50 years, men over the age of 69 years, or men with a life expectancy of less than 10 to 15 years.
ACP: **Screening for Cancer: Advice for High-Value Care from the American College of Physicians**	
41	**Screening for Breast Cancer**: Clinicians should not screen average-risk women younger than 40 years or aged 75 years or older for breast cancer or screen women of any age with a life expectancy less than 10 years.
42	**Screening for Colorectal Cancer:** Clinicians should encourage colorectal cancer screening [in persons aged 50-75 years] by 1 of 4 strategies: high-sensitivity fecal occult blood test (FOBT) or fecal immunochemical test (FIT) (every year); sigmoidoscopy (every 5 years); combined high-sensitivity FOBT or FIT (every 3 years) plus sigmoidoscopy (every 5 years); or optical colonoscopy (every 10 years) in average-risk adults aged 50 to 75 years.
43	**Screening for Colorectal Cancer:** For adults aged <50 or >75 or who have a life expectancy <10yr, do not screen for colorectal cancer.
ACP:	

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Cardiac Screening with Electrocardiography, Stress Echocardiography, or Myocardial Perfusion Imaging: Advice for High-Value Care From the American College of Physicians	
44	**Cardiac Screening:** Clinicians should not screen for cardiac disease in asymptomatic, low-risk adults with resting or stress electrocardiography, stress echocardiography, or stress myocardial perfusion imaging.
ADA: **Standards of Medical Care in Diabetes - 2016**	
45	**Type 2 Diabetes Testing**: Testing to detect type 2 diabetes in asymptomatic people should be considered in adults of any age who are overweight or obese (BMI ≥25 kg/m2 or≥23 kg/m2 in Asian Americans) and who have one or more additional risk factors for diabetes.
46	**Nutritional therapy recommendations - Micronutrients & herbal supplements:** There is no clear evidence that dietary supplementation with vitamins, minerals, herbs, or spices can improve diabetes, and there may be safety concerns regarding the long-term use of antioxidant supplements such as vitamins E and C and carotene.
47	**Hypoglycemia:** Hypoglycemia unawareness or one or more episodes of severe hypoglycemia should trigger reevaluation of the treatment regimen.
48	**Hypertension/Blood Pressure Control:** Lower systolic targets, such as <130 mmHg, may be appropriate for certain individuals with diabetes, such as younger patients, those with albuminuria, and/or those with hypertension and one or more additional atherosclerotic cardiovascular disease risk factors, if they can be achieved without undue treatment burden.
49	**Hypertension/Blood Pressure Control:** In older adults, pharmacological therapy to achieve treatment goals of <130/70 mmHg is not recommended; treating to systolic blood pressure <130 mmHg has not been shown to improve cardiovascular outcomes and treating to diastolic blood pressure <70 mmHg has been associated with higher mortality.
50	**Lipid Management**: Combination therapy (statin/fibrate) has not been shown to improve atherosclerotic cardiovascular disease outcomes and is generally not recommended. However, therapy with statin and fenofibrate may be considered for men with both triglyceride level ≥204 mg/dL (2.3 mmol/L) and HDL cholesterol level ≥34 mg/dL (0.9 mmol/L).
51	**Lipid Management:** Combination therapy (statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone and may increase the risk of stroke and is not generally recommended.
52	**Lipid Management:** For patients of all ages with diabetes and atherosclerotic cardiovascular disease, high-intensity statin therapy should be added to lifestyle therapy.
53	**Antiplatelet Agents**: Aspirin should not be recommended for atherosclerotic cardiovascular disease prevention for adults with diabetes at low atherosclerotic cardiovascular disease risk (10-year atherosclerotic cardiovascular disease risk <5%), such as in men or women with diabetes aged <50 years with no major additional atherosclerotic cardiovascular disease risk factors, as the potential adverse effects from bleeding likely offset the potential benefits.
54	**Coronary Heart Disease**: In patients with type 2 diabetes with stable congestive heart failure, metformin may be used if renal function is normal but should be avoided in unstable or hospitalized patients with congestive heart failure.
55	**Diabetic Kidney Disease:** At least once a year, assess urinary albumin (e.g., spot urinary albumin–to–creatinine ratio) and estimated glomerular filtration rate in patients with type 1 diabetes with duration of ≥5 years, in all patients with type 2 diabetes, and in all patients with comorbid hypertension**.**
56	**Diabetic Retinopathy:** If there is no evidence of retinopathy for one or more annual eye exams, then exams every 2 years may be considered. If any level of diabetic retinopathy is present, subsequent

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	dilated retinal examinations for patients with type 1 or type 2 diabetes should be repeated at least annually by an ophthalmologist or optometrist. If retinopathy is progressing or sight-threatening, then examinations will be required more frequently.
57	**Older Adults:** Other cardiovascular risk factors should be treated in older adults with consideration of the time frame of benefit and the individual patient. Treatment of hypertension is indicated in virtually all older adults, and lipid-lowering and aspirin therapy may benefit those with life expectancy at least equal to the time frame of primary or secondary prevention trials.
AGS: **Guidelines Abstracted from the American Geriatrics Society: Guidelines for Improving the Care of Older Adults with Diabetes Mellitus (DM): 2013 Update**	
58	**Hypertension**: Older adults with DM and hypertension should be offered a therapeutic intervention to lower blood pressure within 3 months if systolic blood pressure is 140 to 160 mmHg or diastolic blood pressure is 90 to 100 mmHg or within 1 month if blood pressure is greater than 160/100 mmHg.
59	**Glycemic Control Medications**: Use estimated glomerular filtration rate (eGFR) rather than serum creatinine levels to guide metformin use. Specifically, do not use metformin in patients with an eGFR of less than 30 mL/min per 1.73 m2. For individuals with an eGFR between 30 and 60 mL/min per 1.73 m2, check renal function more frequently and use lower dosages.
60	**Glycemic Control Monitoring:** Older adults with DM whose individual targets are not being met should have their HbA1c levels measured at least every 6 months and more frequently as needed or indicated. For older adults with stable HbA1c over several years, measurement every 12 months may be appropriate.
AGS: **American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults**	
61	**Anticholinergics (First generation antihistamines):** Avoid use of: Brompheniramine, Carbinoxamine, Chlorpheniramine, Clemastine, Cyproheptadine, Dexbrompheniramine, Dexchlorpheniramine, Dimenhydrinate, Diphenhydramine (oral), Doxylamine, Hydroxyzine, Meclizine, Promethazine, Triprolidine.
62	**Anticholinergics (Antiparkinsonian Agents):** Avoid use of: Benztropine (oral), Trihexyphenidyl.
63	**Anticholinergics (Antispasmodics):** Avoid use of: Atropine (excludes ophthalmic), Belladonna alkaloids, Clidinium-Chlordiazepoxide, Dicyclomine, Hyoscyamine, Propantheline, Scopolamine.
64	**Antithrombotics (Dipyridamole):** Avoid use of Dipyridamole (oral short-acting [does not apply to extended-release combination with aspirin]).
65	**Antithrombotics (Ticlopidine):** Avoid use of Ticlopidine.
66	**Anti-infective Medications:** Avoid use of Nitrofurantoin in individuals with creatinine clearance <30 mL/min or for long-term suppression of bacteria.
67	**Cardiovascular Medications (Peripheral alpha-1 blockers):** Avoid use as an antihypertensive: Doxazosin, Prazosin, Terazosin.
68	**Cardiovascular Medications (Central Alpha Blockers):** Avoid use of: Clonidine (as a first-line antihypertensive), Guanabenz, Guanfacine, Methyldopa, Reserpine (>0.1mg/d).
69	**Cardiovascular Medications (Digoxin):** Avoid use of Digoxin at dosages >0.125mg/d when used for atrial fibrillation or heart failure.
70	**Cardiovascular Medications (Nifedipine):** Avoid use of Nifedipine (immediate release).
71	**Central Nervous System Medications (Barbiturates):** Avoid use of: Amobarbital, Butabarbital, Butalbital, Mephobarbital, Pentobarbital, Phenobarbital, Secobarbital.

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72	**Central Nervous System Medications (Antidepressants):** Avoid use of single or combined: Amitriptyline, Amoxapine, Clomipramine, Desipramine, Doxepin (>6 mg/d), Imipramine, Nortriptyline, Paroxetine, Protriptyline, Trimipramine.
73	**Central Nervous System Medications (Meprobamate):** Avoid use of Meprobamate.
74	**Central Nervous System Medications (Ergoloid mesylates):** Avoid use of ergoloid mesylates, (dehydrogenated ergot alkaloids), Isoxuprine.
75	**Endocrine Medications (Desiccated Thyroid):** Avoid use of desiccated thyroid.
76	**Endocrine Medications (Estrogen):** Avoid use of estrogens (with or without progestins) with administration by oral and topical patch; or administration by vaginal cream or tablets [acceptable to use low-dose intravaginal estrogen for management of dyspareunia, lower urinary tract infections, and other vaginal symptoms].
77	**Endocrine Medications (Insulin):** Avoid use of sliding scale insulin.
78	**Endocrine Medications (Megestrol):** Avoid use of Megestrol.
79	**Gastrointestinal Medications (Metoclopramide):** Avoid use of Metoclopramide except for the indication of gastroparesis.
80	**Gastrointestinal Medications (Mineral Oil):** Avoid use of mineral oil given orally.
81	**Pain Medications (Pentazocine):** Avoid use of Pentazocine.
82	**Pain Medications (Skeletal Muscle Relaxants):** Avoid use of: Carisoprodol, Chlorzoxazone, Cyclobenzaprine, Metaxalone, Methocarbamol, Orphenadrine.
83	**Pain Medications (Genitourinary):** Avoid use of Desmopressin for treatment of nocturia or nocturnal polyuria.
84	**Cardiovascular (In Patients with Syncope):** Avoid use of anticholinesterase inhibitors; tertiary TCAs; peripheral alpha-1 blockers (Doxazosin, Prazosin, Terazosin); and antipsychotics: Chlorpromazine, Thioridazine, Olanzapine.
85	**Central Nervous System (In Patients with Dementia or Cognitive Dementia):** Avoid use of: Anticholinergics (Brompheniramine, Carbinoxamine, Chlorpheniramine, Clemastine, Cyproheptadine, Dexbrompheniramine, Dexchlorpheniramine, Dimenhydrinate, Diphenhydramine [oral], Doxylamine, Hydroxyzine, Meclizine, Triprolidine), Benzodiazepines, H2-receptor antagonists (nonbenzodiazepine benzodiazepine receptor agonist hypnotics, Eszopiclone, Zolpidem, Zaleplon), Antipsychotics [chronic and as-needed use].
86	**Central Nervous System (In Patients with Insomnia):** In patients with insomnia, avoid use of: Oral decongestants (Pseudoephedrine, Phenylephrine), Stimulants (Amphetamine, Armodafinil, Methylphenidate, Modafinil), Theobromines (Theophylline, Caffeine).
87	**ACE-Inhibitors:** Avoid routine use in patients taking Amiloride or Triamterene, except in those with demonstrated hypokalemia while taking an ACE-inhibitor.
88	**Theophylline:** Avoid use in patients taking Cimetidine.
89	**Warfarin:** Avoid in patients taking Amiodarone.
90	**Warfarin:** Avoid use in patients taking NSAIDs (nonsteroidal anti-inflammatory drugs)
91	**Cardiovascular Medications (Amiloride):** Avoid use of Amiloride in patients with CrCl (creatine clearance) <30 mL/min.
92	**Cardiovascular Medications (Apixaban):** Avoid use of Apixaban in patients with CrCl <25 mL/min.
93	**Cardiovascular Medications (Edoxaban):** Reduce dose of Edoxaban in patients with CrCl between 30 and 50 mL/min; avoid use in those with CrCl <30 mL/min or >95 mL/min.
94	**Cardiovascular Medications (Enoxaparin):** Reduce dose of Enoxaparin in patients with CrCl <30 mL/min.
95	**Cardiovascular Medications (Fondaparinux):** Avoid use of Fondaparinux in patients with CrCl <30 mL/min.

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96	**Cardiovascular Medications (Spironolactone):** Avoid use of Spironolactone in patients with CrCl <30 mL/min.
97	**Cardiovascular Medications (Triamterene):** Avoid use of Triamterene in patients with CrCl <30 mL/min.
98	**Central Nervous System Medication (Duloxetine):** Avoid use of Duloxetine in patients with CrCl <30 mL/min.
99	**Central Nervous System Medications (Gabapentin):** Reduce dose of Gabapentin in patients with CrCl <60 mL/min.
100	**Central Nervous System Medications (Levetiracetam):** Reduce dose of Levetiracetam in patients with CrCl ≤80 mL/min.
101	**Central Nervous System Medication (Pregabalin):** Reduce dose of Pregabalin in patients with CrCl <60 mL/min.
102	**Central Nervous System Medications (Tramadol):** Reduce dose of immediate-release Tramadol, and avoid use of extended-release Tramadol, in patients with CrCl <30 mL/min.
103	**Gastrointestinal Medications (Cimetidine):** Reduce dose of Cimetidine in patients with CrCl <50 mL/min.
104	**Gastrointestinal Medications (Famotidine):** Reduce dose of Famotidine in patients with CrCl <50 mL/min.
105	**Gastrointestinal Medications (Nizatidine):** Reduce dose of Nizatidine in patients with CrCl <50 mL/min.
106	**Gastrointestinal Medications (Ranitidine):** Reduce dose of Ranitidine in patients with CrCl <50 mL/min.
107	**Hyperuricemia Medications (Colchicine):** Reduce dose of Colchicine, and monitor for adverse effects, in patients with CrCl <30 mL/min.
108	**Hyperuricemia Medications (Probenecid):** Avoid use of Probenecid in patients with CrCl <30 mL/min.
CDC: **CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016**	
109	**Assessing Risk and Addressing Harms of Opioid Use:** Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.
110	**Opioid Selection, Dosage, Duration, Follow-Up, and Discontinuation:** When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day.
NICE: **Atrial fibrillation: the management of atrial fibrillation [CG]**	
111	**Atrial Fibrillation Management:** Do not offer stroke prevention therapy to people aged under 65 years with atrial fibrillation and no risk factors other than their sex (that is, very low risk of stroke equating to a CHA2DS2-VASc score of 0 for men or 1 for women).
NICE: **Lipid Modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease [CG181]**	
112	**Statin for Prevention of CVD:** Do not offer coenzyme Q10 or vitamin D to increase adherence to statin treatment.
NICE: **MI-secondary prevention: Secondary prevention in primary and secondary care for patients following a myocardial infarction [update of CG48]**	

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113	**Secondary Prevention of Myocardial Infarction (MI):** Do not routinely offer warfarin in combination with prasugrel or ticagrelor to people who need anticoagulation who have had an MI.
NICE: **Type 2 diabetes in adults: management [NG28]**	
114	**In Patients with Type 2 Diabetes:** Do not combine an ACE inhibitor with an angiotensin II-receptor antagonist to treat hypertension in adults with type 2 diabetes.
NICE: **Depression: The Treatment and Management of depression in adults [CPG90]**	
115	**In Patients with Depression:** Do not use antidepressants routinely to treat persistent subthreshold depressive symptoms or mild depression because the risk-benefit ratio is poor, but consider them for people with: a past history of moderate or severe depression; an initial presentation of subthreshold depressive symptoms that have been present for a long period (usually 2+ years); subthreshold depressive symptoms or mild depression that persist(s) after other interventions.
116	**In Patients with Depression:** Although there is evidence that St. John's wort may be of benefit in mild or moderate depression, practitioners should not prescribe or advise its use by people with depression because of uncertainty about appropriate doses, persistence of effect, variation in the nature of preparations and potential serious interactions with other drugs (including oral contraceptives, anticoagulants and anticonvulsants).
117	**In Patients with Depression:** Augmentation of an antidepressant with buspirone, carbamazepine, lamotrigine or valproate should not be used routinely as there is insufficient evidence for their use.
118	**In Patients with Depression:** Current evidence suggests that there are no major safety concerns associated with transcranial magnetic stimulation (TMS) for severe depression. There is uncertainty about the procedure's clinical efficacy, which may depend on higher intensity, greater frequency, bilateral application and/or longer treatment durations than have appeared in the evidence to date. TMS should therefore be performed only in research studies designed to investigate these factors.
NICE: **Depression in Adults [Q28]**	
119	**In Patients with Stable Angina:** Do not routinely offer anti-anginal drugs other than beta blockers or calcium channel blockers as first-line treatment for stable angina.
U.S Multi-Society Task Force: **Colonoscopy surveillance after colorectal cancer resection: recommendations of the US multi-society task force on colorectal cancer**	
120	**Colonoscopy Surveillance:** We recommend that, after the 1-year colonoscopy post-curative resection, the interval to the next colonoscopy should be 3 years, and then 5 years. Subsequent colonoscopies should occur at 5-year intervals until the benefit of continued surveillance is outweighed by diminishing life expectancy. If neoplastic polyps are detected, the intervals between colonoscopies should be in accordance with published guidelines for polyp surveillance intervals. These intervals do not apply to patients with Lynch syndrome.
U.S. Preventive Services Task Force: **Screening for Coronary Heart Disease With Electrocardiography**	
121	**Screening for Coronary Heart Disease with Electrocardiography:** The USPSTF recommends against screening with resting or exercise electrocardiography (ECG) for the prediction of coronary heart disease (CHD) events in asymptomatic adults at low risk for CHD events.
U.S. Preventive Services Task Force: **Screening for Abdominal Aortic Aneurysm**	

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122	**Screening for Abdominal Aortic Aneurysm:** The USPSTF recommends one-time screening for abdominal aortic aneurysm (AAA) with ultrasonography in men ages 65 to 75 years who have ever smoked.
U.S. Preventive Services Task Force: **Aspirin Use for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer**	
123	**Aspirin Use for the Primary Prevention of CHD and CRC:** The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.
U.S. Preventive Services Task Force: **Screening for Testicular Cancer**	
124	**Screening for Testicular Cancer:** The USPSTF recommends against screening for testicular cancer in adolescent or adult males.
U.S. Preventive Services Task Force: **Screening for Chronic Obstructive Pulmonary Disease**	
125	**Screening for Chronic Obstructive Pulmonary Disease:** The USPSTF recommends against screening for COPD in asymptomatic adults.
U.S. Preventive Services Task Force: **Vitamin D and Calcium Supplementation to Prevent Fractures in Adults**	
126	**Vitamin D and Calcium Supplementation to Prevent Factures:** The USPSTF concludes that the current evidence is insufficient to assess the balance of the benefits and harms of daily supplementation with greater than 400 IU of vitamin D3 and greater than 1000mg of calcium for the primary prevention of fractures in noninstitutionalized postmenopausal women. The USPSTF recommends against daily supplementation with 400 IU or less of vitamin D3 and 1000mg or less of calcium for the primary prevention of fractures in noninstitutionalized postmenopausal women.
U.S. Preventive Services Task Force: **Menopausal Hormone Therapy for the Primary Prevention of Chronic Conditions**	
127	**Menopausal Hormone Therapy:** The USPSTF recommends against the use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women.
U.S. Preventive Services Task Force: **Screening for Chlamydia and Gonorrhea**	
128	**Screening for Chlamydia and Gonorrhea:** The USPSTF recommends screening for chlamydia in sexually active females aged 24 years or younger and in older women who are at increased risk for infection. The USPSTF recommends screening for gonorrhea in sexually active females aged 24 years or younger and in older women who are at increased risk for infection.
U.S. Preventive Services Task Force: **Screening for Cervical Cancer**	
129	**Screening for Cervical Cancer:** The USPSTF recommends against screening for cervical cancer in women older than age 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer.
130	**Screening for Cervical Cancer:** The USPSTF recommends against screening for cervical cancer in women who have had a hysterectomy with removal of the cervix and who do not have a history of a high-grade precancerous lesion (cervical intraepithelial neoplasia [CIN] grade 2 or 3) or cervical cancer.
131	**Screening for Cervical Cancer:** The USPSTF recommends against screening for cervical cancer in women younger than age 21 years.

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132	**Screening for Cervical Cancer:** The USPSTF recommends screening for cervical cancer in women aged 21 to 65 years with cytology (Papanicolaou smear) every 3 years or, for women aged 30 to 65 years who want to lengthen the screening interval, screening with a combination of cytology and HPV (human papilloma virus) testing every 5 years.
133	**Screening for Cervical Cancer:** The USPSTF recommends against screening for cervical cancer with HPV testing, alone or in combination with cytology, in women younger than age 30 years.
Department of Veterans Affairs: **VA/DoD Clinical Practice Guideline for the Management of Dyslipidemia for Cardiovascular Risk Reduction**	
134	**Management of Dyslipidemia for Cardiovascular Risk Reduction:** We recommend against routinely measuring LFTs or CK after a moderate-dose statin is initiated.
135	**Management of Dyslipidemia for Cardiovascular Risk Reduction:** We suggest initiation of a moderate-dose statin for patients with an estimated 10-year CVD risk of 12% or greater.
136	**Management of Dyslipidemia for Cardiovascular Risk Reduction:** We suggest considering a moderate-dose statin for patients with a 10-year CVD risk between 6% and 12% following a discussion of the known minimal harms, benefits derived from limited evidence, and an exploration of the patients values and preferences.
137	**Management of Dyslipidemia for Cardiovascular Risk Reduction:** We suggest CVD risk assessment every five years for patients with low CVD risk and not on statin therapy.
Department of Veterans Affairs: **VA/DoD Clinical Practice Guideline for the Diagnosis and Management of Hypertension in the Primary Care Setting**	
138	**Management of Hypertension:** We recommend against the use of more than one of the following three drug classes together in the same patient: angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, or direct renin inhibitors.
139	**Management of Hypertension:** We recommend against the use of alpha-adrenergic blockers as monotherapy, but this class of agents may be used as supplemental therapy or if warranted by comorbid conditions (e.g., symptomatic prostatic hypertrophy).
Choosing Wisely	
140	**Thyroid Ultrasound (American Association of Clinical Endocrinologist & The Endocrine Society):** Don't routinely order a thyroid ultrasound in patients with abnormal thyroid function tests if there is no palpable abnormality of the thyroid gland.
141	**In patients with Hypothyroidism (American Association of Clinical Endocrinologists & The Endocrine Society):** Don't order a total or free T3 level when assessing levothyroxine (T4) dose in hypothyroid patients.
142	**Testosterone (American Association of Clinical Endocrinologists & The Endocrine Society):** Don't prescribe testosterone therapy unless there is biochemical evidence of testosterone deficiency.
143	**Corticosteroids (American Academy of Dermatology):** Don't use systemic (oral or injected) corticosteroids as a long-term treatment for dermatitis.
144	**DEXA Screening (American Academy of Family Physicians):** Don't use dual-energy x-ray absorptiometry (DEXA) screening for osteoporosis in women younger than 65 or men younger than 70 with no risk factors.
145	**Screening for Carotid Artery Stenosis (American Academy of Family Physicians):** Don't screen for carotid artery stenosis in asymptomatic adult patients.
146	**Screening for Cervical Cancer (American Academy of Family Physicians):** Don't screen women younger than 30 years of age for cervical cancer with HPV testing, alone or in combination with cytology.

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147	**Screening for Hepatitis C (American Association of the Society of Liver Disease):** Don't repeat hepatitis C viral load testing outside of antiviral therapy.
148	**Echocardiography (American College of Cardiology):** Don't perform echocardiography as routine follow-up for mild, asymptomatic native valve disease in adult patients with no change in signs or symptoms.
149	**Lung Cancer Screening (American College of Chest Physicians & American Thoracic Society):** Don't perform CT screening for lung cancer among patients at low risk for lung cancer.
150	**Screening for Alzheimer Disease (American College of Medical Genetics and Genomics):** Don't order APOE genetic testing as a predictive test for Alzheimer disease.
151	**Screening for Ovarian Cancer (The American College of Obstetricians and Gynecologists):** Don't screen for ovarian cancer in asymptomatic women at average risk.
152	**Low Back Pain (American College of Physicians):** Don't obtain imaging studies in patients with non-specific low back pain.
153	**Screening for Prostate Cancer (American College of Preventive Medicine):** Don't routinely perform PSA-based screening for prostate cancer.
154	**Screening for Cervical Cancer (American College of Preventive Medicine):** Don't perform screening for cervical cancer in low-risk women aged 65 years or older and in women who have had a total hysterectomy for benign disease.
155	**Screening for Lyme Disease (American College of Rheumatology):** Don't test for Lyme disease as a cause of musculoskeletal symptoms without an exposure history and appropriate exam findings.
156	**DXA Scans (American College of Rheumatology):** Don't routinely repeat DXA scans more often than once every two years.
157	**Long-term Acid Suppression Therapy (American Gastroenterological Association):** For pharmacological treatment of patients with gastroesophageal reflux disease (GERD), long-term acid suppression therapy (proton pump inhibitors or histamine2 receptor antagonists) should be titrated to the lowest effective dose needed to achieve therapeutic goals.
158	**Endoscopy (American Gastroenterological Association):** For a patient who is diagnosed with Barrett's esophagus, who has undergone a second endoscopy that confirms the absence of dysplasia on biopsy, a follow-up surveillance examination should not be performed in less than three years as per published guidelines.
159	**Diabetes Management (American Geriatrics Society):** Avoid using medications other than metformin to achieve hemoglobin A1c <7.5% in most older adults; moderate control is generally better.
160	**Benzodiazepines (American Geriatrics Society):** Don't use benzodiazepines or other sedative-hypnotics in older adults as first choice for insomnia, agitation or delirium.
161	**Antipsychotics (American Geriatrics Society):** Don't use antipsychotics as the first choice to treat behavioral and psychological symptoms of dementia.
162	**Cholinesterase Inhibitors (American Geriatrics Society):** Don't prescribe cholinesterase inhibitors for dementia without periodic assessment for perceived cognitive benefits and adverse gastrointestinal effects.
163	**Antipsychotics (AMDA – The Society for Post-Acute and Long-term Care Medicine):** Don't prescribe antipsychotic medications for behavioral and psychological symptoms of dementia (BPSD) in individuals with dementia without an assessment for an underlying cause of the behavior.
164	**Lipid Management (AMDA – The Society for Post-Acute and Long-Term Care Medicine):** Don't routinely prescribe lipid-lowering medications in individuals with a limited life expectancy.
165	**Antipsychotics (American Psychiatric Association):** Don't routinely prescribe two or more antipsychotic medications concurrently.

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166	**Cancer Screening (American Society of Clinical Oncology):** Don't perform surveillance testing (biomarkers) or imaging (PET, CT, and radionuclide bone scans) for asymptomatic individuals who have been treated for breast cancer with curative intent.
167	**Cancer Surveillance (American Society of Clinical Oncology):** Avoid using PET or PET-CT scanning as part of routine follow-up care to monitor for a cancer recurrence in asymptomatic patients who have finished initial treatment to eliminate the cancer unless there is high-level evidence that such imaging will change the outcome.
168	**Vitamin D Screening (American Society for Clinical Pathology):** Don't perform population-based screening for 25-OH-Vitamin D deficiency.
169	**Anticoagulants (American Society of Hematology):** Don't treat with an anticoagulant for more than three months in a patient with a first venous thromboembolism (VTE) occurring in the setting of a major transient risk factor.
170	**NSAIDS (American Society of Nephrology):** Avoid nonsteroidal anti-inflammatory drugs (NSAIDS) in individuals with hypertension or heart failure or CKD of all causes, including diabetes.
171	**Breast Cancer Surveillance (American Society for Radiation Oncology):** Don't routinely recommend follow-up mammograms more often than annually for women who have had radiotherapy following breast conserving surgery.
172	**Antibiotics (American Urological Association):** Don't treat an elevated PSA with antibiotics for patients not experiencing other symptoms.
173	**Screening for Coronary Artery Disease (Society of Cardiovascular Computed Tomography):** Don't order coronary artery calcium scoring for screening purposes on low risk asymptomatic individuals except for those with a family history of premature coronary artery disease.
174	**Diabetes Monitoring (Society of General Internal Medicine):** Don't recommend daily home finger glucose testing in patients with Type 2 diabetes mellitus not using insulin.
175	**Screening for Gynecologic Cancer (Society of Gynecologic Oncology):** Avoid routine imaging for cancer surveillance in women with gynecologic cancer, specifically ovarian, endometrial, cervical, vulvar and vaginal cancer.
176	**Cancer Screening (Society of Nuclear Medicine and Molecular Imaging):** Don't use PET/CT for cancer screening in healthy individuals.
177	**PET Imaging (Society of Nuclear Medicine and Molecular Imaging):** Don't use PET imaging in the evaluation of patients with dementia unless the patient has been assessed by a specialist in this field.
178	**Testosterone (American Urological Association):** Don't prescribe testosterone to men with erectile dysfunction who have normal testosterone levels.

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eTable 5. Characteristics of the panelists and panels

	Panel 1	Panel 2
Panelist Information		
Participation, N or N (%)		
Panelists invited to participate	29	26
Panelists agreeing to participate	14 (48)	12 (46)
Panelists who participated	13 (45)	12 (46)
Of those participating…		
Gender, N (%)		
Female	5 (38)	8 (67)
Primary Specialty, N (%)		
General internal medicine	9 (69)	9 (75)
Geriatric medicine	1 (8)	3 (25)
Other internal medicine subspecialties (cardiology, endocrinology)	3 (23)	0
Dept. of Veterans Affairs (VA) Affiliation, N (%)		
VA affiliation	10 (77)	8 (67)
Panel information		
Activities, dates/times		
Review of candidate recommendations[†]	April 25 – May 8, 2017	Oct. 23 – Nov. 6, 2017
Meeting #1[*]	May 16, 2017 (3 hours)	Nov. 15, 2017 (3.5 hours)
Initial rating activity[†]	May 26 - June 5, 2017	Nov. 21 - 29, 2017
Meeting #2, including (second) rating[*]	June 20, 2017 (3 hours)	Dec. 13, 2017 (3.5 hours)

[*]*virtual meeting using ThinkTank*
[†]*independent, asynchronous work*

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eTable 6. Original de-intensification recommendation, recommendation as specified by the study team, changes made by the expert panel, and validity ratings

No.	Original recommendation	Initial specification of the actionable recommendation (by the study team)	Final specification of the actionable recommendation (by the expert panel)	Exclusions (for the actionable recommendation by the expert panel)	Definitions (for the actionable recommendation by the expert panel)	Changes made by the expert panel[a,b]	Validity Rating (Median) 1-9
Medication (older adults)							
1-3	Avoid using medications other than metformin to achieve hemoglobin A1c <7.5% in most older adults; moderate control is generally better. *Primary recommendation (above) from: Choosing Wisely (American Geriatrics Society)* *Additional recommendation(s) (listed in eMethods 3 and 4) – source(s): American Geriatrics Society, American Diabetes Association, American College of Cardiology/American Heart Association*	Action (A): Stop or decrease hypoglycemic agents other than metformin within 6 months of a low A1c Population (P): Older adults (>65 years old) with an A1c <7	A {**For Recs 1-3**}: Stop or decrease dose of insulin, sulfonylureas, and/or thiazolidinediones within 3 months of a low HbA1c P {**For Rec 1**}: Older adults (>=65 years old) with an HbA1c <7 at high risk for hypoglycemia (CKD stage 3 or greater, cognitive impairment, or dementia) P {**For Rec 2**}: Older adults (>=75 years old) with an HbA1c <7 at high risk for hypoglycemia (CKD stage 3 or greater, cognitive impairment, or dementia) P {**For Rec 3**}: Older adults (>=65 years old) with an HbA1c <6.5			A: 2,3 P: 1 P: 1 P: 1	 8 8 7.5
4	Don't use benzodiazepines or other sedative-hypnotics in older adults as first choice for insomnia, agitation or delirium.	A: Stop or decrease dose of benzodiazepines or other sedative-hypnotics P: Patients older than 65	A: Decrease the dose of benzodiazepines or other sedative-hypnotics or justify continuation of the current dose P: Patients older than 65 on long-term benzodiazepines or other sedative-		Justification needs to include mention that other modalities (e.g., other medications or therapies and/or a previous attempt at tapering) had been tried and failed	A: 1,4 P: 1	8

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	Choosing Wisely (American Geriatrics Society) *Additional recommendation(s) – source(s): American Geriatrics Society, Choosing Wisely (American Academy of Sleep Medicine)*		hypnotics for the treatment of insomnia				
5	The USPSTF recommends against the use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women. [Evidence: Grade D] *US Preventive Services Task Force* *Additional recommendation(s) – source(s): US Preventive Services Task Force, American Geriatrics Society, American College of Physicians*	A: Stop estrogen or combined estrogen/progestin therapy P: Women on hormonal therapy who are over age 60 or more than 10 years after menopause	A: Stop or decrease estrogen or combined estrogen/progestin therapy P: Women on hormonal therapy who are over age 60 or more than 10 years after menopause			A: 4 P: None	8
6	In patients older than 65 with dementia or cognitive impairment, avoid use of anticholinergics. [Quality of Evidence: Moderate; Strength: Strong]	A: Stop or decrease dose of anticholinergics P: Patients older than 65 with dementia or cognitive impairment	A: Stop or decrease dose of anticholinergics P: Patients older than 65 with dementia or cognitive impairment treated with long-term anticholinergic medications		Anticholinergics include: Brompheniramine, Carbinoxamine, Chlorpheniramine, Clemastine, Cyproheptadine, Dexbrompheniramine, Dexchlorpheniramine, Dimenhydrinate, Diphenhydramine	A: None P: 1	7

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	American Geriatrics Society – Beers Criteria *Additional recommendation(s) – source(s): American Geriatrics Society (Beers Criteria)*				[oral], Doxylamine, Hydroxyzine, Meclizine, Triprolidine		
7	In patients older than 65, avoid use of skeletal muscle relaxants. [Quality of Evidence: Moderate; Strength: Strong] *American Geriatrics Society – Beers Criteria* *Additional recommendation(s) – source(s): None*	A: Stop or decrease the dose of skeletal muscle relaxants P: Patients older than 65	A: Decrease the dose of skeletal muscle relaxants P: Patients older than 65 on long term use of skeletal muscle relaxants Excluded: Patients diagnosed with spasticity disorder	Patients diagnosed with spasticity disorder	Skeletal muscle relaxants include: Carisoprodol, Chlorzoxazone, Cyclobenzaprine, Metaxalone, Methocarbamol, Orphenadrine	A: 4 P: 1	7
8	In patients older than 65, avoid use of single or combined antidepressants. [Quality of Evidence: High; Strength: Strong] *American Geriatrics Society – Beers Criteria* *Additional recommendation(s) – source(s): American Psychiatric Association*	A: Stop or decrease dose of single or combined antidepressants (tricyclics and paroxetine) P: Patients older than 65	A: Stop or decrease dose of single or combined antidepressants (tricyclics) P: Patients older than 65		Antidepressants include: Amitriptyline, Amoxapine, Clomipramine, Desipramine, Doxepin (>6 mg/d), Imipramine, Nortriptyline, Protriptyline, Trimipramine	A: 3 P: None	7
9-10	In older adults with Type 2 diabetes, pharmacological therapy to achieve	A: Decrease the dose or number of antihypertensive medications within	A {**For Recs 9-10**}: Decrease the dose or number of antihypertensive medications within 3 months			A: 2	

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	treatment goals of <130/70 mmHg is not recommended. Treating to systolic blood pressure <130 has not been shown to improve cardiovascular outcomes and treating to diastolic blood pressure <70 has been associated with higher mortality. [Level of Evidence: C] *American Diabetes Association* *Additional recommendation(s) – source(s): American College of Physicians and the American Academy of Family Physicians*	six months of the last prescription issue date P: Older adults with Type 2 diabetes on hypertension therapy who have a SBP<130 or DBP<70	P {**For Rec 9**}: Older adults (>=65 years old) with Type 2 diabetes on hypertension therapy who have two consecutive ambulatory DBP readings <60 P {**For Rec 10**}: Older adults (>=65 years old) with Type 2 diabetes on hypertension therapy who have two consecutive ambulatory SBP readings <130 or two consecutive ambulatory DBP readings <70			P: 1,3 P: 1,3	5 (not validated) 4.5 (not validated)
			MEDICATION (ALL ADULTS)				
11	In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended. [Strength: Class I Strong; Level of Evidence: Category B-NR] *American Heart Association/American College of Cardiology* *Additional recommendation(s) – source(s): American College of*	A: Decrease daily aspirin dose to <=100 mg within 6 months of the last prescription issue date P: Patients with DAPT and daily aspirin dose>100 mg	A: Decrease daily aspirin dose to <=100 mg within 3 months P: Patients with DAPT and daily aspirin dose>100 mg			A: 2 P: None	9

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	Cardiology/American Heart Association						
12-13	In patients with SIHD without prior history of ACS, coronary stent implantation, or recent (within 12 months) CABG, treatment with DAPT is not beneficial. [Strength: Class III No Benefit; Level of Evidence: Category B-R] *American Heart Association/American College of Cardiology* *Additional recommendation(s) – source(s): American Heart Association/American College of Cardiology, American Diabetes Association*	A: Stop either aspirin or alternate antiplatelet therapy within 6 months of the last prescription issue date P: Patients on DAPT (dual anti-platelet regimen) with stable IHD without prior history (in the last 12 months) of ACS, coronary stent implantation, or CABG	A {**For Rec 12**}: Stop the alternate antiplatelet therapy within 3 months unless a reason is documented for longer continuation A {**For Rec 13**}: Stop either aspirin or alternate antiplatelet therapy within 3 months unless a reason is documented for longer continuation P {**For Recs 12-13**}: Patients on DAPT (dual anti-platelet regimen) with stable IHD without prior history (in the last 12 months) of ACS, coronary stent implantation, or CABG		Stable IHD is defined as confirmed obstructive coronary artery disease without recent (<1 year) ACS or PCI	A: 1,2,3 A: 1,2 P: 3	8 7
14	We recommend against the use of more than one of the following three drug classes together in the same patient: angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, or direct renin inhibitors. [Strength: Strongly Against]	A: Stop all but 1 class of the renin-angiotensin system agents (i.e., ACEIs, ARBs, or DRIs) within 6 months of the last prescription issue date P: Patients on combination therapy from two or more of the following classes: ACEIs, ARBs, or DRIs	A: Stop all but 1 class of the renin-angiotensin system agents (i.e., ACEIs, ARBs, or DRIs) within 3 months P: Patients on combination therapy from two or more of the following classes: ACEIs, ARBs, or DRIs			A: 2 P: None	8

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	Dept. of Veterans Affairs and Dept. of Defense *Additional recommendation(s) – source(s): National Institute for Health and Care Excellence, American College of Cardiology/American Heart Association*						
15	Combination therapy (statin/fibrate) has not been shown to improve atherosclerotic cardiovascular disease outcomes and is generally not recommended. However, therapy with statin and fenofibrate may be considered for men with both triglyceride level >=204 mg/dL (2.3 mmol/L) and HDL cholesterol level <=34 mg/dL (0.9 mmol/L). [Level of Evidence: Category B] Combination therapy (statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone and may increase the risk of stroke and is not generally recommended. [Level	A: Stop the non-statin medications within 6 months of the last prescription issue date of niacin or fibrate P: All patients on combination lipid lowering therapy (i.e., statin/fibrate or statin/niacin) Excluded: Men with diabetes and HDL<35 mg/dL	A: Stop the non-statin medications within 3 months P: All patients on combination lipid lowering therapy (i.e., stain/fibrate or statin/niacin) Excluded: Patients, on fibrates, who have a history of triglycerides >=1,000 mg/dL	Patients, on fibrates, who have a history of triglycerides >=1,000 mg/dL		A: 2 P: 1	8

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	of Evidence: Category A] *American Diabetes Association* *Additional recommendation(s) – source(s): The National Institute for Health and Care Excellence, American College of Cardiology/American Heart Association*						
16	Don't prescribe testosterone to men with erectile dysfunction who have normal testosterone levels. *Choosing Wisely (American Urological Society)* *Additional recommendation(s) – source(s): American Geriatrics Society (Beers Criteria), Choosing Wisely (American Association of Clinical Endocrinologists and the Endocrine Society)*	A: Stop testosterone therapy P: Men with erectile dysfunction (ED) who have normal testosterone levels prior to testosterone initiation	A: Stop or decrease testosterone therapy P: Men with erectile dysfunction who have normal testosterone levels prior to testosterone initiation			A: 4 P: None	8
17	Don't prescribe testosterone to men with erectile dysfunction who have normal testosterone levels.	A: Stop testosterone and recheck testosterone levels within 3 months P: Men with ED on testosterone	A: Stop or decrease testosterone and recheck testosterone levels within 3 months P: Men with ED on testosterone			A: 4 P: None	8

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	Choosing Wisely (American Urological Society) *Additional recommendation(s) – source(s): American Geriatrics Society (Beers Criteria), Choosing Wisely (American Association of Clinical Endocrinologists and the Endocrine Society)*						
18	When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day. [Evidence: Type 3] *Centers for Disease Control and Prevention*	A: Stop or decrease the opioid dose P: Patients on ≥90 morphine milligram equivalents/day	A: Decrease the opioid dose or justify continuation of the current dose P: Patients with chronic, non-cancer pain who are on a long-term daily dose of ≥90 morphine milligram equivalents Excluded: Patients receiving hospice or palliative care	Patients receiving hospice or palliative care	Justification needs to include mention that other modalities (e.g., other medications or therapies, a previous attempt at tapering) had been tried and failed	A: 1,4 P: 1	7

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	Additional recommendation(s) – source(s): Department of Veterans Affairs/Department of Defense						
19	Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible. [Evidence: Type 3] *Centers for Disease Control and Prevention* *Additional recommendation(s) – source(s): Department of Veterans Affairs*	A: Stop or decrease the dose of at least one of the two medications P: All patients, 18 years and older, who are on both opioids and benzodiazepines	A: Decrease the dose of at least one of the two medications or justify continuation of the current dose P: Patients with chronic, non-cancer pain who are on both long-term opioids and benzodiazepines Excluded: Patients receiving hospice or palliative care	Patients receiving hospice or palliative care	Justification needs to include mention that other modalities (e.g., other medications or therapies and/or a previous attempt at tapering) had been tried and failed	A: 1,4 P: 1	7
20	Don't use antipsychotics as the first choice to treat behavioral and psychological symptoms of dementia. *Choosing Wisely (American Geriatrics Society)* *Additional recommendation(s) – source(s): Choosing Wisely (American Medical Directors Association - The*	A: Stop or decrease dose of antipsychotics P: Patients older than 65 with dementia Population exclusions: Patients with schizophrenia, bipolar disorder, major depression, or using antipsychotics (short-term) as antiemetics during chemotherapy	A: Initiate a decrease in dose of the antipsychotic after 4 months of daily use or justification of continued use at the same dose P: Patients with dementia Excluded: Patients with schizophrenia, bipolar disorder, major depression, or using antipsychotics (short-term) as antiemetics during chemotherapy	Patients with schizophrenia, bipolar disorder, major depression, or using antipsychotics (short-term) as antiemetics during chemotherapy	Daily use is defined as: continuous use at a constant dose without tapering attempt	A: 1,2,4 P: 2	7

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	Society for Post-Acute and Long-Term Care Medicine; American Psychiatric Association), American Geriatrics Society (Beers Criteria), Pharmacy Quality Alliance, Food and Drug Administration						
21	Inappropriate use of aldosterone receptor antagonists is potentially harmful because of life-threatening hyperkalemia or renal insufficiency when serum creatinine is greater than 2.5 mg/dL in men or greater than 2.0 mg/dL in women (or estimated glomerular filtration rate <30 mL/min/1.73 m2), and/or potassium greater than 5.0 mEq/L. [Strength: Class III Harm; Level of Evidence: Category B] *American Heart Association/American College of Cardiology* *Additional recommendation(s) – source(s): American College of*	A: Reduce dose or stop aldosterone receptor antagonists within 6 months of the last prescription issue date P: Patients on aldosterone receptor antagonists with renal insufficiency (estimated glomerular filtration rate <30 mL/min/1.73 m2) and/or potassium greater than 5.0 mEq/L	A: Reduce dose or stop aldosterone receptor antagonists within one week of the 2nd abnormal laboratory value P: Patients on aldosterone receptor antagonists with renal insufficiency (2 estimated glomerular filtration rates<30 mL/min/1.73 m2) and/or 2 potassium values greater than 5.0 mEq/L Excluded: Patients with primary hyperaldosteronism	Patients with primary hyperaldosteronism		A: 2 P: 1	6.5 (not validated)

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	Cardiology/American Heart Association						
22	Don't routinely prescribe lipid-lowering medications in individuals with a limited life expectancy. *Choosing Wisely (American Medical Directors Association – The Society for Post-Acute and Long-Term Care Medicine)* *Additional recommendation(s) – source(s): US Preventive Services Task Force, American Diabetes Association*	A: Stop lipid lowering therapy within 6 months of the last prescription issue date P: Patients who are on lipid lowering therapy with life expectancy <5 years due to non-cardiovascular disease	A: Stop lipid lowering therapy within 3 months P: Patients who are on lipid lowering therapy with life expectancy <1 year			A: 2 P: 1	5 (not validated)
23	Don't routinely prescribe lipid-lowering medications in individuals with a limited life expectancy. *Choosing Wisely (American Medical Directors Association – The Society for Post-Acute and Long-Term Care Medicine)* *Additional recommendation(s) – source(s): US Preventive Services Task Force, American Diabetes Association*	A: Stop lipid lowering therapy within 6 months of the last prescription issue date P: Patients who are on lipid lowering therapy with life expectancy <5 years	A: Stop lipid lowering therapy within 3 months P: Patients who are on lipid lowering therapy with life expectancy <5 years			A: 2 P: None	3 (not validated)
24	The clinical effectiveness of	A: Stop the use of pentoxifylline within	A: Stop the use of pentoxifylline within 3 months			A: 2	4.5 (not validated)

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	pentoxifylline as therapy for claudication is marginal and not well established. [Level of Evidence: Category C] *American Heart Association/American College of Cardiology* *Additional recommendation(s) – source(s): None*	6 months of the last prescription issue date P: All patients	P: All patients			P: None	
CANCER SCREENING							
25	ACP recommends that clinicians should not screen for prostate cancer using the prostate-specific antigen test in average-risk men under the age of 50 years, men over the age of 69 years, or men with a life expectancy of less than 10 years. *American College of Physicians* *Additional recommendation(s) – source(s): US Preventive Services Task Force, American College of Physicians*	A: Don't screen for prostate cancer using prostate specific antigen (PSA) P: Men younger than 55, older than 69, or with a life expectancy of less than 10 years	A: Don't screen for prostate cancer using prostate specific antigen P: Men younger than 50, older than 69, or with a life expectancy of less than 15 years Excluded: African Americans and men with a family history of prostate cancer	African Americans and men with a family history of prostate cancer		A: None P: 1,2	8.5
26	Clinicians should encourage colorectal cancer screening [in persons aged 50-75 years] by 1 of 4 strategies: high-	A: Don't screen more than every 10 years with colonoscopy, every 5 years with sigmoidoscopy, or yearly with FOBT/FIT	A: Don't screen more often than every 10 years with colonoscopy, every 5 years with sigmoidoscopy, or yearly with FOBT/FIT	Patients whose prior colonoscopy was incomplete due to inadequate bowel preparation	Average-risk is defined as: (1) no prior colectomy; (2) no history of colorectal cancer; (3) no history of colon	A: None P: 1	8.5

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	sensitivity FOBT or FIT (every year); sigmoidoscopy (every 5 years); combined high-sensitivity FOBT or FIT (every 3 years) plus sigmoidoscopy (every 5 years); or optical colonoscopy (every 10 years) in average-risk adults aged 50 to 75 years. *American College of Physicians* *Additional recommendation(s) – source(s): American College of Physicians, US Preventive Services Task Force, US Multi-Society Task Force, Choosing Wisely (American Gastroenterological Association), American Cancer Society, American Gastroenterological Association*	P: Patients with average-risk of colorectal cancer	P: Patients with average-risk of colorectal cancer Excluded: Patients whose prior colonoscopy was incomplete due to inadequate bowel preparation		polyps; (4) no history of inflammatory bowel disease; and (5) no family history of colorectal cancer		
27-28	Clinicians should not screen for colorectal cancer in average-risk adults younger than 50 years or older than 75 years or those with an estimated life expectancy of less than 10 years. *American College of Physicians*	A: Do not do screening colonoscopy, screening sigmoidoscopy, fecal immunochemical test (FIT), or fecal occult blood test (FOBT) P: Average-risk adults younger than 50 years, older than 75	A {**For Recs 27-28**}: Do not do screening colonoscopy, screening sigmoidoscopy, FIT, or FOBT P {**For Rec 27**}: Average-risk adults younger than 50 years or with a life expectancy less than 10 years P {**For Rec 28**}: Average-risk adults younger than 50 or 80 or older		Average-risk is defined as: (1) no prior colectomy; (2) no history of colorectal cancer; (3) no history of colon polyps; (4) no history of inflammatory bowel disease; and (5) no family history of colorectal cancer	A: None P: 1 P: 1	 8 7.5

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	Additional recommendation(s) – source(s): US Preventive Services Task Force, American College of Physicians, Choosing Wisely (American College of Surgeons; Society for General Internal Medicine; Society for Post-acute and Long-term Care Medicine; American Geriatrics Society)	years, or with a life expectancy less than 10 years					
29-30	Clinicians should not screen average-risk women younger than 40 years or aged 75 years or older for breast cancer or screen women of any age with a life expectancy less than 10 years. *American College of Physicians* *Additional recommendation(s) – source(s): US Preventive Services Task Force, American College of Physicians, American Cancer Society, Choosing Wisely (American Geriatrics Society; Society for General Internal Medicine; Society for Post-acute*	A: Do not do screening mammography P: Average-risk women younger than 40, 75 years or older, or with a life expectancy less than 10 years	A {**For Recs 29-30**}: Do not do screening mammography P {**For Rec 29**}: Average-risk women younger than 40 or with a life expectancy less than 10 years P {**For Rec 30**}: Average-risk women younger than 40 or 80 or older		Average-risk is defined as those without a personal history of breast cancer, a genetic mutation known to increase risk of breast cancer [e.g., BRCA], or a history of previous radiotherapy to the chest at a young age	A: None P: 1 P: 1	 8.5 8

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	and Long-term Care Medicine)						
31	The USPSTF recommends: 1) screening for cervical cancer in women age 21 to 65 years with cytology (Pap smear) every 3 years or, for women age 30 to 65 years who want to lengthen the screening interval, screening with a combination of cytology and human papillomavirus (HPV) testing every 5 years [Grade A]; 2) against screening for cervical cancer with HPV testing, alone or in combination with cytology, in women younger than age 30 years [Grade D]; 3) against screening for cervical cancer in women younger than age 21 years [Grade D]; 4) against screening for cervical cancer in women older than age 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer [Grade D]; and 5) against screening for cervical cancer in women who have had a hysterectomy	A: Do not perform cervical cancer screening more often than every 3 years with cytology OR every 5 years with HPV + cervical cytology P: Women who are 30-65 years old Population exclusions: patients with a prior history of exposure to diethylstilbestrol before birth, diagnosis of HIV, a weakened immune system, high-grade precancerous lesion, or cervical cancer (including total hysterectomy with a history of high-grade precancerous lesion or cervical cancer)	A: Do not perform cervical cancer screening more often than every 3 years with cytology OR every 5 years with HPV + cervical cytology P: Women who are 30-65 years old Excluded: Patients with a prior history of exposure to diethylstilbestrol before birth, diagnosis of HIV, a weakened immune system, high-grade precancerous lesion, history of colposcopy, or cervical cancer (including total hysterectomy with a history of high-grade precancerous lesion or cervical cancer)	Patients with a prior history of exposure to diethylstilbestrol before birth, diagnosis of HIV, a weakened immune system, high-grade precancerous lesion, history of colposcopy, or cervical cancer (including total hysterectomy with a history of high-grade precancerous lesion or cervical cancer)	A high-grade precancerous lesion is defined as: CIN 2, CIN 3, HSIL	A: None P: 1,3	8

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	with removal of the cervix and who do not have a history of a high-grade precancerous lesion (cervical intraepithelial neoplasia [CIN] grade 2 or 3) or cervical cancer [Grade D]. *US Preventive Services Task Force* *Additional recommendation(s) – source(s): American College of Physicians, American College of Obstetrics and Gynecology, American Cancer Society/American Society for Colposcopy and Cervical Pathology/American Society for Clinical Pathology, American College of Preventive Medicine, American Academy of Family Physicians*						
32	The USPSTF recommends: 1) screening for cervical cancer in women age 21 to 65 years with cytology (Pap smear) every 3 years or, for women age 30 to 65 years who want to lengthen the screening interval,	A: Do not perform cervical cancer screening (cervical cytology or Human Papilloma Virus (HPV) testing) P: Women under 21 years, over 65 years and at low risk, or with a history of total	A: Do not perform cervical cancer screening (cervical cytology or HPV testing) P: Women under 21 years, over 65 years and at low risk, or with a history of total hysterectomy for benign disease Excluded: Patients with a prior history of exposure to diethylstilbestrol	Patients with a prior history of exposure to diethylstilbestrol before birth, diagnosis of HIV, a weakened immune system, high-grade precancerous lesion, or cervical cancer	Low risk is defined as: no history of a high-grade precancerous lesion and either [(3 negative pap test results in a row) or (2 negative co-test results in a row), with the most recent test performed after age 60]	A: None P: 3	8

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	screening with a combination of cytology and human papillomavirus (HPV) testing every 5 years [Grade A]; 2) against screening for cervical cancer with HPV testing, alone or in combination with cytology, in women younger than age 30 years [Grade D]; 3) against screening for cervical cancer in women younger than age 21 years [Grade D]; 4) against screening for cervical cancer in women older than age 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer [Grade D]; and 5) against screening for cervical cancer in women who have had a hysterectomy with removal of the cervix and who do not have a history of a high-grade precancerous lesion (cervical intraepithelial neoplasia [CIN] grade 2 or 3) or cervical cancer [Grade D]. *US Preventive Services Task Force*	hysterectomy for benign disease Population exclusions: patients with a prior history of exposure to diethylstilbestrol before birth, diagnosis of HIV, a weakened immune system, high-grade precancerous lesion, or cervical cancer	before birth, diagnosis of HIV, a weakened immune system, high-grade precancerous lesion, or cervical cancer		A high-grade precancerous lesion is defined as: CIN 2, CIN 3, or HSIL		

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	Additional recommendation(s) – source(s): American College of Physicians, American College of Obstetrics and Gynecology, American Cancer Society/American Society for Colposcopy and Cervical Pathology/American Society for Clinical Pathology, American College of Preventive Medicine, American Academy of Family Physicians						
33	Don’t perform computer tomography (CT) screening for lung cancer among patients at low risk for lung cancer. *Choosing Wisely (American College of Chest Physicians and American Thoracic Society)* *Additional recommendation(s) – source(s): US Preventive Services Task Force, American Association for Thoracic Surgery, American Cancer Society/American College of Chest*	A: Don't perform a screening CT for lung cancer P: Patients who would receive little benefit from lung cancer screening	A: Don't perform screening for lung cancer using low dose computerized tomography P: Patients for whom the harms of screening (including downstream harms) would exceed the potential mortality benefit of screening		Population definition - Patients older than 80, with a life expectancy less than 5 years, or with severe comorbidities that would preclude potentially curative treatment	A: 3 P: 1	8

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	Physicians/American Society of Clinical Oncology/National Comp Cancer Network, Choosing Wisely (American Geriatrics Society)						
34	Don't perform computer tomography (CT) screening for lung cancer among patients at low risk for lung cancer. *Choosing Wisely (American College of Chest Physicians and American Thoracic Society)* *Additional recommendation(s) – source(s): US Preventive Services Task Force, American Association for Thoracic Surgery, American Cancer Society/American College of Chest Physicians/American Society of Clinical Oncology/National Comp Cancer Network, Choosing Wisely (American Geriatrics Society)*	A: Don't perform a screening computerized tomography (CT) for lung cancer P: Patients at low risk for lung cancer	A: Don't perform screening for lung cancer using low dose computerized tomography P: Patients at low risk for lung cancer		Low risk is defined as: Patients younger than 55, with fewer than 30 pack year history, or who quit smoking more than 15 years ago	A: 3 P: None	8
			OTHER SCREENING				
35	Don't perform population based screening for 25-OH-Vitamin D deficiency.	A: Don't perform 25-OH-Vitamin D testing P: All patients	A: Don't perform 25-OH-Vitamin D screening P: All patients	Patients with a diagnosis of chronic kidney disease, osteomalacia, osteoporosis, active		A: None P: None	8

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	Choosing Wisely (American Society of Clinical Pathology) *Additional recommendation(s) – source(s): US Preventive Services Task Force, The Endocrine Society, Choosing Wisely (American Association of Clinical Endocrinologists and the Endocrine Society)*	Population exclusions: Patients with a diagnosis of chronic kidney disease, osteomalacia, osteoporosis, active rickets, malabsorption, inflammatory bowel disease, obesity, or Crohn's disease. Patients with a history of bariatric surgery or with >30 days of prednisone use (in the study year) also excluded.	Excluded: Patients with a diagnosis of chronic kidney disease, osteomalacia, osteoporosis, active rickets, malabsorption, inflammatory bowel disease, obesity, or Crohn's disease. Patients with a history of bariatric surgery or with >30 days of prednisone use (in the study year) also excluded.	rickets, malabsorption, inflammatory bowel disease, obesity, or Crohn's disease. Patients with a history of bariatric surgery or with >30 days of prednisone use (in the study year) also excluded.			
36	Don't routinely repeat DXA scans more often than once every two years. *Choosing Wisely (American Academy of Rheumatology)* *Additional recommendation(s) – source(s): US Preventive Services Task Force*	A: Don't repeat DEXA screening within 2 years of the previous scan P: Patients who have had a DEXA scan	A: Don't repeat DEXA scans within 2 years of the previous scan P: Patients who have had a DEXA scan Excluded: Patients currently being treated with high dose steroids	Patients currently being treated with high dose steroids		A: None P: 1	8
37	Don't use dual-energy x-ray absorptiometry (DEXA) screening for osteoporosis in women younger than 65 or men younger than 70 with no risk factors. *Choosing Wisely*	A: Don't screen for osteoporosis using Dual-energy X-ray Absorptiometry (DXA/DEXA) screening P: Women younger than 65 with no risk factors and Men under 70 with no risk factors	A: Don't screen for osteoporosis using DEXA screening P: Women younger than 65 with no risk factors and Men under 70 with no risk factors Excluded: Patient with: Osteopenia, Primary hyperparathyroidism, Osteoporosis, Hypercalcemia, or Malabsorption. Patients on prednisone for >30 days during the	Patient with: Osteopenia, Primary hyperparathyroidism, Osteoporosis, Hypercalcemia, or Malabsorption. Patients on prednisone for >30 days during the study year, on androgen deprivation therapy, who had a Glomerular Filtration		A: None P: 1	8

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	(American Academy of Family Physicians) *Additional recommendation(s) – source(s): US Preventive Services Task Force*	Exclusions: Osteopenia, Primary hyperparathyroidism, Osteoporosis, Hypercalcemia, or Malabsorption. Patients on prednisone for >30 days during the study year, on androgen deprivation therapy, or who had a Glomerular Filtration Rate (GFR) < 30 were also excluded.	study year, on androgen deprivation therapy, who had a Glomerular Filtration Rate < 30, or who had a prior fracture at age 50 years or older are also excluded.	Rate < 30, or who had a prior fracture at age 50 years or older are also excluded.			
38	Don't screen for carotid artery stenosis (CAS) in asymptomatic adult patients. *Choosing Wisely (American Academy of Family Physicians)* *Additional recommendation(s) – source(s): US Preventive Services Task Force, American College of Cardiology/American Heart Association*	A: Stop screening for carotid artery stenosis P: Asymptomatic adult patients without a history of cerebrovascular disease	A: Stop screening for carotid artery stenosis P: Asymptomatic adult patients without a history of cerebrovascular disease			A: None P: None	8
39	The USPSTF recommends against screening with resting or exercise electrocardiography (ECG) for the prediction of coronary heart disease (CHD) events in asymptomatic	A: Stop annual (or more frequent) screening with resting or stress electrocardiography, stress echocardiography, or stress myocardial perfusion imaging	A: Stop annual (or more frequent) screening with stress electrocardiography, stress echocardiography, or stress myocardial perfusion imaging P: Asymptomatic adults at low risk for CHD events		Low risk for CHD events defined as an ASCVD score <=5%	A: 3 P: 3	8

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	adults at low risk for CHD events. [Level of Evidence: Grade D] Clinicians should not screen for cardiac disease in asymptomatic, low-risk adults with resting or stress electrocardiography, stress echocardiography, or stress myocardial perfusion imaging. *USPSTF and American College of Physicians* *Additional recommendation(s) – source(s): Choosing Wisely (American Academy of Family Physicians; American College of Physicians; American Society of Echocardiography; American Society of Nuclear Cardiology; American College of Cardiology), American College of Cardiology*	P: Asymptomatic adults at low risk for CHD events					
				ALL OTHER			
40	In patients who have no new or worsening symptoms or no prior evidence of silent ischemia and are not at high risk for a recurrent cardiac event, the usefulness of annual surveillance	A: Stop annual surveillance testing using exercise ECG P: Patients with IHD who are asymptomatic	A: Stop annual surveillance testing using stress electrocardiography, stress echocardiography, or stress myocardial perfusion imaging P: Patients with asymptomatic stable IHD without a history of silent ischemia in the past 12 months or a high-risk occupation		Stable IHD is defined as confirmed obstructive coronary artery disease without recent (<1 year) ACS or PCI	A: 3 P: 1,3	8

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	exercise ECG testing is not well established. [Strength: Class IIB; Level of Evidence: Category C] *American Heart Association/American College of Cardiology* *Additional recommendation(s) – source(s): American College of Cardiology/American Heart Association*						
41-42	Don't perform echocardiography as routine follow-up for mild, asymptomatic native valve disease in adult patients with no change in signs or symptoms. *Choosing Wisely (American College of Cardiology)* *Additional recommendation(s) – source(s): American College of Cardiology/American Heart Association, Choosing Wisely (American Society of Echocardiography)*	A: Stop annual echocardiography P: Adult patients with asymptomatic native valve disease	A {**For Rec 41**}: Do not use echocardiography for screening more often than every 3 years A {**For Rec 42**}: Stop annual echocardiography P {**For Recs 41-42**}: Adult patients with mild, asymptomatic native valve disease		Mild as defined by the American College of Cardiology/American Heart Association criteria	A: 2 A: None P: 1,3	7.5 7
43-44	Don't recommend daily home finger glucose testing in patients with Type 2	A: Decrease the number of prescribed glucose test strips to 10 or fewer per month OR	A {**For Rec 43**}: Decrease the number of prescribed glucose test strips to 15 or fewer per month OR document patient preference for more frequent			A: 2,3	7.5

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	diabetes mellitus not using insulin. *Choosing Wisely (Society of General Internal Medicine)* *Additional recommendation(s) – source(s): National Institute for Health Care and Excellence, Choosing Wisely (American Association of Clinical Endocrinologists and the Endocrine Society)*	document patient preference for more frequent testing (i.e., more than 10 test strips per month) within 6 months of the last prescription issue date P: Patients with Type 2 diabetes not on insulin	testing (i.e., more than 15 test strips per month) within 3 months P {**For Rec 43**}: Patients with established Type 2 diabetes not on insulin A {**For Rec 44**}: Stop prescribing glucose test strips P {**For Rec 44**}: Patients with established Type 2 diabetes treated with metformin or diet alone			P: 1 A: 3 P: 1	4 (not validated)

[a]A: Action [1. Required justification for the continuation of the service; 2. Changed the timeframe; 3. More specifically defined the service [medication, screening, testing] (e.g., specified the exact diabetes medications to include in the action, modified the stress testing modalities to include in the action); 4. Other changes not listed in 1-3 (e.g., changed from 'stop or decrease' to only 'decrease' or only 'stop'; defined a term or phrase such as 'daily use')]

[b]P: Population [1. More specifically defined the eligible population by adding exclusions or otherwise narrowing the persons eligible; 2. Expanded the population; 3. Other changes not listed in 1-2 (e.g., defined a term or phrase such as 'high-grade precancerous lesion,' 'older adults,' 'low risk for CHD events,' or 'stable IHD')]

Abbreviations: ACEI = angiotensin-converting enzyme inhibitors; ACS = acute coronary syndrome; ARB = angiotensin-receptor blockers; ASCVD = atherosclerotic cardiovascular disease; CABG = coronary artery bypass surgery; CHD = coronary heart disease; CIN = cervical intraepithelial neoplasia; CKD = chronic kidney disease; DAPT = dual antiplatelet therapy; DBP = diastolic blood pressure; DEXA = dual-energy X-ray absorptiometry; DRI = direct renin inhibitor; FIT = fecal immunochemical test; FOBT = fecal occult blood test; HbA1c = Hemoglobin A1c; HIV = human immunodeficiency virus; HPV = human papillomavirus; HSIL = high grade squamous intraepithelial lesion; IHD = ischemic heart disease; PCI = percutaneous coronary intervention; SBP = systolic blood pressure

Note: The following recommendation was dropped prior to the second rating, so it does not appear in Table 1: Action: Stop or decrease dose of antipsychotics; Population: Patients older than 65; Population exclusions: Patients with schizophrenia, bipolar disorder, major depression, or using antipsychotics (short-term) as antiemetics during chemotherapy

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