Supplementary Online Content


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This supplementary material has been provided by the authors to give readers additional information about their work.
eMethods. Literature Search Strategies for Primary Literature

Key:
/ = MeSH subject heading
$ = truncation
* = truncation
? = wildcard
ab = word in abstract
adj# = adjacent within x number of words
ae = adverse effects
hw = subject heading word
id = identifier
kw = keyword
md = methodology
near/# = adjacent within x number of words
ti = word in title

CENTRAL
#1 (peripheral next arter*) near/2 disease*:ti,ab,kw
#2 (lower next (limb or extremity) near/2 disease*):ti,ab,kw
#3 (leg next artery next disease*):ti,ab,kw
#4 (ankle near/1 (brachial or arm) near/4 (index* or indices or ratio or gradient or pressure)):ti,ab,kw
#5 (ankle next (index* or indices)):ti,ab,kw
#6 ABPI:ti,ab,kw
#7 #1 or #2 or #3 or #4 or #5 or #6 Publication Year from 2012 to May 2, 2017, in Trials

MEDLINE (via Ovid)

Screening
Database: Ovid MEDLINE(R) Epub Ahead of Print <May 2, 2017>, Ovid MEDLINE(R) <1946 to May Week 1 2017>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 2, 2017>, Ovid MEDLINE(R) Daily Update <May 2, 2017>
1 Peripheral Arterial Disease/
2 Arterial Occlusive Diseases/
3 Peripheral Vascular Diseases/
4 peripheral arter$ disease$.ti,ab.
5 peripheral arter$ occlusive disease$.ti,ab.
6 (lower adj (limb or extremity) adj2 disease$).ti,ab.
7 leg artery disease$.ti,ab.
8 or/1-7
9 Ankle Brachial Index/
10 (brachial adj1 ankle adj4 (ratio$ or index$ or indices or gradient$ or pressure)).ti,ab.
11 (arm adj1 ankle adj4 (ratio$ or index$ or indices or gradient$ or pressure)).ti,ab.

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(ankle adj (index$ or indices)).ti,ab.
Ankle/blood supply
Brachial Artery/physiology, physiology, ultrasonography
Blood pressure/
Ankle/
15 and 16
9 or 10 or 11 or 12 or 13 or 14 or 17
Mass screening/
screen$.ti,ab.
(detect$ or predict$ or diagnost$ or diagnostic$).ti.
or/19-21
8 and 18 and 22
clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/
clinical trials as meta-analysis as topic/
(clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt.
Random$.ti,ab.
control groups/ or double-blind method/ or single-blind method/
clinical trial$.ti,ab.
controlled trial$.ti,ab.
meta analysis$.ti,ab.
or/24-30
23 and 31
"Sensitivity and Specificity"/
"Predictive Value of Tests"/
ROC curve/
False Negative Reactions/
False Positive Reactions/
Diagnostic Errors/
"Reproducibility of Results"/
Reference Values/
Reference Standards/
Observer Variation/
Receiver operating characteristic curve$.ti,ab.
Sensitivity$.ti,ab.
specificity$.ti,ab.
predictive value$.ti,ab.
Accuracy$.ti,ab.
false positive$.ti,ab.
false negative$.ti,ab.
miss rate$.ti,ab.
error rate$.ti,ab.
33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52
18 and 53
32 or 54
limit 55 to (english language and yr="2012 -Current")
remove duplicates from 56

Treatment
1  Peripheral Arterial Disease/
2  Arterial Occlusive Diseases/
3  Peripheral Vascular Diseases/
4  peripheral arter$ disease$.ti,ab.
5  peripheral arter$ occlusive disease$.ti,ab.
6  (lower adj (limb or extremity) adj2 disease$).ti,ab.
7  leg artery disease$.ti,ab.
8  or/1-7
9  ((abnormal$ or low) adj4 (brachial adj1 ankle adj4 (ratio$ or index$ or indices or gradient$ or pressure))).ti,ab.
10  ((abnormal$ or low) adj4 (arm adj1 ankle adj4 (ratio$ or index$ or indices or gradient$ or pressure))).ti,ab.
11  ((abnormal$ or low) adj4 (ankle index$ or ankle indices)).ti,ab.
12  ((abnormal$ or low) adj ABI).ti,ab.
13  or/9-12
14  "tobacco use cessation"/ or smoking cessation/
15  smoking cessation.ti,ab.
16  Hypercholesterolemia/dh, dt, pc, rh, th [Diet Therapy, Drug Therapy, Prevention & Control, Rehabilitation, Therapy]
17  Hyperlipidemias/dh, dt, pc, rh, th [Diet Therapy, Drug Therapy, Prevention & Control, Rehabilitation, Therapy]
18  Anticholesteremic Agents/
19  (lower$ adj3 cholesterol).ti,ab.
20  (reduc$ adj3 cholesterol).ti,ab.
21  Diabetes Mellitus/dh, dt, pc, rh, th [Diet Therapy, Drug Therapy, Prevention & Control, Rehabilitation, Therapy]
22  Diabetes Mellitus, Type 2/dh, dt, pc, rh, th [Diet Therapy, Drug Therapy, Prevention & Control, Rehabilitation, Therapy]
23  Hypoglycemic Agents/
24  Hemoglobin A, Glycosylated/
25  Blood Glucose/an, me [Analysis, Metabolism]
Glycemic Index/
glycemic control$.ti,ab.
glycaemic control$.ti,ab.
glucose control$.ti,ab.
body weight changes/ or weight loss/
weight loss.ti,ab.
Hypertension/dh, dt, pc, rh, th [Diet Therapy, Drug Therapy, Prevention & Control, Rehabilitation, Therapy]
Antihypertensive Agents/
blood pressure control$.ti,ab.
(hypertension adj2 control$).ti,ab.
Platelet Aggregation Inhibitors/
Blood Platelets/de [Drug Effects]
((anti platelet or antiplatelet) adj2 (therapy or treatment$)).ti,ab.
physical activit$.ti,ab.
Exercise/
exercis$.ti.
Physical Fitness/
Walking/
walking.ti.
treadmill.ti,ab.
Resistance Training/
Motor Activity/
Physical Therapy Modalities/
Exercise Therapy/
Exercise Movement Techniques/
physical therap$.ti,ab.
physiotherapy$.ti,ab.
(or/14-52
(8 or 13) and 53
clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/
or meta-analysis as topic/
(clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt.
Random$.ti,ab.
control groups/ or double-blind method/ or single-blind method/
clinical trial$.ti,ab.
controlled trial$.ti,ab.
meta analy$.ti,ab.
or/55-61
54 and 62
"Drug-Related Side Effects and Adverse Reactions"/
harm$.ti,ab.

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toxicity.ti,ab.
complication$.ti,ab.
(adverse adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
adverse effects.fs.
toxicity.fs.
mortality.fs.
Safety/
safety.ti,ab.
product surveillance, postmarketing/
side effect$.ti,ab.
Emergency Service, Hospital/
Hospitalization/
(unexpected$ adj3 (emergency or hospital$ or medical attention)).ti,ab.
or/64-78
54 and 79
63 or 80
limit 81 to (english language and yr="2012 -Current")
remove duplicates from 82

SEARCH (((#6) AND publisher[sb]) AND English[Language]) AND ("2012/01/01"[Date - Publication] : "3000"[Date - Publication])
#6 Search #1 OR #4 OR #5
#4 Search #2 AND #3
#1 Search (peripheral artery disease[tiab] OR peripheral arterial disease[tiab] OR lower extremity disease[tiab] OR leg artery disease[tiab]) AND screen*[tiab]
### eTable 1. Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Category</th>
<th>Included</th>
<th>Excluded</th>
</tr>
</thead>
</table>
| **Population** | **KQs 1–3:** Unselected or community-dwelling, generally asymptomatic adults<sup>a</sup>  
**KQs 4, 5:** Screen-detected or generally asymptomatic adults with PAD or an abnormal ABI<sup>b</sup>  
A priori subpopulations at greater risk for PAD will be examined based on the following factors: age (particularly ≥65 years), sex, race/ethnicity, diabetes, smoking, and hypertension status | Symptomatic adults; study populations consisting exclusively of adults with known CVD or severe chronic kidney disease (stages 4 and 5) |
| **Setting** | Primary care and outpatient settings (i.e., ambulatory care) | Vascular surgery clinics (KQs 1, 2); hospital/inpatient settings |
| **Disease/Condition** | Lower-extremity PAD secondary to atherosclerosis<sup>c</sup> | Other anatomic locations for vascular disease (e.g., coronary artery stenosis, abdominal aortic aneurysm) |
| **Screening** | Resting ABI | History taking, physical examination, questionnaires, digital subtraction arteriography (DSA), duplex ultrasonography, magnetic resonance angiography (MRA), computed tomographic angiography (CTA), toe pressure measurement, treadmill testing (exercise ABI), pulse oximetry, near-infrared spectroscopy, and all invasive diagnostic testing |
| **Treatment or management interventions** | Pharmacologic or lifestyle interventions primarily aimed at CVD reduction: interventions for smoking cessation, cholesterol-lowering therapy, diet and exercise (with or without weight loss), blood pressure control, and antiplatelet therapy  
Exercise or physical therapy interventions aimed at improving lower limb function | Vitamins or nutritional or herbal supplements  
Interventions aimed only at symptomatic adults or adults with critical limb ischemia: pharmacologic symptom management (pentoxifylline, cilostazol, prostaglandins), nonpharmacologic symptom management, and revascularization (angioplasty, thrombolytics, stenting, bypass) |
| **Comparisons** | **KQ 1:** No screening  
**KQ 2:** Reference standard (DSA, diagnostic imaging of atherosclerosis [e.g., MRA, CTA]) or degree of impaired blood flow (e.g., duplex ultrasonography)  
**KQ 4:** True control group (receives placebo, no intervention, or usual care); intervention/treatment at later or symptomatic stage of disease (vs. earlier or asymptomatic stage) | |
### eTable 1. Inclusion and Exclusion Criteria Continued

<table>
<thead>
<tr>
<th>Category</th>
<th>Included</th>
<th>Excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcomes</strong></td>
<td><strong>KQ 1</strong>: Cardiovascular morbidity (myocardial infarction, cerebrovascular accident), PAD morbidity (ambulation impairment, amputation) or mortality (all-cause, PAD-related, or CVD-related), and health-related quality of life</td>
<td>Surrogate markers for atherosclerosis, including imaging (e.g., carotid intima-media thickness) or biochemical markers (e.g., high-sensitivity C-reactive protein) Patient satisfaction Cost-related outcomes (for screening and treatment) Intermediate cardiovascular outcomes (e.g., blood pressure, cholesterol); behavior changes (e.g., smoking cessation, physical activity level); and intermediate measures of lower limb function (e.g., 6-minute walking test, lower-extremity strength) Change in ABI</td>
</tr>
<tr>
<td></td>
<td><strong>KQ 2</strong>: Sensitivity, specificity, positive and negative predictive value for PAD, and incidence or prevalence</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>KQ 4</strong>: Patient health outcomes (listed above for KQ 1)</td>
<td></td>
</tr>
<tr>
<td><strong>Harms</strong></td>
<td><strong>KQ 3</strong>: Adverse outcomes related to ABI test (diagnostic inaccuracy) or harms of subsequent testing</td>
<td>Patient satisfaction</td>
</tr>
<tr>
<td></td>
<td><strong>KQ 5</strong>: Serious adverse events (e.g., death, serious adverse drug reactions) and unexpected medical attention (e.g., emergency department visits, hospitalizations)</td>
<td></td>
</tr>
<tr>
<td><strong>Study designs</strong></td>
<td><strong>KQs 1, 4</strong>: Good-quality systematic reviews and randomized or clinically controlled trials</td>
<td>Poor-quality studies based on established design-specific quality criteria</td>
</tr>
<tr>
<td></td>
<td><strong>KQ 2</strong>: Good-quality systematic reviews and diagnostic accuracy studies</td>
<td>KQ 2: Case-control studies of diagnostic accuracy</td>
</tr>
<tr>
<td></td>
<td><strong>KQs 3, 5</strong>: Good-quality systematic reviews, randomized or clinically controlled trials, and cohort or case-control studies</td>
<td>KQ 4: Studies with less than 3 months of followup</td>
</tr>
<tr>
<td><strong>Countries</strong></td>
<td>Economically developed countries, defined as member countries of the Organisation for Economic Co-operation and Development (2015): Australia, Austria, Belgium, Canada, Chile, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Luxembourg, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom, and United States</td>
<td>Studies performed in countries with populations not similar to the United States Countries that are not a member of the Organisation for Economic Co-operation and Development</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td>English only</td>
<td>Non-English languages</td>
</tr>
</tbody>
</table>

*Adults without lower extremity symptoms or with vague symptoms not attributed to PAD.
*Defined as an ABI of \( \leq 0.90 \) or \( >1.40 \).
*The condition definition for PAD would ideally be confirmed by diagnostic imaging (MRA, CTA, or DSA); however, the review will include trials that recruit participants with an abnormal ABI.

**Abbreviations:** ABI = ankle-brachial index; CTA = computed tomographic angiography; CVD = cardiovascular disease; DSA = digital subtraction arteriography; MRA = magnetic resonance angiography; PAD = peripheral artery disease
### eTable 2. Quality Rating Criteria

<table>
<thead>
<tr>
<th>Study type and source of criteria</th>
<th>Criteria</th>
</tr>
</thead>
</table>
| • USPSTF quality rating criteria for trials<sup>1</sup> | • Initial assembly of comparable groups  
• Employs adequate randomization, including first concealment and whether potential confounders were distributed equally among groups  
• Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)  
• Important differential loss to followup or overall high loss to followup  
• Measurements: equal, reliable, and valid (includes masking of outcome assessment)  
• Clear definition of the interventions  
• All important outcomes considered  
• Intention-to-treat analysis |
| • QUADAS-2 quality criteria for diagnostic accuracy studies<sup>2</sup> | • Were tests clearly described (or referenced)?  
• Domain 1: Patient Selection (Could the selection of patients have introduced bias?)<sup>a</sup>  
  o Was the spectrum of patients representative of the patients who will receive the test in primary care?  
  o Was the selection process clearly defined?  
  o Are there concerns that the included patients and setting do not match the review question?  
• Domain 2: Index Test (Could the conduct or interpretation of the index test have introduced bias?)  
  o Was the index test interpreted without knowledge of the reference standard results?  
  o If a threshold was used, was it prespecified?  
  o Are there concerns that the index test, its conduct, or its interpretation differ from the review question?  
• Domain 3: Reference Standard (Could the conduct or interpretation of the reference standard have introduced bias?)  
  o Is the reference standard acceptable for correctly classifying the target condition?  
  o Was the reference standard interpreted without knowledge of the index test results?  
  o Are there concerns that the target condition as defined by the reference standard does not match the review question?  
  o Did the whole or partial selection of patients receive the reference standard?  
• Domain 4: Flow and Timing (Could the patient flow have introduced bias?)  
  o Was there an appropriate interval between the index test and reference standard?  
  o Did all patients receive the same reference standard?  
  o Were all patients included in the analysis? |

<sup>a</sup> Domain 1 questions minimally adapted.

**Abbreviations:** QUADAS = Quality Assessment of Diagnostic Accuracy Studies; USPSTF = United States Preventive Services Task Force
### eTable 3. Additional Outcomes From KQ 4 Aspirin Studies

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trial Name</th>
<th>Author, Year</th>
<th>IG N Events (%)</th>
<th>CG N Events (%)</th>
<th>IG vs. CG HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal MI + coronary death</td>
<td>AAA</td>
<td>Fowkes, 2010 2</td>
<td>90 (5.4)a</td>
<td>86 (5.1)a</td>
<td>1.05 (0.78 to 1.40)a,b</td>
</tr>
<tr>
<td></td>
<td>POPADAD</td>
<td>Belch, 20084</td>
<td>90 (14.1)a</td>
<td>82 (12.9)a</td>
<td>1.10 (0.83 to 1.45)a,b</td>
</tr>
<tr>
<td>Fatal coronary event</td>
<td>AAA</td>
<td>Fowkes, 2010 2</td>
<td>28 (1.7)</td>
<td>18 (1.1)</td>
<td>1.56 (0.86 to 2.80)a,b</td>
</tr>
<tr>
<td></td>
<td>POPADAD</td>
<td>Belch, 20084</td>
<td>35 (5.5)</td>
<td>26 (4.1)</td>
<td>1.35 (0.81 to 2.25)</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>AAA</td>
<td>Fowkes, 2010 2</td>
<td>62 (3.7)</td>
<td>68 (4.1)</td>
<td>0.91 (0.65 to 1.28)a,b</td>
</tr>
<tr>
<td></td>
<td>POPADAD</td>
<td>Belch, 20084</td>
<td>55 (8.6)</td>
<td>56 (8.8)</td>
<td>0.98 (0.68 to 1.43)</td>
</tr>
<tr>
<td>Total CVA</td>
<td>AAA</td>
<td>Fowkes, 2010 2</td>
<td>44 (2.6)a</td>
<td>50 (3.0)a</td>
<td>0.88 (0.59 to 1.31)a,b</td>
</tr>
<tr>
<td></td>
<td>POPADAD</td>
<td>Belch, 20084</td>
<td>37 (5.8)a</td>
<td>50 (7.8)a</td>
<td>0.74 (0.49 to 1.12)a,b</td>
</tr>
<tr>
<td>Fatal CVA</td>
<td>AAA</td>
<td>Fowkes, 2010 2</td>
<td>7 (0.4)</td>
<td>12 (0.7)</td>
<td>0.58 (0.23 to 1.48)a,b</td>
</tr>
<tr>
<td></td>
<td>POPADAD</td>
<td>Belch, 20084</td>
<td>8 (1.3)</td>
<td>9 (1.4)</td>
<td>0.89 (0.34 to 2.30)</td>
</tr>
<tr>
<td>Nonfatal CVA</td>
<td>AAA</td>
<td>Fowkes, 2010 2</td>
<td>37 (2.2)</td>
<td>38 (2.3)</td>
<td>0.97 (0.62 to 1.52)a,b</td>
</tr>
<tr>
<td></td>
<td>POPADAD</td>
<td>Belch, 20084</td>
<td>29 (4.6)</td>
<td>41 (6.4)</td>
<td>0.71 (0.44 to 1.14)</td>
</tr>
<tr>
<td>Total ischemic CVA</td>
<td>AAA</td>
<td>Fowkes, 2010 2</td>
<td>30 (1.8)a</td>
<td>37 (2.2)a</td>
<td>0.81 (0.50 to 1.31)a,b</td>
</tr>
<tr>
<td>Fatal ischemic CVA</td>
<td>AAA</td>
<td>Fowkes, 2010 2</td>
<td>2 (0.1)</td>
<td>7 (0.4)</td>
<td>0.29 (0.06 to 1.37)a,b</td>
</tr>
<tr>
<td></td>
<td>POPADAD</td>
<td>Belch, 20084</td>
<td>3 (0.5)</td>
<td>5 (0.8)</td>
<td>0.60 (0.14 to 2.50)a,b</td>
</tr>
<tr>
<td>Nonfatal ischemic CVA</td>
<td>AAA</td>
<td>Fowkes, 2010 2</td>
<td>28 (1.7)</td>
<td>30 (1.8)</td>
<td>0.93 (0.56 to 1.56)a,b</td>
</tr>
<tr>
<td>Development of IC</td>
<td>AAA</td>
<td>Fowkes, 2010 2</td>
<td>53 (3.2)</td>
<td>53 (3.2)</td>
<td>1.00 (1.00 to 1.00)a,b</td>
</tr>
<tr>
<td></td>
<td>POPADAD</td>
<td>Belch, 20084</td>
<td>97 (15.2)</td>
<td>107 (16.8)</td>
<td>0.89 (0.68 to 1.18)</td>
</tr>
<tr>
<td>Peripheral revascularization</td>
<td>AAA</td>
<td>Fowkes, 2010 2</td>
<td>23 (1.4)</td>
<td>20 (1.2)</td>
<td>1.15 (0.63 to 2.09)a,b</td>
</tr>
<tr>
<td>Peripheral arterial bypass surgery</td>
<td>POPADAD</td>
<td>Belch, 20084</td>
<td>7 (1.1)</td>
<td>5 (0.8)</td>
<td>1.41 (0.45 to 4.43)</td>
</tr>
<tr>
<td>Peripheral arterial angioplasty</td>
<td>POPADAD</td>
<td>Belch, 20084</td>
<td>11 (1.7)</td>
<td>13 (2.0)</td>
<td>0.85 (0.38 to 1.89)</td>
</tr>
<tr>
<td>Above ankle amputation for critical limb ischemia</td>
<td>POPADAD</td>
<td>Belch, 20084</td>
<td>11 (1.7)</td>
<td>9 (1.4)</td>
<td>1.23 (0.51 to 2.97)</td>
</tr>
</tbody>
</table>

a Calculated.
b RR

**Abbreviations:** AAA = Aspirin for Asymptomatic Atherosclerosis Trial; CG = control group; CI = confidence interval; CVA = cerebrovascular accident; HR = hazard ratio; IC = intermittent claudication; IG = intervention group; MI = myocardial infarction; N = population; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; RR = relative risk
eTable 4. Age Subgroup Analyses for Reported Outcomes in Included Aspirin Studies for KQ 4

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Mean F/U, Years</th>
<th>Type of Analysis</th>
<th>Outcome</th>
<th>Age, Years</th>
<th>IG N Analyzed</th>
<th>IG N Events (%)</th>
<th>CG N Analyzed</th>
<th>CG N Events (%)</th>
<th>IG vs. CG HR (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAA</td>
<td>8.2</td>
<td>A priori</td>
<td>Primary composite: Initial fatal or nonfatal coronary event, CVA or revascularization</td>
<td>&lt;62</td>
<td>NR</td>
<td>57 (NR)*</td>
<td>NR</td>
<td>70 (NR)*</td>
<td>0.85 (0.60 to 1.20)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥62</td>
<td>NR</td>
<td>124 (NR)*</td>
<td>NR</td>
<td>106 (NR)*</td>
<td>1.13 (0.87 to 1.47)</td>
<td>.44</td>
</tr>
<tr>
<td>POPADAD</td>
<td>6.7*</td>
<td>Specification unclear</td>
<td>Fatal coronary events + Fatal CVA</td>
<td>&lt;60</td>
<td>297</td>
<td>10 (3.4)</td>
<td>315</td>
<td>10 (3.2)</td>
<td>1.07 (0.44 to 2.56)</td>
<td>.77</td>
</tr>
<tr>
<td>Belch, 2008</td>
<td></td>
<td></td>
<td></td>
<td>≥60</td>
<td>341</td>
<td>33 (9.7)</td>
<td>323</td>
<td>25 (7.7)</td>
<td>1.24 (0.74 to 2.09)</td>
<td>.77</td>
</tr>
<tr>
<td>POPADAD</td>
<td>6.7*</td>
<td>Specification unclear</td>
<td>Primary composite: death from CHD or CVA, nonfatal MI or CVA, or above-ankle amputation for critical limb ischemia</td>
<td>&lt;60</td>
<td>297</td>
<td>38 (12.8)</td>
<td>315</td>
<td>36 (11.4)</td>
<td>1.11 (0.70 to 1.75)</td>
<td>.77</td>
</tr>
<tr>
<td>Belch, 2008</td>
<td></td>
<td></td>
<td></td>
<td>≥60</td>
<td>341</td>
<td>78 (22.9)</td>
<td>323</td>
<td>81 (25.1)</td>
<td>0.89 (0.65 to 1.21)</td>
<td>.77</td>
</tr>
</tbody>
</table>

* 8.6 per 1,000 p-y (95% CI, 6.5 to 11.2)
* a 10.2 per 1,000 p-y (95% CI, 8.0 to 12.9)
* b 18.8 per 1,000 p-y (95% CI, 15.6 to 22.4)
* c 16.6 per 1,000 p-y (95% CI, 13.6 to 20.1)
* d Median.

**Abbreviations:** AAA = Aspirin for Asymptomatic Atherosclerosis Trial; CG = control group; CI = confidence interval; CHD = coronary heart disease; CVA = cerebrovascular accident; F/U = followup; HR = hazard ratio; IG = intervention group; MI = myocardial infarction; N = number; NR = not reported; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; p-y: person-years
### eTable 5. Sex Subgroup Analyses for Reported Outcomes in Included Aspirin Studies for KQ4

<table>
<thead>
<tr>
<th>Trial Name Author, Year</th>
<th>Mean F/U, Years</th>
<th>Type of Analysis</th>
<th>Outcome</th>
<th>Sex</th>
<th>IG N Analyzed</th>
<th>IG N Events (%)</th>
<th>CG N Analyzed</th>
<th>CG N Events (%)</th>
<th>IG vs. CG HR (95% CI)</th>
<th>P-Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAA Fowkes, 2010[^2]</td>
<td>8.2</td>
<td>A priori</td>
<td>Primary composite: initial (earliest) fatal or nonfatal coronary event or CVA or revascularization</td>
<td>Men</td>
<td>481</td>
<td>96 (20.0)</td>
<td>473</td>
<td>83 (17.5)</td>
<td>1.15 (0.86 to 1.54)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Women</td>
<td>1,194</td>
<td>85 (7.1)</td>
<td>1,202</td>
<td>93 (7.7)</td>
<td>0.92 (0.68 to 1.23)</td>
<td>NR</td>
</tr>
<tr>
<td>POPADAD Belch, 2008[^4]</td>
<td>6.7[^c]</td>
<td>Specification unclear</td>
<td>Fatal coronary events + fatal CVA + CVD death</td>
<td>Men</td>
<td>286</td>
<td>26 (9.1)</td>
<td>277</td>
<td>19 (6.9)</td>
<td>1.33 (0.73 to 2.40)</td>
<td>.68</td>
</tr>
<tr>
<td>POPADAD Belch, 2008[^4]</td>
<td>6.7[^c]</td>
<td>Specification unclear</td>
<td>Primary composite: death from CHD or CVA, nonfatal MI or CVA, or above ankle amputation for critical limb ischemia</td>
<td>Men</td>
<td>286</td>
<td>68 (23.8)</td>
<td>277</td>
<td>62 (22.4)</td>
<td>1.04 (0.74 to 1.47)</td>
<td>.54</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Women</td>
<td>352</td>
<td>17 (4.8)</td>
<td>361</td>
<td>16 (4.4)</td>
<td>1.09 (0.55 to 2.16)</td>
<td>.54</td>
</tr>
</tbody>
</table>

[^2] Calculated  
[^4] RR  
[^c] Median  

**Abbreviations:** AAA = Aspirin for Asymptomatic Atherosclerosis Trial; CG = control group; CI = confidence interval; CHD = coronary heart disease; CVA = cerebrovascular accident; RR = Relative Risk; HR = hazard ratio; IG = intervention group; MI = myocardial infarction; NR = not reported; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; p-y: person-years
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>IG Description</th>
<th>CG Description</th>
<th>Format</th>
<th>Delivered by</th>
<th>Duration, Weeks</th>
<th># sessions</th>
<th>Session Length, Mins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collins, 2007&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Advice to continue routine care with primary care physician, plus 2 intervention components: risk factor modification and improvement in physical activity (PA). Risk factor modification: “Recognize, identify, and manage” (RIM) approach used to assess risk factors. During initial 5-minute assessment, nurse used RIM to assess medication adherence. Nurse then assessed dietary needs specific to risk-factor profile, advised about HbA1c and LDL-C goals, and counseled on reading food labels, increasing fiber, and reducing calories. Participants were asked to share examples of appropriate behavior change related to their specific risk factors. PA: PACE protocol, which included PA assessment of stage of readiness to change and handout tailored to help patient identify ways to increase PA based on stage of change, followed by “extensive discussion” with nurse to encourage regular PA.</td>
<td>Usual care: patients advised to continue routine care with their primary care physician</td>
<td>Individual, in-person with phone F/U</td>
<td>Nurse</td>
<td>12</td>
<td>6 (initial session + 5 F/U phone visits)</td>
<td>Initial session: NR, F/U sessions: &lt;30</td>
</tr>
<tr>
<td>Fowler, 2002&lt;sup&gt;8&lt;/sup&gt;</td>
<td>“Stop smoking and keep walking”. Intervention components included: 1) education, 2) letter to GP recommending smoking cessation, and 3) referral to a community PT intervention. Participants told that “your ABI or ECQ test showed a reduced blood flow to the muscles in your leg or legs caused by partial blockage of the arteries and this often results in pain on walking.” Participants provided with educational package including information on PAD, a brochure on the community PT service, information on smoking cessation (if applicable), and a copy of the letter from the clinic to their GP, and were advised to consult GP about management. GP sent a package of written materials about smoking cessation, notes on obtaining optimal results from nicotine replacement products, and a fact sheet on PAD. GP asked to discuss smoking and to refer each man with early PAD to community PT service. The community PT contacted each referred man within approximately 3 weeks of screening exam. The community PT intervention offered options to increase PA either independently or through an organized program. Participants could attend a weekly mixed-gender group session as part of the established program, a men-only session, or a home-based PA program devised specifically for them by the senior PT. Additionally, all men in IG advised by PT to walk for ≥30 minutes/day. In certain cases, men were referred to hydrotherapy classes or special exercise sessions for those with disabilities.</td>
<td>Usual care: patients told by nurse at screening clinic that “the blood flow to your feet and legs is lower than normal. This is not uncommon for men of your age but there is presently no evidence to suggest you should do anything about it at this time.” ABI and ECQ results were not mentioned in letters to the patient or GP regarding results of the AAA screening.</td>
<td>Individual initial session with print materials, PA was participants choice of individual home-based PA or weekly group sessions</td>
<td>Nurse, GP, PT</td>
<td>52</td>
<td>For participants choosing group format: 51 (initial session with nurse, initial session with PT + 49 supervised PA sessions [52 weeks-3 week lead time])&lt;sup&gt;a&lt;/sup&gt; For participants choosing home-based PA: 2 (initial session with nurse, initial session with PT)</td>
<td>Initial session with nurse: NR, Initial session with PT NR, Group PA sessions: 45</td>
</tr>
</tbody>
</table>

<sup>a</sup>16.5% of IG reported being in exercise group at 12 months
Abbreviations: AAA = abdominal aortic aneurysm; ECQ = Edinburgh Claudication Questionnaire; F/U = followup; GP = general practitioner; HbA1c = glycated hemoglobin; LDL-C = low-density lipoprotein cholesterol; NR = not reported; PA = physical activity; PACE = Physician-based Assessment and Counseling for Exercise; PAD = peripheral artery disease; PT = physical therapy/physical therapist
eReferences


