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

Subject eligibility

We included patients ≥18 and <85 years of age who: (1) were receiving care from an Atrius primary care provider and who were insured by one of 4 large health insurers with whom Atrius had risk-sharing contracts, (2) had a diagnosis hyperlipidemia, hypertension or diabetes based on their having filled a prescription for a medication used to treat one of these conditions (i.e. statins, anti-hypertensives, or oral glucose-lowering agents), (3) had evidence of poor or worsening disease control for at least one of these conditions, (4) were non-adherent to the medication(s) used to treat that condition (defined as being less than 80% adherent to these medications) and (5) if their average adherence all for all medications for all eligible study drugs was less than 80%. As such, patients with hyperlipidemia, hypertension or diabetes who were not poorly controlled or were non-adherent were ineligible for inclusion on the basis of that particular condition but could still be eligible if they satisfied the inclusion criteria for either of the other two conditions.

Disease control was evaluated using the most recent lab or blood pressure values in the electronic health record at the time of enrollment and was based on clinical guideline targets established by the Eighth Joint National Committee (JNC 8), the American Diabetes Association, and the American Heart Association/American College of Cardiology for hypertension, diabetes and cholesterol, respectively (see eAppendix 1).[1-3]

Adherence was assessed using prescription claims data, a validated measure of medication taking that is widely used in quality improvement efforts.[4] For each medication used to treat any one of the conditions for which a patient was eligible, the

proportion of days covered (PDC) is calculated as the number of days of medication that a patient filled between the first fill date and the randomization date divided by the number of days in that same period (up to a maximum of 365 days).[5] We consider drugs that are chemically-related and not intended for use in combination to be interchangeable (e.g., two different statins). The specific list of medications we included is listed in eAppendix 2. Using previously described methods,[6] after calculating adherence for individual medications, we averaged the PDC for all of the medications used to treat a single condition (e.g., all oral hypoglycemics) and then calculated an overall average adherence for all conditions that a patient had at the time of their identification.

We defined a patient as being non-adherent if they were less than 80% adherent to a medication for at least one of the conditions for which they had been identified as being poorly controlled and their "average of averages" PDC for all medications for all eligible study drugs was less than 80%, consistent with the level that is associated with clinically-meaningful reductions in cardiovascular events and which is widely used in quality measures.[4] For example, consider a woman with diabetes (on metformin) and hyperlipidemia (on atorvastatin), who had a high A1c, was non-adherent to her metformin (e.g. a PDC of 50%) but was adherent to atorvastatin (e.g. a PDC of 90%). In order to be eligible for inclusion we required her average adherence (to both metformin and atorvastatin) to be less than 80% (in this case, it would have been 70%).

Randomization

We chose to use cluster randomization at the practice level to minimize contamination by clinical pharmacist and primary care provider. The central component of the multi-faceted intervention was an individually-tailored clinical-pharmacist delivered telephone consultation, at the conclusion of which, recommendations were provided to the patient's treating provider. Should we have chosen patient-level randomization, pharmacist recommendations for intervention patients could have been applied by primary care providers to control patients. Further, since the intervention was delivered by site-based pharmacists who are available for consultation to all patients in a practice upon request, individual randomization would have resulted in the same clinical pharmacist providing care to both intervention and control patients. The clinical pharmacists worked at multiple clinical sites; they were restricted to providing clinical services only at intervention sites during the study.

Practice sites were categorized into blocks based on their size (i.e., small or large, based on the number of patients receiving care at each site) and whether, prior to randomization, clinical pharmacists at the sites offered disease management counseling directly to patients (i.e., yes or no). Within the resultant 4 blocks, practices were randomized in a 1:1 ratio to intervention or control using a random number generator.

Intervention

The central component of the multi-faceted intervention was an individually-tailored telephone consultation conducted by a staff clinical pharmacist at the primary care practices. During this consultation, the clinical pharmacist used a semi-structured guide to confirm the patient's treatment regimen, engaged the patient in sharing

potential barriers to adherence or other factors that may be contributing to poor disease control, discussed the patient's readiness to modify behaviors, and worked with the patient to agree upon a shared plan of strategies to improve adherence and disease control. The structure of these phone consultations was developed by the study team using Brief Negotiated Interviewing,[7-9] a behavioral interviewing technique with foundations in motivational interviewing.

The strategies offered to patients by the clinical pharmacists were tailored to their activation level and their identified adherence barrier(s) (see eAppendix 3) and included: (1) recommendations sent using structured notes with the electronic health record to patients' primary care physicians to modify treatment regimens and coordinate care, (2) follow-up consultations and (3) strategies to promote adherence including text messages and pillboxes. Consultation notes were sent to the primary care physician after all initial and follow-up clinical pharmacist consultations. Follow-up consultations were scheduled based on patients' levels of activation and clinical need, with the intention that most participants with high activation would receive a maximum of two telephone visits.

For patients for whom the clinical pharmacist felt that forgetfulness or motivation were barriers to adherence were offered the opportunity to receive automated SMS text messages via a secure messaging platform (Mobile Commons; Brooklyn, NY).

The content and frequency of the text messages differed depending on patients' PAM levels and adherence barrier (see eAppendix 4).[10] A total of 50 unique text messages were developed by the study team and grouped in the 6 messaging streams (A through F) that delivered automatically by the messaging platform over the year after

enrollment. Examples of these text messages are presented in eAppendix 5. Periodically, text messages were sent asking questions about their adherence behavior to which they could respond and received automated responses using a feedback response system. For example, patients with lower levels of activation were asked about their adherence behaviors frequently, were encouraged to reply to the texts, and were also offered the choice of receiving daily or weekly texts, whereas patients with higher levels of activation were only offered weekly texts. Patients were sent monthly text messages providing them with the option of opting-out of receiving additional text messages. During follow-up, 30 (15%) patients who were sent text messages opted out of receiving them.

Patients for whom forgetfulness or treatment complexity were felt by the clinical pharmacist to be barriers to adherence were sent pillboxes with enough daily compartments to accommodate the number of times per day the particular patient's medications were to be taken.

Mailed progress reports were sent to intervention patients at 6 months and 9 months after randomization on behalf of their primary care provider and summarized personalized and updated information about disease control generated using data from the electronic health record and administrative claims. These reports were sent regardless of whether patients had agreed to participate in the pharmacist consultation, with the exception of patients: (1) who had been actively opted out of participation by their primary care providers or who had asked not to be contacted after receiving the invation to participate, (2) who were no longer receiving care at Atrius Health at the time the mailings were sent, and (3) who, in the opinion of a clinical pharmacist after

completing a telephone consultation, were felt to not require a report card to be mailed. The progress reports include a phone number and invitation for patients who had previously declined participation or were unreachable to call in to schedule a consultation with a clinical pharmacist.

In those cases where the clinical pharmacists felt patients were adherent to their prescribed medications, they were instructed to provide recommendations to improve the patient's disease control, such as diet modification or scheduling a primary care appointment, using their own clinical judgement.

Patients cared for at sites allocated to usual care did not receive any of these study-specific interventions. In those clinics, clinical pharmacists were available for consultation upon request by a patient's primary care provider, but outreach was not done routinely. In addition, usual care clinical pharmacists were not trained in the motivational interviewing method used as part of the intervention, did not have access to detailed adherence information for each patient or activation levels, nor did they have the ability to offer text messages or progress reports.

Outcomes

The trial's primary outcome was medication adherence assessed at 12 months after randomization. This outcome was assessed using prescription claims data and measured as the mean PDC over the 12 months after randomization using the "average of averages" approach used for study eligibility. Adherence was measured only for medications that qualified a patient for inclusion in the study beginning at the time of randomization.[6] Medications that were filled prior to randomization but had a supply that

extended into the follow-up period had their carry-over supply included in the adherence calculation. In a sensitivity analysis of this outcome, we evaluated adherence: (1) beginning from the first fill of a medication after randomization until the end of the 12-month follow-up period, (2) including medications newly-started after randomization and (3) censoring patients with diabetes when they initiated insulin, if they were not on insulin at baseline, since there are no standardized claims-based algorithms to measure insulin adherence.

The prespecified secondary clinical outcome were disease control and rates of healthcare utilization. Disease control was measured in the following two different ways: (1) the proportion of patients achieving good disease control for at least one of their eligible conditions and (2) the proportion of patients achieving "good" disease control based on guideline-specified targets for all of their eligible conditions.

Based on the Eighth Joint National Committee (JNC 8) hypertension guidelines, good blood pressure control was defined a systolic blood pressure <150 mgHg for individuals ≥60 years of age and <140 for individuals <60 years of age.[2] Based on gidelines from the American Diabetes Association, good diabetes control was defined as a hemoglobin A_{1c} <8.[1] For hyperlipidemia, despite the emphasis on statin adherence rather than achieved LDL cholesterol levels in the 2013 American Heart Association/American College of Cardiology stain guidelines,[3] we defined disease control based upon risk-based LDL cholesterol levels as set forth in the National Cholesterol Education Program Adult Treatment Panel III guidelines.[11] This approach was motivated by the fact that adherence was already being evaluated in the trial's primary outcome, because many clinicians continue to monitor cholesterol levels[12] and

because any reduction in cholesterol monitoring, and hence missing data, should be non-differential between the treatment arms.

We chose binary measures of disease control to facilitate the combination of disease-specific measures from different conditions into single outcomes. In secondary analyses, we also evaluated absolute changes in LDL cholesterol, systolic blood pressure, and hemoglobin A_{1c}. Because we evaluated disease control using biometrics that were collected during routine care and recorded in the electronic health record, rather than at study-prescribed intervals, we used those values that were closest to the end of each patient's 12-month follow-up period.

Sample size and power calculations

Based on intention-to-treat and pragmatic trial principles, we powered the study to detect a change in adherence that we expected would also translate into clinical meaningful changes in our secondary biometric outcomes, regardless of whether patients randomized to intervention actually received it or not.

Our estimate was based upon several assumptions. First, because there is limited prior data correlating changes in medication adherence with improvements in biometric outcomes for non-adherent patients with poorly-controlled cardiometabolic conditions, we relied on the results from a large, contemporary trial of post-myocardial infarction patients, which found that a 4-5% improvement in adherence was associated with statistically significant improvements in cardiovascular clinical outcomes.[13] Second, we assumed that 95% of potentially eligible intervention patients would be approved for study inclusion by their PCPs and that 50% of these patients would agree to a

pharmacist consultation. Or, in other words, to see a mean 5% change in adherence, our intervention would need to result in an approximate 10% improvement among those who actually received all of it. Small prior studies of pharmacist-led adherence improvement interventions have reported effect sizes of this magnitude.[14,15] Third, we conservatively assumed a standard deviation in adherence of 25%, clustering at the practice level with a design effect of 1.10,[16,17] and a 15% non-differential loss to follow-up rate. Finally, independent of our ability to detect a change in adherence that we hypothesized would result in an improvement in disease control, we wished to have at least 80% power to detect a 20% between-group difference in the relative risk of our secondary clinical outcome, achieving good disease control, assuming a baseline rate of good control of 23%.

Based upon these assumptions we planned to at least 4000 patients over a 1-year period and to follow them for a 1 year period, which would in fact provide sufficient power to detect a 2.5% mean change in adherence between the intervention and control groups.

Statistical Analyses

As anticipated with the use of routinely-collected data to evaluate clinical outcomes, clinical data was missing for some (15.7%) patients. Accordingly, we used multiple imputation with 20 imputations. This approach achieved in-range values and a 99% relative efficiency. All analyses were conducted on each imputed dataset. We used generalized estimating equations with logit link functions with binary errors for the proportion of patients achieving good control on at least one and all eligible conditions.

We used an identify link with normally distributed errors for the mean disease specific measures. The results were then combined using Rubin's rules.[18] As a sensitivity analysis, we conducted a complete-case analysis on all non-missing values.

We explored whether particular patient subgroups were more likely to have missing data and found that while men were more likely to have missing BPs in follow-up (13.8% vs. 8.7%, p=0.02, chi-square test), there was no significant difference by sex on A_{1c} (5.5% male vs. 6.6% female, p=0.70, chi-square test) or on LDL (18.4% male vs. 19.3% female, p=0.57). There were also no differences in blood pressure missing data by sites (p=0.19), although one site was more likely to have missing A1c and LDL values (ANOVA p=0.04 and p=0.01, respectively,). In exploratory analysis, excluding this site from the outcome analysis did not change the disease control results. For example, the adjusted OR for achieving improvement on at least 1 condition would be 1.03 (0.99-1.08) compared with 1.03 (0.98-1.07) in the full dataset.

Rates of healthcare utilization were compared using using generalized estimating equations with log link functions and Poisson distributed errors.

eAppendix 1. Definitions of poor and worsening disease control

Condition	Age (in years)	Definition
Diabetes[1]	…	Latest HbA1c > 8 or Latest HbA_{1c} 7.5 ≤ to ≤ 8 and previous HbA_{1c} 1% lower
Hypertension[2]	≥ 60	Latest BP > 150/90 or Latest BP 140/80 ≤ to ≤ 150/90, and previous BP 20 mmHg lower
	< 60	Latest BP > 140/90 or Latest BP 130/80 ≤ to ≤ 140/90, and previous systolic or diastolic BP 20 mmHg lower
Hyperlipidemia[3]	…	Diagnoses of ASCVD
	40-75	Type 1 or 2 diabetes and use of glucose lowering agent
	40-79	ASCVD risk > 7.5%
	…	LDL>190 mg/dl or Latest LDL 175 ≤ to ≤ 190, and previous LDL 30 mg/dl lower

…= N/A; Abbreviations: HbA1c, hemoglobin A_{1c}; BP, blood pressure; ASCVD, atherosclerotic cardiovascular disease; LDL, low-density lipoprotein

eAppendix 2. Medications included

1: **Anti-hypertensive drugs**

ACE Inhibitors and ARBs

Benazepril
Captopril
Enalapril
Fosinopril
Lisinopril
Moexipril
Perindopril
Quinapril
Ramipril
Trandolapril
Candesartan
Eprostartan
Irebsartan
Losartan
Olmesartan
Telmisartan
Valsartan

CCBs
Diltiazem
Mibefradil
Verapamil
Amlodipine
Bepridil
Felodipine
Isradipine
Nicardipine
Nifedipine
Nimodipine
Nisoldipine

Diuretics
Bendroflumethiazide
Benzthiazide
Chlorothiazide
Chlorthalidone
Cyclothiazide
Hydrochlorothiazide
Hydroflumethiazide
Indapamide
Methyclothiazide
Polythiazide
Quinethazone
Trichlormethiazide
Triamterene
Beta-blockers

Acebutolol
Atenolol

Betaxolol
Bisprolol
Bucindolol Carteolol
Labetalol
Landiolol
Levobunolol
Metipranolol
Metoprolol
Penbutolol
Pindolol
Timolol
Nebivolol

Others
Methyldopa
Hydralazine
Doxazosin
Terazosin
Minoxidil
Reserpine

2: Lipid lowering drugs (HMG CoA reductase inhibitors [Statins])
Atorvastatin
Fluvastatin
Lovastatin
Pravastatin
Rosuvastatin
Pitivastatin
Simvastatin

3: Anti-diabetic drugs

Sulfonylureas
Chlorpropamide
Tolbutamide
Tolazamide
Gliclazide
Glipizide
Glyburide
Glibencalamide
Glimepiride

Meglitinides
Repaglinide Nateglinide

Biguanides
Metformin

Thiazolidinediones
Rosiglitazone
Pioglitazone
Troglitazone

Alpha-glucosidase inhibitors

Acarbose Miglitol

SGLT-2 inhibitors
Canagliflozin
Dapagliflozin
Empagliflozin

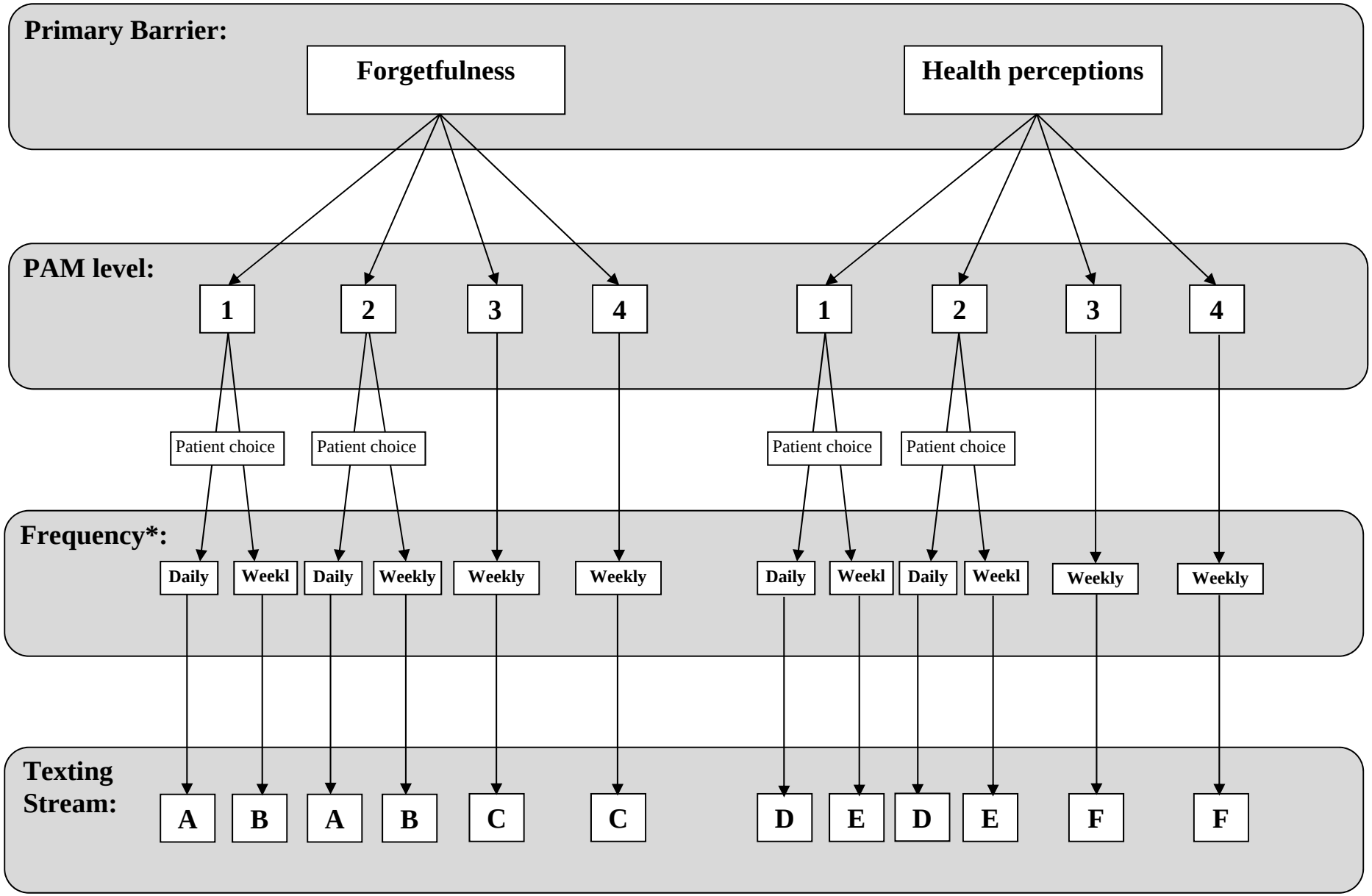
DPP-4 Inhibitors
Sitagliptin
Saxagliptin
Linagliptin
Alogliptin

eAppendix 3. Patient barriers to adherence and available solutions

BARRIER	SOLUTION	SPECIFIC STRATEGY	
		LOW ACTIVATION (PAM 1 and PAM 2)	**HIGH ACTIVATION (PAM 3 and PAM 4)**
Treatment complexity and/or forgetfulness	***Medication review***	▪ Reduce dosing frequency ▪ Switch to combination ▪ Stop unnecessary medications	▪ Reduce dosing frequency ▪ Switch to combination ▪ Stop unnecessary medications
	Pill organization and reminders	▪ Pill box reminder ▪ Use of apps/alarms ▪ Mail order service	▪ Pill box reminder
	Counseling	▪ Counsel about disease/medications as needed	▪ Counsel about disease/medications as needed
	Text messaging	▪ Reminder text messages (weekly or daily)	▪ Reminder text messages (weekly)
	Family and/or social work involvement	▪ Family member support ▪ Social work referral	▪ None
Health perception	***Counseling***	▪ Counsel as needed	▪ Counsel as needed
	Text messaging	▪ Motivational text messages (daily or weekly)	▪ Motivational texts (weekly)
Cognitive impairment	***Family and/or social work involvement***	▪ Family member support ▪ Social work referral	▪ Family member support ▪ Social work referral
	Counseling, education	▪ Counsel using simplified teach-back method	▪ Counsel using simplified teach-back method
Lack of knowledge and/or poor health literacy	***Counseling***	▪ Counsel about disease/medications using teach-back method	▪ Counsel about disease/medications using teach-back method
	Family and/or social work involvement	▪ Family member support ▪ Social work referral	▪ None
Experiencing side effects	***Medication review***	▪ Switch to alternative, adjust dose, or stop ▪ Other strategies to reduce side effects ▪ Refer to PCP if needed	▪ Switch to alternative, adjust dose, or stop ▪ Other strategies to reduce side effects ▪ Refer to PCP if needed
	Counseling	▪ Counsel about expected side effects ▪ Plan for contact if side effects persist	▪ Counsel about expected side effects ▪ Plan for contact if side effects persist
Costs	***Medication review***	▪ Switch to less expensive option/generic ▪ Switch to combination medication ▪ Stop unnecessary meds	▪ Switch to less expensive option/generic ▪ Switch to combination medication ▪ Stop unnecessary meds
	Mail order, social work support	▪ Use of mail order service ▪ Social work referral ▪ Refer Medicare patients to co-pay assistance program	▪ Use of mail order service ▪ Refer Medicare patients to co-pay assistance program
	Counseling	▪ Counsel about disease/medications as needed	▪ Counsel about disease/medications as needed
All barriers	***Follow-up calls***	▪ All patients receive follow-up calls	▪ Follow-up calls only if clinically indicated

PAM = Patient Activation Measure; PCP = Primary Care Physician

eAppendix 4. Text messaging flowchart and sample texts



eAppendix 5. Examples of trial text messages for patients' primary barriers and PAM levels

Primary barrier	PAM levels	Text
Forgetfulness	1, 2	Hello from your Harvard Vanguard team! Here's your daily reminder to take your medication.
Forgetfulness	1, 2	Think about the last time you didn't take your medication. What can you do to keep it from happening again?
Forgetfulness	1, 2	Do you drink coffee in the morning? Try to put your medication by your coffee pot to help you remember to take your medication.
Health perceptions	1, 2	When you are feeling well, do you sometimes stop taking your medications? Skipping medications may affect your long-term health.
Health perceptions	1, 2	Managing your health can be difficult. But taking your medications regularly can help prevent complications down the road. Stick to it!
Health perceptions	1, 2	Set short term goals. Try to take your medications every day for the next 7 days. Remember, missing doses is missing out on better health.
Forgetfulness	3, 4	When you fill each prescription, check the bottle for the number of refills. Call your doctor for a new prescription when you have only one refill left.
Forgetfulness	3, 4	Some people find using automated reminder, such as their phone's alarm or a medication tracker app on a smart phone to be useful.
Forgetfulness	3, 4	Try to make your medication schedule a part of your daily routine. This will help you remember to take your medication on time.
Health perceptions	3, 4	You can't always feel your medications working. It's important to take them for long-term benefit.
Health perceptions	3, 4	As a former US Surgeon General has said: "Drugs don't work in patients who don't take them". Keep it up!
Health perceptions	3, 4	If you skip doses of your scheduled medications, it can be hard for your Harvard Vanguard team to safely adjust your medicine doses at your next visit.

eReferences

1. American Diabetes Association. 5. Glycemic Targets. *Diabetes care.* 2016;39 Suppl 1:S39-46.
2. James PA, Oparil S, Carter BL, et al. 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 (JNC 8). *Jama.* 2014;311(5):507-520.
3. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;129(25 Suppl 2):S1-45.
4. Brown MT, Bussell JK. Medication Adherence: WHO Cares? *Mayo Clinic Proceedings.* 2011;86(4):304-314.
5. Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J. Long-term persistence in use of statin therapy in elderly patients. *Jama.* 2002;288(4):455-461.
6. Choudhry NK, Shrank WH, Levin RL, et al. Measuring concurrent adherence to multiple related medications. *The American journal of managed care.* 2009;15(7):457-464.
7. Rollnick S, Kinnersley P, Stott N. Methods of helping patients with behaviour change. *BMJ (Clinical research ed).* 1993;307(6897):188-190.
8. Heather N, Rollnick S, Bell A, Richmond R. Effects of brief counselling among male heavy drinkers identified on general hospital wards. *Drug and alcohol review.* 1996;15(1):29-38.
9. Samet JH, Rollnick S, Barnes H. Beyond CAGE. A brief clinical approach after detection of substance abuse. *Archives of internal medicine.* 1996;156(20):2287-2293.
10. Choudhry NK, Isaac T, Lauffenburger JC, et al. Rationale and design of the Study of a Tele-pharmacy Intervention for Chronic diseases to Improve Treatment adherence

(STIC2IT): A cluster-randomized pragmatic trial. *American heart journal.* 2016;180:90-97.

11. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation.* 2002;106(25):3143.
12. Pokharel Y, Tang F, Jones PG, et al. Adoption of the 2013 American College of Cardiology/American Heart Association Cholesterol Management Guideline in Cardiology Practices Nationwide. *JAMA Cardiol.* 2017;2(4):361-369.
13. Choudhry NK, Avorn J, Glynn RJ, et al. Full coverage for preventive medications after myocardial infarction. *The New England journal of medicine.* 2011;365(22):2088-2097.
14. Hedegaard U, Kjeldsen LJ, Pottegard A, et al. Improving Medication Adherence in Patients with Hypertension: A Randomized Trial. *The American journal of medicine.* 2015;128(12):1351-1361.
15. Korcegez EI, Sancar M, Demirkan K. Effect of a Pharmacist-Led Program on Improving Outcomes in Patients with Type 2 Diabetes Mellitus from Northern Cyprus: A Randomized Controlled Trial. *J Manag Care Spec Pharm.* 2017;23(5):573-582.
16. Glynn RJ, Brookhart MA, Stedman M, Avorn J, Solomon DH. Design of cluster-randomized trials of quality improvement interventions aimed at medical care providers. *Medical care.* 2007;45(10 Supl 2):S38-43.
17. Choudhry NK, Shrank WH. Implementing randomized effectiveness trials in large insurance systems. *Journal of clinical epidemiology.* 2013;66(8 Suppl):S5-11.
18. Newgard CD, Lewis RJ. Missing Data: How to Best Account for What Is Not Known. *Jama.* 2015;314(9):940-941.

eTable 1. Characteristics of patients who were included and excluded by their primary care providers from a clinical pharmacist consultation[a]

CHARACTERISTIC	Included by Provider (N=1911)	Excluded by Provider (N=127)
Age, mean (SD), y	60.1 (11.5)	63.4 (12.6)
Male gender, n (%)	1063 (55.7)	57 (45.0)
White race, n (%)	1017 (53.2)	73 (57.7)
English language speaker, n (%)	1744 (91.2)	114 (90.0)
Qualifying conditions, n (%)		
Hyperlipidemia	1377 (72.0)	91 (71.4)
Hypertension	492 (25.7)	36 (28.0)
Diabetes	241 (12.6)	9 (6.9)
Number of eligible conditions, mean (SD)	1.1 (0.3)	1.1 (0.2)
Comorbidities, n (%)[b]		
Prior acute coronary syndrome	29 (1.5)	5 (3.7)
Heart failure	79 (4.2)	7 (5.8)
Dementia	19 (1.0)	8 (6.4)
Depression	110 (5.7)	12 (9.5)
Chronic kidney disease	79 (4.2)	7 (5.8)
Smoking	64 (3.4)	6 (4.8)
Charlson comorbidity score, mean (SD)	0.83 (1.6)	1.59 (2.7)
Unique prescription medication filled, mean (SD)	7.8 (5.4)	8.8 (6.0)
Baseline disease control[c]		
LDL cholesterol, mean (SD), mg/dL,	113.9 (39.0)	106.1 (33.5)
Systolic blood pressure, mean (SD), mmHg	149.7 (12.8)	150.9 (15.7)
Glycosylated hemoglobin, mean (SD)	9.9 (1.8)	9.2 (1.4)
Baseline adherence, mean (SD)[d]	57.1 (17.9)	56.1 (18.8)

[a] Standardized mean difference between groups for gender, diabetes, no. of eligible conditions, coronary artery syndrome, dementia, depression, Charlson and baseline glycosylated hemoglobin were >0.1; otherwise, there were no significant differences between the groups. LDL = low density lipoprotein

[b] Comorbidities were assessed based on all available diagnoses in the 12-month period before each patient's date of randomization.

[c] Among patients for whom the listed condition qualified them for inclusion into the study.

[d] Calculated as the average of condition-specific adherence prior to randomization. See text for more details

eTable 2. Reasons that primary care providers excluded patients from a clinical pharmacist consultation (n=127)

REASON PROVIDED BY PRIMARY CARE PROVIDER	N (%)
Patient has well-controlled lab/BP values	19 (15.0)
Patient has limited life expectancy	13 (10.2)
Other:	
Medication regimen change	8 (6.3)
Recently hospitalized	4 (3.2)
Other complicating conditions (dementia, mental health issues, cancer)	4 (3.2)
Physician does not believe patient meets criteria for study	3 (2.4)
Living in nursing home	1 (0.8)
Financial issues	1 (0.8)
Patient does not like intervention from multiple sources	1 (0.8)
Unspecified[a]	73 (57.5)

[a] At the time that patients were excluded from participation, primary care providers were asked to provide a reason for the exclusion. When no specific reason was provided, primary care providers were contacted, via the electronic health record, to clarify. Despite this, in many cases no further clarification of the reason for exclusion was provided.

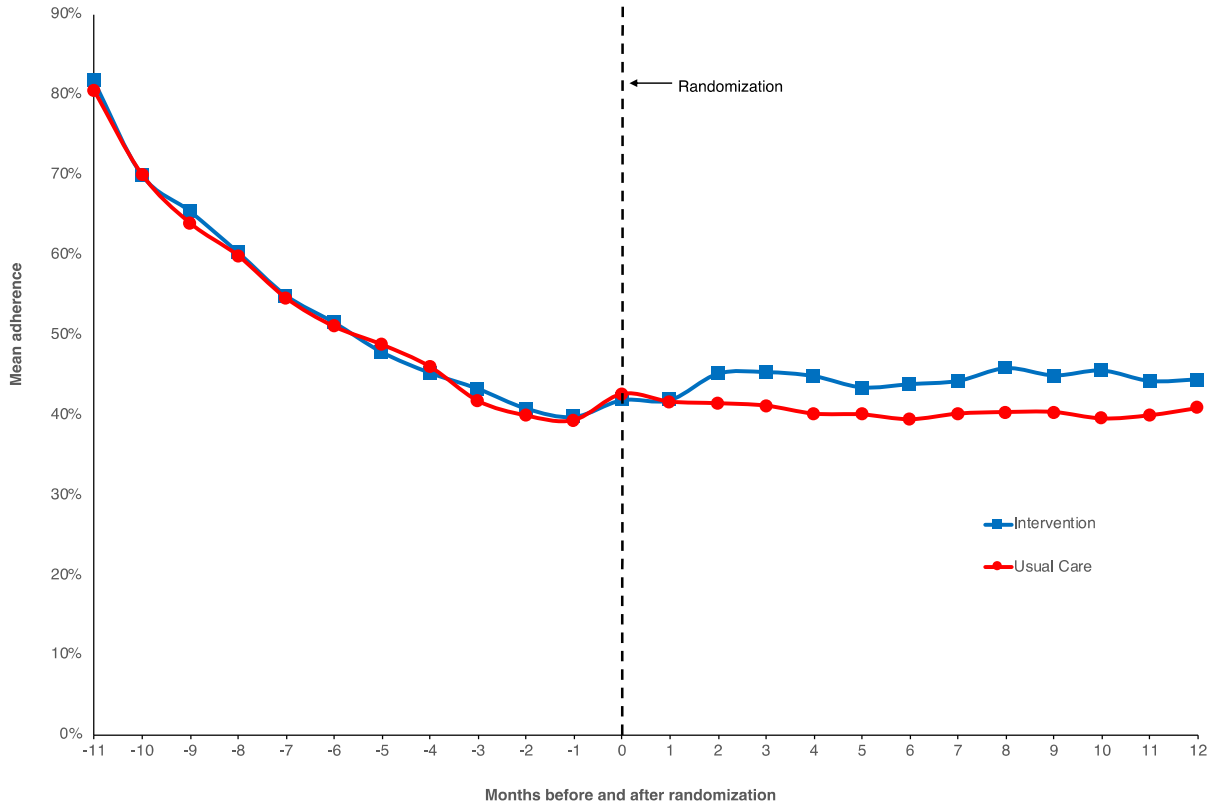
eTable 3. Characteristics of intervention patients agreeing and not agreeing to clinical-pharmacist consultation[a]

CHARACTERISTIC	Agreed to Consultation (N=1069)	Did Not Agree to Consultation (N=969)
Age, mean (SD), y	61.09 (11.0)	59.71 (12.3)
Male gender, n (%)	615 (57.5)	499 (51.5)
White race, n (%)	550 (51.4)	543 (56.0)
English language speaker, n (%)	990 (92.6)	867 (89.5)
Qualifying conditions, n (%)		
Hyperlipidemia	791 (74.0)	676 (70.0)
Hypertension	260 (24.3)	269 (27.8)
Diabetes	131 (12.3)	115 (11.9)
Number of eligible conditions, mean (SD)	1.11 (0.3)	1.09 (0.3)
Comorbidities, n (%)[b]		
Prior acute coronary syndrome	14 (1.3)	21 (2.2)
Heart failure	36 (3.4)	52 (5.4)
Dementia	9 (0.8)	21 (2.2)
Depression	65 (6.1)	59 (6.1)
Chronic kidney disease	70 (6.5)	85 (8.8)
Smoking	34 (3.2)	37 (3.8)
Charlson comorbidity score, mean (SD)	0.8 (1.6)	1.0 (1.9)
Unique prescription medication filled, mean (SD)	8.2 (5.5)	7.6 (5.5)
Baseline disease control[c]		
LDL cholesterol, mean (SD), mg/dL,	110.9 (35.9)	116.1 (41.4)
Systolic blood pressure, mean (SD), mmHg	149.0 (12.3)	150.7 (13.8)
Glycosylated hemoglobin, mean (SD)	9.7 (1.6)	9.9 (2.0)
Baseline adherence, mean (SD)[d]	58.3 (17.3)	55.7 (18.7)

[a] Standardized mean difference between intervention and control for age, race/ethnicity, gender, language, hypertension, dementia, Charlson and baseline adherence were >0.1; otherwise, there were no significant differences between the groups. LDL = low density lipoproteinl

[b] Comorbidities were assessed based upon all available diagnoses during the 12-month period preceding each patient's date of randomization.
[c] Among patients for whom the listed condition qualified them for inclusion into the study.
[d] Calculated as the average of condition-specific adherence prior to randomization. See text for more details

eFigure 1. Medication Adherence by Treatment Group Over Time For Medications Used for Outcome Assessment[a]



[a]This plot shows mean monthly medication adherence over time for those medications that qualified patients for study eligibility (i.e. medications to treat conditions for which patients had sub-optimal disease control). Because patients had to fill medications in order to be potentially eligible and because many patients fill 30 or more days supply of medication in their first month of cohort entry, by definition, adherence at the beginning of the study eligibility window is high and falls over time.

eTable 4. Medication adherence sensitivity analysis

	Intervention, mean adherence (SD)	Usual care, mean (SD) adherence	Unadjusted absolute difference (95% CI)	Adjusted absolute difference[a] (95% CI)
As-treated/ per-protocol analysis[b]	58.3 (17.3)	46.0 (33.7)	10.4 (8.2 – 12.5)	10.3 (8.7 – 11.8)
Adherence to medications only filled after randomization	49.5 (33.1)	46.0 (33.7)	4.0 (1.8 – 6.1)	4.2 (2.3 – 6.2)
Censoring patients on oral hypoglycemic at the time of insulin initiation	46.1 (33.9)	42.1 (33.8)	4.6 (2.9 - 6.4)	4.8 (3.3 – 6.3)

[a] Adjusted for age and race/ethnicity
[b] The baseline adherence among intervention patients agreed to a consultation was 58.3% (see Table e3). In contrast, the baseline adherence among control subjects was 57.2%.

eTable 5. Medication adherence subgroup analyses

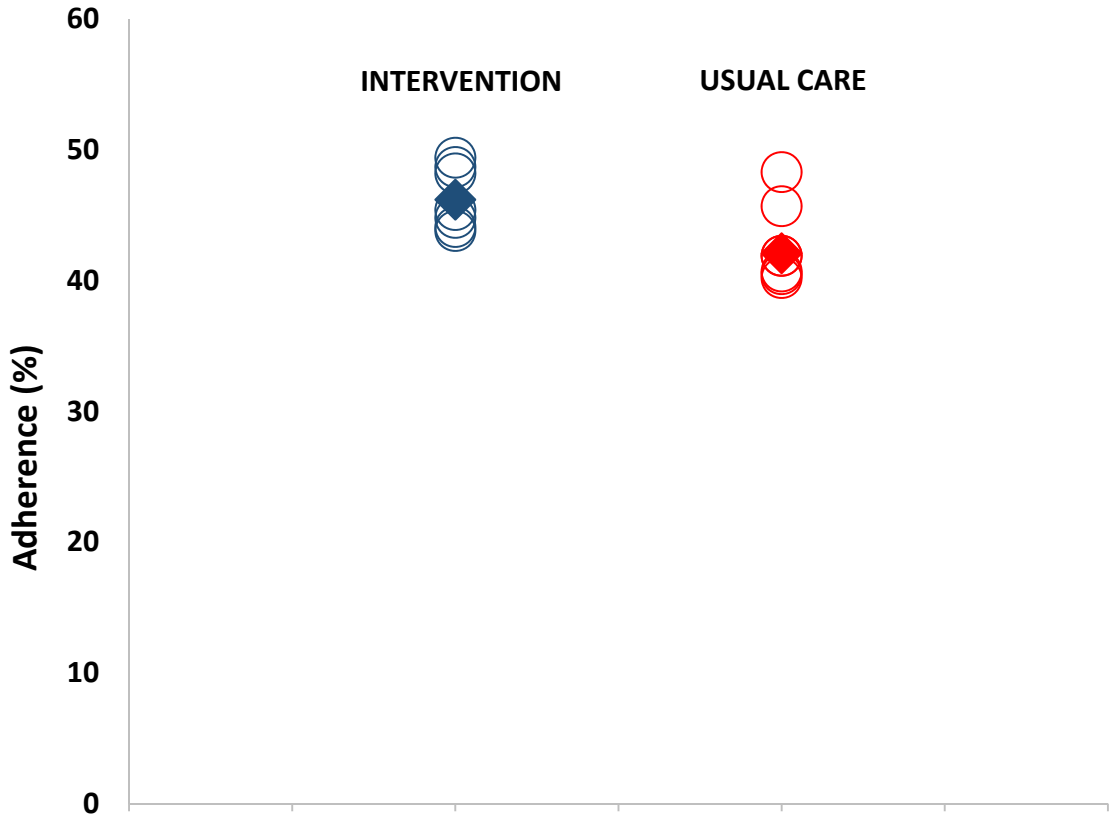
	Number of patients	Intervention, mean adherence (SD)	Usual care, mean adherence (SD)	Unadjusted absolute difference (95% CI)	Adjusted absolute difference[a] (95% CI)	P value for Interaction
Overall	4078	46.2 (33.9)	42.1 (33.8)	4.7 (3.0 - 6.4)	4.9 (3.3 - 6.4)	
Age						
≥ 65 years	1321	48.9 (35.1)	46.2 (35.5)	2.6 (0.3 - 5.0)	4.0 (1.5 - 6.4)	0.19
< 65 years	2757	44.6 (33.1)	40.4 (32.9)	5.0 (3.7 - 6.4)	5.4 (3.7 - 7.1)	
Sex						
Female	1841	43.3 (33.8)	41.5 (33.8)	1.2 (-0.1 - 2.4)	1.7 (0.1 - 3.3)	0.03
Male	2237	48.5 (33.8)	42.5 (33.7)	6.7 (3.8 - 9.5)	7.0 (4.5 - 9.5)	
Race						
White	2329	47.5 (35.6)	43.3 (34.8)	4.8 (2.5 - 7.1)	4.4 (2.3 - 6.5)	0.56
Black	1027	44.8 (30.6)	39.3 (30.3)	6.7 (6.0 - 7.3)	6.0 (5.4 - 7.7)	
Other	722	44.3 (33.4)	41.3 (34.0)	6.0 (1.1 - 10.9)	6.0 (1.3 - 10.7)	
Baseline adherence[b]						
< 50%	1209	34.1 (31.4)	28.9 (30.7)	4.2 (3.8 - 4.6)	4.5 (3.3 - 5.7)	0.44
≥ 50%	2869	51.4 (33.6)	47.6 (33.5)	5.3 (3.7 - 6.9)	5.5 (3.6 - 7.4)	
Number of eligible conditions						
1 condition	3703	46.3 (34.4)	42.1 (34.2)	4.7 (2.9 - 6.5)	4.8 (3.1 - 6.5)	0.77

	2 or 3 conditions	375	45.0 (28.6)	41.6 (28.7)	5.7 (2.8 - 8.7)	6.1 (2.3 - 9.8)	
Number of eligible medications							
	1 medication	3286	47.0 (34.5)	42.6 (34.3)	4.9 (2.6 - 7.1)	5.1 (3.1 – 7.2)	0.35
	≥ 2 medications	792	42.5 (31.2)	39.8 (31.4)	4.3 (2.8 – 5.7)	4.1 (1.8 – 6.3)	

[a] Adjusted for age and race/ethnicity

[b] Calculated as the average of condition-specific adherence prior to randomization. See text for more details

eFigure 2. Average adherence for intervention and control subjects broken down by study site



The open circles represent site-specific adherence results. The solid diamonds are the average adherence results for intervention and usual care sites.

eTable 6. Clinical outcomes sensitivity analysis: as-treated analysis/per-protocol analysis

	Intervention (n=1069)	Usual care (n=2040)	Unadjusted effect estimate[b] (95% CI)	Adjusted effect estimate[c] (95% CI)
Percent of patients achieving good control[a]				
On at least 1 condition, n (%)	808 (75.6)	1452 (71.2)	1.24 (1.03 –1.50)	1.26 (1.04 –1.52)
On all eligible conditions, n (%)	749 (70.1)	1350 (66.2)	1.18 (0.99 –1.41)	1.19 (0.99 –1.43)
Mean disease-specific measures[d]				
Hyperlipidemia, LDL cholesterol (mg/dL)	99.3 (31.2)	108.5 (35.7)	-9.4 (-12.8 – -5.9)	-8.5 (-9.7 – -5.0)
Hypertension, Systolic blood pressure (mmHg)	135.6 (15.6)	134.8 (15.9)	0.4 (-2.4 – 3.3)	0.3 (-2.6 – 3.2)
Diabetes, Hemoglobin A_{1c}	9.1 (1.9)	9.2 (1.8)	0.1 (-0.3 – 0.4)	0.1 (-0.3 – 0.5)

LDL = low density lipoprotein; ASCVD = atherosclerotic cardiovascular disease

[a] Defined by Hemoglobin A1c<8%, Systolic blood pressure <150 mmHg (for age ≥60 yrs) or <140 mmHg (for age <60 years), and LDL cholesterol <100 mg/dL (for ASCVD risk >20%), LDL<130 mg/dL (for ASCVD risk 10-20%), or LDL md/dL <160 (for ASCVD risk <10%)

[b] Effect estimates are odds ratios for the % of patients achieving good control on at least one and all eligible outcomes. For mean disease-specific measures, the effect estimates are absolute differences.

[c] Adjusted for age and race/ethnicity

[d] Hyperlipidemia (n=2970), Hypertension (n=1015), Diabetes (n=488)

eTable 7. Clinical outcomes sensitivity analysis: complete case analysis

	Intervention (n=1750)	Usual care (1686)	Unadjusted effect estimate[b] (95% CI)	Adjusted effect estimate[c] (95% CI)
Percent of patients achieving good control[a]				
On at least 1 condition, n (%)	1239 (70.8)	1167 (69.2)	1.17 (0.97 –1.41)	1.17 (0.98 –1.40)
On all eligible conditions, n (%)	1136 (64.9)	1075 (63.8)	1.12 (0.94 –1.35)	1.12 (0.94 –1.34)
Mean disease-specific measures[d]				
Hyperlipidemia, LDL cholesterol (mg/dL)	102.4 (34.4)	108.0 (38.2)	-6.1 (-9.7 – -2.6)	-5.6 (-9.2 – -2.1)
Hypertension, Systolic blood pressure (mmHg)	137.5 (17.9)	134.9 (16.6)	2.5 (-1.0 – 6.0)	2.2 (-1.4 – 5.7)
Diabetes, Hemoglobin A_{1c}	9.3 (2.0)	9.1 (1.8)	0.2 (-0.1 – 0.5)	0.2 (-0.1 – 0.5)

LDL = low density lipoprotein; ASCVD = atherosclerotic cardiovascular disease

[a] Defined by Hemoglobin A1c<8%, Systolic blood pressure <150 mmHg (for age ≥60 yrs) or <140 mmHg (for age <60 years), and LDL cholesterol <100 mg/dL (for ASCVD risk >20%), LDL<130 mg/dL (for ASCVD risk 10-20%), or LDL md/dL <160 (for ASCVD risk <10%)

[b] Effect estimates are odds ratios for the % of patients achieving good control on at least one and all eligible outcomes. For mean disease-specific measures, the effect estimates are absolute differences.

[c] Adjusted for age and race/ethnicity

[d] Hyperlipidemia (n=2970), Hypertension (n=1015), Diabetes (n=488)

eTable 8. Healthcare utilization outcomes sensitivity analysis: as-treated analysis/per-protocol analysis

	Intervention, N (%) (N=1069)	Usual care, N (%) (N=2040)	Unadjusted odds (95% CI)	Adjusted[a] odds (95% CI)
Emergency room visits	47 (4.4)	113 (5.5)	0.69 (0.47-0.99)	0.69 (0.49-0.97)
Office visits	330 (30.9)	594 (29.1)	1.18 (0.95-1.48)	1.03 (0.93-1.13)
Hospitalizations	89 (8.3)	156 (7.7)	1.03 (0.74-1.42)	0.99 (0.77-1.27)

[a] Adjusted for age and race/ethnicity