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Improving Adherence to Cardiovascular Disease Medications With Information Technology

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Abstract

Objectives—Evaluate the utility of 2 electronic medical record (EMR)-linked, automated phone reminder interventions for improving adherence to cardiovascular disease medications.

Study Design—A 1-year, parallel arm, pragmatic clinical trial in which 21,752 adults were randomized to receive either usual care (UC) or 1 of 2 interventions in the form of interactive voice recognition calls—regular (IVR) or enhanced (IVR+). The interventions used automated phone reminders to increase adherence to cardiovascular disease medications. The primary outcome was medication adherence; blood pressure and lipid levels were secondary outcomes.

Methods—The study took place in 3 large health maintenance organizations. We enrolled participants who were 40 years or older, had diabetes mellitus or atherosclerotic cardiovascular disease, and were suboptimally adherent. IVR participants received automated phone calls when they were due or overdue for a refill. IVR+ participants received these phone calls, plus personalized reminder letters, live outreach calls, EMR-based feedback to their primary care providers, and additional mailed materials.

Results—Both interventions significantly increased adherence to statins and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) compared with UC (1.6 to 3.7 percent-age points). Adherence to ACEIs/ARBs was also significantly higher for IVR+ relative to IVR participants. These differences persisted across subgroups. Among statin users, IVR+ participants had significantly lower low-density lipoprotein (LDL) levels at follow-up compared with UC (Δ = −1.5; 95% CI, −2.7 to −0.2 mg/dL); this effect was seen mainly in those with baseline LDL levels >100 mg/dL (Δ = −3.6; 95% CI, −5.9 to −1.3 mg/dL).

Conclusions—Technology-based tools, in conjunction with an EMR, can improve adherence to chronic disease medications and measured cardiovascular disease risk factors.

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Nonadherence to chronic cardiovascular disease (CVD) therapy is well-documented and contributes to increased CVD risk and morbidity.[1,2] Low adherence is often the broken link between new therapies and improved health outcomes,[3] and is a target for reducing healthcare costs.[4,5]

The most effective adherence interventions include both educational and behavioral strategies[6]; however, these can be costly. Further, most interventions thus far have enrolled select patient populations, limiting generalizability. Recently, research has focused on using health information technologies (HITs) to develop low-cost interventions for large populations.[7,8]

We recently reported on a trial to improve adherence to inhaled corticosteroids in 8517 adult health plan members with asthma.[9] That study used automated telephone reminder calls linked with an electronic medical record (EMR). It found a small (2 percentage point) but statistically significant improvement over 18 months in the intent-to-treat analysis, and an increase of 6 percentage points in adherence and decreased asthma symptoms among patients who took the calls. Derose and colleagues[10] tested automated reminder calls followed by mailed letters to increase adherence among 5216 adults who received a new statin prescription. The intervention improved fill rates over the next 25 days by 16 percentage points. These and other studies[11-14] suggest that HIT/EMR-based reminder interventions offer a promising population-based approach to promoting adherence.

We present the main outcomes for PATIENT (Promoting Adherence to Improve Effectiveness of Cardiovasular Disease Therapies), a pragmatic trial involving members of a health maintenance organization that evaluated the effectiveness of 2 EMR-linked, automated reminder interventions, compared with usual care (UC), in increasing adherence to cardiovascular medications.

METHODS

Additional methods, details, and results are included in the eAppendix, available at www.ajmc.com.

Study Design

PATIENT was a parallel arm, pragmatic clinical trial in which 21,752 adults were randomized to receive either UC or 1 of 2 interventions designed to increase adherence to statins, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs). The study was funded as a CHOICE (Clinical and Health Outcomes Initiative in Comparative Effectiveness) grant[15] by the Agency for Healthcare Research and Quality, and had a mandate to carry out comparative effectiveness research in large, “real-world” populations and to assess treatment effects overall and in relevant subgroups.

Assuming a standard deviation of 0.28 (ie, 28 percentage points), the study had 95% power to detect deltas of 0.025 (2.5 percentage points) in adherence to statins and 0.029 (2.9 percentage points) to ACEIs/ARBs for each active intervention arm relative to UC for the cohort as a whole. Subgroup power is shown in the eAppendix A.

Research Setting

Participants were members of one of 3 regions of the Kaiser Permanente (KP) health plan—Northwest (KPNW), Hawaii (KPH), and Georgia (KPG)—which collectively serve about 944,000 individuals. The Institutional Review Boards of each region approved the study and waived informed consent. An external Data and Safety Monitoring Board and local clinician advisory boards at each site approved the study protocol and monitored the study for safety and data quality.

Participant Selection and Randomization

Using each region's EMR, we identified participants 40 years and older with diabetes mellitus and/or cardiovascular disease (CVD), suboptimally (<90%) adherent to a statin or ACEI/ARB during the previous 12 months, and due or overdue for a refill. We excluded only individuals with medical conditions that might contraindicate the use of these medications, such as medication allergies, liver failure, cirrhosis, rhabdomyolysis, end-stage renal disease, chronic kidney disease (see eAppendix Table A1 for complete list) and those on KP's "do not contact" list.

Within each region, we randomly assigned a sample of eligible members to the 3 primary study arms (usual care and 2 intervention arms) in a 1:1:1 ratio at the study outset and repeated this process for previously ineligible members who subsequently met eligibility criteria over the following 5 months. Computer-generated randomization assignments were stratified by region and blocked to assure balance across treatment arms. Neither participants nor providers were blinded to treatment assignment.

Study enrollment began in December 2011 and continued through May 2012. Intervention and outcome assessment continued through November 2012.

Study Interventions

UC participants had access to the full range of usual services, including each region's normal education and care management outreach efforts to encourage statin and ACEI/ARB use.

Interactive Voice Recognition (IVR) Calls—IVR participants received automated phone calls when they were due or overdue for a refill. The calls used speech-recognition technology to educate patients about their medications and help them refill prescriptions (we created separate "refill" and "tardy" calls). The flow of each call was determined by participants' responses; each call lasted 2 to 3 minutes. At randomization, IVR participants received a pamphlet explaining these calls.

Both call types offered a transfer to KP's automated pharmacy refill line. The tardy call also offered a transfer to a live pharmacist. With permission, obtained at the first successful call contact, the program left detailed messages on answering machines or with another household member.

Enhanced IVR (IVR+)—In addition to IVR calls, participants in the IVR+ arm received a personalized reminder letter if they were 60 to 89 days overdue and a live outreach call if they were ≥90 days overdue, as well as EMR-based feedback to their primary care provider. IVR+ participants received additional materials, including a personalized health report with their latest BP and cholesterol levels, a pill organizer, and bimonthly mailings (Table A2 in eAppendix).

Study Measurements

Medication Adherence—We used a modified version of the Proportion of Days Covered (PDC),[16] defined from pharmacy dispensing records, for our primary measure. Because we were measuring adherence to chronic medications patients were known to be taking at randomization, we modified the PDC (mPDC) to include the whole follow-up period as the denominator time frame rather than time from first dispensing.[17] We accounted for medication on hand at randomization and ignored any medication remaining at the end of follow-up. We computed mPDCs separately for statins and ACEI/ARBs. To simplify enrollment logistics, we defined eligibility at baseline using the simpler Medication Possession Ratio (MPR), which we computed by dividing total days' dispensed supply by 365 and capping at 1.

Other EMR-Based Data—We used the EMR to capture age, race, gender, healthcare utilization for diabetes and CVD, and BP and lipid levels. Consistent with the Healthcare Effectiveness Data and Information Set reporting guidelines,[18,19] we defined BP control as systolic BP (SBP)/diastolic BP <140/90 mm Hg and lipid control as an low-density lipoprotein (LDL) <100 mg/dL. Pre-and post BP measurements were available for 91.6% of ACEI/ARB users, while pre-and post LDL measurements were available for 84.2% of statin users; missing values were ignored.

Statistical Analysis

We used an intention-to-treat analysis to compare primary and secondary outcomes between intervention and UC participants. All adherence analyses were conducted separately for users of statins and users of ACEIs/ARBs. We compared each intervention against UC using an α-level of 0.025. We then compared the IVR and IVR+ interventions against each other at an α-level of 0.05 only if either of these initial contrasts was statistically significant, thus assuring a trialwide α-level of 0.05. We used a similar adjustment procedure for all secondary analyses of treatment effects.

The primary analytic model compared post intervention adherence between intervention and UC participants using a general linear model that adjusted for site, gender, age (40-60 years, 61-70 years, 71+ years), number of baseline medications (1-5, 6-10, 11-15, 16+), comorbid diabetes/CVD status, and baseline adherence (≤.4, .4-.75, >.75 for statins; ≤.5, .5-.75, >.75 for ACEIs/ARBs) as fixed main effects. We assessed follow-up from randomization to end-of-study or loss of health plan coverage, whichever came first; baseline refers to the 12 months prior to randomization.

In prespecified secondary analyses, we added interaction terms to our models to estimate subgroup-specific treatment effects and to test for treatment by subgroup interactions. We used similar analytic models to assess the impact of the interventions on BP and LDL-cholesterol levels as continuous variables. We used logistic regression for analyses of BP control and LDL-cholesterol control. All analyses were conducted using SAS version 9.2[20] or Stata version 11.2.[21]

RESULTS

Of the 45,051 individuals who met inclusion criteria, we excluded 13.7% due to medical contraindications and another 6.2% for administrative reasons (Figure A1 in eAppendix). From the remaining 36,115 individuals, we randomly selected 25,323 for study inclusion and randomized those people into one of the main study arms (n = 21,752) or to one of the 2 ancillary treatment arms (n = 3571; see eAppendix). Of the former group, 16,380 qualified for statin calls at randomization and are included in the statin analyses; 13,036 qualified for the ACEI/ARB analyses.

Comparison of Intervention and UC Groups

Baseline characteristics of the intervention and UC groups for the pooled statin and ACEI/ARB analysis samples were very similar (Table 1). Among individuals included in the statin analysis, the mean baseline MPR was 0.51. For ACEI/ARB users, mean baseline MPR was 0.53.

Participant Follow-Up and Intervention Process Data

Mean duration of follow-up was 9.6 months and did not vary by treatment arm (Table A3 in eAppendix). IVR participants received, on average, 3.7 call attempts, including 2.4 direct connects or detailed messages; IVR+ participants received an average of 10.1 contact attempts, including 3.3 call attempts (2.2 resulting in direct connects or detailed messages), 5.9 educational mailings, 0.6 reminder letters, and 0.3 live pharmacy outreach call attempts.

Statin Adherence

While statin adherence increased significantly for both IVR and IVR+ participants compared with UC, adherence did not differ significantly between IVR and IVR+ (Table 2). On average, adherence among IVR participants was 2.2 percentage points higher than for UC (95% CI, 1.1-3.4), while the difference was 3.0 (95% CI, 1.9-4.2) percentage points for IVR +. These differences generally persisted in subgroups defined by gender, age, number of baseline medications, and baseline adherence; however, we saw little or no effect among individuals whose baseline adherence was greater than 0.75 or among those with comorbid diabetes and CVD (Table A4 in eAppendix). The intervention effects were present in all sites and differed significantly by site.

Both the IVR and IVR+ arms also significantly increased the proportion of individuals with good adherence (≥0.80), with odds ratios (ORs) of 1.16 and 1.14 for IVR+ and IVR versus UC, respectively (Table 2). The same patterns were observed for those with mid-level

baseline adherence (0.40-0.70) and for those with baseline adherence >0.75, although only the former were statistically significant.

ACEI/ARB Adherence

The results for ACEI/ARB adherence were similar to those for statin adherence (Table 2). Compared with UC, ACEI/ARB adherence also increased significantly for both IVR (1.6 percentage points) and IVR+ (3.7 percentage points) participants, within this case, the difference between IVR+ and IVR also statistically significant. As with the statin analyses, these patterns generally persisted across subgroups, and we found no evidence of an intervention effect among those with baseline adherence above 0.75 and among those with both diabetes and CVD (Table A6 in eAppendix). Unlike in the statin analysis, the interventions' effects on ACEI/ARB use were very similar across regions.

Both interventions also resulted in significantly higher levels of "good" ACEI/ARB adherence (>0.80) compared with UC, with ORs (95% CIs) of 1.21 (1.10-1.32) and 1.12 (1.02-1.23) for IVR+ and IVR versus UC, respectively (Table 2). The difference between IVR+ and IVR was not statistically significant.

Impact on Lipids and Blood Pressure

Among statin users, we observed a statistically significant reduction in LDL-cholesterol levels among IVR+ relative to UC participants (mean difference = −1.5; 95% CI, −2.7 to −0.2 mg/dL: Table 3). These differences appeared to vary by baseline LDL level, with the greatest reductions occurring in those whose initial LDL levels were above 100 mg/dL (mean difference = −3.6; 95% CI, −5.9 to −1.3 mg/dL) and no indication of an intervention effect in those with baseline LDL level below 80 mg/dL. The corresponding interaction test, however, was not significant. These reductions in LDL levels were reflected in improved LDL control for IVR+ versus UC, with significant increases ($P = .015$) in those whose initial LDL levels were above 100 mg/dL (mean difference = 1.21; 95% CI 1.04-1.42) and borderline significant increases ($P = .058$) overall [mean difference = 1.10, 95% CI, 1.00-1.22).

We observed no evidence of any impact on SBP or overall BP control among ACEI/ARB users, either overall or in subgroups defined by initial SBP levels (Table 3).

Participant Safety

During the 1-year follow-up period (Table A9 in eAppendix), 427 study participants (2.0%) died; 0.3% of participants were hospitalized for conditions potentially related to ACEI/ARB use; and 0.02% were hospitalized for conditions potentially related to statin use. These patterns were similar for the 3 intervention arms.

DISCUSSION

The PATIENT trial demonstrated that a low-cost EMR-based intervention, utilizing HIT tools, can improve adherence among patients with diabetes and/or CVD as part of a

population-based disease management strategy, and extends our previous work showing similar improvements among patients with asthma.[9]

Although the improvements were statistically significant across subgroups, the overall effect was small (1.6-3.7 percentage points). This may, however, still have important public health implications. For instance, a 2 mm Hg drop in blood pressure, on a population basis, translates into long-term cardiovascular risk reduction.[22] Unfortunately, little is known about the public health impact of small changes in medication adherence.

Of note in this regard, we observed a statistically significant reduction in LDL-cholesterol levels among IVR+ participants who were taking statins. This effect was most pronounced among those with poorly controlled LDL at baseline, for whom the IVR+ and IVR interventions resulted in LDL reductions of 3.6 and 1.7 mg/dL versus UC, respectively. A recent meta-analysis of 26 randomized trials suggests that each 39 mg/dL decrease in LDL leads to annual reductions in all-cause mortality and major vascular events of 10% and 21%, respectively.[23] Assuming a sustained effect, the 3.6 mg/dL reduction in LDL we observed for IVR+ would be associated with a nearly 1% annual reduction in mortality and 2% reduction in major vascular events. Therefore, while modest, these LDL reductions could have meaningful public health impact. We did not observe significant improvements in BP control, despite increases in ACEI/ARB adherence similar to those we observed with statins. This may reflect a different adherence threshold for clinical impact or the complexity of BP control.[24]

Reminder interventions show promise for improving adherence with CVD medications.[10,25-28] The PATIENT intervention also showed an impact on lipid levels. Together these studies reinforce the value of IVR/EMR strategies to support adherence among new and established users of statins.

The sustainability of such strategies, however, is likely dependent on patient perceptions of the usefulness versus intrusiveness of the calls. To assess this, we conducted qualitative, semi-structured follow-up interviews with 49 study participants. Most (70%) indicated they appreciated the calls, while only 8% said they were annoyed by them. In addition, 70% reported listening to at least 1 call in its entirely, though 22% reported hanging up on subsequent calls. Only 6% described the calls as “not useful,” while 43% reported that the calls made them feel cared for and supported by the health plan. Close to 60% reported that the calls prompted them to check the status of their medication and take follow-up action. And while intervention “fatigue” might certainly be a barrier to continued efficacy, 94% reported that the service should continue for all health plan members. However, as patients increasingly rely on diverse communication technologies, including email and texting, effective reminder interventions will need to be flexible, adaptive, and personally tailored to match patients’ preferences.

This study’s strengths are a large, real-world patient population, a randomized design, and near-complete participant primary and secondary outcome data derived directly from the EMR. Also, in this trial we show evidence that change in EMR-derived pharmacy dispensing is associated with change in CVD risk factors, supporting the validity of this approach.

Limitations should also be noted: a substantial number of participants were never reached by phone, thus diluting delivery and potentially the effectiveness of the IVR intervention. Indeed, the IVR+ intervention was designed largely in recognition of this limitation, although the incremental effect of the added IVR+ components was also small. Post hoc analyses suggested much more substantial effects for those participants who actually received 2 or more calls (Tables A5, A7, A8 in eAppendix); however, the PATIENT intervention model was by design relatively passive and "light-touch." More actively engaging patients in their own self-care and adherence might have increased the impact of the reminder intervention. Finally, constraints imposed by the funding agency precluded a longer follow-up.

Barriers to adherence can include cost, low health literacy, depression, patient-provider communication, and health beliefs.[29] The PATIENT intervention was not designed to address these complex barriers, but to overcome simpler barriers. Our results support the benefit of such programs in improving adherence and provide preliminary evidence for clinical impact. Future interventions that combine HIT-based systems, perhaps with strategies customized to patient preference and more tailored clinical support, offer a promising next step.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Take-Away Points

PATIENT (Promoting Adherence to Improve Effectiveness of Cardiovasular Disease Therapies) was a pragmatic clinical trial designed to improve adherence to cardiovascular disease medications using a low-cost, electronic medical record linked telephone reminder intervention. Using broad eligibility criteria, we enrolled 21,752 adult members of a health maintenance organization in a randomized trial to evaluate whether 2 phone reminder interventions, compared with usual care, could improve adherence to statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers.

- We saw small but statistically significant improvements in adherence.
- Among statin users, intervention participants had significantly reduced follow-up lipid levels and improved lipid control compared with usual care.
- The public health impact of these changes, applied across large populations, is uncertain.

Table 1

Characteristics[a] of the PATIENT Study Participants

	Usual Care	IVR	IVR+	Total
Randomized, N	7255	7247	7250	21,752
Male	52.7%	53.5%	52.9%	53.0%
Age (years); mean (SD)	63.6 (12.2)	63.6 (12.1)	63.5 (12.2)	63.6 (12.2)
Race				
White	46.9%	46.9%	47.0%	46.9%
African American	16.1%	15.1%	15.3%	15.5%
Asian	17.5%	17.8%	17.3%	17.5%
Native Hawaiian/Pacific Islander	11.0%	11.3%	10.8%	11.0%
American Indian/Alaskan Native	0.7%	0.6%	0.6%	0.6%
Unknown	7.8%	8.3%	9.0%	8.4%
Ever a smoker?	48.0%	48.8%	49.1%	48.6%
Comorbid diabetes mellitus (DM)[b]	78.1%	78.7%	77.6%	78.1%
Comorbid cardiovascular disease (CVD)[c]	36.2%	36.1%	36.7%	36.3%
ED visit or hospitalization for comorbid CVD or DM[d]	16.5%	18.0%	17.5%	17.3%
LDL cholesterol among statin users (mg/dL); mean (SD)	94.0 (35.3)	92.4 (34.0)	93.8 (34.8)	93.4 (34.7)
Systolic blood pressure among ACEI/ARB users (mm Hg); mean (SD)	129.4 (13.1)	129.2 (13.3)	129.0 (13.1)	129.2 (13.2)
Target medication use				
Statin only	40.3%	39.6%	40.3%	40.1%
ACEI/ARB only	24.4%	24.7%	25.1%	24.7%
Statin and ACEI/ARB	35.3%	35.7%	34.7%	35.2%
No. different medications dispensed,[e] **median (25th-75th percentile)**	8 (3-15)	8 (3-15)	9 (3-16)	8 (3-15)
0-5	47.3%	47.3%	46.9%	47.2%
6-10	26.0%	25.1%	25.2%	25.4%
11-15	15.5%	16.5%	16.2%	16.1%
16+	11.3%	11.1%	11.6%	11.3%
Statin adherence among users[f]**; mean (SD)**	0.51 (0.24)	0.51 (0.24)	0.51 (0.24)	0.51 (0.24)
0-20%	11.6%	10.7%	12.3%	11.5%
>20-40%	22.7%	22.8%	21.7%	22.4%
>40-60%	22.7%	23.7%	22.7%	23.1%
>60-80%	35.1%	34.0%	34.8%	34.6%
>80-90%	7.9%	8.8%	8.6%	8.4%
ACEI/ARB adherence among users[f]**; mean (SD)**	0.53 (0.23)	0.53 (0.24)	0.53 (0.23)	0.53 (0.23)
0-20%	7.7%	7.7%	7.0%	7.5%
>20-40%	23.8%	23.4%	23.2%	23.5%
>40-60%	22.2%	21.8%	23.0%	22.5%

	Usual Care	IVR	IVR+	Total
>60-80%	37.5%	37.8%	38.1%	37.8%
>80-90%	8.2%	9.3%	8.6%	8.7%
Months since last dispense				
Statin users, median (25th-75th percentile)	3 (2-4)	3 (2-5)	3 (2-4)	3 (2-4)
ACEI/ARB users, median (25th-75th percentile)	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)

[a]Based on chart information for the 12 months prior to randomization.

[b]Presence in site-specific diabetes disease registry.

[c]Presence in site-specific cardiovascular disease registry.

[d]Primary inpatient or emergency visit diagnosis of diabetes (*International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]* 250.x) or CVD (*ICD-9-CM* 390.x-459.x).

[e]Number of unique generic medication names dispensed during the 12 months prior to baseline.

[f]Medication possession ratio for 12 months prior to baseline (see Methods in eAppendix A).

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ED, emergency department; IVR, interactive voice recognition; LDL, low-density lipoprotein; PATIENT, Promoting Adherence to Improve Effectiveness of Cardiovascular Disease Therapies.

Table 2

Analysis of Follow-up Adherence

				IVR+ vs UC		IVR vs UC		IVR+ vs IVR	
	IVR+	IVR	UC	Δ[a]	Sig[b]	Δ[a]	Sig[b]	Δ[a]	Sig[b]
Statin users: Follow-up adherence overall and by initial level of statin adherence									
Overall	0.58 ± 0.34[c] (n = 5429)	0.57 ± 0.34 (n = 5453)	0.55 ± 0.35 (n = 5484)	0.030 (0.019-0.042)	0.000	0.022 (0.011-0.034)	0.000	0.008 (−0.004 to 0.020)	0.183
≤0.40	0.41 ± 0.36 (n = 1842)	0.41 ± 0.36 (n = 1827)	0.38 ± 0.37 (n = 1880)	0.031 (0.011-0.051)	0.002	0.027 (0.007-0.047)	0.009	0.004 (−0.016 to 0.024)	0.683
0.40-0.75	0.65 ± 0.30 (n = 3122)	0.63 ± 0.31 (n = 3141)	0.61 ± 0.31 (n = 3165)	0.034 (0.019-0.050)	0.000	0.020 (0.004-0.035)	0.013	0.015 (−0.001 to 0.030)	0.063
>0.75-0.90	0.75 ± 0.29 (n = 465)	0.77 ± 0.27 (n = 485)	0.75 ± 0.27 (n = 439)	0.000 (−0.041 to 0.041)	0.991	0.022 (−0.018 to 0.062)	0.287	−0.022 (−0.061 to 0.018)	0.285
Statin users: Percentage with good (>80%) adherence at follow-up									
Overall	35.8%[d]	35.9%	32.9%	1.16 (1.06-1.26)	0.000	1.14 (1.05-1.24)	0.002	1.01 (0.93-1.10)	0.793
≤0.40	21.8%	22.6%	21.5%	1.05 (0.89-1.23)	0.594	1.06 (0.91-1.25)	0.449	0.98 (0.85-1.15)	0.824
0.40-0.75	40.1%	39.4%	36.2%	1.19 (1.07-1.32)	0.001	1.16 (1.04-1.29)	0.007	1.03 (0.93-1.14)	0.611
>0.75-0.90	62.6%	63.5%	58.1%	1.27 (0.96-1.67)	0.091	1.28 (0.98-1.69)	0.074	0.99 (0.75-1.30)	0.937
ACEI/ARB users: Follow-up adherence overall and by initial level of ACEI/ARB adherence									
Overall	0.61 ± 0.34[c] (n = 4323)	0.59 ± 0.35 (n = 4370)	0.57 ± 0.36 (n = 4330)	0.037 (0.023-0.050)	0.000	0.016 (0.002-0.029)	0.022	0.021 (0.008-0.035)	0.002
≤0.50	0.50 ± 0.36 (n = 2127)	0.47 ± 0.37 (n = 2133)	0.45 ± 0.37 (n = 2164)	0.050 (0.030-0.069)	0.000	0.019 (−0.001 to 0.038)	0.057	0.031 (0.012-0.050)	0.002
0.50-0.75	0.71 ± 0.29 (n = 1817)	0.70 ± .029 (n = 1816)	0.69 ± 0.30 (n = 1806)	0.028 (0.007-0.049)	0.009	0.016 (−0.005 to 0.037)	0.128	0.012 (−0.009 to 0.033)	0.270
>0.75-0.90	0.77 ± 0.29 (n = 379)	0.76 ± 0.28 (n = 421)	0.76 ± 0.26 (n = 360)	0.007 (−0.039 to 0.054)	0.752	−0.003 (−0.048 to 0.042)	0.893	0.011 (−0.034 to 0.055)	0.642
ACEI/ARB users: Percentage with good (>80%) adherence at follow-up									
Overall	41.6%[d]	40.3%	37.4%	1.21 (1.10-1.32)	0.000	1.12 (1.02-1.23)	0.014	1.08 (0.98-1.18)	0.119
≤0.50	28.2%	27.0%	24.5%	1.21 (1.05-1.39)	0.008	1.13 (0.99-1.30)	0.081	1.07 (0.93-1.23)	0.352

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				IVR+ vs UC		IVR vs UC		IVR+ vs IVR	
	IVR+	IVR	UC	Δ[a]	Sig[b]	Δ[a]	Sig[b]	Δ[a]	Sig[b]
0.50-0.75	52.0%	51.1%	48.4%	1.18 (1.03-1.35)	0.015	1.12 (0.98-1.28)	0.104	1.06 (0.92-1.21)	0.420
>0.75-0.90	66.8%	62.0%	59.7%	1.34 (0.99-1.83)	0.061	1.11 (0.82-1.49)	0.510	1.22 (0.90-1.64)	0.199

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ED, emergency department; IVR, interactive voice recognition; LDL, low-density lipoprotein; PATIENT, Promoting Adherence to Improve Effectiveness of Cardiovascular Disease Therapies; Sig, significance; UC, usual care.

[a] Intervention effect (either absolute difference or, for proportions, odds ratios) expressed as mean and 95% CI.

[b] 2-tailed significance level based on linear (mean adherence) or logistic (proportion good adherence) regression analysis adjusting for site, gender, age, total number of prescription medications dispensed at baseline, comorbid diabetes/CVD, and baseline adherence as fixed main effects. Subgroup analyses also include the corresponding treatment by subgroup interaction.

[c] Raw, unadjusted adherence (mean ± SD).

[d] Raw, unadjusted proportions.

Table 3

Analysis of Follow-up Blood Pressure and Lipid Levels From the EMR

				IVR+ vs UC		IVR vs UC		IVR+ vs IVR	
	IVR+	IVR	UC	Δ[a]	Sig[b]	Δ[a]	Sig[b]	Δ[a]	Sig[b]
Follow-up SBP by initial SBP level (ACEI/ARB users only)									
Overall	129.0 ± 13.2[c] (n = 3971)	128.6 ± 13.2 (n = 3980)	129.2 ± 13.1 (n = 3980)	0.0 (−0.5 to 0.5)	0.931	−0.5 (−1.0 to −0.0)	0.041	0.5 (0.0-1.0)	0.033
≤130 mm Hg	123.4 ± 11.1 (n = 2155)	122.8 ± 11.1 (n = 2123)	123.5 ± 10.7 (n = 2111)	−0.1 (−0.8 to 0.6)	0.776	−0.6 (−1.3 to 0.1)	0.069	0.5 (−0.1 to 1.2)	0.122
130-140 mm Hg	132.7 ± 10.1 (n = 1058)	132.2 ± 10.1 (n = 1059)	132.8 ± 10.7 (n = 1049)	0.0 (−1.0 to 1.0)	0.988	−0.6 (−1.5 to 0.4)	0.239	0.6 (−0.4 to 1.6)	0.232
>140 mm Hg	140.9 ± 13.2 (n = 657)	140.4 ± 13.2 (n = 680)	140.6 ± 13.3 (n = 723)	0.2 (−1.0 to 1.4)	0.709	−0.2 (−1.4 to 1.0)	0.717	0.4 (−0.8 to 1.7)	0.471
Follow-up BP control (<140/90) by initial SBP level (ACEI/ARB users only)									
Overall	81.3%[d]	82.1%	81.1%	0.96 (0.85-1.09)	0.535	1.05 (0.93-1.19)	0.404	0.91 (0.81-1.03)	0.148
≤130 mm Hg	92.9%	94.0%	93.7%	0.87 (0.68-1.10)	0.247	1.04 (0.81-1.34)	0.739	0.83 (0.65-1.06)	0.136
130-140 mm Hg	78.3%	78.4%	78.4%	1.04 (0.85-1.30)	0.673	1.13 (0.92-1.40)	0.257	0.93 (0.75-1.15)	0.489
>140 mm Hg	50.2%	52.4%	49.2%	0.98 (0.80-1.21)	0.877	1.00 (0.81-1.24)	0.979	0.98 (0.80-1.21)	0.855
Follow-up LDL by initial LDL level (statin users only)									
Overall	91.3 ± 33.3[c] (n = 4545)	91.8 ± 34.0 (n = 4610)	92.4 ± 35.3 (n = 4621)	−1.5 (−2.7 to −0.2)	0.019	−0.6 (−1.8 to 0.7)	0.379	−0.9 (−2.2 to 0.3)	0.142
≤80 mg/dL	75.6 ± 26.1 (n = 1734)	75.5 ± 25.7 (n = 1769)	75.5 ± 26.1 (n = 1815)	−0.0 (−2.0 to 2.0)	0.975	0.1 (−1.9 to 2.0)	0.945	−0.1 (−2.1 to 1.9)	0.921
80-100 mg/dL	90.7 ± 24.9 (n = 1193)	91.5 ± 25.9 (n = 1224)	92.0 ± 27.8 (n = 1155)	−1.3 (−3.7 to −1.1)	0.298	−0.6 (−3.1 to 1.8)	0.609	−0.7 (−3.1 to 1.7)	0.589
>100 mg/dL	111.4 ± 36.6 (n = 1346)	113.0 ± 37.9 (n = 1329)	114.9 ± 37.9 (n = 1352)	−3.6 (−5.9 to −1.3)	0.002	−1.7 (−3.9 to 0.6)	0.116	−1.9 (−4.2 to 0.4)	0.097
Follow-up LDL control (<100 mg/dL) by initial LDL level (statin users only)									
Overall	70.4%[d]	69.8%	69.1%	1.10 (1.00-1.22)	0.058	1.03 (0.93-1.13)	0.594	1.07 (0.97-1.18)	0.173
≤80 mg/dL	88.1%	88.0%	88.4%	0.98 (0.80-1.21)	0.873	0.96 (0.78-1.18)	0.679	1.03 (0.84-1.26)	0.797

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				IVR+ vs UC		IVR vs UC		IVR+ vs IVR	
	IVR+	IVR	UC	Δ[a]	Sig[b]	Δ[a]	Sig[b]	Δ[a]	Sig[b]
80-100 mg/dL	74.9%	74.0%	73.7%	1.08 (0.89-1.30)	0.440	1.03 (0.85-1.24)	0.764	1.05 (0.87-1.26)	0.630
>100 mg/dL	44.1%	43.5%	39.9%	1.21 (1.04-1.42)	0.015	1.14 (0.97-1.33)	0.103	1.07 (0.91-1.24)	0.429

ACEI indicates angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CVD, cardiovascular disease; EMR, electronic medical record; IVR, interactive voice recognition; SBP, systolic blood pressure; Sig, significance; UC, usual care.

[a] Intervention effect (either absolute difference or, for proportions, odds ratios) expressed as mean and 95% CI.

[b] 2-tailed significance level based on linear (mean adherence) or logistic (proportion good adherence) regression analysis adjusting for site, gender, age, total number of prescription medications dispensed at baseline, comorbid diabetes/CVD, and baseline SBP or LDL subgroup, as appropriate, as fixed main effects. Subgroup analyses also include the corresponding treatment by subgroup interaction.

[c] Raw, unadjusted adherence (mean ± SD).

[d] Raw, unadjusted proportions.