

# Improving Adherence to Cardiovascular Disease Medications With Information Technology

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

The most effective adherence interventions include both educational and behavioral strategies<sup>6</sup>; 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.<sup>7,8</sup>

We recently reported on a trial to improve adherence to inhaled corticosteroids in 8517 adult health plan members with asthma.<sup>9</sup> 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<sup>10</sup> 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<sup>11-14</sup> 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 Cardiovascular 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.

## 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 percentage 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 ( $\Delta = -1.5$ ; 95% CI,  $-2.7$  to  $-0.2$  mg/dL); this effect was seen mainly in those with baseline LDL levels  $>100$  mg/dL ( $\Delta = -3.6$ ; 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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## METHODS

Additional methods, details, and results are included in the [eAppendix](#), available at [www.ajmc.com](http://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<sup>15</sup> 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.

### Take-Away Points

PATIENT (Promoting Adherence to Improve Effectiveness of Cardiovascular 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.

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 re-

minder letter if they were 60 to 89 days overdue and a live outreach call if they were  $\geq 90$  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),<sup>16</sup> 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.<sup>17</sup> 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,<sup>18,19</sup> we defined BP control as systolic BP (SBP)/diastolic BP  $< 140/90$  mm Hg and lipid control as a 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  $\alpha$ -level of 0.025. We then compared the IVR and IVR+ interventions against each other at an  $\alpha$ -level of 0.05 only if either of these initial contrasts was statistically significant, thus assuring a trialwide  $\alpha$ -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 partici-

pants 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 ( $\leq .4$ ,  $.4$ -.75,  $> .75$  for statins;  $\leq .5$ ,  $.5$ -.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<sup>20</sup> or Stata version 11.2.<sup>21</sup>

## 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.

■ **Table 1.** Characteristics<sup>a</sup> of the PATIENT Study Participants

	Usual Care	IVR	IVR+	Total
<b>Randomized, N</b>	7255	7247	7250	21,752
<b>Male</b>	52.7%	53.5%	52.9%	53.0%
<b>Age (years); mean (SD)</b>	63.6 (12.2)	63.6 (12.1)	63.5 (12.2)	63.6 (12.2)
<b>Race</b>				
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%
<b>Ever a smoker?</b>	48.0%	48.8%	49.1%	48.6%
<b>Comorbid diabetes mellitus (DM)<sup>b</sup></b>	78.1%	78.7%	77.6%	78.1%
<b>Comorbid cardiovascular disease (CVD)<sup>c</sup></b>	36.2%	36.1%	36.7%	36.3%
<b>ED visit or hospitalization for comorbid CVD or DM<sup>d</sup></b>	16.5%	18.0%	17.5%	17.3%
<b>LDL cholesterol among statin users (mg/dL); mean (SD)</b>	94.0 (35.3)	92.4 (34.0)	93.8 (34.8)	93.4 (34.7)
<b>Systolic blood pressure among ACEI/ARB users (mm Hg); mean (SD)</b>	129.4 (13.1)	129.2 (13.3)	129.0 (13.1)	129.2 (13.2)
<b>Target medication use</b>				
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%
<b>No. different medications dispensed,<sup>e</sup> median (25th-75th percentile)</b>				
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%
<b>Statin adherence among users<sup>f</sup>; mean (SD)</b>				
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%
<b>ACEI/ARB adherence among users<sup>f</sup>; mean (SD)</b>				
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%
>60-80%	37.5%	37.8%	38.1%	37.8%
>80-90%	8.2%	9.3%	8.6%	8.7%
<b>Months since last dispense</b>				
<b>Statin users, median (25th-75th percentile)</b>	3 (2-4)	3 (2-5)	3 (2-4)	3 (2-4)
<b>ACEI/ARB users, median (25th-75th percentile)</b>	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)

<sup>a</sup>Based on chart information for the 12 months prior to randomization.

<sup>b</sup>Presence in site-specific diabetes disease registry.

<sup>c</sup>Presence in site-specific cardiovascular disease registry.

<sup>d</sup>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*).

<sup>e</sup>Number of unique generic medication names dispensed during the 12 months prior to baseline.

<sup>f</sup>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.

### 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 ( $\geq 0.80$ ), 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 ( $\geq 0.80$ ) 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 ap-

peared 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.<sup>9</sup>

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.<sup>22</sup> 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.<sup>23</sup> Assum-

■ **Table 2.** Analysis of Follow-up Adherence

	IVR+	IVR	UC	IVR+ vs UC		IVR vs UC		IVR+ vs IVR	
				$\Delta^a$	Sig <sup>b</sup>	$\Delta^a$	Sig <sup>b</sup>	$\Delta^a$	Sig <sup>b</sup>
<b>Statin users: Follow-up adherence overall and by initial level of statin adherence</b>									
Overall	0.58 ± 0.34 <sup>c</sup> (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
<b>Statin users: Percentage with good (&gt;80%) adherence at follow-up</b>									
Overall	35.8% <sup>d</sup>	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
<b>ACEI/ARB users: Follow-up adherence overall and by initial level of ACEI/ARB adherence</b>									
Overall	0.61 ± 0.34 <sup>c</sup> (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
<b>ACEI/ARB users: Percentage with good (&gt;80%) adherence at follow-up</b>									
Overall	41.6% <sup>d</sup>	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
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.

<sup>a</sup>Intervention effect (either absolute difference or, for proportions, odds ratios) expressed as mean and 95% CI.

<sup>b</sup>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.

<sup>c</sup>Raw, unadjusted adherence (mean ± SD).

<sup>d</sup>Raw, unadjusted proportions.

ing 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.<sup>24</sup>

Reminder interventions show promise for improving adherence with CVD medications.<sup>10,25-28</sup> The PATIENT intervention also showed an impact on lipid levels. Together these studies reinforce the value of IVR/EMR

**Table 3.** Analysis of Follow-up Blood Pressure and Lipid Levels From the EMR

	IVR+	IVR	UC	IVR+ vs UC		IVR vs UC		IVR+ vs IVR	
				Δ <sup>a</sup>	Sig <sup>b</sup>	Δ <sup>a</sup>	Sig <sup>b</sup>	Δ <sup>a</sup>	Sig <sup>b</sup>
<b>Follow-up SBP by initial SBP level (ACEI/ARB users only)</b>									
Overall	129.0 ± 13.2 <sup>c</sup> (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
<b>Follow-up BP control (&lt;140/90) by initial SBP level (ACEI/ARB users only)</b>									
Overall	81.3% <sup>d</sup>	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
<b>Follow-up LDL by initial LDL level (statin users only)</b>									
Overall	91.3 ± 33.3 <sup>c</sup> (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
<b>Follow-up LDL control (&lt;100 mg/dL) by initial LDL level (statin users only)</b>									
Overall	70.4% <sup>d</sup>	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
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.

<sup>a</sup>Intervention effect (either absolute difference or, for proportions, odds ratios) expressed as mean and 95% CI.

<sup>b</sup>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.

<sup>c</sup>Raw, unadjusted adherence (mean ± SD).

<sup>d</sup>Raw, unadjusted proportions.

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 entirety, 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 medi-

cation 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.<sup>29</sup> 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.

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## REFERENCES

- Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. *Am J Med.* 2012;125(9):882-887.
- Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation.* 2009;119(23):3028-3035.
- The Network for Excellence in Health Innovation. Thinking outside the pillbox: a system-wide approach to improving patient medication

adherence for chronic disease. [http://www.nehi.net/writable/publication\\_files/file/pa\\_issue\\_brief\\_final.pdf](http://www.nehi.net/writable/publication_files/file/pa_issue_brief_final.pdf). Published August 12, 2009. Accessed November 4, 2010.

4. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Med Care*. 2005;43(6):521-530.
5. Steiner JF. Rethinking adherence. *Ann Intern Med*. 2012;157(8):580-585.
6. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev*. 2008;2:CD000011.
7. Misono AS, Cutrona SL, Choudhry NK, et al. Healthcare information technology interventions to improve cardiovascular and diabetes medication adherence. *Am J Manag Care*. 2010;16(12 suppl HIT):SP82-SP92.
8. Howren MB, Van Liew JR, Christensen AJ. Advances in patient adherence to medical treatment regimens: the emerging role of technology in adherence monitoring and management. *Social and Personality Psychology Compass*. 2013;7(7):427-443.
9. Vollmer WM, Feldstein A, Smith DH, et al. Use of health information technology to improve medication adherence. *Am J Manag Care*. 2011;17(12 Spec No.):SP79-SP87.
10. Derose SF, Green K, Marrett E, et al. Automated outreach to increase primary adherence to cholesterol-lowering medications. *JAMA Intern Med*. 2013;173(1):38-43.
11. Piette JD, Weinberger M, Kraemer FB, McPhee SJ. Impact of automated calls with nurse follow-up on diabetes treatment outcomes in a Department of Veterans Affairs Health Care System: a randomized controlled trial. *Diabetes Care*. 2001;24(2):202-208.
12. Vervloet M, Linn AJ, van Weert JC, de Bakker DH, Bouvy ML, van Dijk L. The effectiveness of interventions using electronic reminders to improve adherence to chronic medication: a systematic review of the literature. *J Am Med Inform Assoc*. 2012;19(5):696-704.
13. Christakis DA, Garrison MM, Lozano P, Meischke H, Zhou C, Zimmerman FJ. Improving parental adherence with asthma treatment guidelines: a randomized controlled trial of an interactive website. *Acad Pediatr*. 2012;12(4):302-311.
14. McMahon GT, Fonda SJ, Gomes HE, Alexis G, Conlin PR. A randomized comparison of online- and telephone-based care management with internet training alone in adult patients with poorly controlled type 2 diabetes. *Diabetes Technol Ther*. 2012;14(11):1060-1067.
15. Friedly J, Bauer Z, Comstock BA, et al. Challenges conducting comparative effectiveness research: Clinical and Health Outcomes Initiative in Comparative Effectiveness (CHOICE) experience. *Comparative Effectiveness Research*. 2014;4:1-12.
16. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf*. 2006;15(8):565-574.
17. Vollmer WM, Xu M, Feldstein A, Smith D, Waterbury A, Rand C. Comparison of pharmacy-based measures of medication adherence. *BMC Health Serv Res*. 2012;12:155.
18. National Committee for Quality Assurance (NCQA). HEDIS 2014, Healthcare Effectiveness Data and Information Set. Vol. 1, narrative. Washington, DC: National Committee for Quality Assurance; 2013.
19. National Committee for Quality Assurance (NCQA). HEDIS 2014: Healthcare Effectiveness Data and Information Set. Vol. 2, technical specifications for health plans. Washington, DC, National Committee for Quality Assurance; 2013.
20. SAS *Enhanced Logging Facilities* [computer program]. Version 9.2. Cary, NC: SAS Institute Inc; 2008.
21. *STATA Data Analysis and Statistical Software*. Version 11.2. College Station, TX: StataCorp; 2011.
22. Stamler J, Rose G, Stamler R, Elliott P, Dyer A, Marmot M. INTER-SALT study findings. public health and medical care implications. *Hypertension*. 1989;14(5):570-577.
23. Cholesterol Treatment Trialists' (CTT) Collaboration; Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376(9753):1670-1681.
24. Daugherty SL, Powers JD, Magid DJ, et al. The association between medication adherence and treatment intensification with blood pressure control in resistant hypertension. *Hypertension* 2012;60(2):303-309.
25. Schedlbauer A, Davies P, Fahey T. Interventions to improve adherence to lipid lowering medication. *Cochrane Database Syst Rev*. 2010;3:CD004371.
26. Lieu TA, Capra AM, Makol J, Black SB, Shinefield HR. Effectiveness and cost-effectiveness of letters, automated telephone messages, or both for underimmunized children in a health maintenance organization. *Pediatrics*. 1998;101(4):E3.
27. Mosen DM, Feldstein AC, Perrin N, et al. Automated telephone calls improved completion of fecal occult blood testing. *Med Care*. 2010;48(7):604-610.
28. Ho PM, Lambert-Kerzner A, Carey EP, et al. Multifaceted intervention to improve medication adherence and secondary prevention measures after acute coronary syndrome hospital discharge: a randomized clinical trial. *JAMA Intern Med*.
29. Gellad WF, Grenard J, McGlynn EA. *A Review of Barriers to Medication Adherence: A Framework for Driving Policy Options*. Santa Monica, CA; RAND Corporation, 2009. ■

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## **APPENDIX A: Online Supplement for “Improving Adherence to Cardiovascular Disease Medications with Information Technology”**

This document contains more detailed information regarding study methods and results, including cost and qualitative analyses not included in the main text.

### Online Supplement Elements:

Methods

Study Measurements

Economic Analysis

Qualitative Analyses

References (6)

Table A1. PATIENT eligibility criteria

Table A2. Summary of bimonthly participant mailings for IVR+ arm

Table A3. Participant follow-up and intervention process data

Table A4. Subgroup Analysis of follow-up statin adherence– statin users

Table A5. Analysis of follow-up statin adherence– statin users with 2 or more detailed messages or, for UC, would have been triggered for 2 or more calls

Table A6. Subgroup analysis of follow-up ACEI/ARB adherence– ACEI/ARB users

Table A7. Analysis of follow-up ACEI/ARB adherence– ACEI/ARB users with 2 or more detailed messages or, for UC, would have been triggered for 2 or more calls

Table A8. Analysis of follow-up lipid levels for statin users with 2+ detailed msgs or contacts or, for UC, who would have been triggered for 2 or more calls

Table A9. Safety data

Figure A1. Participant flow diagram

Figure A2. Flowchart for suspension or termination of intervention activity due to safety concerns

## **METHODS**

### ***Power for Subgroup Analyses***

The study had roughly 90% power to detect effects of 0.032 (3.2 percentage points) in adherence for statins and 0.045 (4.5 percentage points) for ACEI/ARBs in gender-specific subgroup analyses, and effects of 0.039 (statins) and 0.045 (ACEI/ARBs) in subgroups defined by tertiles of some baseline factor.

### ***Study Interventions***

#### **Interactive Voice Recognition Calls (IVR)**

Call lists were generated monthly. If a participant received tardy calls for three consecutive months and still had not refilled, no further reminders were given for that medication class until a new dispensing was observed, at which time normal call rules applied. Call activity ceased at the request of any provider or participant, or if a participant discontinued membership or died. In addition, calling could be stopped, temporarily or permanently, due to evidence of stop orders, allergy or intolerance, or other medical contraindications (Figure A2).

In instances when a participant indicated they wished to speak with a live pharmacist and it was after hours, the transfer was only made in regions where a voicemail was available (KPNW and KPH). In regions where a voicemail was not available (KPG), members were not transferred but were instead provided the phone number and hours of operation for the pharmacy department.

When possible, the calling program left messages on answering machines or with another household member if the target participant was not at home. As part of the first direct contact with each participant, the scripted IVR call asked for permission to leave detailed messages that included the name of the target medication. Lacking this authorization, the phone messages simply noted it was the Kaiser Permanente “Prompt Program” (our branding of the intervention within the health plan) calling with an important medication reminder and asked the participant to call back on a toll-free number.

The call-eligibility algorithms used in each region were designed to reflect that region's rules for when prescriptions can be refilled. For instance, KPNW requires that participants have used up at least 75% of their previous supply. Participants were only flagged for a refill reminder for a medication if this criterion was met.

### **Enhanced IVR (IVR+)**

In addition to the IVR calls, the IVR+ arm included mailed educational materials; personalized, mailed "reminder letters" and live outreach calls to patients who failed to fill prescriptions following the IVR calls; and EMR-based feedback to primary care providers, as described in greater detail below.

**Educational mailings.** Beginning at the time of randomization, all participants in the IVR+ arm received a series of bimonthly informational/educational mailings for up to ten months (see Table A2). These mailings included both "static" informational brochures (e.g., FAQ booklet about heart conditions and medications, a pamphlet on barriers to adherence and solutions, and a step-by-step guide to refilling medications online) as well as a periodic "Personal Health Report" that contained personalized health information including recent dispensings, refill information, and clinical measurements of blood pressure, lipid levels, and hemoglobin A1c (HbA1c) levels. Along with the educational materials, the initial mailing included a plastic pill organizer, a Prompt Program magnet with regional automated refill line phone number, and a brief overview of the IVR+ program, including contact information should the participant have any questions or concerns about the program.

**Reminder letter.** If, after receiving an IVR tardy reminder call for a given medication class, a participant qualified for another tardy reminder for the same medication class the following month (i.e., had not filled the medication and there was no indication of allergy/intolerance or of the medication having been formally discontinued), that person also received a reminder letter via US Postal Service. Consistent with local practice, KPNW pharmacy staff conducted chart reviews before sending the letters to assure their appropriateness.

**Live outreach calls.** Participants who failed to fill their medication in response to the reminder letter next received a call from a KP pharmacist or pharmacy technician the following month. The purpose of the call was to encourage use of the medication, facilitate a refill, and to answer any questions about the medication. As with the reminder letters, KPNW staff first reviewed the chart to assure the appropriateness of the outreach. Similar to the protocol for the IVR arm, no further reminders were made for that medication class until a new dispensing occurred for it. The participant could still continue to receive calls for the other medication class, however.

**EMR-based feedback to primary care providers.** Participants randomized to receive IVR calls (as part of either the IVR or IVR+ arms) were flagged as such in the EMR. In addition, for IVR+ participants a copy of the reminder letter was placed into the EMR. For both KPH and KPNW, this was a passive documentation only, whereas in KPG it included active notification of the primary care physician to draw their attention to this letter and their patient's noncompliance. In addition, "live" calls were documented in the EMR consistent with standard protocol for telephone encounters and staff communicated with the individual providers as-needed to determine, for example, if a discontinuation order needed to be entered into the EMR or if a medication adjustment was needed.

### **Ancillary Arms**

The study also incorporated two ancillary arms. In KPG, we randomized an additional 1122 participants to receive an **IVR\_lite** intervention that used KP's own automated messaging service, which did not incorporate speech recognition technology. In KPNW, we randomized an additional 2449 participants to a scaled back version of the **IVR+** intervention (**IVR+\_lite**) that did not include the live pharmacist calls or educational mailings, although it did use the same IVR call technology used in the **IVR** and **IVR+** study arms and included the personalized reminder letter to refill overdue medications. Inclusion of these two ancillary arms, which were added at the outset of the study, helped secure organizational buy-in for the study and allowed us to test whether scaled back versions of the primary interventions would work as well as the primary interventions.

## **STUDY MEASUREMENTS**

### ***Medication Adherence***

We used dispensing information from the EMR to construct our primary measures of medication adherence. The vast majority of prescriptions filled by KP members in these three regions are filled at KP pharmacies. While the use

of non-KP pharmacies may have biased our overall estimates of adherence, this bias should have been distributed evenly across the three treatment arms. We believe that our eligibility requirement that participants have at least one dispensing of a target medication from a KP outpatient pharmacy in the baseline year helped to minimize this problem.

The Proportion of Days Covered (PDC)<sup>1</sup> is nominally a measure of the proportion of time in some well-defined interval that an individual used a specific medication as prescribed. It is a refinement over the cruder medication possession ratio (MPR), which is calculated merely as total days' supply dispensed divided by elapsed time from first to last dispensing. By contrast, the PDC accounts for the timing of the dispensings. Assuming that medications are used as prescribed, one can theoretically calculate for a given interval of time those days on which a participant is adherent or nonadherent, and this information is used to calculate the PDC.

Since we know that all of our participants should be taking these medications on an ongoing basis and, at the time of randomization, had a dispensing from at least one of our two target classes in the preceding 12 months, we used a modified PDC (mPDC) that included the whole follow-up period as the denominator timeframe. This has the dual advantage of (1) avoiding the upward bias inherent in requiring an initial (and potentially two) dispensing and (2) not having to exclude totally nonadherent individuals who don't have any dispensings during the follow-up year.<sup>2</sup> As a further refinement, we accounted for medication still on hand at the time of randomization and excluded any dispensed medication that would theoretically be remaining at the end of follow-up. We computed these mPDCs separately for statin use and for ACEI/ARB use, treating all statin (ACEI/ARB) products interchangeably. While we recognize that some individuals will be taking both an ACE inhibitor and an ARB, we believe that this is the exception and that those with both types of dispensing will more typically have shifted off of one product and on to the other.

Because we only looked back 12 months prior to randomization to determine eligibility, we were not able to distinguish new from ongoing users and as an operational rule defined baseline adherence as the total days supply dispensed in this timeframe divided by 365 and capped at a value of 1, which we refer to as the MPR. We realize this may underestimate true baseline adherence.

### ***Blood Pressure***

We defined baseline systolic (SBP) and diastolic (DBP) blood pressure levels as the mean of the six most recent measurements taken during the 12 months before randomization, and follow-up BP as the mean of the six most recent measurements taken during follow-up. We defined baseline (follow-up) LDL-cholesterol as the last available LDL measurement (fasting or nonfasting) during the 12 months before (after) randomization.

## **RESULTS: ANCILLARY STUDY ARMS AND POST-HOC ANALYSES**

### ***Participant Follow-Up and Intervention Process Data***

A total of 51,013 IVR calls were triggered (Table A3). We connected with participants on 56% of IVR call attempts. We left a detailed voice message on another 10% of calls. This translated, on average, to 2.3 direct connects or detailed messages per person delivered.

### ***Ancillary Study Findings***

We found no evidence that the IVR calls were more effective than those made using KPG's in-house calling technology. For KPNW, the **IVR+<sub>lite</sub>** intervention resulted in effect size estimates intermediate to those of the full **IVR** and **IVR+** interventions, although it did not differ significantly from either.

### ***Post-Hoc Analyses***

The intervention effects on adherence were 2-3 times greater in *post hoc* analyses restricted to participants whom we were able to reach directly or leave detailed phone messages for at least twice (Tables A5, A7). Due to the potential for selection bias in such analyses, caution should be used in interpreting these findings. Nonetheless it is understandable that IVR calls would have little to no impact for those patients whom we did not reach, and that the most pronounced impact would be amongst those we successfully contacted.

The LDL effects also were more pronounced in these *post hoc* analyses (Table A8). LDL levels in both the **IVR+** and **IVR** groups declined significantly compared to **UC** overall (-2.8 and -1.9 mg/dl, respectively). Corresponding odds ratios for LDL control were 1.26 and 1.14 (both p-values  $\leq 0.028$ ).

## **ECONOMIC ANALYSIS**

### ***Intervention Delivery Costs: Methods***

Intervention delivery costs are the costs of identifying patients, introductory mailings, intervention phone contacts, staff training, and (for IVR+) the bimonthly mailings. Other intervention delivery costs include the costs of incremental primary care visits, prescriptions, and laboratory testing induced by the program. We estimated the costs of delivering the interventions in two ways. Our contract with Eliza, the provider of the automated phone calls, provided the cost of making calls for this study. Working with Eliza staff, we determined the cost of making calls at different calling volumes for use in sensitivity analysis and replication cost estimates. We conducted similar calculations for the mailing costs in the IVR+ arm. We used several systems to collect the costs associated with the development and delivery of the interventions. A patient enrollment and tracking system was developed to track intervention calls and follow-up mailings. Allocation of staff effort to development and implementation activities was estimated based on interviews with program staff. Staff unit costs came from research budgets, adjusted for appropriate staff level in the health care delivery setting if needed.

### ***Intervention Cost: Results***

Using data collected during the clinical trial (including staff time logs, IVR call costs and mailing and printing costs), we estimated the cost to deliver and maintain the research intervention over the trial time frame. Our cost estimates assume the entire trial population size for each arm. Because research intervention costs can overstate clinical replication costs, we simulated an implementation scenario to obtain replication costs.<sup>3</sup>

We estimated costs of \$9 to \$17 per participant per year for IVR (replication and research intervention costs, respectively) and \$36 to \$47 for IVR+.

A manuscript summarizing the results of a more comprehensive economic analysis is in preparation.

## **QUALITATIVE ANALYSES**

### ***Health Plan and Participant Feedback***

We conducted qualitative interviews across all three intervention sites with 45 health plan stakeholders (physicians, health plan leaders/managers, and pharmacy staff), and 49 participants to obtain their reactions to the intervention. Interviewees were recruited by email or letter, followed by a phone call, for open-ended, semi-structured interviews. Interviews were conducted either in person or by phone, using an interview guide.<sup>4</sup> Interviews were transcribed, and were content-analyzed by a trained qualitative research specialist (JS). All interviews were analyzed using standard qualitative analysis techniques,<sup>4,5</sup> and aided by the use of a qualitative research software package.<sup>6</sup> We also surveyed 498 participants at the end of the study regarding overall satisfaction with various elements of the program.

### ***Participant and Health Plan Stakeholder Reaction to the Intervention***

Among the 459 survey participants who reported receiving a call, 68% reported the calls as either useful or very useful; and 71% indicated they would like to receive similar calls in the future. Of the 379 IVR+ participants surveyed who received mailed materials, 78% found the mailed materials useful or very useful, with 77% indicating a desire to receive similar mailings in the future. Overall, 87% of survey respondents indicated they would like the program to continue as an ongoing service.

In-depth qualitative interviews with participants (n=49) revealed similar findings with 63% identifying the calls as a personally helpful service for staying on track with their medication refills, and 31% reporting the calls as a valuable service as one ages and becomes forgetful. Thirty of the 49 interviews were with participants in the IVR+ arm, and 57% of these respondents described the materials as personally helpful for increasing understanding and awareness of the importance of their medications. Of the 49 interviewed participants, 94% felt the calls should be sustained as an ongoing service, and 68% felt that it was worth continuing at least some of the more personalized mailings.

Among the 45 stakeholders (physicians, pharmacy, and other health plan staff) interviewed, 69% perceived the program as a useful and important tool for improving adherence that was appreciated by participants. Additionally, 47% thought the program was a good use of lower-cost technology, and 27% felt that it likely provided outreach to members who might otherwise slip through the cracks.

## REFERENCES

1. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf* 2006;15:565-574.
2. Vollmer WM, Xu M, Feldstein A, Smith D, Waterbury A, Rand C. Comparison of pharmacy-based measures of medication adherence. *BMC Health Serv Res* 2012;12:155.
3. Meenan R, Stevens V, Hornbrook M et al. Cost-effectiveness of a hospital-based smoking cessation intervention. *Med Care* 1998;36:670-678.
4. Erlandson D, Harris EL, Skipper B, Allen S. *Doing naturalistic inquiry: a guide to methods*. Thousand Oaks, CA: Sage Publications, 1993.
5. Patton M. *Qualitative research and evaluation methods*. 3rd ed. Thousand Oaks, CA: Sage publications, 2002.
6. *ATLAS.ti Visual Qualitative Data Analysis*. Version 5.9. Berlin: 1997.

## **Table A1. PATIENT eligibility criteria**

### **Inclusion criteria**

- Aged 40 years or older at time of randomization
- Documented diabetes or CVD (defined as Coronary Artery Disease (CAD), Peripheral Vascular Disease (PVD), or a history of atherosclerotic stroke) at the time of randomization
- At least one dispensing of an ACEI, ARB, or statin in the preceding 12 months
- Suboptimal adherence (MPR<0.9) to either statins or ACEI/ARBs in the preceding 12 months
- Continuous health plan membership for the 12 months prior to randomization
- Qualifies for an intervention call at the time of randomization

### **Exclusion criteria**

- Medical contraindications for statins: evidence of liver failure, cirrhosis, pregnancy or rhabdomyolysis at any time during the preceding 12 months, or evidence of allergy or intolerance to all statins (participant could still be randomized if taking ACEI/ARBs)
- Medical contraindications for ACEI/ARBs: evidence of end-stage renal disease, chronic kidney disease (stage 4 or above), pregnancy or acute renal failure at any time during the preceding 12 months, or evidence of allergy or intolerance to both of ACEIs and ARBs (participant could still be randomized if taking statins)
- Absence of either phone number or mailing address in the EHR
- For KPH, clinics whose patients fill prescriptions primarily at non-KP pharmacies
- On KP “do not contact” list or in other research studies that could add undue burden

**Table A2. Summary of bimonthly participant mailings for IVR+ arm**

Mailing Timing	Intervention Arm	Contents*
Introductory Mailing (sent as close to first IVR call as possible, prior to call is ideal)	IVR IVR+ Local (NW) IVR Local (GA)	IVR Brochure ( <i>region specific</i> )
Introductory Mailing (sent as close to first IVR call as possible, prior to call is ideal)	IVR+	Materials are generic but some are region specific <ul style="list-style-type: none"> <li>• Prompt Program Folder</li> <li>• Introduction Letter (<i>region specific</i>)</li> <li>• IVR Brochure (<i>region specific</i>)</li> <li>• My Medication List Wallet Card (<i>region specific</i>)</li> <li>• FAQ Booklet</li> <li>• Questions for your Doctor/Pharmacy (wallet card) (<i>region specific</i>)</li> <li>• Weekly pill organizing container (pill box)</li> <li>• Daily Medication Schedule</li> <li>• Prompt Magnet adhered to postcard</li> </ul>
2 weeks	IVR+	Personalized, includes health information merge <ul style="list-style-type: none"> <li>• My Heart Health Report (8 x 11)</li> <li>• Daily Medication Schedule (8 x 11)</li> </ul>
2 month mailing	IVR+	Materials are generic but some are region specific <ul style="list-style-type: none"> <li>• Follow up note (6 x 9) (<i>region specific</i>)</li> <li>• Getting my medications/Setting up my kp.org account insert (<i>region specific</i>)</li> <li>• Learning About KP.org brochure</li> </ul>
4 month mailing	IVR+	Materials are generic but some are region specific <ul style="list-style-type: none"> <li>• Follow up note (4 x 9) (<i>region specific</i>)</li> <li>• Medication reminders (4 x 9)</li> <li>• My medications: connecting me to health (4 x 9) (<i>region specific</i>)</li> <li>• Questions for your Doctor Pharmacy Wallet Card</li> <li>• My Medication List Wallet Card (<i>region specific</i>)</li> </ul>
6 month mailing	IVR+	Personalized, includes health information merge <ul style="list-style-type: none"> <li>• My Heart Health Report (8 x11)</li> <li>• Daily Medication Schedule (8x11)</li> </ul> Flat windowed envelope.
8 month mailing	IVR+	Materials are generic but some are region specific <ul style="list-style-type: none"> <li>• Follow up note (<i>region specific</i>)</li> <li>• Barriers and Solutions insert</li> </ul>
10 month mailing	IVR+	Materials are generic but some are region specific <ul style="list-style-type: none"> <li>• Follow up note (<i>region specific</i>)</li> <li>• Questions for your Doctor Pharmacy Wallet Card</li> <li>• My Medication List Wallet Card (<i>region specific</i>)</li> </ul>

**\*Material Descriptions**

Barriers and Solutions insert

Addresses and suggests solutions to common barriers to medication taking including trouble remembering, side effects, and cost.

Daily Medication Schedule (generic)

A blank form designed to help participants organize their medications, divided into sections for morning and evening medicines, with spaces for participants to write medication names, times taken, dosage, and other notes.

Follow-up note

Brief letter that accompanied later mailings and explained their contents.

FAQ Booklet

Provides information to address frequently asked questions about high blood pressure, cholesterol, diabetes, pre-diabetes, and benefits of aspirin.

Getting my medications/Setting up my kp.org account insert (region specific)

This mailed piece explains the different ways participants can get their medications – either by mail or pharmacy pickup. Explains how to log on to the kp.org website and register, so participants can order medications online.

Introduction Letter (region specific)

A letter welcoming participants to the program, signed by the region's director of pharmacy.

IVR Brochure (region specific)

A plain-language, color brochure that orients participants to the purpose of the Prompt program, why they are being enrolled, and what they can expect when the IVR program calls them.

Learning About KP.org brochure

This brochure explains how participants can use [www.kp.org](http://www.kp.org), the health plan's member website, to get general information on their condition (e.g., heart health or diabetes), email their doctor, look up medications in a drug encyclopedia, request refills, or request that reminder emails be sent to them.

Medication Reminders

A card with suggestions and resources to help participants remember to take medications.

My Heart Health Report (personalized) (8 x 11)

Offers information on high blood pressure, cholesterol, and diabetes. Personalized with each participants' recent test results for these conditions.

My Medications: Connecting me to health (region specific)

Explains the benefits of statins, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs).

My Medication List Wallet Card (region specific)

A card to carry in a purse or wallet with places to record medication name, prescription number, dose, and time of day taken. Includes pharmacy phone number and hours.

Questions for your Doctor/Pharmacy (wallet card) (region specific)

A card to carry in a wallet or purse that suggests questions participants might want to ask their doctor or pharmacist about their medications and provides a place to write down new questions.

**Additional Tools**

Prompt program folder to keep materials in

Weekly pill organizing container (pill box)

Prompt program magnet

**Table A3. Participant follow-up and intervention process data**

	Statin Users			ACEI/ARB Users			Overall		
	UC	IVR	IVR+	UC	IVR	IVR+	UC	IVR	IVR+
<b># Randomized</b>	5486	5460	5434	4331	4374	4331	7255	7247	7250
<b>Follow-up (mos)</b>	9.7 (2.3)	9.6 (2.4)	9.5 (2.5)	9.7 (2.4)	9.6 (2.4)	9.6 (2.5)	9.7 (2.3)	9.6 (2.4)	9.6 (2.5)
<b>Number and type of intervention contacts attempted per participant</b>									
IVR calls		3.8 (1.7)	3.4 (1.5)		3.8 (1.7)	3.4 (1.6)		3.7 (1.7)	3.3 (1.5)
Reminder letters		--	0.6 (0.7)		--	0.6 (0.7)		--	0.6 (0.7)
Live calls		--	0.3 (0.6)		--	0.4 (0.6)		--	0.3 (0.5)
Educ. mailings		--	5.9 (1.4)		--	5.9 (1.4)		--	5.9 (1.4)
Total contacts		3.8 (1.7)	10.2 (3.1)		3.8 (1.7)	10.3 (3.2)		3.7 (1.7)	10.1 (3.1)
<b># IVR calls attempted</b>		20613	18416		16513	14850		26734	24279
<b>Type of call</b>									
Simple refill		45.4%	51.0%		45.5%	51.5%		47.6%	53.6%
Tardy		54.6%	49.0%		54.5%	48.5%		52.4%	46.4%
<b>Medication classes discussed</b>									
One		77.6%	78.4%		74.5%	75.1%		79.7%	80.4%
Two		22.4%	21.6%		25.5%	24.9%		20.3%	19.6%
<b>Type of reminder (categories not mutually exclusive)</b>									
Statin nearly due		31.2%	35.0%		27.0%	30.9%		30.3%	34.1%
Statin overdue		41.7%	37.6%		28.3%	25.2%		34.2%	30.4%
ACEI/ARB refill		27.0%	30.0%		32.5%	36.4%		29.6%	32.9%
Tardy ACEI/ARB		22.4%	18.9%		37.8%	32.4%		26.1%	22.2%
<b>Call outcomes</b>									
Participant reached		53.6%	54.9%		53.7%	54.8%		55.0%	56.3%
Detailed msg left		10.5%	10.3%		10.6%	10.3%		10.4%	10.4%
Nondetailed msg		20.5%	20.8%		20.2%	21.0%		19.9%	19.9%
<b># Reminder letters and live calls</b>			5135			4139			6409

**Table A4. Subgroup Analysis of follow-up statin adherence– statin users**

	IVR+	IVR	UC	IVR+ vs. UC $\Delta^1$	Sig <sup>2</sup>	IVR vs. UC $\Delta^1$	Sig <sup>2</sup>	IVR+ vs. IVR $\Delta^1$	Sig <sup>2</sup>
<b>By gender</b>									
Male	.58±.34 (n=2871)	.59±.34 (n=2908)	.56±.35 (n=2886)	0.023 ( 0.007, 0.039)	0.006	0.021 ( 0.005, 0.037)	0.010	0.002 ( -0.015, 0.018)	0.846
Female	.57±.34 (n=2558)	.56±.35 (n=2545)	.53±.35 (n=2598)	0.039 ( 0.022, 0.056)	0.000	0.024 ( 0.007, 0.041)	0.007	0.015 ( -0.002, 0.032)	0.083
<b>By age</b>									
40-60	.50±.34 (n=2471)	.49±.34 (n=2389)	.47±.35 (n=2420)	0.030 ( 0.013, 0.048)	0.001	0.021 ( 0.003, 0.038)	0.022	0.009 ( -0.008, 0.027)	0.291
61-70	.62±.33 (n=1532)	.62±.34 (n=1602)	.60±.34 (n=1595)	0.027 ( 0.005, 0.048)	0.018	0.019 ( -0.003, 0.041)	0.085	0.008 ( -0.014, 0.029)	0.499
≥71	.66±.33 (n=1426)	.65±.33 (n=1462)	.62±.34 (n=1469)	0.035 ( 0.012, 0.058)	0.003	0.029 ( 0.006, 0.051)	0.013	0.006 ( -0.017, 0.029)	0.606
<b>By co-morbid diabetes and CVD status</b>									
Diabetes only	.55±.34 (n=3451)	.54±.34 (n=3535)	.52±.35 (n=3526)	0.038 ( 0.023, 0.052)	0.000	0.024 ( 0.009, 0.038)	0.002	0.014 ( -0.001, 0.029)	0.059
CVD only	.63±.34 (n=1220)	.63±.34 (n=1159)	.59±.35 (n=1203)	0.033 ( 0.008, 0.058)	0.010	0.027 ( 0.002, 0.052)	0.035	0.006 ( -0.019, 0.031)	0.658
Both	.61±.34 (n=758)	.63±.34 (n=759)	.61±.33 (n=755)	-0.008 (-0.039, 0.024)	0.640	0.009 ( -0.022, 0.040)	0.575	-0.017 ( -0.048, 0.015)	0.303
<b>By number of baseline medications</b>									
1-5	.58±.33 (n=2534)	.57±.34 (n=2588)	.55±.33 (n=2590)	0.029 ( 0.012, 0.047)	0.001	0.011 ( -0.006, 0.028)	0.192	0.018 ( 0.001, 0.035)	0.038
6-10	.55±.35 (n=1394)	.56±.35 (n=1378)	.51±.36 (n=1423)	0.042 ( 0.019, 0.066)	0.000	0.053 ( 0.030, 0.076)	0.000	-0.010 ( -0.034, 0.013)	0.386
11-15	.59±.34 (n=877)	.60±.34 (n=903)	.58±.36 (n=870)	0.013 ( -0.017, 0.042)	0.395	0.011 ( -0.019, 0.040)	0.479	0.002 ( -0.027, 0.031)	0.882
16+	.60±.34 (n=624)	.58±.36 (n=584)	.56±.36 (n=601)	0.031 ( -0.004, 0.066)	0.079	0.016 ( -0.019, 0.052)	0.369	0.015 ( -0.020, 0.050)	0.402
<b>By site</b>									
KPG	.48±.34 (n=1756)	.50±.34 (n=1737)	.47±.35 (n=1734)	0.014 ( -0.007, 0.035)	0.182	0.024 ( 0.003, 0.044)	0.026	-0.010 ( -0.030, 0.011)	0.365
KPH	.60±.32 (n=1908)	.59±.33 (n=1962)	.58±.32 (n=1957)	0.024 ( 0.004, 0.044)	0.016	0.008 ( -0.012, 0.027)	0.437	0.016 ( -0.003, 0.036)	0.103
KPNW	.64±.34 (n=1765)	.63±.36 (n=1754)	.59±.37 (n=1793)	0.053 ( 0.033, 0.074)	0.000	0.037 ( 0.017, 0.058)	0.000	0.016 ( -0.005, 0.037)	0.127

1 Intervention effect adjusted for baseline covariates and expressed as mean and 95% confidence interval

2 Two-tailed significance level based on linear 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.

3 Raw, unadjusted adherence (mean±sd)

**Table A5. Analysis of follow-up statin adherence– statin users with 2 or more detailed messages or, for UC, would have been triggered for 2 or more calls**

	IVR+	IVR	UC	IVR+ vs UC $\Delta^1$	Sig <sup>2</sup>	IVR vs UC $\Delta^1$	Sig <sup>2</sup>	IVR+ vs IVR $\Delta^1$	Sig <sup>2</sup>
<b>Overall</b>	.64±.31 <sup>3</sup> (n=3320)	.63±.32 (n=3525)	.54±.35 (n=5031)	0.080 (0.067, 0.094)	0.000	0.064 (0.051, 0.077)	0.000	0.017 (0.002, 0.031)	0.022
<b>By baseline statin adherence</b>									
≤ 0.40	.51±.35 (n=1016)	.49±.36 (n=1108)	.38±.36 (n=1753)	0.118 (0.095, 0.142)	0.000	0.094 (0.071, 0.116)	0.000	0.025 (-0.001, 0.050)	0.057
0.40-0.75	.69±.27 (n=2006)	.67±.29 (n=2076)	.61±.30 (n=2899)	0.068 (0.051, 0.085)	0.000	0.049 (0.032, 0.066)	0.000	0.019 (0.001, 0.037)	0.044
0.75- 0.9	.79±.25 (n=298)	.82±.23 (n=341)	.76±.25 (n=379)	0.018 (-0.027, 0.064)	0.434	0.043 (-0.001, 0.087)	0.055	-0.025 (-0.072, 0.022)	0.296
<b>By gender</b>									
Male	.66±.31 (n=1698)	.65±.32 (n=1829)	.56±.34 (n=2645)	0.076 (0.058, 0.095)	0.000	0.068 (0.050, 0.086)	0.000	0.008 (-0.012, 0.028)	0.411
Female	.63±.31 (n=1622)	.60±.33 (n=1696)	.53±.35 (n=2386)	0.084 (0.066, 0.103)	0.000	0.059 (0.040, 0.078)	0.000	0.025 (0.005, 0.046)	0.015
<b>By age</b>									
40-60	.58±.31 (n=1220)	.56±.33 (n=1269)	.47±.34 (n=2228)	0.098 (0.077, 0.119)	0.000	0.077 (0.056, 0.097)	0.000	0.022 (-0.002, 0.045)	0.074
61-70	.67±.31 (n=1027)	.65±.32 (n=1127)	.59±.33 (n=1465)	0.073 (0.049, 0.097)	0.000	0.051 (0.028, 0.075)	0.000	0.021 (-0.004, 0.047)	0.099
≥71	.69±.30 (n=1073)	.68±.31 (n=1129)	.62±.34 (n=1338)	0.064 (0.040, 0.088)	0.000	0.058 (0.034, 0.082)	0.000	0.006 (-0.019, 0.031)	0.633
<b>By co-morbid diabetes and CVD status</b>									
Diabetes only	.62±.31 (n=2010)	.60±.33 (n=2205)	.51±.35 (n=3244)	0.092 (0.075, 0.108)	0.000	0.066 (0.050, 0.082)	0.000	0.026 (0.007, 0.044)	0.006
CVD only	.68±.30 (n=801)	.68±.31 (n=797)	.59±.34 (n=1086)	0.073 (0.045, 0.100)	0.000	0.064 (0.037, 0.092)	0.000	0.008 (-0.021, 0.038)	0.583
Both	.67±.31 (n=509)	.68±.32 (n=523)	.61±.33 (n=701)	0.045 (0.010, 0.079)	0.011	0.051 (0.017, 0.085)	0.003	-0.006 (-0.043, 0.030)	0.735
<b>By number of baseline medications</b>									
1-5	.66±.29 (n=1483)	.63±.31 (n=1580)	.55±.33 (n=2404)	0.085 (0.066, 0.105)	0.000	0.060 (0.041, 0.079)	0.000	0.025 (0.004, 0.046)	0.022
6-10	.63±.33 (n=838)	.61±.34 (n=904)	.51±.36 (n=1294)	0.093 (0.067, 0.120)	0.000	0.082 (0.056, 0.107)	0.000	0.011 (-0.017, 0.04)	0.425
11-15	.64±.32 (n=573)	.64±.32 (n=614)	.57±.35 (n=796)	0.05 (0.018, 0.082)	0.002	0.049 (0.017, 0.080)	0.003	0.001 (-0.033, 0.035)	0.950
16+	.65±.32	.62±.34	.55±.36	0.076 (0.038, 0.115)	0.000	0.057 (0.019, 0.095)	0.003	0.019 (-0.021, 0.060)	0.348

	(n=426)	(n=427)	(n=537)						
<b>By site</b>									
KPG	.55±.32 (n=989)	.54±.33 (n=1077)	.47±.35 (n=1588)	0.057 (0.033, 0.081)	0.000	0.055 (0.031, 0.078)	0.000	0.002 (-0.024, 0.028)	0.869
KPH	.67±.28 (n=1157)	.65±.30 (n=1222)	.57±.32 (n=1822)	0.073 (0.051, 0.095)	0.000	0.054 (0.032, 0.076)	0.000	0.019 (-0.005, 0.043)	0.116
KPNW	.70±.31 (n=1174)	.68±.33 (n=1226)	.58±.36 (n=1621)	0.109 (0.086, 0.131)	0.000	0.083 (0.061, 0.105)	0.000	0.026 (0.002, 0.050)	0.034

1 Intervention effect adjusted for baseline covariates and expressed as mean and 95% confidence interval

2 Two-tailed significance level based on linear 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

3 Raw, unadjusted adherence (mean±sd)

**Table A6. Subgroup analysis of follow-up ACEI/ARB adherence– ACEI/ARB users**

	IVR+	IVR	UC	IVR+ vs. UC $\Delta^1$	Sig <sup>2</sup>	IVR vs. UC $\Delta^1$	Sig <sup>2</sup>	IVR+ vs. IVR $\Delta^1$	Sig <sup>2</sup>
<b>By gender</b>									
Male	.61±.35 (n=2278)	.59±.36 (n=2318)	.58±.36 (n=2322)	0.036 ( 0.018, 0.055)	0.000	0.016 ( -0.002, 0.034)	0.089	0.02 ( 0.002, 0.039)	0.033
Female	.61±.34 (n=2045)	.59±.35 (n=2052)	.57±.35 (n=2008)	0.038 ( 0.018, 0.058)	0.000	0.016 ( -0.004, 0.035)	0.122	0.022 ( 0.003, 0.042)	0.027
<b>By age</b>									
40-60	.56±.35 (n=1910)	.52±.35 (n=1862)	.51±.35 (n=1924)	0.043 ( 0.023, 0.063)	0.000	0.014 ( -0.006, 0.034)	0.179	0.029 ( 0.008, 0.049)	0.006
61-70	.66±.33 (n=1246)	.64±.35 (n=1289)	.61±.35 (n=1234)	0.049 ( 0.024, 0.075)	0.000	0.024 ( -0.001, 0.049)	0.060	0.025 ( 0.000, 0.050)	0.047
≥71	.65±.35 (n=1167)	.65±.35 (n=1219)	.63±.35 (n=1172)	0.014 ( -0.012, 0.04)	0.296	0.010 ( -0.016, 0.035)	0.457	0.004 ( -0.022, 0.03)	0.754
<b>By co-morbid diabetes and CVD status</b>									
Diabetes only	.61±.34 (n=2835)	.58±.35 (n=2875)	.56±.35 (n=2863)	0.051 ( 0.035, 0.068)	0.000	0.019 ( 0.003, 0.036)	0.022	0.032 ( 0.015, 0.049)	0.000
CVD only	.62±.36 (n=851)	.63±.36 (n=829)	.60±.37 (n=809)	0.006 ( -0.025, 0.036)	0.722	0.017 ( -0.014, 0.048)	0.294	-0.011 ( -0.042, 0.020)	0.480
Both	.62±.35 (n=637)	.60±.36 (n=666)	.60±.35 (n=658)	0.014 ( -0.021, 0.049)	0.430	-0.001 ( -0.036, 0.033)	0.948	0.015 ( -0.02, 0.05)	0.392
<b>By number of baseline medications</b>									
0-5	.61±.33 (n=2013)	.59±.34 (n=2032)	.57±.35 (n=2002)	0.041 ( 0.021, 0.060)	0.000	0.020 ( 0.000, 0.039)	0.054	0.021 ( 0.001, 0.041)	0.037
6-10	.61±.36 (n=1099)	.59±.36 (n=1100)	.57±.37 (n=1142)	0.040 ( 0.013, 0.066)	0.003	0.018 ( -0.009, 0.044)	0.194	0.022 ( -0.005, 0.049)	0.0107
11-15	.61±.36 (n=697)	.58±.37 (n=724)	.57±.37 (n=686)	0.026 ( -0.008, 0.06)	0.128	-0.007 ( -0.041, 0.026)	0.681	0.033 ( 0, 0.0670)	0.051
16+	.62±.36 (n=514)	.62±.36 (n=514)	.60±.36 (n=500)	0.031 ( -0.008, 0.071)	0.121	0.029 ( -0.011, 0.068)	0.153	0.002 ( -0.037, 0.042)	0.903
<b>Change in adherence by site</b>									
KPG	.53±.36 (n=1306)	.51±.36 (n=1365)	.48±.36 (n=1335)	0.034 ( 0.010, 0.059)	0.006	0.019 ( -0.006, 0.043)	0.130	0.015 ( -0.009, 0.040)	0.213
KPH	.63±.32 (n=1575)	.61±.33 (n=1542)	.59±.34 (n=1511)	0.045 ( 0.023, 0.068)	0.000	0.018 ( -0.005, 0.040)	0.127	0.028 ( 0.005, 0.050)	0.017
KPNW	.67±.35 (n=1442)	.65±.35 (n=1463)	.64±.36 (n=1484)	0.031 ( 0.007, 0.054)	0.010	0.011 ( -0.012, 0.034)	0.341	0.019 ( -0.004, 0.043)	0.104

1 Net intervention effect, expressed as mean and 95% confidence interval

2 Two-tailed significance level based on linear 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.

3 Raw, unadjusted adherence (mean±sd)

**Table A7. Analysis of follow-up ACEI/ARB adherence– ACEI/ARB users with 2 or more detailed messages or, for UC, would have been triggered for 2 or more calls**

	IVR+	IVR	UC	IVR+ vs UC $\Delta^1$	Sig <sup>2</sup>	IVR vs UC $\Delta^1$	Sig <sup>2</sup>	IVR+ vs IVR $\Delta^1$	Sig <sup>2</sup>
<b>Overall</b>	.68±.31 <sup>3</sup> (n=2661)	.64±.33 (n=2835)	.57±.35 (n=4000)	0.083 (0.068, 0.098)	0.000	0.050 (0.036, 0.065)	0.000	0.032 (0.016, 0.049)	0.000
<b>By baseline ACEI/ARB adherence</b>									
≤ 0.50	.58±.34 (n=1258)	.53±.36 (n=1339)	.45±.37 (n=2043)	0.119 (0.097, 0.140)	0.000	0.07 (0.049, 0.091)	0.000	0.049 (0.025, 0.072)	0.000
0.5-0.75	.75±.26 (n=1168)	.74±.27 (n=1230)	.70±.29 (n=1646)	0.048 (0.025, 0.071)	0.000	0.033 (0.010, 0.055)	0.005	0.016 (-0.009, 0.040)	0.209
0.75-0.9	.83±.23 (n=235)	.80±.25 (n=266)	.76±.26 (n=311)	0.049 (-0.003, 0.101)	0.063	0.023 (-0.027, 0.073)	0.365	0.026 (-0.028, 0.080)	0.342
<b>By gender</b>									
Male	.68±.31 (n=1366)	.65±.33 (n=1477)	.58±.36 (n=2148)	0.083 (0.062, 0.104)	0.000	0.052 (0.032, 0.072)	0.000	0.031 (0.008, 0.053)	0.008
Female	.67±.31 (n=1295)	.64±.33 (n=1358)	.57±.35 (n=1852)	0.083 (0.061, 0.104)	0.000	0.049 (0.027, 0.070)	0.000	0.034 (0.011, 0.057)	0.004
<b>By age</b>									
40-60	.63±.31 (n=985)	.58±.33 (n=975)	.51±.35 (n=1788)	0.105 (0.082, 0.129)	0.000	0.055 (0.031, 0.079)	0.000	0.051 (0.023, 0.078)	0.000
61-70	.71±.29 (n=831)	.68±.33 (n=928)	.61±.35 (n=1139)	0.091 (0.064, 0.119)	0.000	0.057 (0.031, 0.084)	0.000	0.034 (0.005, 0.063)	0.020
≥71	.69±.32 (n=845)	.68±.33 (n=932)	.63±.35 (n=1073)	0.044 (0.017, 0.072)	0.002	0.035 (0.008, 0.061)	0.012	0.010 (-0.019, 0.038)	0.509
<b>By co-morbid diabetes and CVD status</b>									
Diabetes only	.68±.30 (n=1652)	.64±.32 (n=1772)	.56±.35 (n=2645)	0.100 (0.081, 0.119)	0.000	0.062 (0.044, 0.081)	0.000	0.037 (0.017, 0.058)	0.000
CVD only	.67±.33 (n=583)	.66±.35 (n=615)	.61±.36 (n=747)	0.039 (0.006, 0.073)	0.020	0.023 (-0.009, 0.056)	0.164	0.016 (-0.019, 0.051)	0.362
Both	.68±.32 (n=426)	.65±.34 (n=448)	.60±.35 (n=608)	0.070 (0.032, 0.108)	0.000	0.034 (-0.003, 0.072)	0.072	0.036 (-0.005, 0.076)	0.086
<b>By number of baseline medications</b>									
0-5	.68±.28 (n=1197)	.65±.31 (n=1249)	.57±.34 (n=1869)	0.092 (0.069, 0.114)	0.000	0.064 (0.042, 0.086)	0.000	0.028 (0.003, 0.052)	0.026
6-10	.68±.32 (n=654)	.63±.35 (n=728)	.58±.36 (n=1043)	0.089 (0.059, 0.119)	0.000	0.038 (0.009, 0.067)	0.010	0.051 (0.019, 0.084)	0.002
11-15	.66±.34 (n=458)	.63±.35 (n=476)	.57±.36 (n=634)	0.063 (0.026, 0.100)	0.001	0.027 (-0.009, 0.064)	0.145	0.036 (-0.004, 0.075)	0.075
16+	.67±.33 (n=352)	.67±.34 (n=382)	.61±.35 (n=454)	0.065 (0.022, 0.107)	0.003	0.057 (0.016, 0.099)	0.007	0.007 (-0.037, 0.052)	0.754
<b>By site</b>									

KPG	.59±.33 (n=735)	.55±.35 (n=816)	.48±.36 (n=1230)	0.084 (0.056, 0.112)	0.000	0.043 (0.016, 0.070)	0.002	0.041 (0.010, 0.071)	0.009
KPH	.70±.27 (n=965)	.67±.30 (n=969)	.59±.33 (n=1409)	0.095 (0.070, 0.120)	0.000	0.063 (0.038, 0.088)	0.000	0.032 (0.004, 0.059)	0.023
KPNW	.72±.32 (n=961)	.70±.33 (n=1050)	.64±.35 (n=1361)	0.070 (0.045, 0.096)	0.000	0.044 (0.020, 0.069)	0.001	0.026 (-0.001, 0.053)	0.058

1 Net intervention effect, expressed as mean and 95% confidence interval

2 Two-tailed significance level based on linear 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

3 Raw, unadjusted adherence (mean±sd)

**Table A8. Analysis of follow-up lipid levels for statin users with 2+ detailed msgs or contacts or, for UC, who would have been triggered for 2 or more calls**

	IVR+	IVR	UC	IVR+ vs UC $\Delta^1$	Sig <sup>2</sup>	IVR vs UC $\Delta^1$	Sig <sup>2</sup>	IVR+ vs IVR $\Delta^1$	Sig <sup>2</sup>
<b>Follow-up LDL by initial LDL level</b>									
Overall	88.7±31.3 (2946)	89.4±31.7 (3139)	92.7±35.4 (4301)	-2.8 (-4.2, -1.4)	0.000	-1.9 (-3.2, -0.6)	0.006	-0.9 (-2.3, 0.6)	0.237
≤80 mg/dl	73.9±22.5 (n=1208)	74.6±24.4 (n=1286)	75.5±25.9 (n=1683)	-1.5 (-3.6, 0.7)	0.186	-0.7 (-2.8, 1.4)	0.519	-0.8 (-3.0, 1.5)	0.517
80-100 mg/dl	89.0±24.1 (n=803)	91.0±25.4 (n=864)	92.6±28.4 (n=1074)	-3.0 (-5.6, -0.3)	0.029	-1.2 (-3.8, 1.5)	0.387	-1.8 (-4.6, 1.0)	0.201
>100 mg/dl	110.3±35.4 (n=790)	110.6±35.1 (n=818)	115.1±38.0 (n=1261)	-4.4 (-7.0, -1.8)	0.001	-3.9 (-6.5, -1.4)	0.003	-0.4 (-3.3, 2.4)	0.767
<b>Follow-up LDL control (&lt;100 mg/dl) by initial LDL level</b>									
Overall	74.1%	72.7%	68.8%	1.26 (1.12, 1.42)	0.000	1.14 (1.01, 1.27)	0.028	1.11 (0.98, 1.26)	0.097
≤80 mg/dl	90.3%	88.8%	88.1%	1.25 (0.98, 1.59)	0.072	1.06 (0.84, 1.33)	0.645	1.18 (0.91, 1.54)	0.202
80-100 mg/dl	78.1%	75.1%	73.1%	1.28 (1.03, 1.59)	0.026	1.09 (0.89, 1.35)	0.402	1.17 (0.93, 1.48)	0.179
>100 mg/dl	45.3%	45.8%	39.9%	1.25 (1.04, 1.50)	0.019	1.24 (1.03, 1.49)	0.020	1.00 (0.82, 1.23)	0.967

1 Net intervention effect (absolute difference or, or proportions, odds ratio) expressed as mean and 95% confidence interval

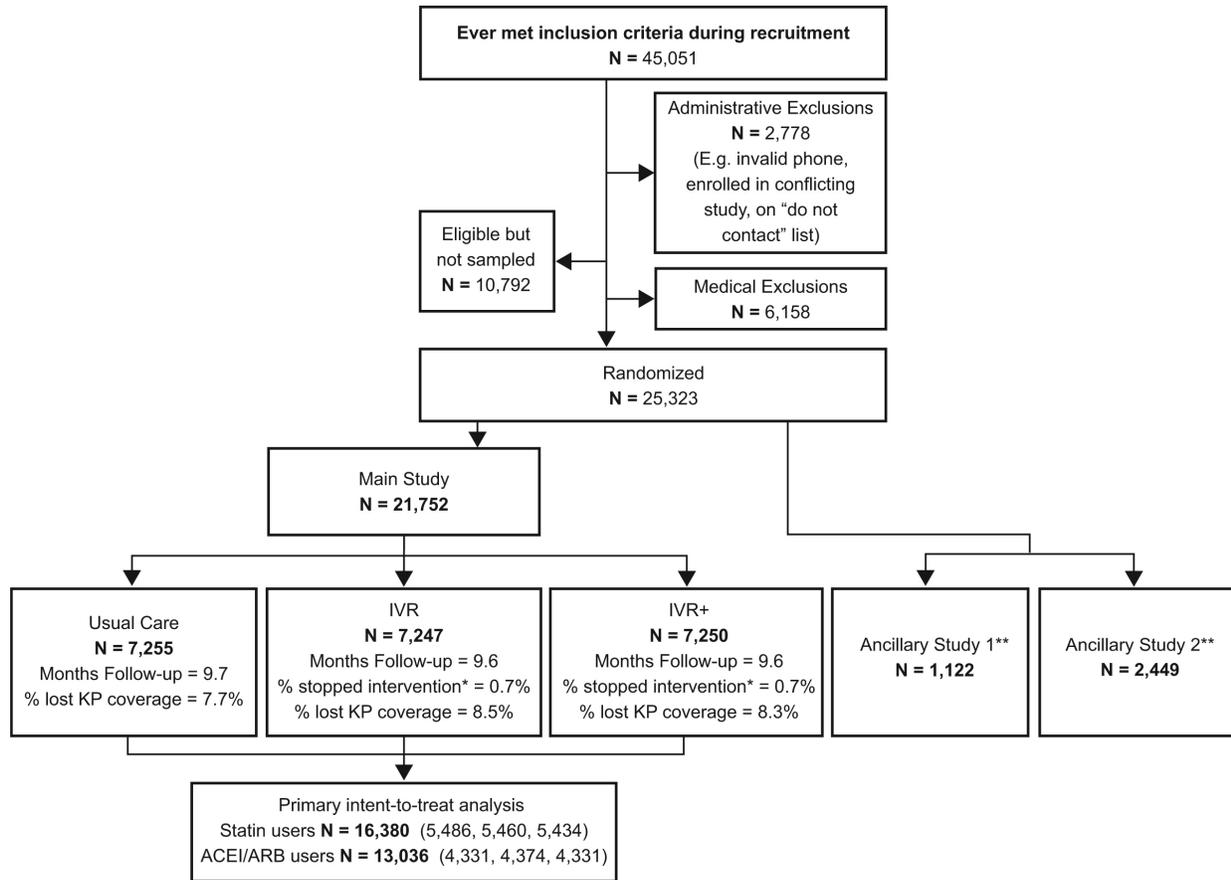
2 Two-tailed significance level based on linear regression analysis adjusting for site, gender, age, total number of prescription medications dispensed at baseline, comorbid diabetes/CVD, and baseline adherence as fixed main effects. Subgroup analyses also include the corresponding treatment by subgroup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

3 Raw, unadjusted adherence (mean±sd)

**Table A9. Safety data**

	<b>UC</b>	<b>IVR</b>	<b>IVR+</b>	<b>Total</b>
<b># Randomized</b>	7255	7247	7250	21752
<b>Died</b>	141 (1.94%)	146 (2.01%)	140 (1.93%)	427 (1.96%)
<b>Potential ACEI/ARB related hospitalization</b>	24 (0.33%)	19 (0.26%)	20 (0.28%)	63 (0.29%)
<b>Potential statin related hospitalization</b>	1 (0.01%)	2 (0.03%)	2 (0.03%)	5 (0.02%)
<b>Serum K&gt;6 (mEq/L)</b>	13 (0.18%)	26 (0.36%)	31 (0.43%)	70 (0.32%)
<b>Serum Cr&gt;3 (mg/dL)</b>	34 (0.47%)	47 (0.65%)	35 (0.48%)	116 (0.53%)

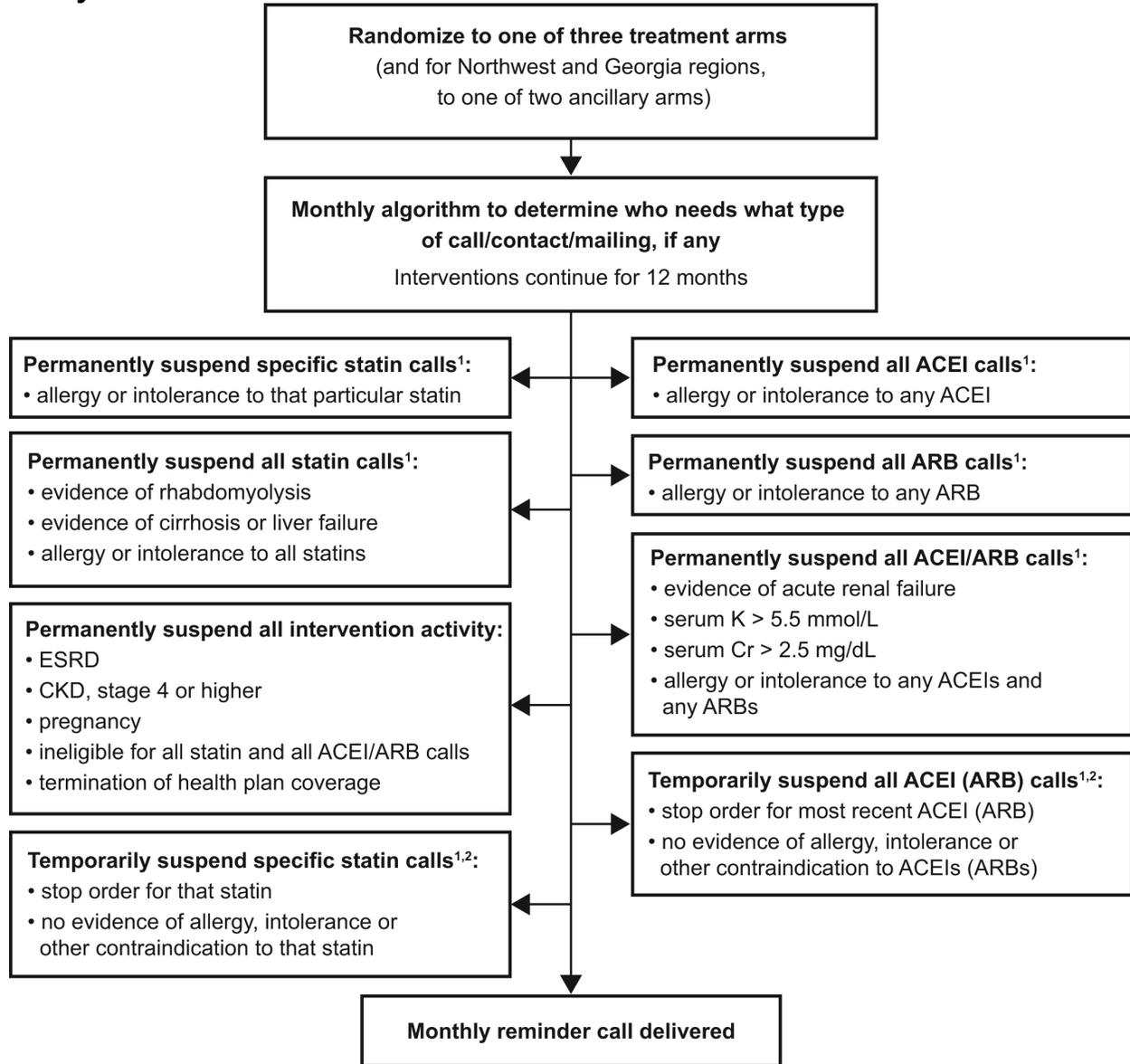
**Figure A1. Participant flow diagram**



\* Intervention activity stopped per patient request or due to stop orders or medical contraindications.

\*\* Ancillary study 1 tested the **IVR\_lite** intervention (KPG only) and ancillary study 2 tested the **IVR+\_lite** intervention (KPNW only).

**Figure A2. Flowchart for suspension or termination of intervention activity due to safety concerns**



1 Includes cessation of reminder letters and live calls, but not (for IVR+) the educational mailings

2 Suspension ceases after a subsequent dispensing of any medication in that class