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.

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)[1] 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.[2] 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+_lite** 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.[3]

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.[4] Interviews were transcribed, and were content-analyzed by a trained qualitative research specialist (JS). All interviews were analyzed using standard qualitative analysis techniques,[4;5] and aided by the use of a qualitative research software package.[6] 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 *(region specific)*
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 • Prompt Program Folder • Introduction Letter *(region specific)* • IVR Brochure *(region specific)* • My Medication List Wallet Card (*region specific)* • FAQ Booklet • Questions for your Doctor/Pharmacy (wallet card) (*region specific)* • Weekly pill organizing container (pill box) • Daily Medication Schedule • Prompt Magnet adhered to postcard
2 weeks	IVR+	Personalized, includes health information merge • My Heart Health Report (8 x 11) • Daily Medication Schedule (8 x 11)
2 month mailing	IVR+	Materials are generic but some are region specific • Follow up note (6 x 9) (*region specific*) • Getting my medications/Setting up my kp.org account insert (*region specific)* • Learning About KP.org brochure
4 month mailing	IVR+	Materials are generic but some are region specific • Follow up note (4 x 9) (*region specific*) • Medication reminders (4 x 9) • My medications: connecting me to health (4 x 9) *(region specific)* • Questions for your Doctor Pharmacy Wallet Card • My Medication List Wallet Card *(region specific)*
6 month mailing	IVR+	Personalized, includes health information merge • My Heart Health Report (8 x11) • Daily Medication Schedule (8x11) Flat windowed envelope.
8 month mailing	IVR+	Materials are generic but some are region specific • Follow up note *(region specific)* • Barriers and Solutions insert
10 month mailing	IVR+	Materials are generic but some are region specific • Follow up note *(region specific)* • Questions for your Doctor Pharmacy Wallet Card • My Medication List Wallet Card *(region specific)*

***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, 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+**
# Randomized	5486	5460	5434	4331	4374	4331	7255	7247	7250
Follow-up (mos)	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)
Number and type of intervention contacts attempted per participant									
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)
# IVR calls attempted		20613	18416		16513	14850		26734	24279
Type of call									
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%
Medication classes discussed									
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%
Type of reminder (categories not mutually exclusive)									
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%
Call outcomes									
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%
# Reminder letters and live calls			5135			4139			6409

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

	IVR+	IVR	UC	IVR+ vs. UC Δ[1]	Sig[2]	IVR vs. UC Δ[1]	Sig[2]	IVR+ vs. IVR Δ[1]	Sig[2]
By gender									
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
By age									
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
By co-morbid diabetes and CVD status									
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
By number of baseline medications									
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
By site									
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 Δ[1]	IVR+ vs UC Sig[2]	IVR vs UC Δ[1]	IVR vs UC Sig[2]	IVR+ vs IVR Δ[1]	IVR+ vs IVR Sig[2]
Overall	.64±.31[3] (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
By baseline statin adherence									
≤ 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
By gender									
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
By age									
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
By co-morbid diabetes and CVD status									
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
By number of baseline medications									
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)						
By site									
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 Δ[1]	IVR+ vs. UC Sig[2]	IVR vs. UC Δ[1]	IVR vs. UC Sig[2]	IVR+ vs. IVR Δ[1]	IVR+ vs. IVR Sig[2]
By gender									
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
By age									
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
By co-morbid diabetes and CVD status									
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
By number of baseline medications									
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
Change in adherence by site									
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 Δ[1]	IVR+ vs UC Sig[2]	IVR vs UC Δ[1]	IVR vs UC Sig[2]	IVR+ vs IVR Δ[1]	IVR+ vs IVR Sig[2]
Overall	.68±.31[3] (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
By baseline ACEI/ARB adherence									
≤ 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
By gender									
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
By age									
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
By co-morbid diabetes and CVD status									
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
By number of baseline medications									
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
By site									

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 Δ[1]	IVR+ vs UC Sig[2]	IVR vs UC Δ[1]	IVR vs UC Sig[2]	IVR+ vs IVR Δ[1]	IVR+ vs IVR Sig[2]
Follow-up LDL by initial LDL level									
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
Follow-up LDL control (<100 mg/dl) by initial LDL level									
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

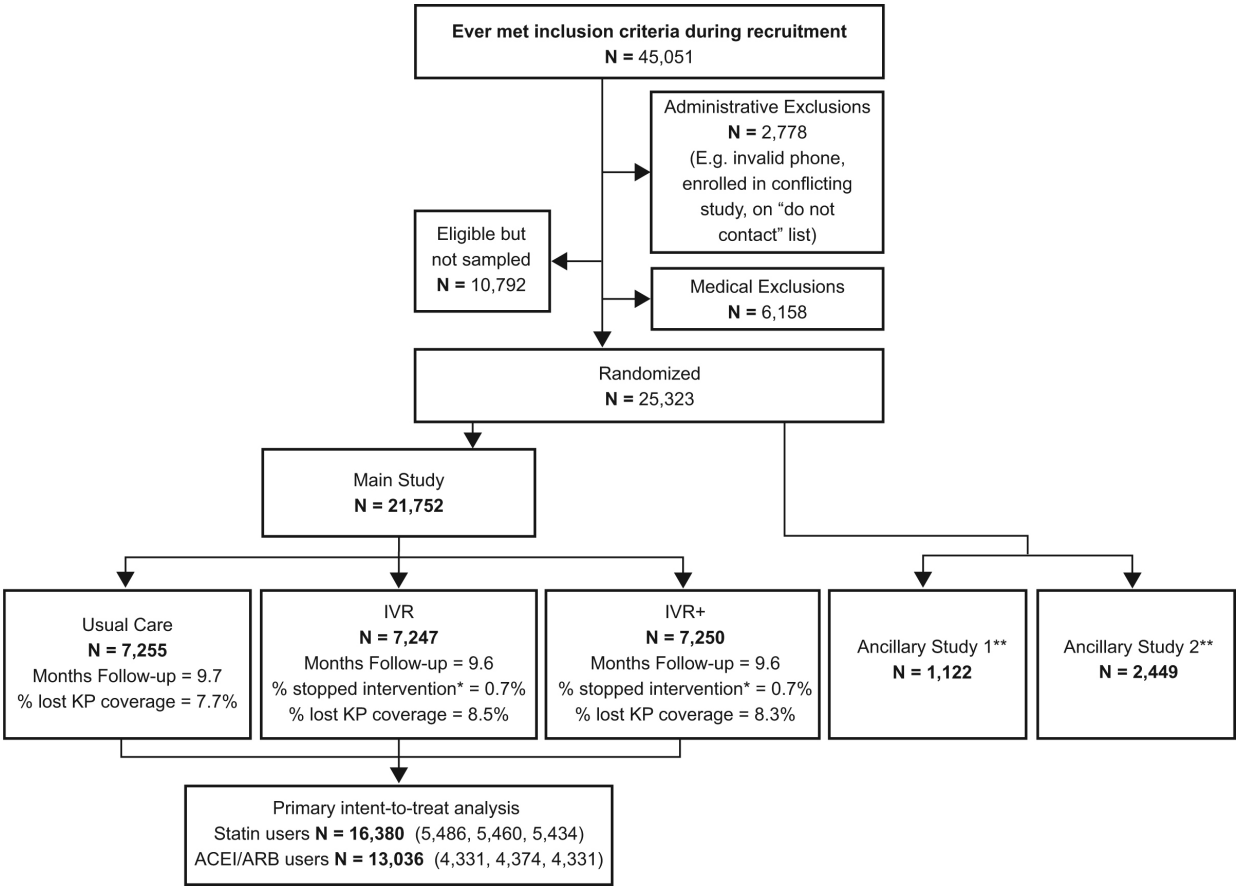
2 Two-tailed significance level based on linear regression analysis adjusting for site, gender, age, total number of prescription medications dispensed at baseline, comorbid diabetes/CVD, and baseline adherence as fixed main effects. Subgroup analyses also include the corresponding treatment by subgroup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

3 Raw, unadjusted adherence (mean±sd)

Table A9. Safety data

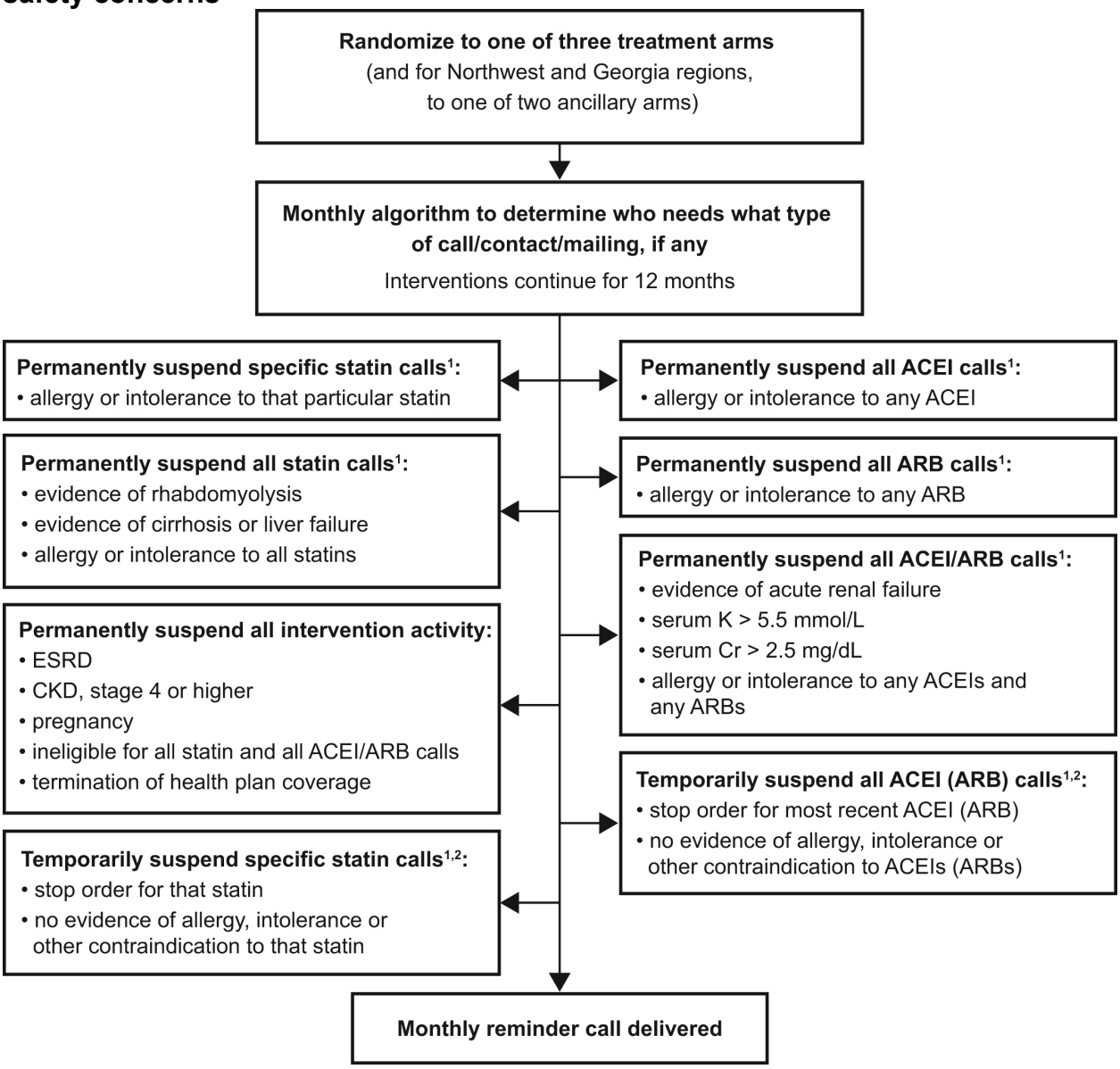
	UC	IVR	IVR+	Total
# Randomized	7255	7247	7250	21752
Died	141 (1.94%)	146 (2.01%)	140 (1.93%)	427 (1.96%)
Potential ACEI/ARB related hospitalization	24 (0.33%)	19 (0.26%)	20 (0.28%)	63 (0.29%)
Potential statin related hospitalization	1 (0.01%)	2 (0.03%)	2 (0.03%)	5 (0.02%)
Serum K>6 (mEq/L)	13 (0.18%)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