Randomized Trial of Telephone Outreach to Improve Medication Adherence and Metabolic Control in Adults With Diabetes

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OBJECTIVE
Medication nonadherence is a major obstacle to better control of glucose, blood pressure (BP), and LDL cholesterol in adults with diabetes. Inexpensive effective strategies to increase medication adherence are needed.

RESEARCH DESIGN AND METHODS
In a pragmatic randomized trial, we randomly assigned 2,378 adults with diabetes mellitus who had recently been prescribed a new class of medication for treating elevated levels of glycated hemoglobin (A1C) ≥8% (64 mmol/mol), BP ≥140/90 mmHg, or LDL cholesterol ≥100 mg/dL, to receive 1) one scripted telephone call from a diabetes educator or clinical pharmacist to identify and address nonadherence to the new medication or 2) usual care. Hierarchical linear and logistic regression models were used to assess the impact on 1) the first medication fill within 60 days of the prescription; 2) two or more medication fills within 180 days of the prescription; and 3) clinically significant improvement in levels of A1C, BP, or LDL cholesterol.

RESULTS
Of the 2,378 subjects, 89.3% in the intervention group and 87.4% in the usual-care group had sufficient data to analyze study outcomes. In intent-to-treat analyses, intervention was not associated with significant improvement in primary adherence, medication persistence, or intermediate outcomes of care. Results were similar across subgroups of patients defined by age, sex, race/ethnicity, and study site, and when limiting the analysis to those who completed the intended intervention.

CONCLUSIONS
This low-intensity intervention did not significantly improve medication adherence or control of glucose, BP, or LDL cholesterol. Wide use of this strategy does not appear to be warranted; alternative approaches to identify and improve medication adherence and persistence are needed.
However, medication adherence and persistence vary depending on age, sex, number of prescribed medications, and seriousness of the medical condition.

Published reports indicate that medication adherence may be effectively improved through case management by nurses or clinical pharmacists, financial incentives, or other strategies (6,7). However, many of the effective case-management strategies require ongoing contact and are quite expensive (8,9). Despite these encouraging reports of interventions that improve medication adherence and persistence in adults with diabetes, the need for more cost-effective, sustainable intervention strategies is widely recognized. This must be balanced against the need for interventions that are potent enough to achieve their aims. Recent reports (10–12) suggest that low-intensity, well-timed telephone contact may improve primary adherence to statins or other medications.

This multisite pragmatic clinical trial was designed to assess the effectiveness of a single scripted telephone call to diabetics patients who 1) were currently above the recommended clinical goals for glucose, BP, or lipids, and 2) had recently been prescribed a new medication for that specific clinical domain. The goals of the intervention were to improve the primary adherence and persistence to the newly prescribed medication, and to improve control of glucose, BP, and lipids.

RESEARCH DESIGN AND METHODS
Hypothesis, Study Design, and Study Sites
This randomized trial tested the hypothesis that a telephone contact with a patient who had recently been prescribed a new medication for uncontrolled glycated hemoglobin (A1C), BP, or LDL cholesterol would improve 1) primary medication adherence; 2) medication persistence; 3) medication possession ratio (MPR); and 4) A1C, BP, or LDL cholesterol control. This study was part of the larger Agency for Healthcare Research and Quality–funded SUPREME-DM study. The clinical trial reported here was coordinated and led by HealthPartners Institute for Education and Research, while data collection was coordinated through Kaiser Permanente Northwest and analysis was conducted at Kaiser Permanente Colorado. The clinical intervention sites for this study included Kaiser Permanente Northern California (KPNC), Group Health Cooperative (GHC), Marshfield Clinic, and Geisinger Clinic. These are large multispecialty medical groups that have sophisticated health informatics systems and use electronic medical records (EMRs). Nearly all patients have health insurance with modest copays for visits and prescription medications. Diabetes care is provided by primary care providers, with referrals to diabetes educators and endocrinologists as needed.

Study Subjects
At each clinical intervention site, study subjects were selected if they met the following criteria: 1) they were 18–75 years of age; 2) they met study criteria for diabetes before study enrollment (13,14); 3) they had received clinical care at a designated clinic or medical center involved in this study for at least 15 months before study enrollment; and 4) they were prescribed a new class of medication (not filled in the past 180 days) for A1C, BP, or LDL cholesterol uncontrolled at the time of medication prescription (A1C ≥8% [64 mmol/mol], systolic BP [SBP] ≥140 mmHg, or LDL cholesterol ≥100 mg/dL).

Randomization Procedure
We randomized each cluster to receive usual care or intervention. We defined clusters of patients based on their linkage to primary care physicians at KPNC and Marshfield Clinic; linkage to primary care clinics at GHC; or linkage to certified diabetes educators at Geisinger Clinic. Every 2 weeks during the 12-month intervention period, programmers at each study site identified newly eligible study subjects, assigned an index date on which each was identified, and determined whether they were in a usual-care or intervention cluster. The “prescription date” was defined as the date on which a new class of medication was prescribed for uncontrolled A1C, BP, or LDL cholesterol.

Description of Intervention
Those subjects in the intervention arm received a single protocol-structured telephone call from an interventionist who was a nurse health manager (one site); diabetes educator or diabetes educator trainee (one site); or pharmacist (two sites). All interventionists followed the same structured telephone interview protocol to ascertain whether the subject had started to take the newly prescribed medication; this protocol was modified from one that was effectively used in a prior study (15,16). If the patient was taking the new medication as prescribed, positive reinforcement was provided. If the new medication prescription had not been filled, or was filled but the patient was not taking the medication as directed, the interventionist probed for reasons for nonadherence and worked with the patient to identify and resolve barriers to adherence. The calls were designed to last a median time of <5 min, and up to three call attempts were made to reach each intervention patient. Most intervention telephone calls occurred within 2–6 weeks after the prescription date. Subjects who had filled and those who had not filled their prescription before the index date were identified.

Data Sources
Most study data were obtained directly from extracts of EMR data. These data included demographics, vital signs, laboratory values, encounter dates, and pharmacy prescriptions. Other data, including pharmacy fill data and study enrollment data, were obtained from medical group administrative databases.

Variable Definitions
“Primary medication adherence” was defined as having at least one prescription fill of the index medication within 60 days of the prescription date. “Medication persistence” was defined as having two or more fills of the index medication within 180 days of the prescription date. The MPR denominator was the number of days between the first prescription fill for the new medication and the last day of supplied drug from the last prescription fill for the new medication; the numerator was defined as the number of days of medication supplied in all fills in the denominator time period.

Plan of Analysis
The hypotheses that the intervention would improve 1) primary medication adherence; 2) medication persistence; 3) MPR; and 4) A1C, BP, and LDL cholesterol control were tested using hierarchical logistic regression models and nested linear regression models to assess the proportion of patients who
met medication and care-improvement goals and mean changes in clinical values. If a patient had more than one out-of-control intermediate outcome at the time of the index date, we included all treated intermediate outcomes in the main analyses. If a subject was initially assigned to the intervention or control group and then had a second eligible episode of care during the study period, the patient remained in the initial assignment group. If a subject had insufficient data to assess the change in intermediate outcomes, their adherence and persistence were still assessed if they had sufficient pharmacy coverage.

The principal dependent variable was a composite of improvement from prerandomization to postrandomization values of the clinical domain of interest. To be classified as “improved,” each patient had to meet or exceed the following prespecified thresholds for improvement calculated as the difference between the postrandomization value and prerandomization value: A1C greater than or equal to -0.2% (-2 mmol/mol), SBP greater than or equal to -5 mmHg, or LDL cholesterol greater than or equal to -5 mg/dl. These thresholds were assigned a priori to assure that smaller improvements were not classified as clinically significant. These specified changes have a measurable impact on the occurrence of major clinical end points based on prior intervention studies (17–19). We also examined the mean changes in A1C, SBP, and LDL cholesterol levels among the subset of eligible subjects who had been prescribed a new medication for A1C, BP, or LDL cholesterol.

After completion of the primary analysis, a second prespecified analysis was conducted to identify whether the intervention effect varied in subgroups based on age, sex, race, and study site. After completing the intent-to-treat analysis that included all randomized subjects, we conducted a per-protocol analysis in which changes in study outcomes were compared for all usual-care patients versus only intervention-group patients who had been successfully contacted by the interventionist. For this analysis, successful contact was defined as a telephone conversation between the interventionist and the target patient. A last post hoc analysis was conducted to assess the impact of the intervention in the subgroup of ~20% of subjects in both study arms who had not filled their new prescription between the prescription date and the index date.

**Protection of Human Research Subjects**

The institutional review boards at KPNC, GHC, Marshfield Clinic, and Geisinger Clinic reviewed and approved all aspects of the randomized trial reported here, including the intervention, the randomization procedure, data collection, data-transfer protocols, and analysis. This study is registered at ClinicalTrials.gov (NCT02192255).

**RESULTS**

The study randomization resulted in 1,220 eligible patients assigned to the intervention and 1,158 assigned to the control arm, with no significant differences in baseline clinical and demographic characteristics between groups (Table 1). Table 2 shows that, among all study subjects, 1,102 subjects were prescribed a new class of medications to control elevated glucose levels; of these, 969 subjects (88.0%) had both baseline and follow-up A1C values, and 892 (80.9%) had at least 180 days of follow-up and pharmacy coverage. Overall, 76% of subjects in both the intervention and control groups had already filled their new prescription before the index date. There were no significant differences between the intervention and control arms in primary medication adherence within 60 days of the prescription date (intervention arm 85.9%, control arm 87.6%, P = 0.54), medication persistence at 180 days (intervention arm 66.9%, control arm 62.2%, P = 0.14), MPR (intervention arm 0.80, control arm 0.79, P = 0.90), change in A1C level from baseline (intervention arm -1.16% [-12 mmol/mol], control arm -1.33% [-13 mmol/mol], P = 0.15), or the proportion of subjects with a ≥ 0.2% (2 mmol/mol) improvement in A1C level (intervention arm 73.7%, control arm 75.2%, P = 0.64). Among the 195 subjects whose new prescription was not filled before the index date, the change in A1C level from baseline was -1.08% (-11 mmol/mol) in the intervention arm vs. -0.90% (-9 mmol/mol) in the control arm (P = 0.48). Table 2 also shows that, among all study subjects, 791 were prescribed a new class of medications to control hypertension; of these, 731 subjects (92.4%) had both baseline and follow-up BP values, and 570 subjects (72.1%) had at least 180 days of follow-up and pharmacy coverage, among whom 76.0% (control arm) and 79.1% (intervention arm) had filled their new prescription before the index date (P = 0.39). There were no significant differences between the intervention and control study arms in primary medication adherence within 60 days of the prescription date (intervention arm 85.8%, control arm 83.0%, P = 0.35), medication persistence at 180 days (intervention arm 64.0%, control arm 60.3%, P = 0.30), MPR (intervention arm 0.90, control arm 0.92, P = 0.13), SBP change from baseline (intervention arm -18.1 mmHg, control arm -16.4 mmHg, P = 0.26), or the proportion of subjects with a ≥ 4 mmHg drop in SBP (intervention arm 78.5%, control arm 75.8%, P = 0.38). Among the 129 subjects whose new prescription was not filled before the index date, the change in SBP from baseline was -19.6 mmHg in the intervention arm vs. -15.6 mmHg in the control arm (P = 0.25).

Table 2 also shows that, among all study subjects, 663 subjects were prescribed a new class of medications to control lipid levels, which was almost always a new statin prescription. Of these, 539 subjects (81.3%) had both baseline and follow-up LDL cholesterol values, and 549 subjects (82.8%) had at least 180 days of follow-up and pharmacy coverage, among whom 70.0% (control arm) and 60.9% (intervention arm) had filled their new prescription before the index date (P = 0.02) — a difference observed before the intervention. There were no significant differences between the intervention and control arms of the study in primary medication adherence within 60 days of the prescription date (intervention arm 79.6%, control arm 81.9%, P = 0.47), medication persistence at 180 days (intervention arm 49.1%, control arm 49.5%, P = 0.73), MPR (intervention arm 0.851, control arm 0.846, P = 0.84), mean LDL cholesterol change from baseline (intervention arm -30.4 mg/dL, control arm -33.0 mg/dL, P = 0.44), or the proportion of subjects with a ≥ 5 mg/dL drop in LDL cholesterol.
Table 1—Baseline patient characteristics shown for 1) all patients and 2) three subsets of patients within both the intervention and the control group who met specific criteria for baseline elevated A1C, LDL cholesterol, or SBP

|                  | Intervention | Control | P value |
|------------------|--------------|---------|---------|
|                  | All patients | A1C ≥8% (64 mmol/mol) | LDL cholesterol ≥100 mg/dL | SBP ≥140/90 mmHg | All patients | A1C ≥8% (64 mmol/mol) | LDL cholesterol ≥100 mg/dL | SBP ≥140/90 mmHg | (all patients) |
| Site, n (%)      |              | (n = 1,220) | (n = 569) | (n = 348) | (n = 388) | (n = 1,158) | (n = 533) | (n = 315) | (n = 403) |
| Site A           | 161 (13.2)   | 52 (9.1)   | 31 (8.9)   | 91 (23.5)  | 136 (11.7) | 46 (8.6)   | 25 (7.9)  | 73 (18.1)  | 0.576     |
| Site B           | 834 (68.4)   | 421 (74.0) | 269 (77.3) | 203 (52.3) | 806 (69.6) | 400 (75.0) | 246 (78.1) | 228 (56.6) |          |
| Site C           | 152 (12.5)   | 57 (10.0)  | 38 (10.9)  | 67 (17.3)  | 137 (11.8) | 49 (9.2)   | 31 (8.9)  | 67 (16.6)  |          |
| Site D           | 73 (6.0)     | 39 (6.9)   | 10 (2.9)   | 27 (7.0)   | 79 (6.8)   | 38 (7.1)   | 13 (4.1)  | 35 (8.7)   |          |
| Female sex, n (%)|              |         |           |           |           |           |           |           |           |
| Asian            | 171 (14.0)   | 88 (15.5) | 62 (17.8)  | 35 (9.0)   | 183 (15.8) | 89 (16.7) | 56 (17.8) | 48 (11.9)  | 0.422     |
| Black            | 150 (12.3)   | 64 (11.2) | 50 (14.4)  | 47 (12.1)  | 140 (12.1) | 66 (12.4) | 44 (14.0) | 51 (12.7)  |          |
| Hispanic         | 358 (29.3)   | 134 (23.6) | 77 (22.1)  | 171 (44.1) | 329 (28.4) | 125 (23.5) | 61 (19.4) | 165 (40.9) | 0.825     |
| Other/unknown    | 85 (7.0)     | 46 (8.1)  | 25 (7.2)   | 25 (6.4)   | 66 (5.7)   | 33 (6.2)   | 18 (5.7)  | 21 (5.2)   |          |
| White            | 814 (66.7)   | 371 (65.2) | 211 (60.6) | 281 (72.4) | 769 (66.4) | 345 (64.7) | 197 (62.5) | 283 (70.2) |          |
| Age at new prescription (years), n (%) |          |         |           |           |           |           |           |           |           |
| 18–39            | 59 (4.8)     | 36 (6.3)  | 19 (5.5)   | 6 (1.5)    | 59 (5.1)   | 34 (6.4)   | 18 (5.7)  | 15 (3.7)   | 0.553     |
| 40–64            | 653 (53.5)   | 341 (59.9) | 199 (57.2) | 171 (44.1) | 594 (51.3) | 316 (59.3) | 179 (56.8) | 159 (39.5) |          |
| ≥65              | 508 (41.6)   | 192 (33.7) | 130 (37.4) | 211 (54.4) | 505 (43.6) | 183 (34.3) | 118 (37.5) | 229 (56.8) |          |
| Race, n (%)      |              |         |           |           |           |           |           |           |           |
| Asian            | 171 (14.0)   | 88 (15.5) | 62 (17.8)  | 35 (9.0)   | 183 (15.8) | 89 (16.7) | 56 (17.8) | 48 (11.9)  | 0.422     |
| Black            | 150 (12.3)   | 64 (11.2) | 50 (14.4)  | 47 (12.1)  | 140 (12.1) | 66 (12.4) | 44 (14.0) | 51 (12.7)  |          |
| Hispanic         | 358 (29.3)   | 134 (23.6) | 77 (22.1)  | 171 (44.1) | 329 (28.4) | 125 (23.5) | 61 (19.4) | 165 (40.9) | 0.825     |
| Other/unknown    | 85 (7.0)     | 46 (8.1)  | 25 (7.2)   | 25 (6.4)   | 66 (5.7)   | 33 (6.2)   | 18 (5.7)  | 21 (5.2)   |          |
| White            | 814 (66.7)   | 371 (65.2) | 211 (60.6) | 281 (72.4) | 769 (66.4) | 345 (64.7) | 197 (62.5) | 283 (70.2) |          |
| Age at new prescription (years)* |          |         |           |           |           |           |           |           |           |
| Mean ± SD        | 61.67 ± 13.03 | 59.10 ± 12.43 | 59.70 ± 12.63 | 66.47 ± 12.49 | 62.04 ± 13.37 | 59.24 ± 12.79 | 59.93 ± 13.41 | 66.23 ± 13.22 | 0.390     |
| Median (minimum–maximum) | 62 (19–94) | 60 (19–94) | 60.00 (22–91) | 66 (33–94) | 63 (19–96) | 60 (19–96) | 60 (24–92) | 67 (28–92) |          |
| Drug coverage at new prescription, n (%)* |          |         |           |           |           |           |           |           |           |
| Mean ± SD        | 9.76 ± 1.66% (83 mmol/mol) | 135.1 ± 31.09 | 155.2 ± 13.51 | 9.83 ± 1.65% (84 mmol/mol) | 138.0 ± 30.56 | 154.6 ± 13.78 |          |           |           |
| Median (minimum–maximum) | 9.3% (8.0–17.9%) | 126.5 mg/dL | 152.0 mmHg | 9.4% (8.0–15.7%) | 130.0 mg/dL | 150.0 mmHg |          |           |           |

Note that a given patient could have elevations in more than one clinical domain. *Time of new prescription for first uncontrolled condition when pooled over all conditions.
Table 2—Follow-up time and medication adherence among patients with baseline uncontrolled A1C, BP, or LDL cholesterol by intervention versus control condition

| Drug coverage and follow-up | Patients with uncontrolled A1C (n, %) | Patients with uncontrolled BP (n, %) | Patients with uncontrolled LDL cholesterol (n, %) |
|-----------------------------|--------------------------------------|-------------------------------------|-----------------------------------------------|
| Intervention | 0.08 (268/3377) | 0.08 (274/3489) | 0.08 (384/4728) |
| Control | 0.08 (252/3127) | 0.08 (266/3278) | 0.08 (378/4715) |

Sample sizes are in parentheses. Table A1 provides patients with medication adherence by index date. Nonsignificant differences were observed in primary adherence by the index date, nonpersistence, MPR, and median (minimum–maximum) MPR.
(intervention arm 75.7%, control arm 75.3%, P = 0.90). Among the 164 subjects whose new prescription was not filled before the index date, the change in LDL cholesterol level from baseline was −29.2 mg/dL in the intervention arm vs. −22.3 mg/dL in the control arm (P = 0.23). A post hoc power analysis indicates that substantially larger sample sizes would be required to confirm or refute the observed positive trends in A1C, BP, and LDL cholesterol levels among the subgroup of those subjects who had not filled the new prescription by the index date (Table 3).

In the subgroup of subjects who had not filled their prescription prior to the index date, the differences in LDL cholesterol (6.9 mg/dL) and SBP (4.0 mmHg) are potentially clinically significant, and favored the intervention group. However, the post hoc power analysis shown in Table 3 indicates that substantially larger sample sizes would have been required to adequately assess the statistical significance of these observed differences, and to confirm or refute the observed positive trends in A1C, BP, and LDL cholesterol levels among the subgroup of subjects who had not filled the new prescription by the index date (Table 3).

Table 4 gives the results of the intent-to-treat and per-protocol analyses of the intervention effect on a composite measure of improvement in A1C, BP, and LDL cholesterol control. Sufficient data to assess this measure were available for 1,090 of 1,220 intervention subjects (89.3%) and for 1,012 of 1,158 control subjects (87.4%). Clinically significant improvement in the clinical domain of interest occurred in 76.3% of intervention group subjects and 75.9% of control group subjects, a statistically and clinically nonsignificant difference. Additional analyses were performed by the number of clinical domains; among the combined 2,378 study subjects, 2,933 clinical domains were not at goal and had a new medication prescribed. There were sufficient data to adjudicate clinical improvement for 1,157 of 1,501 clinical domains (77.1%) in the intervention group and 1,082 of 1,432 clinical domains (75.6%) in the control group. Clinical improvement occurred in 75.7% of the 1,157 intervention group clinical domains and in 75.4% of the 1,082 control group clinical domains (P = 0.87). No significant differences in improvement were noted in subgroups defined by patient sex, age group, race, or ethnicity. There were no significant differences in response to the intervention across the four study sites, or based on whether the case manager was a pharmacist, diabetes educator, or nurse health manager. A secondary analysis that compared differences in improvement between intervention subjects who did and did not have successful contact with the case manager showed no significant main effect (P = 0.74) or significant differences in subgroups defined by sex, age group, race, ethnicity, or type of case manager. Results were similar in those with one versus more than one clinical domain targeted by the intervention.

**CONCLUSIONS**

In this population-based, pragmatic randomized controlled trial, we studied the impact of a very brief structured telephone intervention on clinical and adherence measures among patients with diabetes who had been prescribed a new class of medication for the treatment of uncontrolled A1C, BP, or LDL cholesterol. The telephone intervention was delivered by interventionists who were pharmacists, diabetes educators, or nurse health managers trained in the use of the study protocol and intervention. The intervention failed to significantly improve primary adherence, medication persistence, MPR, or the main composite measure of improved glucose, BP, or LDL cholesterol control.

There are several possible explanations for the failure of this intervention to have its desired effect. Although the intervention was grounded in a coherent conceptual model and delivered by clinicians carefully trained and monitored for intervention fidelity, it was brief. The intervention included a single telephone contact with a median duration of <5 min delivered a median time of 2–3 weeks after the patient was prescribed a new class of medication for uncontrolled glucose, BP, or lipids. Successful case-manager interventions in prior randomized trials (7,8) of adults with diabetes have typically included much more patient contact, sometimes delivered by a clinic-based nurse working with the patient’s primary care provider. However, some prior reports (11,12) indicate that brief telephone contact or other brief interventions may be sufficient to improve primary adherence rates.

It is notable that, in our study, an estimated 76%, 78%, and 66% of those subjects prescribed new medications for glucose, BP, and lipids, respectively, had already filled them before the interventionist called. The high medication fill rate before the intervention call in effect reduced the power for the study to detect intervention effects. We observed differences of 0.18% (2 mmol/mol) in A1C, 4 mmHg in SBP, and 6.9 mg/dL in LDL cholesterol in favor of the intervention group when limiting the analysis to

| Outcome | A1C (%) | SBP (mmHg) | LDL cholesterol (mg/dL) |
|---------|---------|------------|------------------------|
| Pooled SD | 1.81 | 19.2 | 36.4 |
| Difference to detect (observed difference) | 0.18 (2 mmol/mol) | 4.0 | 6.9 |

Table 3—Post hoc power analysis to detect observed differences in clinical parameters as significant within the subset of patients who had not filled their new prescription prior to the index date.
of our intervention strategy. More precise identification of early primary nonadherence, and might improve the clinical impact and efficiency of our intervention strategy.

The potential advantages of a more targeted approach are suggested by a recent report that evaluated the impact of an automated telephone call to patients with uncontrolled dyslipidemia who did not fill their new statin prescription within 2 weeks. Compared with a randomized control group, intervention-group patients filled their initial statin prescription more often (42.3% vs. 26.0%, \( P < 0.001 \)), although the impact on subsequent LDL cholesterol levels was not reported (10). However, at present, this type of precisely targeted intervention can be delivered in a timely fashion only in integrated care systems that have close to real-time consolidation of prescription data from EMRs and prescription fill data from pharmacy databases (20).

Notably, only a small fraction of subjects who had levels of A1C \( \geq 8\% \) (64 mmol/mol), BP \( \geq 140/90 \) mmHg, or LDL cholesterol \( > 100 \) mg/dL had a new class of medications prescribed at a given clinical encounter. Similar low rates have been previously reported (21–23) in both primary care and subspecialty outpatient practices, and suggest that more attention needs to be directed to the timely initiation and intensification of medications in patients who are not at key evidence-based clinical goals.

| Table 4—Proportion of patients with improvement in composite measure of improvement in A1C, LDL, or SBP among patients with that clinical condition uncontrolled at baseline |
|---|---|---|---|---|---|
| Control (CTL;\( n = 1,158 \) patients, 1,432 clinical domains) | Intervention (INT;\( n = 1,220 \) patients, 1,501 clinical domains) | SC subgroups (\( n = 563 \) patients, 690 clinical domains) | No SC subgroups (\( n = 657 \) patients, 811 clinical domains) | \( P \) value |
| **Patient-specific analysis** | | | | |
| Baseline and follow-up measurement | | | | |
| Improvement by medication persistence | 1,158 | 1,220 | 563 | 657 | 0.813 0.739 |
| Yes | 1,012 (87.4) | 1,090 (89.3) | 510 (90.6) | 580 (88.3) | 0.676 |
| Improvement | 768 (75.9) | 832 (76.3) | 391 (76.7) | 441 (76.0) | 0.865 0.676 |
| **Condition-specific analysis** | | | | |
| Baseline and follow-up measurement | 1,432 | 1,501 | 690 | 811 | 0.865 0.676 |
| Improvement by age group | 1,082 (75.6) | 1,157 (77.1) | 543 (78.7) | 614 (75.7) | 0.802 0.676 |
| Improvement by race | 816 (75.4) | 876 (75.7) | 414 (76.2) | 462 (75.2) | 0.827 0.676 |
| Improvement by Hispanic ethnicity | 1,022 (72.1) | 1,114 (75.5) | 535 (90.6) | 610 (75.6) | 0.802 0.676 |
| Improvement by sex | 428/564 (75.9) | 441/596 (74.0) | 220/292 (75.3) | 221/304 (72.7) | 0.227 0.962 |
| Male | 388/518 (74.9) | 435/561 (77.5) | 194/251 (77.3) | 241/310 (77.7) | 0.227 0.962 |
| Female | 102/132 (77.3) | 116/148 (78.4) | 82/108 (75.9) | 34/40 (85.0) | 0.536 0.248 |
| Improvement by pharmacist | 126/168 (75.0) | 112/161 (69.6) | 49/66 (74.2) | 63/95 (66.3) | 0.597 0.413 |
| Nurse health manager | 98/136 (72.1) | 114/151 (75.5) | 50/71 (70.4) | 44/52 (84.6) | 0.536 0.248 |
| Pharmacist | 539/713 (77.3) | 581/766 (75.8) | 290/379 (76.5) | 291/387 (75.2) | 0.536 0.248 |
| Improvement by diabetes educator | 38/53 (71.7) | 34/43 (79.1) | 16/20 (80.0) | 18/23 (78.3) | 0.501 0.202 |
| Other/unknown | 221/307 (72.0) | 264/341 (77.4) | 119/155 (76.8) | 145/186 (78.0) | 0.124 0.184 |
| White | 500/653 (76.6) | 508/677 (75.0) | 248/323 (76.8) | 260/354 (73.4) | 0.124 0.184 |
| Black | 95/122 (77.9) | 104/139 (74.8) | 47/65 (72.3) | 57/74 (77.0) | 0.124 0.184 |
| No | 358/469 (76.3) | 380/493 (77.1) | 189/254 (74.4) | 191/239 (79.9) | 0.124 0.184 |

Data are \( n \) (%) or \( n/T \) (%), unless otherwise indicated. CTL, control; INT, intervention; SC, successful contact; T, total number of uncontrolled conditions belonging to the indicated subgroup for which baseline and follow-up measurements are available.
Although primary adherence to newly prescribed medications was in the 75–80% range, the relatively low medication persistence rate we observed at 180 days of follow-up, which was confirmed in data from other studies, underscores the importance of efforts to improve longer-term persistence with key medications (e.g., metformin and statins) that have conferred substantial clinical benefits in multiple randomized trials (19, 24–27). It is possible that synchronizing interventions to the date of a second or third medication refill may be a strategy to consider (28, 29).

A number of factors limit the interpretation of our data. First, the study was conducted at four medical groups with sophisticated health informatics systems, and the generalization of results to other care settings may be limited. Second, the study was underpowered to detect observed clinically meaningful changes in BP and LDL cholesterol control in the subset of patients who had not filled their new prescription before the intervention call (Table 3). Our inability to rapidly link prescription data with claims data at all sites prevented us from implementing an intervention that targeted only those who had not yet filled their new prescription. Future studies that explore a more targeted approach are needed. Finally, our intervention involved resource-intensive personal calls to patients; more experimentation with less expensive automated communication approaches is needed.

In summary, this low-intensity intervention did not significantly improve medication adherence or intermediate outcomes of diabetes care. Wide use of this strategy may not be warranted, and alternative approaches to identify and improve medication adherence are needed.

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