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# Effect of a Remotely Delivered Tailored Multicomponent Approach to Enhance Medication Taking for Patients With Hyperlipidemia, Hypertension, and Diabetes

## The STIC2IT Cluster Randomized Clinical Trial

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**IMPORTANCE** Approximately half of patients with chronic conditions are nonadherent to prescribed medications, and interventions have been only modestly effective.

**OBJECTIVE** To evaluate the effect of a remotely delivered multicomponent behaviorally tailored intervention on adherence to medications for hyperlipidemia, hypertension, and diabetes.

**DESIGN, SETTING, AND PARTICIPANTS** Two-arm pragmatic cluster randomized controlled trial at a multispecialty group practice including participants 18 to 85 years old with suboptimal hyperlipidemia, hypertension, or diabetes disease control, and who were nonadherent to prescribed medications for these conditions.

**INTERVENTIONS** Usual care or a multicomponent intervention using telephone-delivered behavioral interviewing by trained clinical pharmacists, text messaging, pillboxes, and mailed progress reports. The intervention was tailored to individual barriers and level of activation.

**MAIN OUTCOMES AND MEASURES** The primary outcome was medication adherence from pharmacy claims data. Secondary outcomes were disease control based on achieved levels of low-density lipoprotein cholesterol, systolic blood pressure, and hemoglobin A<sub>1c</sub> from electronic health records, and health care resource use from claims data. Outcomes were evaluated using intention-to-treat principles and multiple imputation for missing values.

**RESULTS** Fourteen practice sites with 4078 participants had a mean (SD) age of 59.8 (11.6) years; 45.1% were female. Seven sites were each randomized to intervention or usual care. The intervention resulted in a 4.7% (95% CI, 3.0%-6.4%) improvement in adherence vs usual care but no difference in the odds of achieving good disease control for at least 1 (odds ratio [OR], 1.10; 95% CI, 0.94-1.28) or all eligible conditions (OR, 1.05; 95% CI, 0.91-1.22), hospitalization (OR, 1.02; 95% CI, 0.78-1.34), or having a physician office visit (OR, 1.11; 95% CI, 0.91-1.36). However, intervention participants were significantly less likely to have an emergency department visit (OR, 0.62; 95% CI, 0.45-0.85). In as-treated analyses, the intervention was associated with a 10.4% (95% CI, 8.2%-12.5%) increase in adherence, a significant increase in patients achieving disease control for at least 1 eligible condition (OR, 1.24; 95% CI, 1.03-1.50), and nonsignificantly improved disease control for all eligible conditions (OR, 1.18; 95% CI, 0.99-1.41).

**CONCLUSIONS AND RELEVANCE** A remotely delivered multicomponent behaviorally tailored intervention resulted in a statistically significant increase in medication adherence but did not change clinical outcomes. Future work should focus on identifying which groups derive the most clinical benefit from adherence improvement efforts.

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The underuse of evidence-based therapies for cardiovascular and other chronic conditions imposes a substantial clinical and economic burden on patients and health care systems.<sup>1-3</sup> Because rates of underdiagnosis and underprescribing have improved substantially, much of the ongoing underuse problem is attributable to patients not taking their medications as prescribed.<sup>4</sup>

A wide variety of interventions have been developed to improve medication adherence,<sup>5-7</sup> but, when rigorously tested, many of these approaches have only been moderately successful.<sup>5,8-11</sup> This limited efficacy may reflect the fact that many interventions do not adequately address each individual's unique barriers to adherence and/or only do so at a single point in time.<sup>12</sup> In addition, among those interventions demonstrating success, many have not been widely adopted because of the substantial human resources required to sustain them.<sup>13</sup>

We evaluated the effect of an intervention to improve medication adherence among patients with hypertension, hyperlipidemia, or diabetes. Study participants were nonadherent to their prescribed medications and had clinical evidence of poor disease control. The intervention was behaviorally tailored to their individual needs and was intended to be cost-efficient.

## Methods

### Study Design

The Study of a Telepharmacy Intervention for Chronic Diseases to Improve Treatment Adherence (STIC2IT) trial was a pragmatic, prospective, open-label, intention-to-treat, cluster randomized controlled trial. Details of the study design and protocol have been published previously.<sup>14</sup> The trial protocol was designed, written, and conducted by the investigators and is available in [Supplement 1](#). Additional details of the methods can be found in the eMethods in [Supplement 2](#). The authors analyzed the trial data using an independent copy of the study database and vouch for analytic accuracy and completeness, as well as the fidelity of the report to the study protocol. The study was monitored by an independent data and safety monitoring committee. The trial was approved by the institutional review board of Brigham and Women's Hospital. Requirements to obtain formal informed consent were waived because the risks to participation were deemed no more than minimal. Study enrollment began in August 2015 and was completed after full enrollment in July 2016. Follow-up of all trial participants ended July 2017.

### Study Setting and Randomization

This trial was conducted at Atrius Health, a large multispecialty medical group. Randomization occurred at the level of the primary care practice sites such that all primary care clinicians in a given practice site were assigned to the same study arm. We chose to use cluster randomization at the practice level to minimize contamination by clinical pharmacist and primary care clinician (see eMethods in [Supplement 2](#)).

Study participants, study staff interacting with patients, and the clinical pharmacist were not blinded to group assign-

## Key Points

**Question** Does a remotely delivered multicomponent behaviorally tailored intervention improve adherence to medications for hyperlipidemia, hypertension, and diabetes vs usual care?

**Findings** In this cluster randomized clinical trial of 14 primary care practice sites with 4078 adults with poorly controlled disease who were nonadherent to prescribed medications, the intervention improved medication adherence but did not significantly improve disease control.

**Meaning** A multicomponent, technologically enabled pharmacist intervention tailored to patients' adherence barriers and level of health activation improved medication adherence for patients with common, chronic conditions but did not change clinical outcomes.

ment. Study investigators and data analysts remained blinded until all follow-up data were obtained and the primary analytic strategies were finalized.

### Study Population and Enrollment

We included patients who were at least 18 and younger than 85 years of age who had a diagnosis of hyperlipidemia, hypertension, or diabetes based on their having filled a relevant prescription medication (ie, statins, antihypertensives, or oral glucose-lowering agents), had evidence of poor or worsening disease control for at least 1 of these conditions, and were nonadherent to the prescribed therapy for their uncontrolled conditions.

Disease control was evaluated using the most recent laboratory or blood pressure values in the electronic health record at the time of enrollment and was based on clinical guideline targets (see eAppendix 1 in [Supplement 2](#)).<sup>15-17</sup> Adherence was assessed with prescription claims data, a validated measure of medication taking that is widely used in quality improvement efforts,<sup>18</sup> by calculating a mean proportion of days covered for all conditions that a patient had at the time of their identification.

Patients were excluded if, prior to randomization, they had less than 6 months of continuous enrollment in the health plan (to allow adequate assessment of eligibility) or had no available telephone contact information, which would preclude contact for enrollment and delivery of the intervention.

Once identified, each patient's primary care physician, all of whom had received information about the study prior to the beginning of enrollment, was contacted to ask permission to include their patient(s) in the study. Patients approved for enrollment were sent a letter on behalf of their primary care clinician informing them about the study. They were then contacted by telephone and were invited to participate. Patients who agreed were scheduled to have a telephone consultation with a clinical pharmacist and were administered the Patient Activation Measure, a questionnaire to assess the knowledge, skills, and confidence to manage one's health and health care.<sup>19,20</sup> As described herein, each patient's activation level was subsequently used to tailor the intervention that they received.

## Intervention

The central component of the multifaceted intervention was an individually tailored telephone consultation conducted by a staff clinical pharmacist. During this consultation, the clinical pharmacist used a semistructured guide to confirm the patient's treatment regimen, engaged them in sharing potential barriers to adherence or other factors that may be contributing to poor disease control, discussed the patient's readiness to modify behaviors, and worked with the patient to develop a shared plan to improve adherence and disease control. The structure of these telephone consultations was developed by the study team using brief negotiated interviewing,<sup>21-23</sup> a behavioral interviewing technique with foundations in motivational interviewing.

The strategies were tailored to patients' activation level and their identified adherence barrier(s) and included (1) structured consultation reports sent to patients' primary care physicians with recommendations for modifying treatment regimens and coordinating care, (2) strategies to promote adherence including text messages and pillboxes, and (3) follow-up consultations (eMethods in Supplement 2).

Mailed progress reports were sent to intervention patients at 6 and 9 months after randomization on behalf of their primary care clinician and summarized personalized and updated information about disease control generated using data from the electronic health record and medication adherence from administrative claims.

## Study Outcomes

The trial's primary outcome was medication adherence assessed at 12 months after randomization. This outcome was assessed using prescription claims data and measured as the mean proportion of days covered over the 12 months after randomization using the "average of averages" approach used for study eligibility (eMethods in Supplement 2). Adherence was measured only for medications that qualified a patient for inclusion in the study beginning at the time of randomization.<sup>24</sup>

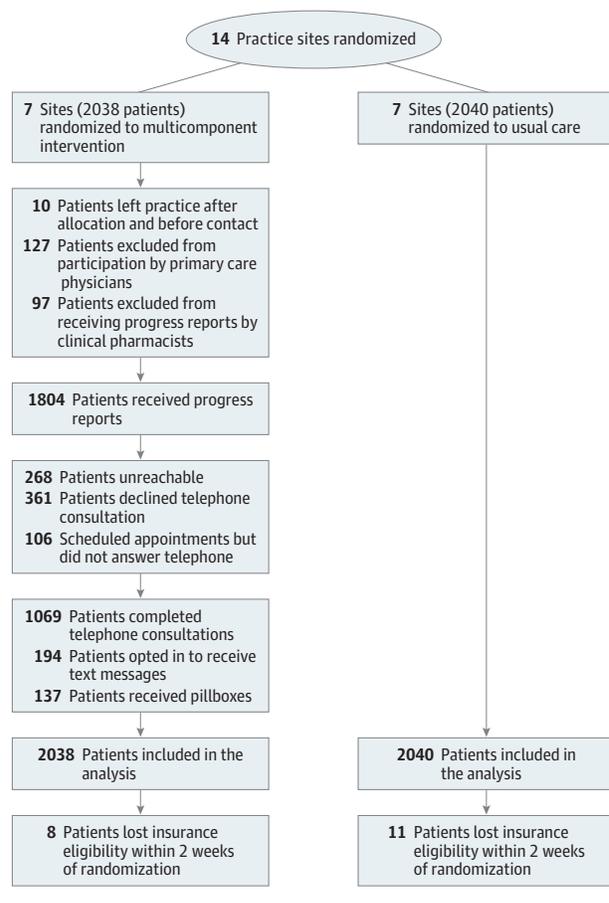
The prespecified secondary clinical outcomes were disease control and rates of health care utilization. As described in the eMethods in Supplement 2, disease control was measured as the proportion of patients achieving "good" disease control based on guideline-specified targets<sup>14-17</sup> for at least 1 and all of their eligible conditions.

Health care utilization was measured using administrative claims data and included all-cause emergency department visits, physician office visits, and hospitalizations during follow-up.

## Statistical Analysis

We powered the study to detect a 2.5% mean change in adherence between the intervention and control groups regardless of whether patients actually received the intervention. We reported the means and frequencies of prerandomization variables separately for intervention and control patients and compared them using standardized mean differences. We used intention-to-treat principles for all randomized patients. In the primary analysis, the outcomes were compared using generalized estimating equations with an identity link function and

Figure 1. Study Flow Diagram



normally distributed errors to account for the clustering of patients within practice sites; these models also adjusted for the block-randomized design. For baseline characteristics between study groups that had a standardized mean difference greater than 0.1, we repeated our analyses after adjusting for these covariates. We also conducted an "as-treated" analysis that compared patients who received the clinical pharmacist intervention with usual care, with and without adjustment for differences in baseline characteristics. Subgroup analyses were also performed according to age, sex, race/ethnicity, baseline adherence levels, and number of conditions and medications that identified the patients for the study. There were no missing data for the primary outcome or for resource utilization. Multiple imputation was used to handle missing data for our clinical outcomes (eMethods in Supplement 2).

## Results

We randomized 2038 patients to receive the intervention and 2040 to usual care (Figure 1). Participants had a mean (SD) age of 59.8 (11.6) years, 1841 (45.1%) were female, and 1749 (42.9%) were of nonwhite race/ethnicity. The baseline characteristics of the intervention patients are presented in Table 1. Intervention patients were slightly older and less likely to be of white

Table 1. Patient Characteristics by Group<sup>a</sup>

Characteristic	Intervention (n = 2038)	Usual Care (n = 2040)
Age, mean (SD), y	60.4 (11.7)	59.2 (11.5)
Male sex, No. (%)	1114 (54.7)	1123 (55.0)
White race, No. (%)	1093 (53.6)	1236 (60.6)
English language speaker, No. (%)	1857 (91.1)	1879 (92.1)
Comorbidities, No. (%) <sup>b</sup>		
Prior acute coronary syndrome	35 (1.7)	44 (2.2)
Heart failure	88 (4.3)	59 (2.9)
Dementia	30 (1.5)	29 (1.4)
Depression	124 (6.1)	135 (6.6)
Chronic kidney disease	155 (7.6)	120 (5.9)
Smoking	71 (3.5)	80 (3.9)
Charlson comorbidity score, mean (SD)	0.90 (1.8)	0.74 (1.6)
Unique prescription medications filled, mean (SD)	7.9 (5.5)	7.7 (5.2)
Qualifying conditions, No. (%)		
Hyperlipidemia	1467 (72.0)	1503 (73.7)
Hypertension	529 (25.9)	486 (23.8)
Diabetes	246 (12.1)	242 (11.9)
No. of qualifying conditions per patient, mean (SD)	1.1 (0.32)	1.1 (0.30)
Baseline disease control <sup>c</sup>		
Low-density lipoprotein cholesterol, mean (SD), mg/dL	113.3 (38.6)	117.9 (41.6)
Systolic blood pressure, mean (SD), mmHg	149.9 (13.1)	149.2 (12.8)
Hemoglobin A <sub>1c</sub> , mean (SD), %	9.8 (1.8)	9.5 (1.4)
No. of medications for qualifying conditions, mean (SD)	1.3 (0.70)	1.3 (0.65)
Baseline adherence, mean % (SD) <sup>d</sup>	57.0 (18.0)	57.2 (18.6)

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; to convert hemoglobin A<sub>1c</sub> to proportion of total hemoglobin, multiply by 0.01.

<sup>a</sup> Standardized mean differences between intervention and control for age and race/ethnicity were greater than 0.1; otherwise, there were no significant differences between treatment arms.

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

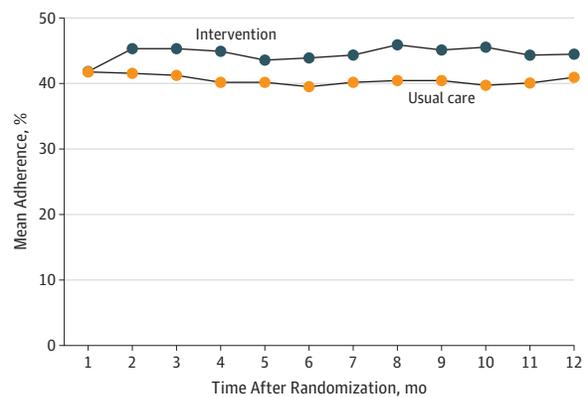
<sup>c</sup> Among patients for whom the listed condition qualified them for inclusion into the study.

<sup>d</sup> Baseline adherence was calculated as the mean adherence prior to randomization for all potentially eligible medication classes. In contrast, the adherence outcome was calculated using only those conditions for which, prior to randomization, they had both poor adherence and suboptimal disease control (see eMethods and eFigure 1 in Supplement 2 for more details).

race/ethnicity but were otherwise similar to usual care patients, including with respect to baseline levels of disease control and medication adherence, with standardized mean differences less than 0.1.

Characteristics of intervention participants who were or were not approved for a clinical pharmacist consultation by their primary care clinicians are provided in eTable 1 in Supplement 2. Reasons for nonapproval are presented in eTable 2 in Supplement 2. Among approved patients, characteristics of participants who did and did not agree to consultation are reported in eTable 3 in Supplement 2. One hundred (4.9%) patients were initially unreachable or declined participation

Figure 2. Medication Adherence by Treatment Group Over Time



but subsequently scheduled a pharmacist consultation after receiving a mailed progress report.

In total, 1069 (52.5%) intervention patients completed a telephone consultation with a clinical pharmacist that lasted a mean (SD) of 24.9 (12.5) minutes; among those who completed the initial telephone consultation, 1050 (98.2%) patients received a second call and 175 (16.4%) patients received 3 or more calls. During these consultations, 654 (61.2%) patients had at least 1 barrier for nonadherence identified and 268 (25.1%) patients had 2 or more barriers identified. The most common were forgetfulness (417 [39.0%]), misperceptions about the benefits of treatment (294 [27.5%]), and adverse effects (148 [13.8%]). The clinical pharmacists provided counseling about the disease being treated and the benefits and risks of their prescribed treatments to 765 (71.6%) patients; recommended reminder aids such as pillboxes or alarms for 620 (58.0%) patients; suggested medication, dosage, or timing changes with the specific intent of enhancing adherence for 216 (20.2%) patients; made a referral to social work or other similar services for 99 (9.3%) patients; offered strategies to reduce medication adverse effects for 87 (8.1%) patients; and offered methods to reduce medication costs for 51 (4.8%) patients.

Among the 415 (38.8%) patients without an identified adherence barrier, 103 patients reported that they had recently become adherent. In the remaining 312 cases, the clinical pharmacists believed that the pattern of medication filling in the prescription claims data did not actually represent nonadherence, either because treatment regimens had been changed (133 [12.4%]), patients paid cash for the medications or used an alternative insurance plan (119 [11.1%]), or they had other potential reasons, such as a hospitalization (61 [5.7%]).

Of the 1069 intervention patients who received a telephone consultation, 194 (18.1%) opted in to receive text messages. Among all 2038 intervention patients, 1804 (88.5%) were sent quarterly progress reports.

Trends in adherence during follow-up in the 2 arms are shown in Figure 2. Mean (SD) adherence during follow-up among patients allocated to usual care was 42.1% (33.8%). The intervention resulted in a 4.7% (95% CI, 3.0%-6.4%) improvement in medication adherence (Table 2). The results remained unchanged after adjustment for imbalances in base-

Table 2. Medication Adherence by Group

Adherence	Adherence, %, Mean (SD)		Absolute Difference, % (95% CI)	
	Intervention	Usual Care	Unadjusted	Adjusted <sup>a</sup>
Overall	46.2 (33.9)	42.1 (33.8)	4.7 (3.0 to 6.4)	4.9 (3.3 to 6.4)
Disease subgroups				
Hyperlipidemia (n = 2970)	48.2 (33.7)	44.1 (33.6)	4.5 (2.1 to 6.8)	4.9 (2.8 to 7.0)
Hypertension (n = 1015)	42.7 (33.4)	35.9 (33.0)	8.5 (5.4 to 11.7)	7.6 (4.1 to 11.1)
Diabetes (n = 488)	39.8 (30.2)	40.9 (31.0)	1.5 (-1.9 to 4.9)	0.1 (-3.6 to 3.8)

<sup>a</sup> Adjusted for age and race/ethnicity.

Table 3. Clinical and Health Care Utilization Outcomes by Group

Outcome	Intervention (n = 2038)	Usual Care (n = 2040)	Unadjusted	Adjusted <sup>a</sup>
Clinical				
Effect Estimate (95% CI) <sup>b</sup>				
Patients achieving good control, No. (%) <sup>c</sup>				
On ≥1 condition	1486 (72.9)	1452 (71.2)	1.10 (0.94 to 1.28)	1.12 (0.96 to 1.30)
On all eligible conditions	1374 (67.4)	1350 (66.2)	1.05 (0.91 to 1.22)	1.07 (0.92 to 1.24)
Disease-specific measures, mean (SD)				
Hyperlipidemia, LDL cholesterol, mg/dL (n = 2970)	103.3 (33.0)	108.5 (35.7)	-5.3 (-8.3 to -2.36)	-4.8 (-7.7 to -1.9)
Hypertension, systolic blood pressure, mmHg (n = 1015)	137.6 (17.0)	134.8 (15.9)	2.8 (0.3 to 5.3)	2.3 (-0.3 to 4.8)
Diabetes, hemoglobin A <sub>1c</sub> (n = 488)	9.3 (2.0)	9.2 (1.8)	0.2 (-0.2 to 0.5)	0.2 (-0.2 to 0.5)
Health Care Utilization				
Odds Ratio (95% CI)				
Emergency department visits	90 (4.4)	113 (5.5)	0.62 (0.45 to 0.85)	0.59 (0.51 to 0.68)
Physician office visits	641 (31.5)	594 (29.1)	1.11 (0.91 to 1.36)	0.99 (0.92 to 1.06)
Hospitalizations	170 (8.3)	156 (7.7)	1.02 (0.78 to 1.34)	1.01 (0.80 to 1.27)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LDL, low-density lipoprotein.

<sup>a</sup> Adjusted for age and race/ethnicity.<sup>b</sup> Effect estimates are odds ratios for the percentage of patients achieving good control on at least 1 and all eligible outcomes. For mean disease-specific measures, the effect estimates are absolute differences.<sup>c</sup> Defined by hemoglobin A<sub>1c</sub> less than 8% (to convert to proportion of total hemoglobin, multiply by 0.01), systolic blood pressure less than 150 mm Hg (for age ≥60 y) or less than 140 mm Hg (for age <60 y), and LDL cholesterol less than 100 mg/dL (for ASCVD risk >20%), LDL less than 130 mg/dL (for ASCVD risk 10%-20%), or LDL less than 160 mg/dL (for ASCVD risk <10%) (to convert to millimoles per liter, multiply by 0.0259).

line characteristics. Within disease-specific subgroups, the intervention significantly improved adherence to antihypertensive medications and statins, but not to oral hypoglycemics.

In the as-treated analysis, mean adherence among patients receiving the intervention was 10.4% higher (95% CI, 8.2%-12.5%) than in the usual care group (eTable 4 in Supplement 2). In sensitivity analyses that evaluated only adherence to medications filled after randomization and which censored patients with diabetes when they started insulin use, the results were similar to the primary analyses (eTable 4 in Supplement 2). The effect of the intervention did not differ based on baseline level of adherence, the number of conditions or medications for which patients were eligible, and race. However, the intervention was more effective in men than in women (eTable 5 in Supplement 2). Adherence results by study site are presented in eFigure 2 in Supplement 2.

Analyses of secondary disease control outcomes are presented in Table 3. The mean (SD) duration of time between randomization and outcome assessment was 229.2 (100.9) days. Among usual care patients, 1350 (66.2%) achieved good disease control for all of their eligible conditions and 1452 (71.2%) achieved good control for at least 1 eligible condition. The intervention did not significantly

change the odds of achieving good disease control for either of these outcomes (≥1 eligible condition: unadjusted odds ratio [OR], 1.10; 95% CI, 0.94-1.28; all eligible conditions: unadjusted OR, 1.05; 95% CI, 0.91-1.22). In disease-specific subgroups, the intervention resulted in a small reduction in low-density lipoprotein cholesterol level (adjusted absolute difference, -4.8 mg/dL; 95% CI, -7.7 to -1.9 mg/dL). Systolic blood pressure was higher among intervention participants, although this effect was no longer significant in multivariable models. In an “as treated” analysis, the intervention significantly improved disease control in at least 1 eligible condition (OR, 1.24; 95% CI, 1.03-1.50). There was a nonsignificant finding of improvement in disease control for all eligible conditions (OR, 1.18; 95% CI, 0.99-1.41) (eTable 6 in Supplement 2). A complete case sensitivity analysis found similar results to the primary analyses of the clinical outcomes (eTable 7 in Supplement 2).

Rates of hospitalization and physician office visits were similar between the 2 groups, although we observed significantly fewer emergency department visits in the intervention group (90 [4.4%]) vs the control group (113 [5.5%]) (unadjusted OR, 0.62; 95% CI, 0.45-0.85) (Table 3). An “as-treated” analysis showed similar results (eTable 8 in Supplement 2).

## Discussion

In this pragmatic, cluster randomized trial of individuals with suboptimally controlled hyperlipidemia, hypertension, and diabetes who were nonadherent to therapy, we found that a tailored, pharmacist-led, multicomponent, technologically enabled intervention resulted in a statistically significant improvement in medication adherence but did not influence clinical outcomes. The intervention significantly reduced emergency department visits but did not affect rates of hospitalizations or physician office visits.

Following intention-to-treat principles, we analyzed the intervention's effectiveness among all patients allocated to intervention, even though only half of patients accepted the most intensive part of the strategy: pharmacist consultation. As such, the actual effect among those exposed to intervention is likely to have been larger than the average treatment effect. In our as-treated analysis, the intervention resulted in a 10% improvement in adherence, which is similar to other studies of pharmacist-led interventions to improve medication adherence conducted with individual-level randomization.<sup>9,25</sup> These studies, which had substantially smaller sample sizes than our trial, have generally involved repeated in-person pharmacist consultations and/or have been conducted in countries with different health systems than in the United States.

In contrast, we tested an intervention that was designed to be scalable in a domestic context. The consultations were conducted on the telephone by clinical pharmacists, already working as clinicians in the integrated practice network where the study was conducted. Most patients received only 2 short consultations. The clinical pharmacists spent a total of 985 hours conducting these calls, or 29 minutes per patient. Assuming a mean annual pharmacist salary of \$120 000, this amounts to \$30 per patient per year. Our intervention also had other components although their marginal costs were small.<sup>26</sup> By comparison, removing financial barriers for evidence-based medication typically improves adherence by 3% to 6% and is one of the most consistently effective adherence interventions reported in the literature.<sup>27</sup> Eliminating patient out-of-pocket costs for just 1 medication, conservatively assuming monthly copayments of \$10,<sup>28,29</sup> would cost \$120 per patient per year.

While we met the trial's primary outcome, we did not observe an overall effect of the intervention on disease control. In the MI FREEE trial, a 4% to 5% increase in adherence, like we observed in the present trial, was sufficient to reduce rates of cardiovascular events. However, that study included higher-risk patients and resulted in improvements in 3 medication classes that work synergistically.<sup>30</sup> For patients with stable hypertension or hyperlipidemia, small trials of pharmacist interventions that improved clinical outcomes were associated with absolute improvements in adherence of 20% or more.<sup>31,32</sup> Patients in these trials had relatively good disease control and were not selected because they were nonadherent to their prescribed therapies.

Our study population falls between these 2 extremes, and our results suggest that larger improvements in adherence

might be necessary to drive clinical effects for similar individuals. This is consistent with our as-treated results, in which the observed 10% improvement in adherence was associated with a significantly greater percentage of patients achieving disease control on at least 1 eligible condition and a nonsignificant finding in this same direction for the outcome of achieving disease control on all eligible conditions. By extension, our intervention may have benefited from being more intensive, for example, by having a greater proportion of patients agree to pharmacist consultation or having more follow-up consultations per patient.

Alternatively, targeting a different patient population might have increased the effectiveness of the intervention as we designed it. We focused on patients whom we hypothesized would be most likely to benefit from adherence improvement. It is possible that the intervention may have been more effective for individuals with suboptimal but better disease control than we included. Or, while the 3 conditions that we studied often coexist, improvements in adherence may have different influences on clinical outcomes. This may explain our observation that patients with hyperlipidemia had improvements in both adherence and clinical outcomes while patients with hypertension had even larger changes in adherence with no effect on clinical outcomes. Conversely, in approximately 30% of cases, the clinical pharmacists believed that patients were not actually nonadherent. This was most commonly because of changes to treatment regimens or patients paying cash for their medications or using alternative insurance. If these patients were less in need of or less responsive to adherence support, this would have reduced the overall effect of the intervention. That said, it is still possible that the intervention benefited these individuals because adherence is highly dynamic. Many patients who are presently adherent will become nonadherent in the future,<sup>33</sup> and the intervention may have prevented this decline. Furthermore, when interacting with patients whom they believed were adherent, the clinical pharmacists focused on lifestyle modifications or addressing other clinical concerns based on their professional judgment.

In keeping with this, we observed a significant reduction in emergency department visits for patients randomized to the intervention. Given the overall null clinical effects, we hypothesize that this resulted from mechanisms unrelated to enhancements in adherence; these may include medication reconciliation, medication therapy management, or other similar activities that clinical pharmacists routinely perform when interacting with patients. These services have been associated with reductions in the need for emergent care, such as that arising from adverse drug events.<sup>34-36</sup> However, they have had mixed effects on disease control,<sup>37</sup> an observation that is consistent with the results of our study.

## Limitations

There are limitations to our study that should be acknowledged. We tested our intervention among insured individuals cared for in a multispecialty group practice, and our results may not be applicable to other patient groups. We evaluated adherence using prescription claims, which have

been demonstrated to be valid measures of medication-taking behavior.<sup>38</sup> Nevertheless, the intervention may have motivated patients to fill additional prescriptions without actually consuming more pills. It is also important to acknowledge that some patients, despite having suboptimal disease control, may have made an informed decision not to take the medications that had been prescribed to them, and thus would not have been expected to respond to the intervention that they were offered. We used electronic health record data to evaluate clinical outcomes, and any missing or inaccurate data, even if nondifferential, would have biased treatment effects to the null. The outcome measures themselves, while widely used as quality metrics, might not have been sufficiently sensitive to detect changes from the

intervention among the patients whom we studied, especially given our decision to combine binary measures to create a single interpretable metric. These biometric outcomes are still only proxies of more clinically meaningful events such as myocardial infarction or stroke.

## Conclusions

In this large cluster randomized pragmatic trial, a remotely delivered, tailored multicomponent intervention resulted in a statistically significant increase in medication adherence for patients with common chronic conditions but did not improve disease control.

### ARTICLE INFORMATION

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**Author Contributions:** Drs Choudhry and Lauffenburger had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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