



Original Investigation | Diabetes and Endocrinology

Effectiveness of Targeted Insulin-Adherence Interventions for Glycemic Control Using Predictive Analytics Among Patients With Type 2 Diabetes

A Randomized Clinical Trial

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Abstract

IMPORTANCE Patient adherence to antidiabetic medications, especially insulin, remains poor, leading to adverse outcomes and increased costs. Most adherence interventions have only been modestly effective, partly because they are not targeted to patients who could benefit most.

OBJECTIVE To evaluate whether delivering more intensive insulin-adherence interventions only to individuals with type 2 diabetes predicted to benefit most was more effective than delivering a lower-intensity intervention to a larger group of unselected individuals.

DESIGN, SETTING, AND PARTICIPANTS This 3-arm pragmatic randomized clinical trial used data from Horizon, the largest health insurer in New Jersey, on 6000 participants 18 years or older with type 2 diabetes who were receiving basal insulin. Patients were excluded if they were insured by Medicaid or Medicare or had fewer than 3 months of continuous enrollment. The study was conducted from July 7, 2016, through October 5, 2017. Analyses were conducted from February 5 to September 24, 2018.

INTERVENTIONS Eligible patients were randomized to 3 arms in a 1:1:1 ratio. Randomization was stratified based on baseline availability of 1 or more glycated hemoglobin A_{1c} (HbA_{1c}) test values. All arms were designed to cost the same, and each cohort received a tailored pharmacist telephone consultation varying based on (1) proportion receiving the intervention and (2) intensity, including follow-up frequency and cointerventions. Arm 1 offered a low-intensity intervention to all patients. Arm 2 offered a moderate-intensity intervention to 60% of patients based on their predicted risk of insulin nonadherence. Arm 3 offered a high-intensity intervention to 40% of patients based on glycemic control and predicted risk of insulin nonadherence.

MAIN OUTCOMES AND MEASURES The primary outcome was insulin persistence. Secondary outcomes were changes in HbA_{1c} level and health care utilization. Outcomes were evaluated in arms 2 and 3 vs arm 1 using claims data, intention-to-treat principles, and multiple imputation for missing values in the 12-month follow-up.

RESULTS Among 6000 participants, mean (SD) age was 55.9 (11.0) years and 3344 (59.8%) were male. Compared with arm 1, insulin nonpersistence did not differ in arm 2 (relative risk, 0.88; 95% CI, 0.75-1.03) or arm 3 (relative risk, 0.91; 95% CI, 0.77-1.06). Glycemic control was similar in arm 2 and arm 1 (absolute HbA_{1c} level difference, -0.15%; 95% CI, -0.34% to 0.05%) but was better in arm 3 (absolute HbA_{1c} level difference, -0.25%; 95% CI, -0.43% to -0.06%). Total spending and office

(continued)

Key Points

Question Is delivering more intensive insulin-adherence interventions to targeted subgroups of patients with type 2 diabetes more effective than delivering a lower-intensity intervention to a larger group of unselected patients?

Findings In this 3-arm randomized clinical trial of 6000 patients with type 2 diabetes receiving basal insulin, delivering a high-intensity intervention to those predicted to benefit most did not improve insulin persistence but improved mean glycemic control compared with a low-intensity intervention for all patients.

Meaning Targeting patients for more intensive interventions based both on predicted risk of nonadherence and level of disease control may be more effective than untargeted approaches.

+ Supplemental content

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Abstract (continued)

visits did not differ, but arm 2 (moderate intensity intervention) had more hospitalizations (odds ratio, 1.22; 95% CI, 1.06-1.41) and emergency department visits (odds ratio, 1.38; 95% CI, 1.24-1.53) than did arm 1 (low intensity intervention).

CONCLUSIONS AND RELEVANCE Compared with an untargeted low-intensity intervention, delivering a highly targeted high-intensity intervention did not improve insulin persistence but modestly improved mean glycemic control. A partially targeted moderate-intensity intervention did not change insulin persistence or HbA_{1c} level but was associated with a small increase in hospitalizations.

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Introduction

Despite numerous new therapies, the management of chronic cardiometabolic diseases remains suboptimal, in part because of poor adherence to medications.¹⁻³ Patients with diabetes requiring insulin therapy are a particularly vulnerable subgroup because of unique administration challenges, including anxiety about self-injection and fear of hypoglycemia, and barriers, such as medication costs attributable, in part, to rising costs of insulin.⁴ Although the barriers to optimal medication use are complex, interventions designed to improve medication use are often simple and broadly delivered.^{5,6} As a result, they have generally only been modestly effective.^{7,8}

The ability to effectively target adherence interventions to patients who are most likely to benefit has the potential to improve their effect and efficiency, but this hypothesis has not been adequately evaluated.^{5,9} Even for patients with complex conditions, such as insulin-requiring diabetes, not all require adherence support.¹⁰ From a population health perspective, focusing efforts on those who are most likely to be nonadherent or those with poor disease control may be more effective. Given that more intensive interventions tend to result in larger improvements in adherence,⁷ focusing only on individuals most likely to benefit may allow more resources to be devoted to fewer individuals without increasing overall costs of an intervention program.^{7,11,12} A more potent effect for a comparatively small subgroup may also make it more likely to observe population-level effects when appropriately analyzing quality improvement trials using intention-to-treat principles, even though patient acceptance of interventions may be less than 30%.^{7,12,13}

To test this hypothesis, we launched the Targeted Adherence Intervention to Reach Glycemic Control With Insulin Therapy for Patients With Diabetes (TARGIT-Diabetes) study, a pragmatic, prospective, intention-to-treat randomized clinical trial.¹⁴ This trial evaluated the effectiveness on insulin persistence and glycemic control of a pharmacist-delivered intervention with 3 levels of increasing intensity to progressively more-targeted groups of patients. The core intervention in this trial (ie, a pharmacist telephone consultation) was similar in design to those that are regularly used by many health care organizations, such as telephonic medication therapy management consultations.^{7,15,16}

Methods

Study Design

The trial protocol is given in [Supplement 1](#). This trial was designed to be pragmatic using Pragmatic Explanatory Continuum Indicator Summary (PRECIS-2) trial guidance and was reported using the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.¹⁷ The investigators analyzed the data using an independent copy and vouch for accuracy, completeness, and fidelity. The trial was

approved by the institutional review board of Brigham and Women's Hospital and the privacy board of Horizon Blue Cross Blue Shield of New Jersey, Newark (Horizon). A waiver of informed consent was granted by the institutional review board and privacy board because of the minimal risk nature of the study. Study enrollment began in July 7, 2016, and was completed after full enrollment in October 5, 2016. Follow-up ended in October 5, 2017. The final study database became available in February 5, 2018, with analyses conducted until September 24, 2018.

Study Population and Randomization

This randomized clinical trial was conducted at Horizon, the largest health insurer in New Jersey. We included patients 18 years or older with type 2 diabetes, established through diagnoses codes^{18,19} for diabetes in claims or previous fills of an oral hypoglycemic medication,¹⁴ who filled 1 or more basal (long-acting) insulin prescriptions in the 6 months before randomization. Insulin detemir, glargine, lispro protamine, and Neutral Protamine Hagedorn (NPH) formulations were all considered to be basal insulins. We excluded patients insured by Medicaid or Medicare and those who had fewer than 3 months of continuous enrollment.

Eligible patients were randomized to 3 arms in a 1:1:1 ratio. Randomization was stratified based on baseline availability of 1 or more glycated hemoglobin A_{1c} (HbA_{1c}) test values, which Horizon receives from more than 200 medical homes and population health programs as part of routine quality improvement monitoring, to ensure equal distribution across the study arms. Study participants and pharmacists interacting with patients were not masked to assignment. Study investigators remained masked until all follow-up data were obtained and analytic strategies were finalized.

Intervention

The 3 arms were designed to be equivalently priced to mirror the type of choice a health insurer or health care system would make to allocate funds for a quality improvement program (ie, no targeting, adherence-based targeting, and glycemic control plus adherence-based targeting). Costs were determined by Magellan Rx Management,²⁰ a pharmacy benefit management company, who also delivered the intervention components.

Once randomized, a patient's predicted risk of future nonpersistence to insulin or continued use of insulin was calculated by applying a proprietary regression-based algorithm to Horizon's enrollment data and pharmacy and medical claims data.^{21,22} In brief, this algorithm uses demographic and clinical information from enrollment data and claims as predictors and indicated high model accuracy (>75% overall accuracy at predicting nonpersistence).^{14,21} These predicted risks and patients' glycemic control were used to identify which patients would be targeted for intervention in each arm, described below and in the **Figure**. In arm 1 (untargeted low intensity), 100% of patients were assigned to a low-intensity intervention. In arm 2 (partially targeted moderate intensity), 60% of patients were assigned to a moderate-intensity intervention based on their future risk of insulin nonpersistence. We selected patients with a risk of nonpersistence predicted to be between 10% and 90% to focus on individuals who were most likely to benefit.¹⁴ This threshold was chosen because patients with very high-predicted adherence would not need intervention and those with extremely low-predicted adherence have often completely stopped the therapy for clinically appropriate reasons. In arm 3 (highly targeted high intensity), 40% of patients were assigned to a high-intensity intervention based on both their risk of future nonpersistence (between 20% and 80%) and baseline HbA_{1c} level (ie, whether they had a value and the actual value).¹⁴ Individuals were assigned to the intervention if their HbA_{1c} level was 8% or more, the minimum threshold recommended by the American Diabetes Association,²³ or if they had missing HbA_{1c} values, because these patients are often poorly engaged in care, therefore requiring intervention.¹⁴ These thresholds were chosen to balance costs across arms.

The primary component of the multifaceted intervention in all arms was an individually tailored telephone consultation conducted by a clinical pharmacist based on patients' barriers. Although the

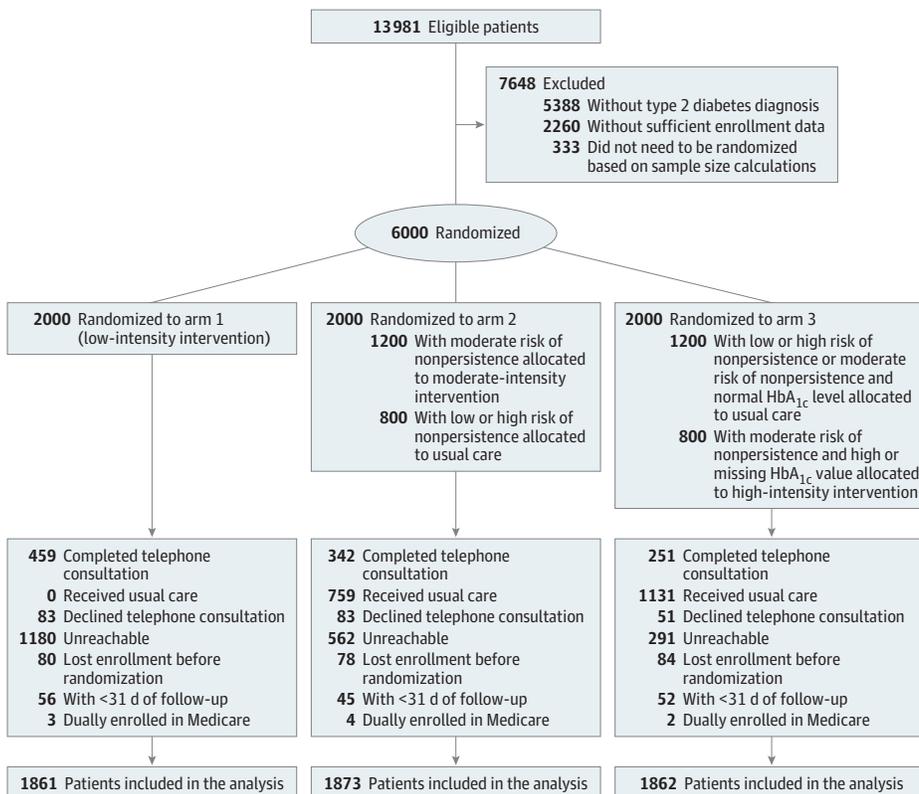
type of outreach and solutions were similar across the arms, they differed in the number of patients receiving the intervention and intensity of the interventions, ranging from low intensity in arm 1 to high intensity in arm 3 (eAppendix 1-4 in Supplement 2). Before study launch, all pharmacists received training in medication therapy management, motivational interviewing, and specific interventions being provided.²⁴ Study staff at the pharmacy benefit-management company regularly monitored the delivery of the intervention to ensure fidelity. During the consultations, pharmacists engaged patients in discussions about their individual beliefs and expectations of treatments and barriers to optimal treatment and provided counseling regarding strategies for achieving good control. Additional detail is provided in the trial protocol (Supplement 1) and published protocol.¹⁴

In arm 1 (untargeted low-intensity), all patients assigned to the treatment arm received a letter informing them about the pharmacist outreach, a reminder postcard, and a small pillbox. Pharmacists attempted to reach everyone in this arm to provide the consultations using the telephone number on record with Horizon. Patients received up to 2 follow-up calls.

In arm 2 (partially targeted moderate intensity), the 1200 patients (60%) selected for outreach received the components in arm 1 but could also receive up to 6 follow-up calls and 2 calls with their primary care clinician and/or pharmacy to clarify treatment issues or receive recommendations for therapeutic changes. Patients were also offered enrollment in a weekly text messaging program focused on medication-taking behaviors, lifestyle choices, and glycemic control. The unselected 40% of patients assigned to arm 2 did not receive any intervention.

In arm 3 (highly targeted high intensity), the 800 patients (40%) selected for outreach received all of the intervention components in arms 1 and 2 and could receive up to 12 follow-up calls; primary care clinicians and/or pharmacies were called as often as necessary. Patients were also offered text messages delivered weekly, every 3 days, or daily. The unselected 60% of patients assigned to arm 3

Figure. CONSORT Flow Diagram



Among 6000 patients randomized to the 3 intervention arms, 2085 had baseline hemoglobin A_{1c} (HbA_{1c}) values (695 in each arm). A total of 242 study subjects (80 in arm 1, 78 in arm 2, and 84 in arm 3) lost insurance eligibility between the time of data pull and randomization; data from these patients were not excluded in the follow-up analyses.

did not receive any intervention. Arm 3 was designed to mimic the most intensive type of strategy that a telephone-based disease management program could offer.

Study Outcomes

The trial's primary outcome was persistence to basal insulin therapy assessed using a previously validated approach in prescription claims data.²¹ Patients were classified as nonpersistent if they did not refill their insulin prescription before a set threshold of time, which was assigned based on historical claims data from Horizon as the 90th percentile of the time between each fill, adjusting for insulin type and quantity dispensed (eAppendix 5 in Supplement 2).¹⁴ Patients were considered to be persistent if they filled a prescription for any basal insulin therapy within that interval and were censored if they lost insurance eligibility.

As described in the eMethods in Supplement 2, the prespecified secondary outcomes included glycemic control, total health care utilization, and health care spending. Glycemic control, only evaluated in patients with baseline HbA_{1c} values, was measured as the change in HbA_{1c} level from baseline to follow-up. Multiple imputation was used to handle missing data for glycemic control (382 [19.6%] of patients).²⁵ Health care utilization was measured using claims data and included all-cause emergency department visits, physician office visits, and hospitalizations during follow-up. There were no missing data on the primary outcome or resource utilization. Follow-up for all outcomes began 1 month after randomization (the earliest patients could receive the intervention because of time required for data processing and mailing), and continued through 12 months after randomization.

Statistical Analysis

We randomized 6000 patients to achieve more than 80% power to detect a 15% relative decrease in the risk of insulin nonpersistence between either targeted arm (arm 2 or 3) and arm 1. We reported the means and frequencies of prerandomization variables separately by arm and compared them using analysis of variance for continuous variables and χ^2 tests for binary variables ($\alpha = .05$, 2-tailed). We also evaluated baseline variables by arm in those with HbA_{1c} values available at baseline and follow-up. We used intention-to-treat principles and evaluated for all randomized patients. In other words, we evaluated outcomes regardless of whether patients were targeted for intervention or actually received the intervention.

All analyses compared patients in arm 2 or 3 separately with arm 1. For each analysis in this study, a 2-sided hypothesis was tested at $\alpha = .05$. In the primary analysis, outcomes were compared using generalized estimating equations with a log-link function and Poisson-distributed errors, accounting for correlations between repeated measurements over time and adjusting for the stratified design. In secondary analyses, we used a time-to-event approach to evaluate the hazard of discontinuing insulin therapy throughout the entire follow-up period. We evaluated change in HbA_{1c} levels using generalized estimating equations with an identity link and normally distributed errors. Health care utilization and cost analyses were performed using generalized estimating equations using a log link with Poisson-distributed errors.

We conducted additional sensitivity and secondary analyses (eMethods in Supplement 2). For insulin persistence, we used alternative measures, such as gaps in insulin supplies. Exploratory subgroup analyses were performed according to age, sex, and baseline HbA_{1c} control. For glycemic control, we conducted a complete case analysis among patients with baseline and follow-up HbA_{1c} values. For resource utilization outcomes, we conducted several sensitivity analyses, including measuring inpatient and outpatient visits for hypoglycemia. For all outcomes, we conducted as-treated analyses, in which we evaluated effects among patients who received the intervention in arms 2 and 3 compared with patients who received the intervention in arm 1. For this analysis, we used propensity score matching to identify reached patients in arm 1 similar to those reached in arms 2 and 3 based on baseline characteristics and predicted risk of nonpersistence, and we compared outcomes using recommended approaches in pragmatic trials.²⁶⁻²⁹

Results

Of the 6000 randomized patients, 404 patients (6.7%) lost insurance eligibility between the time of data collection and 1 month after randomization (the beginning of follow-up); thus, data from these patients were not included in the analyses (Figure). The mean (SD) duration of follow-up was 287 (118) days.

The baseline characteristics of the randomized participants (**Table 1**) and those included in analyses were well-balanced (eTable 1 in the [Supplement 2](#)). The mean (SD) age of participants was 55.9 (11.0) years, and 3344 (59.8%) were male. In total, 2085 patients (34.8%) had mean (SD) baseline HbA_{1c} values of 8.5% (1.8%). Characteristics of those with HbA_{1c} values available at baseline by study arm are shown in eTable 2 in [Supplement 2](#) and within arm 3 in eTable 3 in [Supplement 2](#).

Of those targeted, 459 of 1861 patients (24.7%) in arm 1 (untargeted low intensity), 342 of 1114 patients (30.7%) in arm 2 (partially targeted moderate intensity), and 251 of 731 patients (34.3%) in arm 3 (highly targeted high intensity) completed a telephone consultation with a pharmacist. Patients with an initial consultation received a mean (SD) of 1.7 (0.8) calls in arm 1, 1.8 (1.1) calls in arm 2, and 2.1 (1.1) calls in arm 3. In this consultation, 318 of 459 patients (69.3%) in arm 1, 214 of 342 patients (62.5%) in arm 2, and 148 of 251 patients (59.0%) in arm 3 self-reported optimal insulin adherence. Among patients completing the initial consultation, pharmacists recommended changing

Table 1. Patient Characteristics by Study Arm^a

Characteristic	Arm 1: Untargeted Low Intensity (n = 2000)	Arm 2: Partially Targeted Moderate Intensity (n = 2000)	Arm 3: Highly Targeted High Intensity (n = 2000)	P Value ^b
Age, mean (SD), y	55.9 (11.0)	55.4 (11.3)	55.9 (1.7)	.25
Female	793 (39.7)	786 (39.3)	814 (40.7)	.71
HbA _{1c} level, mean (SD), % ^c	8.5 (1.8)	8.5 (1.8)	8.6 (1.8)	.24
Insulin and hypoglycemic use				
Short- or rapid-acting insulin	974 (48.7)	935 (46.8)	948 (47.4)	.46
No. of basal insulin claims, mean (SD)	2.5 (1.8)	2.6 (1.9)	2.6 (1.9)	.24
Adjunct oral hypoglycemic	1264 (63.2)	(63.3)	(62.8)	.78
Diabetic complications				
Hypoglycemia	97 (4.9)	97 (4.9)	95 (4.8)	.98
Ketoacidosis	54 (2.7)	61 (3.1)	52 (2.6)	.67
Retinopathy	201 (1.1)	176 (8.8)	186 (9.3)	.36
Nephropathy	49 (2.5)	49 (2.5)	51 (2.6)	.98
Neuropathy	472 (23.6)	450 (22.5)	461 (23.1)	.65
Other clinical diagnoses				
Coronary artery disease	435 (21.8)	450 (22.5)	416 (20.8)	.42
Hypertension	1506 (75.3)	1521 (67.1)	1546 (77.3)	.45
Hyperlipidemia	1394 (69.7)	1353 (67.7)	1397 (69.9)	.18
Congestive heart failure	157 (7.9)	159 (8.0)	156 (7.8)	.98
Stroke or transient ischemic attack	108 (5.4)	121 (6.1)	115 (5.8)	.70
Obesity	511 (25.6)	513 (25.7)	537 (26.9)	.62
Asthma or COPD	293 (14.7)	268 (13.4)	246 (12.3)	.08
Liver disease	148 (7.4)	152 (7.6)	157 (7.9)	.89
Chronic kidney disease	1343 (67.2)	1328 (66.4)	1320 (66.0)	.56
Depression	162 (8.1)	147 (7.4)	148 (7.4)	.61
Dementia	52 (2.6)	41 (2.1)	38 (1.9)	.26
Acute stress	78 (3.9)	74 (3.7)	66 (3.3)	.57
Resource utilization, mean (SD)				
Time hospitalized, d	3.3 (15.7)	3.2 (16.1)	2.9 (11.5)	.61
Hospitalizations, No.	0.4 (1.2)	0.4 (1.5)	0.4 (1.1)	.85
Office visits, No.	9.8 (8.0)	9.5 (7.6)	9.6 (7.8)	.57

Abbreviations: COPD, chronic obstructive pulmonary disease; HbA_{1c}, glycated hemoglobin A_{1c}.

^a Data are presented as number (percentage) of patients unless otherwise indicated.

^b Analysis of variance for continuous measures; χ^2 tests for binary and categorical measures.

^c Among patients with at least 1 HbA_{1c} value.

to longer dispensations of medications for 6.2% (65 of 1052), using mail order for 4.4% (46), and diabetes therapy changes for 7.8% (82) of patients. In arm 2, 85 patients (24.9%) opted to receive weekly text messages. In arm 3, 13 patients (5.2%) chose to receive text messages daily, 7 patients (2.8%) chose every 3 days, and 31 patients (12.4%) chose weekly.

In arm 1, the rate of nonpersistence was 5.4% (Table 2). The rate of nonpersistence was 4.7% in arm 2 compared with arm 1 (relative risk, 0.88; 95% CI, 0.75-1.03) and 4.9% in arm 3 compared with arm 1 (relative risk, 0.91; 95% CI, 0.77-1.06). The mean time to insulin nonpersistence was 250 days in arm 1, 255 days in arm 2 (hazard ratio, 0.91; 95% CI, 0.79-1.06), and 258 days in arm 3 (hazard ratio, 0.92; 95% CI, 0.79-1.07). Alternative measures, such as gaps in medication supplies, showed similar findings (eTable 4 in Supplement 2).

Insulin persistence results by key subgroup are presented in Table 3. In arm 2, men (relative risk, 0.81; 95% CI, 0.67-0.99) and patients 55 years or older (relative risk, 0.81; 95% CI, 0.66-0.99) had significantly lower rates of nonpersistence than their counterparts in arm 1. Similar results for both subgroups were also observed in arm 3. However, no subgroups were significantly different when comparing interaction P values.

Analyses of glycemic control outcomes are shown in Table 2. After imputation, glycemic control was not significantly different in arm 2 and arm 1 (absolute difference in HbA_{1c} level, -0.15%; 95% CI, -0.34% to 0.05%). However, patients randomized to arm 3 had significantly lower HbA_{1c} level compared with arm 1 (absolute difference, -0.25%; 95% CI, -0.43% to -0.06%; P = .002). A complete case analysis found similar results (eTable 5 in Supplement 2). Baseline characteristics of patients with nonmissing baseline and follow-up HbA_{1c} values were similar across the study arms (eTable 2 in Supplement 2).

Analyses of resource utilization outcomes are shown in Table 4 and eTables 6-8 in Supplement 2. Total health care spending and office visits did not differ among the arms, but patients in arm 2 had a higher likelihood of hospitalizations (odds ratio, 1.22; 95% CI, 1.06-1.41) and emergency department visits (odds ratio, 1.38; 95% CI, 1.24-1.53). Stratified analyses showed that this increased risk may be associated with baseline hospitalization and HbA_{1c} levels (eTable 7 in Supplement 2). No differences were observed in the risk of hypoglycemia during follow-up (eTable 8 in Supplement 2).

Table 2. Clinical Outcomes by Study Arm

Outcome	Arm 1: Untargeted Low Intensity	Arm 2: Partially Targeted Moderate Intensity	Arm 3: Highly Targeted High Intensity	Relative Risk (95% CI)	
				Arm 2 vs Arm 1	Arm 3 vs Arm 1
Non-insulin persistence, %	5.4	4.7	4.9	0.88 (0.75 to 1.03)	0.91 (0.77 to 1.06)
Change in HbA _{1c} level from baseline, mean (SD)	-0.06 (1.48)	-0.21 (1.37)	-0.31 (1.48)	-0.15 (-0.34 to 0.05)	-0.25 (-0.43 to -0.06)

Abbreviation: HbA_{1c}, glycated hemoglobin A_{1c}.

Table 3. Insulin Persistence by Patient Subgroup

Subgroup	Insulin Persistence vs Arm 1 (Untargeted Low Intensity), Relative Risk (95% CI)			
	Arm 2: Partially Targeted Moderate Intensity	P Value	Arm 3: Highly Targeted High Intensity	P Value
Age, y				
<55	0.99 (0.77-1.29)	.24	0.99 (0.77-1.28)	.37
≥55	0.81 (0.67-0.99)		0.85 (0.70-1.04)	
Sex				
Male	0.81 (0.66-0.99)	.23	0.89 (0.73-1.09)	.79
Female	0.98 (0.77-1.26)		0.93 (0.73-1.19)	
Baseline HbA _{1c} level, %				
<8	0.95 (0.64-1.43)	.70	1.03 (0.69-1.55)	.17
≥8	0.86 (0.60-1.22)		0.72 (0.51-1.02)	

Abbreviation: HbA_{1c}, glycated hemoglobin A_{1c}.

The reasons for hospitalization are shown by study arm in eTable 9 in [Supplement 2](#); no notable differences were observed.

The baseline characteristics of the propensity score–matched population are shown in eTable 10 in [Supplement 2](#), with results from the matching procedures described in eMethods in [Supplement 2](#). Outcomes comparing arm 2 with arm 1 are given in eTable 11 in [Supplement 2](#), and outcomes comparing arm 3 with arm 1 are given in eTable 12 in [Supplement 2](#). In these as-treated analyses, the absolute differences in nonpersistence were 1.5% to 1.9% lower in arms 2 and 3 than in arm 1, but these differences were not statistically significant. Changes in glycemic control were larger compared with those observed in the intention-to-treat analysis. Compared with arm 1, mean HbA_{1c} level was –0.42% (95% CI, –0.84% to 0.01%) lower in arm 2 and –0.61% (95% CI, –1.18% to –0.04%) lower in arm 3. There was also no increased risk of hospitalizations or emergency department visits in arm 2 or arm 3 vs arm 1 (eg, odds ratio, 0.84; 95% CI, 0.57-1.24 for hospitalizations in arm 2 vs arm 1).

Discussion

In this pragmatic trial of patients with type 2 diabetes receiving insulin therapy, we found that increasing the focus and intensity of an intervention for a smaller number of patients based on both the risk of poor adherence and baseline glycemic control did not improve insulin persistence compared with administering a lower-intensity intervention to a larger number of patients. Compared with an untargeted low-intensity intervention, a highly targeted high-intensity intervention improved glycemic control by a statistically significant amount. Also, a partially targeted moderate-intensity intervention resulted in a small increase in the risk of hospitalizations and emergency department visits. The interventions did not impact health care spending or office visits.

Using intention-to-treat principles, we analyzed the effectiveness of the targeted interventions among all randomized patients even though only 28.4% of patients assigned to the intervention accepted the initial consultation. This percentage is similar to that in another telephonic quality improvement study using pharmacists.¹² We chose this approach to evaluate the mean effectiveness of the intervention as it would be administered in a population-based setting and allow for unbiased comparisons.¹³ Nevertheless, the acceptance rate was slightly lower than in our initial power calculations, possibly because the rates were based on a slightly different population, and we specifically targeted patients in this trial who could have been more difficult to engage. The persistence measurement could not have been sufficiently sensitive; the 90th percentile threshold may not have detected enough variation in filling and only detected differences in very nonpersistent patients.³⁰ Moreover, baseline persistence was also fairly high in all 3 arms. Thus, a ceiling effect may have limited any potential benefit from the interventions that we studied. Although we observed small improvements in persistence, we were likely underpowered to see smaller but still clinically significant changes. Finally, whereas the outreach was performed by trained clinical pharmacists skilled at telephonic consultations, these individuals were not a regular part of patients' care teams, which could have reduced effectiveness.

In contrast to persistence, in the group that was targeted based on both the risk of nonpersistence and poor baseline glycemic control, we observed significant improvements in glycemic control, ultimately a more meaningful outcome in diabetes care.³¹ Although the levels of

Table 4. Resource Utilization Outcomes by Study Arm

Resource Utilization Outcome	Mean (SD)			Relative Risk (95% CI)	
	Arm 1: Untargeted Low Intensity	Arm 2: Partially Targeted Moderate Intensity	Arm 3: Highly Targeted High Intensity	Arm 2 vs Arm 1	Arm 3 vs Arm 1
Total health care spending, \$	22 616 (49 250)	23 284 (49 094)	22 545 (44 448)	1.03 (0.95-1.11)	0.99 (0.92-1.06)
Physician office visits	7.66 (7.29)	7.62 (7.17)	7.50 (7.27)	1.00 (0.97-1.02)	0.98 (0.96-1.00)
All-cause emergency department visits	0.31 (1.00)	0.43 (4.40)	0.30 (0.87)	1.38 (1.24-1.53)	0.96 (0.85-1.07)
All-cause hospitalizations	0.19 (0.63)	0.23 (0.72)	0.21 (0.65)	1.22 (1.06-1.41)	1.14 (0.99-1.32)

glycemic control achieved were modest, the improvements were roughly equivalent to those anticipated from the addition of an oral hypoglycemic medication.^{23,32}

Targeting a different patient population might have increased the effectiveness of the interventions that we tested. For example, we focused on patients at moderate risk of nonpersistence. It is possible that the intervention could have been more effective if targeted to patients at highest risk rather than those who we hypothesized would be more impactable. In arm 2, we also included patients with good baseline glycemic control, hypothesizing that even they could benefit, although this could have diluted the effect. Similarly, despite being predicted to be nonadherent based on claims data, 64.6% of patients thought they were optimally adherent, suggesting further weakening of effectiveness and that targeting could be further optimized.

The finding of slightly increased risk of hospitalizations and emergency department visits in the partially targeted moderate-intensity group was unexpected. Unlike the highly targeted high-intensity group, interventions were given to patients with good glycemic control; we speculate that that could have potentially led to the increased risk, perhaps through increased hypoglycemia, although we did not observe a significant difference in overall visits.³³⁻³⁵ In other words, administering interventions to patients who were predicted to be nonpersistent without considering their actual glycemic control could have led to worsened outcomes requiring hospitalization. Propensity score-matched analyses that identified similar patients in both arms did not observe any differences.

Limitations

Several limitations should be acknowledged. Our evaluation of glycemic control was limited to patients for whom Horizon had baseline laboratory data available. We also designed the study with 3 active comparison groups to mimic providing some degree of quality improvement outreach to members with diabetes. Without a true control group, we were unable to test for differences between the untargeted low-intensity intervention and no intervention. The prediction model was proprietary, but the overall approach could be replicated. Moreover, any bias resulting from insufficient targeting would be toward the null, because worse predictions would decrease the success of the targeting and have made it less likely to observe an effect. We also could not evaluate the extent to which the nature of conversations or counseling recommendations differed across the arms, because we did not have access to deidentified versions of the pharmacist consultations. The findings from this study may also not be fully generalizable to other populations, such as those with Medicare or Medicaid coverage; however, it is likely that a similar approach could be used within these populations to potentially target interventions.

Conclusions

By embedding a clinical trial within a large health insurance system and limiting the exclusion criteria, our goal was to mimic a real-world setting to compare 3 equivalent-priced strategies to aid the implementation and dissemination of the most effective strategy given a set amount of resources. Our results suggest that targeting patient populations for more intensive interventions based both on predicted risk of nonadherence and level of glycemic control has the potential to be more effective than untargeted approaches.

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SUPPLEMENT 1.

Trial Protocol

SUPPLEMENT 2.

eMethods. Supplemental Methods

eAppendix 1. Summary of Intervention Components

eAppendix 2. Text Messaging Flowchart

eAppendix 3. Sample Text Messages

eAppendix 4. Example of 3-Month Quarterly Member Mailing

eAppendix 5. Basal Insulins and 90th Percentile Thresholds

eTable 1. Characteristics of Patients Included in Analysis by Study Arm

eTable 2. Pre-Randomization Characteristics Among Those With HbA_{1c} Available

eTable 3. Pre-Randomization Characteristics of Patients by Glycated Hemoglobin A1c in Arm 3 (Highly Targeted High-Intensity Intervention)

eTable 4. Insulin Persistence Sensitivity Analyses

eTable 5. Complete Case Analysis of Glycemic Control

eTable 6. Sensitivity Analyses of Resource Utilization Outcomes

eTable 7. Stratified Analyses of Resource Utilization Outcomes

eTable 8. Risk of Hypoglycemia in Follow-Up

eTable 9. Frequency of Primary Hospitalization Diagnosis by Study Arm (Top 30 Diagnoses)

eTable 10. Patient Characteristics After Propensity Score Matching

eTable 11. Arm 2 vs Arm 1: As-Treated Analyses Using Propensity Score Matching

eTable 12. Arm 3 vs Arm 1: As-Treated Analyses Using Propensity Score Matching

SUPPLEMENT 3.

Data Sharing Statement