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Implementation of a Health Plan Program for Switching From Analogue to Human Insulin and Glycemic Control Among Medicare Beneficiaries With Type 2 Diabetes

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IMPORTANCE Prices for newer analogue insulin products have increased. Lower-cost human insulin may be effective for many patients with type 2 diabetes.

OBJECTIVE To evaluate the association between implementation of a health plan–based intervention of switching patients from analogue to human insulin and glycemic control.

DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort study using population-level interrupted times series analysis of members participating in a Medicare Advantage and prescription drug plan operating in 4 US states. Participants were prescribed insulin between January 1, 2014, and December 31, 2016 (median follow-up, 729 days). The intervention began in February 2015 and was expanded to the entire health plan system by June 2015.

EXPOSURES Implementation of a health plan program to switch patients from analogue to human insulin.

MAIN OUTCOMES AND MEASURES The primary outcome was the change in mean hemoglobin A_{1c} (HbA_{1c}) levels estimated over three 12-month periods: preintervention (baseline) in 2014, intervention in 2015, and postintervention in 2016. Secondary outcomes included rates of serious hypoglycemia or hyperglycemia using *ICD-9-CM* and *ICD-10-CM* diagnostic codes.

RESULTS Over 3 years, 14 635 members (mean [SD] age: 72.5 [9.8] years; 51% women; 93% with type 2 diabetes) filled 221 866 insulin prescriptions. The mean HbA_{1c} was 8.46% (95% CI, 8.40%-8.52%) at baseline and decreased at a rate of −0.02% (95% CI, −0.03% to −0.01%; P <.001) per month before the intervention. There was an association between the start of the intervention and an overall HbA_{1c} level increase of 0.14% (95% CI, 0.05%-0.23%; P = .003) and slope change of 0.02% (95% CI, 0.01%-0.03%; P < .001). After the completion of the intervention, there were no significant differences in changes in the level (0.08% [95% CI, −0.01% to 0.17%]) or slope (<0.001% [95% CI, −0.008% to 0.010%]) of mean HbA_{1c} compared with the intervention period (P = .09 and P = 0.81, respectively). For serious hypoglycemic events, there was no significant association between the start of the intervention and a level (2.66/1000 person-years [95% CI, −3.82 to 9.13]; P = .41) or slope change (−0.66/1000 person-years [95% CI, −1.59 to 0.27]; P = .16). The level (1.64/1000 person-years [95% CI, −4.83 to 8.11]; P = .61) and slope (−0.23/1000 person-years [95% CI, −1.17 to 0.70]; P = .61) changes in the postintervention period were not significantly different compared with the intervention period. The baseline rate of serious hyperglycemia was 22.33 per 1000 person-years (95% CI, 12.70-31.97). For the rate of serious hyperglycemic events, there was no significant association between the start of the intervention and a level (4.23/1000 person-years [95% CI, −8.62 to 17.08]; P = .51) or slope (−0.51/1000 person-years [95% CI, −2.37 to 1.34]; P = .58) change.

CONCLUSIONS AND RELEVANCE Among Medicare beneficiaries with type 2 diabetes, implementation of a health plan program that involved switching patients from analogue to human insulin was associated with a small increase in population-level HbA_{1c}.

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Supplemental content

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The price of insulin has increased substantially in recent years.[1-3] In 2016, Medicare's outpatient prescription drug program (Part D) spent more than $4 billion on just 1 long-acting insulin analogue.[4] These trends are concerning because high prices for insulin often translate into higher out-of-pocket payments for patients with insufficient drug coverage or for Medicare beneficiaries in the Part D coverage gap.[5]

Although newer analogue insulin medications (eg, glargine, lispro) are more expensive than human insulin products (eg, neutral protamine Hagedorn [NPH], regular human insulin), they may not result in substantially improved clinical outcomes for patients with type 2 diabetes.[6-8] Human insulin, when used effectively, may be a viable initial treatment option for many patients with type 2 diabetes.[9,10]

When CareMore, a managed care organization, examined its insulin spending in 2014, the organization found that many of its members were using insulin analogues that had a high daily injection burden (ie, basal-prandial insulin strategies) and were reaching the Medicare Part D coverage gap. Therefore, in early 2015, the organization piloted an intervention to switch members from analogue to human insulin, with a preference for regimens containing fewer daily injections. The goals were to reduce daily injection burden and to delay or avoid the Medicare Part D coverage gap by encouraging members to use a clinically comparable insulin regimen that was less costly. The goal of this study was to evaluate the association between this intervention and clinical outcomes, including hemoglobin A_{1c} (HbA_{1c}) levels and serious hypoglycemic and hyperglycemic events, as well as economic measures, including the proportion of members who reached the Medicare Part D coverage gap and total spending on insulin products.

Key Points

Question Is a health plan program that encourages patients to switch from analogue to human insulin associated with a change in glycemic control among older adults with type 2 diabetes?

Findings In this retrospective cohort study of 14 635 older adults with type 2 diabetes participating in a Medicare Advantage plan, implementation of a health plan intervention that involved switching patients from analogue to human insulin was associated with a population HbA_{1c} level increase of 0.14%.

Meaning Among patients with type 2 diabetes, a health plan intervention that involved switching from analogue to human insulin was significantly associated with a small increase in population-level HbA_{1c}.

Methods

Study Population and Data Sources

This study was approved by the institutional review board at the Brigham and Women's Hospital in Boston. Participants provided written informed consent to the release of deidentified information for research purposes upon enrolling in the plan. The managed care organization providing data for this study is a subsidiary of Anthem Inc, and is a Medicare Advantage plan and medical group based in Cerritos, California, that serves about 130 000 members in 4 states (California, Arizona, Nevada, and Virginia).[11] Any health plan member who filled 1 or more insulin prescriptions between January 1, 2014, and December 31, 2016, was eligible for this study (eTable 1 in the Supplement). We conducted 2 analyses: (1) a prespecified population-level analysis using interrupted times series methods and (2) a post hoc patient-level analysis using a differences-in-differences approach. In the prespecified open cohort analysis, members could enter or leave the cohort (ie, unenroll or die) at any time. In the patient-level analysis, we compared members who switched from analogue insulin to human insulin against members who continued taking analogue insulin. We used a closed cohort for this analysis, excluding members (1) who did not have continuous enrollment, unless the reason for disenrollment was death; (2) whose first prescription claim was for human insulin; (3) who switched back to analogue insulin after switching to human insulin; and (4) who did not have at least 365 days between the first analogue and first human insulin prescription (**Figure 1**). As a sensitivity analysis, we excluded members who died during follow-up. The plan provided deidentified member enrollment files, outpatient (professional) claims, prescription drug claims, inpatient/emergency department claims, and HbA_{1c} results for members who were eligible for study participation using a scrambled unique identification number.

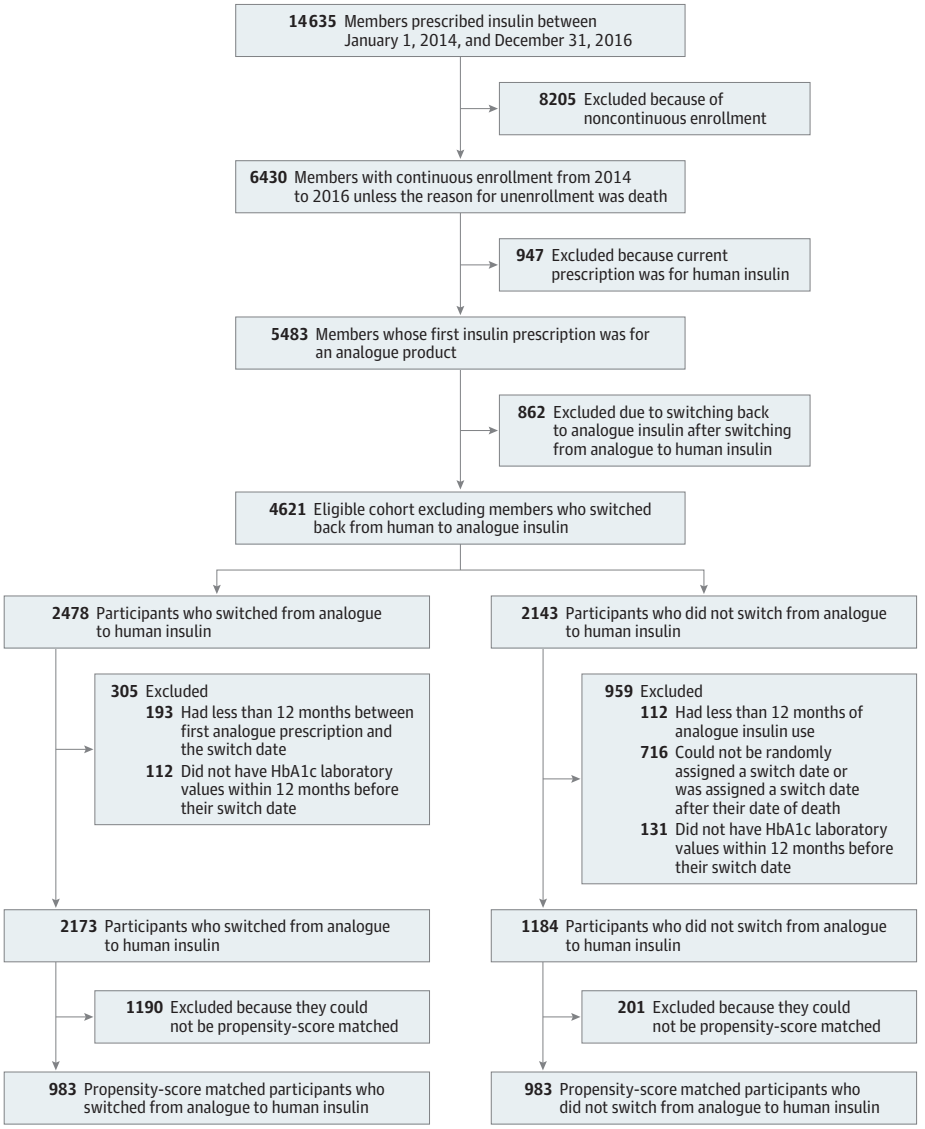
Clinical characteristics, such as markers of disease severity, comorbidities, HbA_{1c} results, and use of other prescription drugs, were defined if members had diagnosis codes or prescription claims for the relevant characteristic at any time during the 3-year study period for the population-level analysis and within 12 months before the switch date or corresponding switch date (or index date) for the patient-level analysis. We classified members as living with type 1 or type 2 diabetes using a decision rule that considered use of oral antidiabetic medications and a ratio of type 1 to type 2 diagnostic codes derived from a validated, optimized algorithm (eTable 2 in the Supplement).[12]

Insulin Switch Intervention

In 2015, the health plan started a program to switch patients from higher-cost analogue insulin regimens to lower-cost human insulin. The protocol-driven intervention was led by plan pharmacists and supported by nurse practitioners, physician assistants, and physicians with experience in chronic disease management at plan health centers. The intervention pilot started in February 2015 in Arizona and was expanded to the entire health plan system by June 2015.

Although the intervention was implemented across the entire health plan system, the following characteristics helped clinicians identify ideal member conditions for an analogue to human insulin switch: using more than 2 injections per day or receiving both basal and prandial insulin analogues, receiving more than 50 U of insulin per day, having a history of nonadherence, and lacking a history of recurrent hypoglycemia. After stopping the basal or prandial insulin analogue and secretagogues (sulfonylureas and meglitinides), the recommended initial dose of human insulin (either premixed human 70/30 or NPH insulin) was 80% of the baseline total daily

Figure 1. Participant Flow Diagram for a Study Examining the Effects of an Intervention Aimed at Switching Medicare Beneficiaries With Type 2 Diabetes From Analogue to Human Insulin



dose of the analogue insulin. For participants starting premixed human 70/30 insulin, two-thirds of the total daily dose was given before breakfast and one-third of the daily dose before dinner (ie, 2 injections per day). The conversion protocol did not have specific recommendations with respect to the frequency of blood glucose self-monitoring. Operationally, conversion progress was tracked using claims data by a director for quality improvement at the health plan organization.

In addition to these clinical changes, plan benefits were altered to financially encourage patients to switch from analogue to human insulin. For example, starting in January 2016, select plans moved analogue insulin products containing glargine, detemir, or aspart from tier 6 ($0 co-pay) to tier 3 ($37.50 co-pay with additional out-of-pocket payments if members were in the Medicare Part D coverage gap), while human insulin products remained on a tier with a $0 co-pay. Not all members experienced this financial incentive equally because some members qualified for a low-income government subsidy or were dually eligible under the Medicaid and Medicare programs and therefore subject to little or no out-of-pocket expenditures.

Outcomes

The primary clinical outcome was overall glycemic control as measured by mean monthly HbA_{1c}. A change in HbA_{1c} by 0.5% has been suggested to be clinically meaningful.[13] Secondary clinical outcomes included serious hypoglycemia or hyperglycemia (event rate per 1000 person-years at risk), defined as a hospital admission or emergency department visit in which the primary diagnosis was hypoglycemia or hyperglycemia, per the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) and the *International Classification of*

Diseases, Tenth Revision, Clinical Modification (*ICD-10-CM*) diagnosis codes (eTable 3 and eTable 4 in the Supplement). We used a modification of a previously validated *ICD-9-CM*–based algorithm for hypoglycemic events before October 1, 2015 (the *ICD-10-CM* transition date).[14] After this date, we used *ICD-10-CM* codes mapped from the *ICD-9-CM*–based algorithm and additional codes obtained from the published literature. For hyperglycemic events, we used both *ICD-9-CM* and *ICD-10-CM* codes drawn from the Agency for Healthcare Research and Quality's Prevention Quality Indicator 01 (diabetes short-term complications) and 14 (uncontrolled diabetes), which are quality indicators for ambulatory care–sensitive conditions in adult populations.[15] To ensure that the *ICD-10-CM* transition date did not affect the apparent incidence of hypoglycemic or hyperglycemic events according to claims, we conducted a validation study using an external database of medical claims from more than 650 000 patients with a history of diabetes 2 quarters before and 2 quarters after the *ICD-10-CM* transition date (eTable 5 in the Supplement).[16] In the patient-level analysis, we also explored the rate of death comparing participants who switched from analogue to human insulin vs participants who did not.

Cost outcomes included total plan spending for analogue and human insulin, independently, and the proportion of patients who were subject to the Part D coverage gap. Total plan spending was defined as follows: amount billed + fill fee - co-pay - low-income cost sharing subsidy amount. Any participant who had annual prescription drug spending (ingredient cost submitted) above the initial coverage limit threshold ($2850 in 2014, $2950 in 2015, and $3310 in 2016) was counted as entering the coverage gap. For this outcome, spending for all prescriptions (insulin and noninsulin) was included.

Statistical Analysis

We used 2 analytic methods to evaluate the clinical outcomes associated with the insulin conversion intervention. Our prespecified analysis plan estimated changes in HbA_{1c} and rates of hypoglycemia or hyperglycemia at the population level using interrupted time series models (without a control) with cut points at the start of 2015 and 2016. In this analysis, study participants contributed HbA_{1c} data if they had an insulin dispensed either in the same month as or 3 months before the laboratory result. Study participants contributed hypoglycemic or hyperglycemic events only if they had been dispensed insulin during the same month as their clinical event. We first plotted outcomes by calendar month. We then defined 3 equal 12-month periods: preintervention period (baseline; 2014), intervention period (2015), and postintervention period (2016). We defined the start of the intervention as January 1, 2015, and the end of the intervention as December 31, 2015. We then created indicators for each period (ie, baseline, intervention, postintervention) and calendar time and used these indicators in a segmented linear regression model to examine changes in the level or slope of study outcomes. We adjusted for autocorrelation of error terms using SAS statistical software.

Our post hoc analysis compared a closed cohort of participants who switched to human insulin vs participants who did not, using a difference-in-differences approach (segmented regression analysis with a control group) for HbA_{1c}. In this analysis, we created regression models with an indicator for participants who switched and for participants who did not and an indicator for time before or after the switch to estimate the differential changes in level and trend. In these analyses, we restricted the outcome measures to the 12 months before and after the switch date. The switch date for participants who switched from analogue to human insulin was the date of their first human insulin dispensing. The switch date for participants who did not switch was assigned by risk-set sampling from available switch dates from participants who did switch, anchored on the calendar month and year of the first analogue prescription, to account for both calendar time and time since the first analogue prescription. We excluded members who were assigned switch dates after their date of death (Figure 1 and eTable 6 in the Supplement). We estimated rate ratios and 95% CIs for serious hypoglycemic and hyperglycemic events among participants 12 months after the switch date.

We used propensity score matching to control for measured baseline differences between participants who did and who did not switch from analogue to human insulin, adjusting for demographic, geographic, economic, and clinical measures, including diabetes type, year of first analogue insulin prescription fill, severity of disease, clinical comorbidities, other prescription medicines, and most recent mean HbA_{1c} (**Table 1**). The propensity score is the predicted probability of being a participant who did or did not switch from an analogue to a human insulin, conditional on covariates measured 12 months before the switch date or assigned switch date, and was estimated using logic regression. We used a 1:1 nearest-neighbor matching algorithm and a caliper of 0.025.

For cost and utilization outcomes, we tabulated total plan spending and proportion of insulin dispenses per calendar month and generated plots stratified by analogue vs human insulin using Excel (Microsoft 2010). We calculated binomial CIs for proportions. For the Medicare Part D coverage gap outcome, we first created 1 new closed subcohort for each calendar year (2014, 2015, and 2016). Non–low income cost sharing members from the population-level cohort could enter a subcohort if they had at least 1 claim for an insulin product in the month of January for each respective year. Patients were followed up until 1 of the following 4 censoring criteria was met: reaching the coverage gap, plan disenrollment, death, or end of the calendar year. We calculated hazard ratios and 95% CIs using Cox proportional hazards regression models using 2014 as the reference and included a robust sandwich estimator to account for the possibility of the same patient entering more than 1 subcohort. We evaluated the proportional hazards assumption by graphically examining survival curves. We did not impute for missing data for outcomes or covariates because claims for dispensed prescriptions, outpatient diagnoses, and emergency department or inpatient encounters are unlikely to be missing. A very small amount (0.11%) of HbA_{1c} results were excluded because of missing values or text entries such as "unable to perform." All analyses were performed using SAS version 9.4. We used a 2-sided significance threshold of .05. Secondary

Table 1. Baseline Characteristics of Insulin Users in the Open Cohort Population-Level Analysis (N = 14 635)

Characteristic	No. (%)
Age at data pull, mean (SD), y	72.5 (9.8)
Women	7429 (50.8)
Men	7206 (49.2)
State	
California	9732 (66.5)
Arizona	3126 (21.4)
Nevada	1148 (7.8)
Virginia	627 (4.3)
Unknown	2 (0.01)
Low-income subsidy	6322 (43.2)
Hospice	1157 (7.9)
Diabetes	
Type 2	13 619 (93.1)
Type 1	109 (0.7)
Unknown[a]	907 (6.2)
Severity of disease	
Nephropathy	5576 (38.1)
Neuropathy	7107 (48.6)
Retinopathy	1274 (8.7)
Foot ulcers	860 (5.9)
Comorbidities[b]	
Hypertension	5206 (35.6)
Hyperlipidemia	2325 (15.9)
Coronary artery disease	2494 (17.0)
Chronic kidney disease	2826 (19.3)
End-stage kidney disease	963 (6.6)
Peripheral artery disease	1427 (9.8)
Obesity	922 (6.3)
Smoker	228 (1.6)
Prescription medicines	
Metformin	7755 (53.0)
Sulfonylurea[c]	5199 (35.5)
Dipeptidyl peptidase-4 inhibitor[d]	1984 (13.6)
Glucagon-like peptide receptor agonist[e]	539 (3.7)
Sodium-glucose cotransporter-2 inhibitor[f]	173 (1.2)
Thiazolidinedione[g]	847 (5.8)
Meglitinide[h]	143 (1.0)
α-Glucosidase inhibitor[i]	110 (0.8)
Combination antidiabetic medicine	450 (3.1)
Angiotensin-converting enzyme inhibitor	8219 (56.2)
Angiotensin receptor blocker	4085 (27.9)
Statin	11 602 (79.3)

[a] 510 People could not be classified because they had no outpatient claims (eg, professional health services paid by a third-party payer) and 397 people had no outpatient claims for type 1 or type 2 diabetes during the study period.

[b] Definitions for clinical comorbidities can be found in eTable 9.

[c] Commonly including glipizide and glimepiride.

[d] Commonly including sitagliptin and linagliptin.

[e] Commonly including exenatide and liraglutide.

[f] Commonly including canagliflozin and dapagliflozin.

[g] Commonly including pioglitazone.

[h] Commonly including nateglinide and repaglinide.

[i] Commonly including acarbose.

outcomes and analyses should be interpreted as exploratory because we did not adjust for multiple comparisons.

Results

Patient Characteristics

Overall, 14 635 plan members filling a total of 221 866 insulin prescriptions between January 1, 2014, and December 31, 2016, were eligible for the population-level study (Table 1). The median follow-up was 729 days. The mean (SD) age of the participants was 72.5 (9.8) years, and 51% were women. Over 93% had type 2 diabetes. Before the intervention, statins, angiotensin-converting enzyme inhibitors, metformin, and sulfonylureas were all commonly used medications of the participants. Forty-three percent of participants qualified for a low-income subsidy.

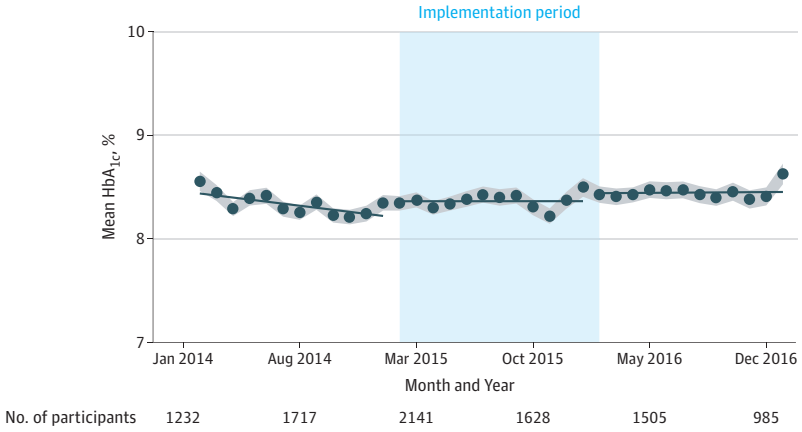
Clinical Outcomes From the Population-Level Analysis

Before the intervention, the baseline mean HbA_{1c} was 8.46% (95% CI, 8.40% to 8.52%), and it decreased at a rate of −0.02% (95% CI, −0.03% to −0.01%) per month during 2014 (**Figure 2**). There was an association between the start of the intervention and an HbA_{1c} level increase of 0.14% (95% CI, 0.05%-0.23%; $P = .003$) and a slope change of 0.02% (95% CI, 0.01%-0.03%; $P < .001$) per month. After the completion of the intervention, changes in the mean HbA_{1c} level (0.08% [95% CI, −0.01% to 0.17%]) and slope (<0.001% [95% CI, −0.008% to 0.010%]) were not statistically significantly different ($P = .09$ and $P = .81$, respectively) compared with the preceding period (ie, the 12-month intervention period).

There were 31 serious hypoglycemic events in 2014, 45 in 2015, and 26 in 2016. The baseline rate of serious hypoglycemia was 4.21 per 1000 person-years at risk (95% CI, −0.64 to 9.06), and it changed at a rate of 0.36 per 1000 person-years per month (95% CI, −0.30 to 1.02) during 2014 (**Figure 3**A). There was no significant association between the start of the intervention and a level change (2.66 per 1000 person-years [95% CI, −3.82 to 9.13]; $P = .41$) or slope change (−0.66 per 1000 person-years [95% CI, −1.59 to 0.27]; $P = .16$). The level (1.64 per 1000 person-years; [95% CI, −4.83 to 8.11]) and slope (−0.23 per 1000 person-years [95% CI, −1.17 to 0.70]) changes in the postintervention period were not significantly different compared with the intervention period ($P = .61$ for both).

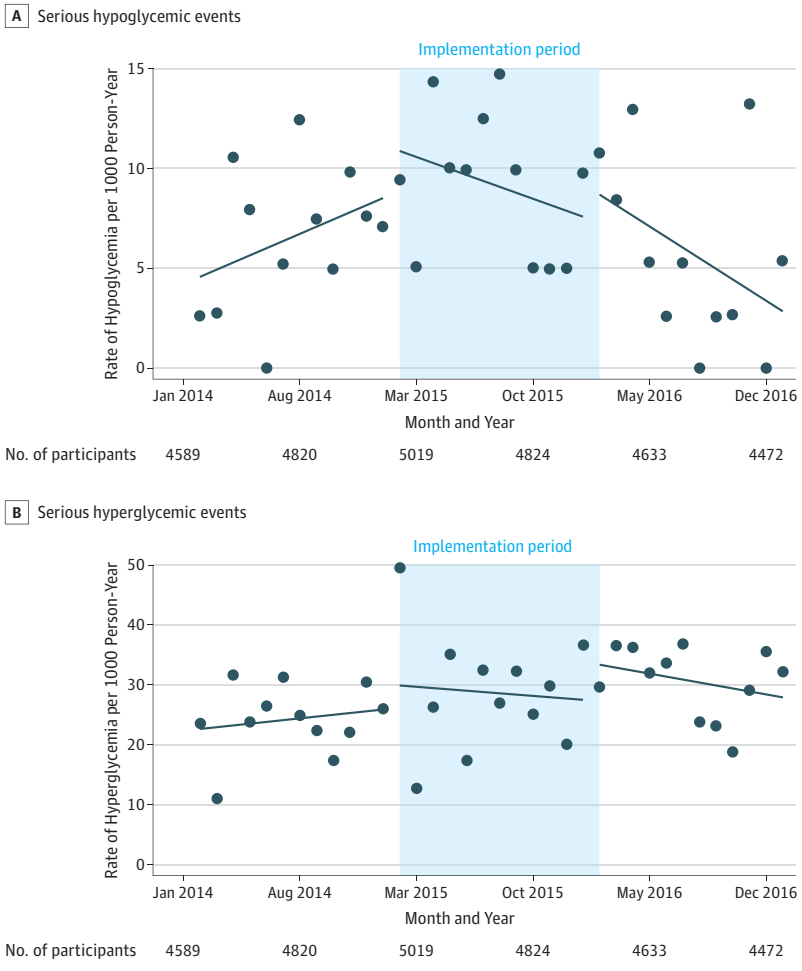
There were 114 serious hyperglycemic events in 2014, 140 in 2015, and 138 in 2016. The baseline rate of serious hyperglycemic events was 22.33 per 1000 person-years (95% CI, 12.70-31.97) and it increased at a rate of 0.30 per 1000 person-years (95% CI, −1.01 to 1.60) (Figure 3B). There was no significant association between the start of the intervention and a level change (4.23 per 1000 person-years [95% CI, −8.62 to 17.08]; $P = .51$) or slope change (−0.51 per 1000 person-years [95% CI, −2.37 to 1.34]; $P = .58$). As with the hypoglycemia results, the level (6.35 per 1000 person-years [95% CI, −6.50 to 19.20]) and slope (−0.28 per 1000 person-years [95% CI, −2.13 to 1.57]) changes comparing the postintervention and intervention periods were not statistically significant ($P = .32$ and $P = .76$, respectively).

Figure 2. Mean Hemoglobin A_{1c} (HbA_{1c}) of Insulin Users Before, During, and After an Insulin Conversion Intervention



The shaded area represents the intervention period of January 1, 2015, through December 31, 2015. The shading around the data points indicate 95% CIs. Changes in the mean level (circles) and slope (solid lines) of HbA_{1c} were estimated using interrupted time series models (segmented regression analysis) with cut points at the start of 2015 and 2016. Because HbA_{1c} may lag up to 3 months, study participants only contributed HbA_{1c} data if they had an insulin dispensed either in the same month of the laboratory result or within 3 months before.

Figure 3. Rate of Serious Hypoglycemic and Hyperglycemic Events Among Insulin Users Before, During, and After an Insulin Conversion Intervention.



The shaded area represents the intervention period of January 1, 2015, through December 31, 2015. Changes in the mean level (circles) and slope (solid lines) of serious hypoglycemic events (A) and hyperglycemic events (B) were estimated using interrupted time series models (segmented regression analysis) with cut points at the start of 2015 and 2016. Study participants contributed hypoglycemic or hyperglycemic events only if they had been dispensed insulin during the same month as their clinical event. Participants could contribute more than 1 event.

Post Hoc Patient-Level Analysis

Of 14 635 members, we identified 2173 participants who switched from analogue to human insulin who could be compared with 1184 participants who did not for the patient-level analysis. After 1:1 propensity-score matching, the final closed cohort included 1966 participants (983 who switched and

Table 2. Baseline Characteristics Comparing Members Before and After Propensity-Score Matching Who Switched From Analogue to Human Insulin vs Members Who Did Not Switch[a]

Characteristic	Unmatched Participants			Propensity-Score Matched Participants		
	Switched	Did Not Switch	Standardized Difference	Switched	Did Not Switch	Standardized Difference
No.	2173	1184		983	983	
Age, mean (SD), y	72.2 (8.1)	73.0 (9.6)	0.09	73.2 (8.4)	72.9 (9.6)	0.03
Women	1010 (46.5)	606 (51.2)	0.09	495 (50.4)	493 (50.2)	0.00
Men	1163 (53.5)	578 (48.8)	0.09	488 (49.6)	490 (49.8)	0.00
State						
California	1655 (76.2)	884 (74.7)	0.03	741 (75.4)	747 (76.0)	0.01
Arizona	317 (14.6)	195 (16.5)	0.05	166 (16.9)	151 (15.4)	0.04
Nevada	154 (7.1)	78 (6.6)	0.02	60 (6.1)	64 (6.5)	0.02
Virginia	47 (2.2)	27 (2.3)	0.01	16 (1.6)	21 (2.1)	0.04
Low-income subsidy	415 (19.1)	484 (40.9)	0.49	330 (33.6)	325 (33.1)	0.01
Hospice	90 (4.1)	85 (7.2)	0.13	62 (6.3)	62 (6.3)	0.00
Type of diabetes						
Type 2	2101 (96.7)	1104 (93.2)	0.16	925 (94.1)	928 (94.4)	0.01
Type 1	31 (1.4)	36 (3.0)	0.11	28 (2.9)	29 (3.0)	0.01
Unknown[b]	41 (1.9)	44 (3.7)	0.11	30 (3.1)	26 (2.6)	0.03
Year of first analogue prescription						
2014	2147 (98.8)	1113 (94.0)	0.26	959 (97.6)	953 (97.0)	0.04
2015	26 (1.2)	71 (6.0)	0.26	24 (2.4)	30 (3.0)	0.04
Severity of disease						
Nephropathy	730 (33.6)	408 (34.5)	0.02	342 (34.8)	339 (34.5)	0.01
Neuropathy	941 (43.3)	415 (35.1)	0.17	338 (34.4)	361 (36.7)	0.05
Retinopathy	138 (6.4)	72 (6.1)	0.01	55 (5.6)	60 (6.1)	0.02
Foot ulcers	88 (4.0)	48 (4.1)	0.01	40 (4.1)	39 (4.0)	0.01
Comorbidities[c]						
Hypertension	482 (22.2)	278 (23.5)	0.03	229 (23.3)	224 (22.8)	0.01
Hyperlipidemia	208 (9.6)	116 (9.8)	0.01	100 (10.2)	98 (10.0)	0.01
Coronary artery disease	317 (14.6)	162 (13.7)	0.03	137 (13.9)	136 (13.8)	0.00
Chronic kidney disease	377 (17.3)	182 (15.4)	0.05	163 (16.6)	157 (16.0)	0.02
End-stage kidney disease	62 (2.9)	73 (6.2)	0.16	47 (4.8)	49 (5.0)	0.01
Peripheral artery disease	158 (7.3)	89 (7.5)	0.01	74 (7.5)	77 (7.8)	0.01
Obesity	101 (4.6)	22 (1.9)	0.15	17 (1.7)	20 (2.0)	0.02
Smoker	21 (1.0)	12 (1.0)	0.00	13 (1.3)	11 (1.1)	0.02
Prescription medications						
Metformin	1072 (49.3)	538 (45.4)	0.08	451 (45.9)	467 (47.5)	0.03
Sulfonylurea[d]	533 (24.5)	416 (35.1)	0.23	312 (31.7)	326 (33.2)	0.03
Dipeptidyl peptidase-4 inhibitor[e]	176 (8.1)	145 (12.2)	0.14	111 (11.3)	109 (11.1)	0.01
Glucagon-like peptide-1 receptor agonist[f]	33 (1.5)	31 (2.6)	0.08	24 (2.4)	19 (1.9)	0.03
Sodium-glucose cotransporter-2 inhibitor[g]	8 (0.4)	14 (1.2)	0.09	5 (0.5)	5 (0.5)	0.00
Thiazolidinedione[h]	65 (3.0)	54 (4.6)	0.08	34 (3.5)	40 (4.1)	0.03
Meglitinide[i]	15 (0.7)	5 (0.4)	0.04	4 (0.4)	5 (0.5)	0.01
α-Glucosidase inhibitor[j]	9 (0.4)	6 (0.5)	0.01	6 (0.6)	5 (0.5)	0.01
Combination antidiabetic medicine	38 (1.7)	29 (2.4)	0.05	24 (2.4)	20 (2.0)	0.03
Angiotensin-converting enzyme inhibitor	1130 (52.0)	573 (48.4)	0.07	467 (47.5)	481 (48.9)	0.03
Angiotensin receptor blocker	551 (25.4)	300 (25.3)	0.00	252 (25.6)	248 (25.2)	0.01
Statin	1743 (80.2)	908 (76.7)	0.09	759 (77.2)	762 (77.5)	0.01
Most recent HbA_{1c}, mean (SD), %	8.3 (1.5)	7.7 (1.4)	0.41	7.9 (1.3)	7.8 (1.4)	0.07

[a] Data are presented as No. (%) unless otherwise noted.

[b] 85 Members in the unmatched cohort and 56 members in the propensity-scored matched cohort had no outpatient or prescription claims specifying type 1 or type 2 diabetes in the covariate assessment period.

[c] Definitions for clinical comorbidities can be found in eTable 9 in the Supplement.

[d] Commonly including glipizide and glimepiride.

[e] Commonly including sitagliptin and linagliptin.

[f] Commonly including exenatide and liraglutide.

[g] Commonly including canagliflozin and dapagliflozin.

[h] Commonly including pioglitazone.

[i] Commonly including nateglinide and repaglinide.

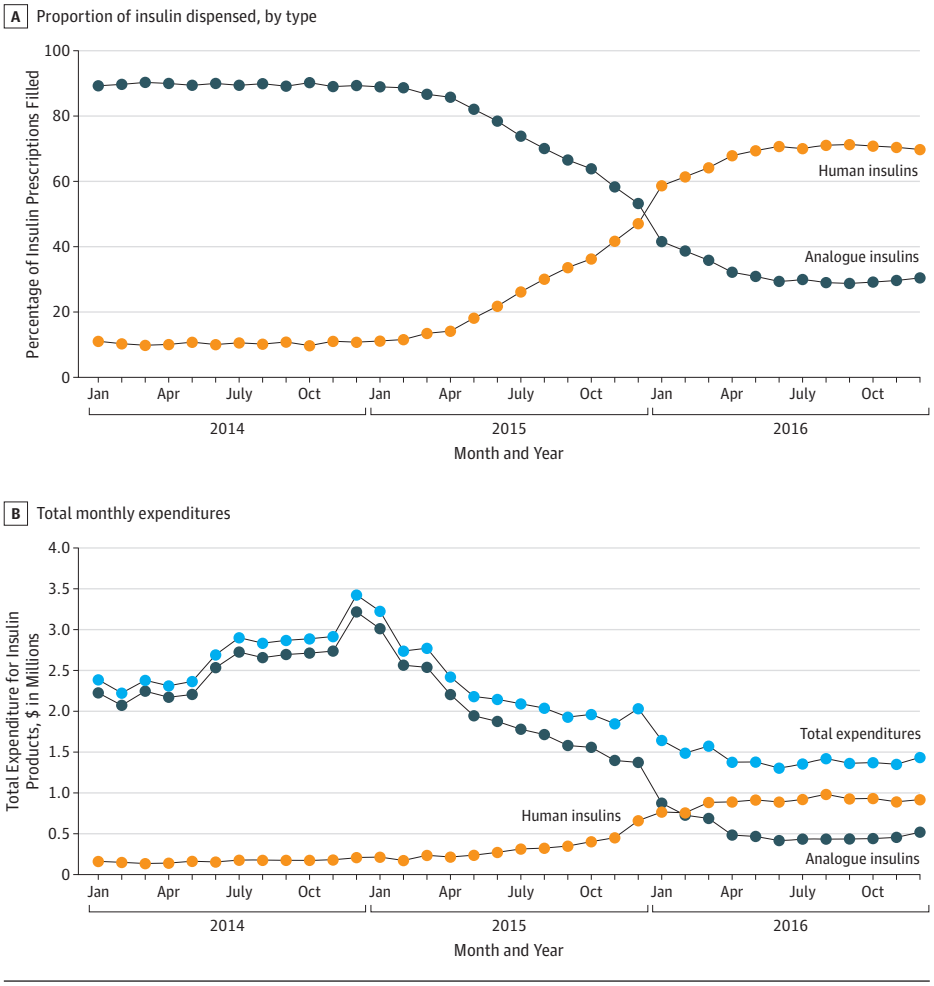
[j] Commonly including acarbose.

Table 3. Differential Changes in Hemoglobin A_{1c} (HbA_{1c}) Comparing Propensity-Score Matched Participants Who Switched From Analogue to Human Insulin vs Participants Who Did Not Switch

	Mean HbA_{1c}, % (95% CI)			
	Before Switch Date		After Switch Date	
Participants	Baseline Level[a]	Baseline Trend	Level change	Trend change
Participants who switched (n=983)	8.13 (8.03 to 8.23)	−0.011 (−0.02 to 0.003)	0.11 (−0.02 to 0.24)	0.001 (−0.02 to 0.02)
Participants who did not switch (n=983)	7.83 (7.73 to 7.94)	0.005 (−0.01 to 0.02)	−0.01 (−0.15 to 0.13)	0.001 (−0.02 to 0.02)
Difference between participants who did and did not switch	0.29 (0.15 to 0.44)	−0.02 (−0.04 to 0.005)	0.12 (−0.08 to 0.32)	<0.001 (−0.03 to 0.03)

[a] Baseline level indicates 12 months before the switch date.

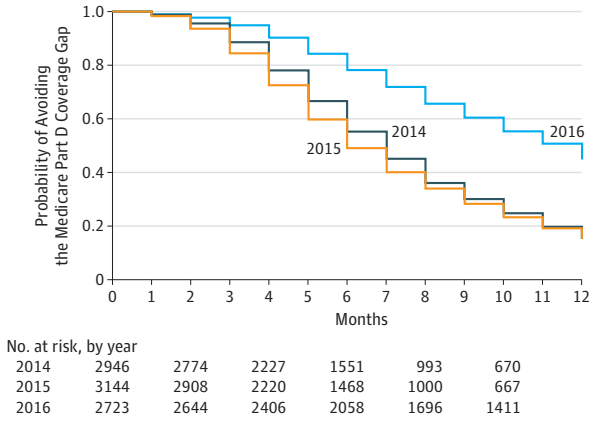
Figure 4. Proportion of Analogue vs Human Insulin Products Dispensed by Calendar Month and Year Among Insulin Users and Total Monthly Expenditures for Insulin Products Dispensed in a Medicare Advantage Plan



The insulin switching intervention was implemented throughout the health system by 2015.

983 who did not), whose baseline characteristics are shown in **Table 2**. Before matching, participants who did not switch from analogue to human insulin were 0.8 years older and more likely to be women; qualify for a low-income subsidy; be enrolled in hospice; have type 1 diabetes; have end-stage kidney disease; and use a dipeptidyl peptidase 4 (DPP-4) inhibitor, a glucagon-like peptide 1 GLP-1 receptor agonist, or a sodium-glucose co-transporter 2 SGLT2 inhibitor than participants who did not switch. After matching, baseline characteristics were well balanced. Matched participants who switched and did not switch had a mean (SD) age of 73 (8.4 and 9.6, respectively) years and mean (SD) most recent HbA_{1c} levels of 7.9% (1.3%) and 7.8% (1.4%), respectively. Of 1966 matched participants, 1853 (>94%) could be definitively classified as living with type 2 diabetes. Six-hundred eighty-one (approximately 35%) had evidence of nephropathy while 338 participants who switched (34%) and 361 participants who did not (37%) had evidence of neuropathy. Of matched participants, 1521 (77%) used a statin at baseline.

Figure 5: Kaplan-Meier Survival Curves for Reaching the Medicare Part D Coverage Gap Comparing Insulin Users in 2014, 2015, and 2016



No. at risk, by year

2014	2946	2774	2227	1551	993	670
2015	3144	2908	2220	1468	1000	667
2016	2723	2644	2406	2058	1696	1411

Reaching the coverage gap indicates that a Medicare beneficiary has surpassed the annual initial coverage threshold, and, from that point on, is responsible for substantially larger out-of-pocket expenses for outpatient prescriptions covered by their Medicare Part D plan. The hazard ratio comparing 2016 and 2014 is 0.45 (95% CI, 0.43-0.48; $P < .001$ using a robust sandwich estimator). Median (interquartile range) length of follow-up was 7 (5-10) months in 2014, 6 (4-10) months in 2015, and 11 (7-12) months in 2016.

Twelve months before their switch dates (index dates), participants who did not switch from an analogue to human insulin had an overall mean HbA_{1c} of 7.83% (95% CI, 7.73%-7.94%), while participants who did switch had an overall mean HbA_{1c} of 8.13% (95% CI, 8.03%-8.23%), corresponding to a difference of 0.29% (95% CI, 0.15%-0.44%; $P = <.001$) (**Table 3**). The trend in mean HbA_{1c} before the intervention was 0.01% (95% CI, −0.02% to 0.003%) per month in participants who switched and 0.005% (95% CI, −0.01% to 0.02%) per month in participants who did not, corresponding to a between-group difference of −0.02% per month (95% CI, −0.04% to 0.005%). After the intervention, the level change in mean HbA_{1c} was 0.11% (95% CI, −0.02% to 0.24%) in participants who switched and −0.01% (95% CI, −0.15% to 0.13%) in participants who did not, corresponding to a between-group difference of 0.12% (95% CI, −0.08% to 0.32%; $P = .22$). The trend change was 0.001% (95% CI, −0.02% to 0.02%) per month in all participants, corresponding to a between-group difference of less than 0.001% (95% CI −0.03% to 0.03%; $P = .99$).

There were 2 serious hypoglycemic events in participants who switched from an analogue to a human insulin (951.4 person-years of follow-up) and in participants who did not (922.1 person-years of follow-up), 12 months after their switch date. The estimated rate ratio comparing participants who did vs did not switch from analogue to human insulin for serious hypoglycemic events was 0.97 (95% CI, 0.14-6.88).

In the 12 months after their switch dates, there were 8 serious hyperglycemic events among participants who switched insulins and 13 among participants who did not. The estimated rate ratio comparing participants who did vs did not switch was 0.60 (95% CI, 0.25-1.44).

Sixty-three participants who switched from analogue to human insulin (6.4%) and 92 participants who did not switch (9.4%) died within 12 months of their switch dates. Results with respect to HbA_{1c}, hypoglycemia, and hyperglycemia from the sensitivity analysis that excluded participants who died during follow-up was not qualitatively different from the results of the primary analysis (eTable 7 and eTable 8 in the Supplement).

Economic Outcomes

During the baseline period, 89% (95% CI, 88%-90%) of filled insulin prescriptions were for analogue insulin products (**Figure 4**A). During the intervention period, the percentage of filled insulin prescriptions for analogue products decreased to 53% (95% CI, 52%-54%), while the human insulin proportion increased from 11% (95% CI, 10%-12%) in the baseline period to 47% (95% CI, 46%-48%). In the postintervention period, analogue prescriptions declined to 30% of filled insulin prescriptions (95% CI, 28%-31%) in June 2016. By December 2016, 70% (95% CI, 68%-71%) of insulin prescriptions were for human insulin products.

Total monthly expenditures for analogue insulin increased from $2 226 389 in January 2014 to a high of $3 214 437 by December 2014 (Figure 4B). Monthly expenditures for analogue insulins decreased to $1 372 942 by December 2015. Expenditures for analogue insulin continued to decline from $875 973 in January 2016 to $515 875 by December 2016. Trends in human insulin expenditures also reflected changes in use. Monthly expenditures for human insulin increased from $160 233 in January 2014 to $209 571 in December 2014. By December 2015, human insulin expenditures were $659 222. Monthly expenditures for human insulin stabilized in 2016, reaching $916 826 by December.

In 2014, 109 of 529 members (20.6%) reached the Part D coverage gap. In 2015, 103 of 549 members (18.8%) reached the gap. In 2016, 143 of 1289 members (11.1%) reached the gap. Comparing the postintervention cohort (2016) against the preintervention cohort (2014), the hazard ratio for reaching the coverage gap or disenrollment was 0.45 (nominal 95% CI, 0.43-0.48; $P < .001$) (**Figure 5**). The hazard ratio was 1.08 (nominal 95% CI, 1.03-1.13) when comparing the intervention cohort (2015) against the preintervention cohort (2014).

Discussion

The managed care organization's intervention encouraging Medicare beneficiaries with diabetes to switch from analogue to human insulin was associated with a small increase in population-level HbA_{1c}. The intervention was not associated with changes in rates of serious hypoglycemia or hyperglycemia. This study provides evidence from a cohort of over 14 000 older patients in routine clinical care assessing the clinical effectiveness of switching patients with type 2 diabetes from analogue to human insulin.

Although it was significant in 1 of 2 analyses, the observed increase in population-level HbA_{1c} may not be clinically important because the value (0.14%) falls within the biological within-patient variation of modern HbA_{1c} assays.[17,18] Results from large randomized trials, including

the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the Action in Diabetes and Vascular Disease (ADVANCE) trial, and the Veterans Affairs Diabetes Trial (VADT), suggest that small changes in HbA_{1c} are unlikely to meaningfully affect rates of macrovascular events or mortality among patients with type 2 diabetes.[19-23] In addition, the association with increases in HbA_{1c} reported in this study may reflect underlying changes in clinical practice occurring during 2015 and 2016 as new data counseled against tight glycemic control among older adults with diabetes.[24,25] However, there is a possibility that small increases in population-level HbA_{1c} could become clinically meaningful for individual patients if continued for prolonged periods.

The results of the current study add to a growing body of literature suggesting that human insulins may result in similar clinical outcomes compared with insulin analogues for many patients with type 2 diabetes. For example, a 2018 observational study using data from over 25 000 patients with type 2 diabetes (mean age, 61 years; mean duration of diabetes, 11 years; mean HbA_{1c}, 9.4%) from Kaiser Permanente of Northern California concluded that initiation with basal analogue insulin was not associated with reduced hypoglycemia-related ED visits or hospital admissions or with improved glycemic control when compared with NPH insulin.[7] Participants in this study were prevalent insulin users, had better HbA_{1c} control at baseline (7.8%), had lower rates of clinical events, and were part of a health system that did not have a strong preference for human insulin. The present study also found that the intervention was associated with a reduced risk of reaching the Part D coverage gap, an important economic outcome for many older adults.

In 2016, 1.9 million Medicare beneficiaries used the long-acting insulin analogue glargine at a cost of $4.6 billion.[26] Because the least expensive versions of human insulin can be obtained at approximately one-tenth of the cost of analogue insulin,[9] if even a small proportion of Medicare beneficiaries with type 2 diabetes who were prescribed analogue insulin were switched to clinically equivalent human insulin (eg, 70/30 or NPH), the resulting savings to the health care system would be substantial.

Strengths of this study include its sample size and inclusion of both prescription/health care encounter claims and laboratory data. A post hoc analysis that matched participants who did and who did not switch from an analogue to human insulin on a propensity score incorporating a large number of patient characteristics, including hemoglobin A_{1c}, provided results consistent with the prespecified primary analysis. Furthermore, the question that this study addresses would be difficult to answer through other study designs or data sources. For example, it would be difficult and costly to enroll thousands of similar patients with type 2 diabetes into a prospective noninferiority or switching trial. Additionally, this study would be difficult to conduct using traditional claims databases alone because of the lack of complete capture of laboratory data, including HbA_{1c} levels.

Limitations

This study has several limitations. First, the observed higher rate of death among participants who did not switch suggests either that switching from analogue to human insulin is protective against death (less likely), or that the patient-level analysis was limited by residual confounding or time-related biases[27] despite the use of propensity scores to control for measured baseline covariates (more likely). It is reassuring that the results presented here with respect to HbA_{1c}, serious hypoglycemic events, and serious hyperglycemic events were not substantially different from the results of a prespecified population-level analysis accounting for time-related biases, nor in a sensitivity analysis excluding members who died. Second, it is possible that small increases in population-level HbA_{1c} could become clinically relevant for certain individual patients if continued for a prolonged period. Third, this study cannot detect differences in rates of minor hypoglycemia episodes or nocturnal hypoglycemic events because the outcome definitions relied on claims. Fourth, the clinical results may not generalize to other health care settings with less intensive pharmacy-level support for chronic disease management.

Conclusions

Among Medicare beneficiaries with type 2 diabetes, implementation of a health plan program that involved switching patients from analogue to human insulin was associated with a small increase in population-level HbA_{1c}.

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Author Contributions: Dr Luo had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Luo, Manetti, Rose, Kaloghlian, Gadhe, Jain, Gagne, Kesselheim.
Acquisition, analysis, or interpretation of data: Luo, Khan, Manetti, Kaloghlian, Gadhe, Jain, Gagne, Kesselheim.
Drafting of the manuscript: Luo, Manetti, Kaloghlian, Jain.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Luo, Khan, Manetti, Gagne.
Obtained funding: Kesselheim.
Administrative, technical, or material support: Luo, Manetti, Rose, Kaloghlian, Gadhe, Jain.
Supervision: Luo, Manetti, Jain, Gagne, Kesselheim.
Other - clinical work for the project: Gadhe.

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