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Association of Initiation of Basal Insulin Analogs vs Neutral Protamine Hagedorn Insulin With Hypoglycemia-Related Emergency Department Visits or Hospital Admissions and With Glycemic Control in Patients With Type 2 Diabetes

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IMPORTANCE In clinical trials of patients with type 2 diabetes, long-acting insulin analogs modestly reduced the risk of nocturnal hypoglycemia compared with human neutral protamine Hagedorn (NPH) insulin, but cost 2 to 10 times more. Outcomes in clinical practice may differ from trial results.

OBJECTIVE To compare the rates of hypoglycemia-related emergency department (ED) visits or hospital admissions associated with initiation of long-acting insulin analogs vs human NPH insulin in patients with type 2 diabetes.

DESIGN, SETTING, AND PARTICIPANTS A retrospective observational study using data from Kaiser Permanente of Northern California from January 1, 2006, through September 30, 2015. Patients with type 2 diabetes who initiated a long-acting insulin analog or NPH insulin were included and censored at death, loss of health plan coverage, change in insulin treatment, or study end on September 30, 2015.

EXPOSURE Initiation of basal insulin analogs (glargine or detemir) vs NPH insulin.

MAIN OUTCOMES AND MEASURES The primary outcome was the time to a hypoglycemia-related ED visit or hospital admission and the secondary outcome was the change in hemoglobin A_{1c} level within 1 year of insulin initiation.

RESULTS There were 25 489 patients with type 2 diabetes who initiated basal insulin therapy (mean age, 60.2 [SD, 11.8] years; 51.9% white; 46.8% female). During a mean follow-up of 1.7 years, there were 39 hypoglycemia-related ED visits or hospital admissions among 1928 patients who initiated insulin analogs (11.9 events [95% CI, 8.1 to 15.6] per 1000 person-years) compared with 354 hypoglycemia-related ED visits or hospital admissions among 23 561 patients who initiated NPH insulin (8.8 events [95% CI, 7.9 to 9.8] per 1000 person-years) (between-group difference, 3.1 events [95% CI, −1.5 to 7.7] per 1000 person-years; $P = .07$). Among 4428 patients matched by propensity score, the adjusted hazard ratio was 1.16 (95% CI, 0.71 to 1.78) for hypoglycemia-related ED visits or hospital admissions associated with insulin analog use. Within 1 year of insulin initiation, hemoglobin A_{1c} level decreased from 9.4% (95% CI, 9.3% to 9.5%) to 8.2% (95% CI, 8.1% to 8.2%) after initiation of insulin analogs and from 9.4% (95% CI, 9.3% to 9.5%) to 7.9% (95% CI, 7.9% to 8.0%) after initiation of NPH insulin (adjusted difference-in-differences for glycemic control, −0.22% [95% CI, −0.09% to −0.37%]).

CONCLUSIONS AND RELEVANCE Among patients with type 2 diabetes, initiation of a basal insulin analog compared with NPH insulin was not associated with a reduced risk of hypoglycemia-related ED visits or hospital admissions or with improved glycemic control. These findings suggest that the use of basal insulin analogs in usual practice settings may not be associated with clinical advantages for these outcomes.

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Editorial
Author Audio Interview

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Treatment of type 2 diabetes typically begins with lifestyle modification and initiation of metformin; however, 14% to 25% of patients eventually require initiation of insulin to reach recommended glycemic targets.[1,2] The mainstay of insulin treatment has long been human synthetic insulin; however, insulin analogs have become increasingly popular in clinical practice during the past decade.[3,4] Insulin analogs are molecularly altered forms of insulin that more closely mimic the pharmacokinetic profile of endogenous insulin.

In clinical trials, long-acting insulin analogs modestly reduce the risk of nocturnal hypoglycemia compared with human insulin, but have not been shown to reduce the risk of severe hypoglycemia or to improve glycemic control among patients with type 2 diabetes.[5] Discrepancies between trial results and outcomes in clinical practice are common and highlight the importance of gathering additional evidence from usual care settings.[6]

Although human insulin products are still used preferentially within Kaiser Permanente of Northern California (KPNC), prior work demonstrated widespread adoption of insulin analogs among US patients during the past 2 decades.[3,4,7] At the same time, the prices of insulin analogs have increased dramatically,[8,9] Medicaid payments for insulin have increased substantially,[10] and patients' out-of-pocket spending on insulin analogs has doubled.[4] In this setting, it is imperative to understand the differences in health outcomes associated with the use of the more expensive insulin analogs vs the more affordable human insulin products.

This study investigated the rates of hypoglycemia-related emergency department (ED) visits or hospital admissions and changes in levels of glycemic control after initiation of long-acting insulin analogs (glargine or detemir) compared with human neutral protamine Hagedorn (NPH) insulin among patients with type 2 diabetes in clinical practice.

Key Points

Question Is initiation of a basal insulin analog compared with human neutral protamine Hagedorn (NPH) insulin associated with a reduced risk of hypoglycemia-related emergency department (ED) visits or hospital admissions in patients with type 2 diabetes?

Findings In this retrospective observational study of 25 489 patients with type 2 diabetes, initiation of basal insulin analogs compared with NPH insulin was not associated with a significant difference in hypoglycemia-related ED visits or hospital admissions among a propensity-score matched cohort of 4428 patients (hazard ratio, 1.16).

Meaning Among patients with type 2 diabetes, the use of basal insulin analogs compared with NPH insulin was not associated with a reduced risk of hypoglycemia-related ED visits or hospital admissions.

Methods

Study Source

The institutional review boards of the Kaiser Foundation Research Institute and the University of Chicago approved the study. Participant informed consent was waived. A large, integrated health care delivery system, KPNC provides care for approximately 30% of the residents in the Northern California service area. The KPNC diabetes registry has been maintained since 1993. The registry now includes more than 350 000 adults with diabetes and is updated annually by identifying all health plan members with diabetes.

The identification of clinically recognized diabetes among health plan members is based on multiple sources of data including pharmacy use; laboratory results; and outpatient, emergency department, and hospitalization diagnoses of diabetes detailed further in a published algorithm.[11] Race/ethnicity was measured because prior studies suggest it is associated with both hypoglycemia and glycemic control.[12,13] Determination of race/ethnicity was based on self-reported race/ethnicity captured in the electronic medical record according to fixed categories. The study methods and a validation study of the KPNC diabetes registry (99% sensitivity for diabetes based on chart review registration) have been published.[14]

Study Population

Using electronic medical records from KPNC, 49 190 adults (aged ≥19 years) with diabetes were identified. Each patient had full health plan and prescription coverage for 24 months prior to initiating insulin between January 1, 2006, and December 31, 2014. Patients with type 1 diabetes were excluded (n = 1838) based on a validated algorithm that uses self-report or age of diabetes onset and drug treatment history to determine diabetes type.[15] Clinicians within KPNC can prescribe either NPH insulin or insulin analogs to patients with type 2 diabetes without obtaining prior approval; however, clinicians are encouraged to start with NPH insulin.

The analytic cohort consisted of patients who initiated basal insulin therapy and had no insulin prescription fills during the prior 12 months (**Figure 1**). Patients started with either NPH insulin or the insulin analog glargine or detemir. Patients using prandial insulin at baseline were excluded from the study. Patients who initiated prandial insulin during the study were censored at that time.

Study Outcomes

The primary outcome was the time to hypoglycemia-related ED visit or hospital admission after initiation of insulin therapy based on a primary or principal discharge diagnosis of hypoglycemia using a validated algorithm (any of the following *International Classification of Diseases, Ninth Revision* codes: 251.0, 251.1, 251.2, 962.3, or 250.8 modified by 259.8, 272.7, 681, 682, 686.9, 707.1-707.9, 709.3, 730.0-730.2, or 731.8).[16]

The secondary outcome was the change in hemoglobin A_{1c} level, which is a marker for the clinical effectiveness of insulin. For the baseline hemoglobin A_{1c} level, the last measure during the 12 months prior to insulin initiation was used. The change from baseline to the last hemoglobin A_{1c} level was

assessed prior to censoring and within 3 to 12 months after insulin initiation. A change in hemoglobin A_{1c} level of 0.5% or greater is typically considered to be clinically significant.[17]

Statistical Analysis

The analysis involved multiple steps. During the first step, a propensity score model was developed, predicting the binary outcome of initiating treatment with basal insulin analogs (compared with NPH insulin) using a flexible, data-adaptive model selection procedure called the deletion, substitution, and addition algorithm by Neugebauer and Bullard (available in R version 3.1.4; R Foundation for Statistical Computing).[18] The deletion, substitution, and addition procedure made use of training and test data sets to select the estimator with the lowest cross-validated risk among a list of candidate estimators developed via machine learning (ie, deletion, substitution, and addition of potential covariates as well as interactions and higher-order parameters).

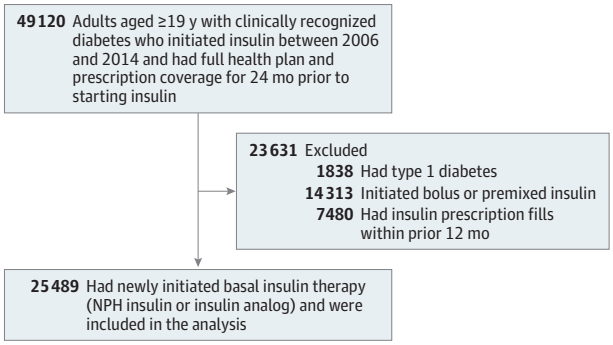
Potential covariates included: demographics, index year, clinical and comorbid characteristics, clinician specialty (primary care, endocrinology, or other specialty), KPNC service area, Charlson comorbidity index, chronic kidney disease stage, chronic liver disease, visual impairment, history of diabetic ketoacidosis, history of depression, glycemic control, the number of hypoglycemia-related ED visits or hospital admissions during the year prior to baseline, the number of ED visits or inpatient stays (for any reason) during the year prior to baseline, medication nonadherence (continuous measure of medication gaps[19,20]), outpatient medical visits (ie, the number of face-to-face visits with a clinician) during the 2 years prior to baseline, the patient co-pay for index insulin dispensed, and indicators of prevalent use for each of the diabetes therapeutic drug classes, statins, angiotensin-converting enzyme inhibitors, and β-blockers.

Missing data for continuous variables were imputed based on the within-group mean. Missing data for categorical variables were treated as a separate category. The C statistic (area under the receiver operating characteristic curve) for this model was 0.81, suggesting good discrimination.

During the second step, the predicted probability (ie, propensity score) of initiating treatment with long-acting insulin analogs was calculated for each patient. Quintiles of the propensity score were created based on the distribution of the propensity scores among the exposed patients (ie, patients who initiated insulin analogs). Using frequency matching (random sampling with replacement), 500 reference patients who initiated NPH insulin were selected from each of the quintiles defined by the exposed group.

This frequency matching created a population in which the distribution of covariates in the NPH insulin cohort was similar to those in the insulin analog cohort, thus minimizing observed confounders. Balance in the covariate distribution in each cohort was assessed by visually inspecting box plots and cumulative probability distributions of the propensity scores between exposed and reference patients and quantitatively through the calculation of the standardized difference, which compares the difference in means or prevalence of baseline covariates in units of the pooled SDs. A standardized difference with the absolute value of less than or equal to 0.1 indicates a negligible difference in the mean or prevalence of a covariate between groups.[21]

Figure 1. Derivation of the Study Cohort



Adults with type 2 diabetes and full health plan and prescription coverage were included if they began basal insulin therapy (neutral protamine Hagedorn [NPH] or insulin analog) between January 1, 2006, and December 31, 2014.

During the third step, a survival analysis was conducted for the outcome of hypoglycemia-related ED visits or hospital admissions. This approach examined time to first event of hypoglycemia-related ED visit or hospital admission. Patients were censored at the earliest event: death, end of KPNC membership, end of prescription drug benefits, discontinuation of NPH insulin or long-acting insulin, addition of any other insulin subtype, or end of follow-up (September 30, 2015). The hazard ratios (HRs) and 95% CIs were calculated from the results of the Cox proportional hazards analyses on 1000 bootstrap samples with replacement, and were created using the methods described above.

The proportional hazard assumption was tested by assessing independence between the Schoenfeld residuals and follow-up time. The primary analysis included the HR after adjusting for baseline covariates that remained unbalanced after propensity score matching (ie, those with the absolute value of the standardized difference >0.1), as well as additional adjustments for prior hypoglycemia-related ED visits or hospital admissions and for time-dependent indicators of diabetes medication use. The use of sulfonylureas, metformin, or thiazolidinediones was based on dispensing of a given medication within 6 months prior to the start of insulin; thereafter, it was based on monthly fills and days' supply dispensed.

In a sensitivity analysis, the HR was additionally calculated using traditional regression adjustment for covariates that were significantly different at baseline for prior hypoglycemia-related ED visits or hospital admissions and for time-dependent indicators of diabetes medication use. Based on a post hoc estimate with a sample size of 25 489 patients, the study had 80% power to detect a HR of 2.1 or greater or of 0.5 or less for the outcome of hypoglycemia-related ED visits or hospital admissions associated with the initiation of insulin analogs vs NPH insulin.

During the fourth step, the change in hemoglobin A_{1c} level following insulin initiation was estimated using a difference-in-differences approach. This approach measured the change

in glycemic control associated with the initiation of long-acting insulin analogs (first difference) after subtracting the background change (second difference [eg, due to secular trends]) among patients who initiated NPH insulin.[22] This model was based on the counterfactual assumption that if patients who initiated insulin analogs had instead initiated NPH insulin, their changes in hemoglobin A_{1c} level would be similar to the changes observed in the NPH insulin reference group, who were frequency matched based on the propensity score quintile. The model was adjusted for baseline covariates that remained unbalanced after propensity score matching.

In the main secondary outcome analysis, participants with missing data for hemoglobin A_{1c} level at baseline and those who were censored within 90 days of baseline were excluded. In a sensitivity analysis, patients also were excluded if the use of any class of diabetes medications changed from baseline until they were censored or until 12 months after initiation of insulin, whichever occurred first. The purpose of this analysis was to isolate the relationship between insulin initiation and change in hemoglobin A_{1c} levels.

The difference-in-differences estimates and 95% CIs were calculated from the results of a least-squares regression analysis on 1000 bootstrap samples with replacement.[23] We used R version 3.3.1 and SAS version 9.3 (SAS Institute Inc) statistical software for all analyses. A P value <.05 was considered statistically significant and all testing was 2-sided.

Results

Patient Characteristics at Baseline

Between 2006 and 2014, a total of 25 489 patients with type 2 diabetes initiated basal insulin therapy (**Table 1**). The mean age was 60.2 years (SD, 11.8 years) and 46.8% were female. The racial/ethnic makeup of the cohort consisted of 51.9% who were white, 9.2% who were black, 17.6% who were Hispanic, and 15.3% who were Asian. The Charlson comorbidity index value was 0 among 28.1%, 1 among 28.5%, 2 among 11.3%, and 3 or greater among 32.1%.

In this cohort, data were missing for race/ethnicity (n = 280), chronic kidney disease stage (n = 213), duration of diabetes (n = 6641), age at diabetes onset (n = 6641), body mass index (n = 1429), elevated serum creatinine level (n = 33), neighborhood deprivation index (n = 242), hemoglobin A_{1c} level (n = 402), KPNC service area (n = 61), and medication nonadherence (n = 5474).

Among the patients who initiated insulin, 23 561 (92%) started with NPH insulin and 1928 (8%) started with insulin analogs. Patients who initiated insulin analogs were more likely to have a greater number of comorbid conditions and had more ED or hospital use events (for any cause) within the prior year, but the magnitude of the differences was small (Table 1). One substantive difference was that the median co-payments for insulin analogs ($20) were significantly higher than for NPH insulin ($10). The mean baseline hemoglobin A_{1c} levels for the 2 groups were 9.41% [SD, 2.0%] among patients who started insulin analogs and 9.40% [SD, 1.8%] among patients who started NPH insulin.

In the propensity score–matched cohort (n = 4428), the differences in the characteristics of patients who initiated insulin analog vs NPH insulin were minimized; however, statistical differences persisted for outpatient medical visits, KPNC service area, and year of index prescription. These differences were not substantive.

Primary Outcome

Among patients who initiated insulin analogs (n = 1928; 3289.8 person-years), there were 32 ED visits and 7 hospital admissions related to hypoglycemia (11.9 events [95% CI, 8.1 to 15.6] per 1000 person-years) during a mean follow-up of 1.71 years (95% CI, 1.62 to 1.79) and a median follow-up of 1.03 years (interquartile range, 0.36 to 2.37). Among patients who initiated NPH insulin (n = 23 561; 40 060.0 person-years), there were 309 ED visits and 45 hospital admissions related to hypoglycemia (8.8 events [95% CI, 7.9 to 9.8] per 1000 person-years) during a mean follow-up of 1.70 years (95% CI, 1.68 to 1.72) and a median follow-up of 1.09 years (interquartile range, 0.41 to 2.38). The between-group difference was 3.1 events (95% CI, −1.5 to 7.7) per 1000 person-years (P = .07).

The Kaplan-Meier curve appears in **Figure 2**. Among all censoring events, 2.8% were due to death, 31.9% were due to discontinuation of insulin, and 31.6% were due to initiation of an additional type of insulin. The proportional hazard assumption was met because the Schoenfeld residuals for the exposure were independent of time (Pearson correlation coefficient, 0.06; P = .20).

After frequency matching the patients who initiated insulin analogs with those who initiated NPH insulin, and after additional adjustment for unbalanced covariates, prior hypoglycemia-related ED visits or hospital admissions, and time-dependent indicators of diabetes medication use, there was no significant difference in hypoglycemia-related ED visits or hospital admissions (HR, 1.16 [95% CI, 0.71 to 1.78]; **Table 2**).

Secondary Outcome

In the main secondary outcome analysis of change in glycemic control, participants with missing data for hemoglobin A_{1c} level at baseline (n = 402) and those who were censored within 90 days of baseline (n = 3665) were excluded (n = 4067). Within 1 year of initiation of insulin analogs, hemoglobin A_{1c} level decreased by 1.26 percentage points (95% CI, 1.16 to 1.36 percentage points) from 9.41% (95% CI, 9.34% to 9.50%) to 8.16% (95% CI, 8.09% to 8.24%).

Within 1 year of initiation of NPH insulin, hemoglobin A_{1c} level decreased by 1.48 percentage points (95% CI, 1.39 to 1.57 percentage points) from 9.39% (95% CI, 9.32% to 9.47%) to 7.92% (95% CI, 7.85% to 7.99%). Between the baseline and post-baseline measures, the mean number of days was 298 (SD, 103 days) among patients who initiated insulin analogs and 288 days (SD, 98 days) among patients who initiated NPH (standardized difference, 0.10). After adjustment, the difference-in-differences for glycemic control was −0.22% (95% CI, −0.09% to −0.37%), indicating that the use of NPH insulin was associated with a statistically significant greater decrease in hemoglobin A_{1c} level (**Table 3**). However, this difference is not considered clinically significant.[17]

Table 1. Baseline Characteristics of 25 489 Patients With Type 2 Diabetes

Characteristic	Before Frequency Matching			After Frequency Matching[a]	
	Insulin Analog (n = 1928)	NPH Insulin (n = 23 561)	Standardized Difference[b]	NPH Insulin (n = 2500)[c]	Standardized Difference[b]
Age, mean (SD), y	60.6 (12.8)	60.2 (11.8)	0.04	60.8 (11.8)	−0.01
Female sex, No. (%)	912 (47)	11 105 (47)	0.01	1140 (46)	0.03
Race/ethnicity, No. (%)[d]					
Asian	332 (17)	3534 (15)	0.06	383 (15)	0.05
Black	214 (11)	2109 (9)	0.07	231 (9)	0.06
White	957 (50)	12 136 (52)	−0.04	1265 (51)	−0.02
Hispanic	293 (15)	4130 (18)	−0.06	446 (18)	−0.07
Other	114 (6)	1390 (6)	−0.04	133 (5)	−0.04
Neighborhood deprivation index by quartile, No. (%)[d,e]					
First (least deprived)	374 (20)	4643 (20)	−0.01	486 (19)	−0.002
Second	538 (28)	6695 (29)	−0.01	702 (28)	−0.004
Third	572 (30)	7030 (30)	−0.004	760 (30)	−0.02
Fourth (most deprived)	423 (22)	4972 (21)	0.02	532 (21)	0.02
Comorbidities, No. (%)					
Charlson comorbidity index[f]					
0	501 (26)	6654 (28)	−0.05	690 (28)	−0.04
1	533 (28)	6736 (29)	−0.02	735 (29)	−0.04
2	228 (12)	2652 (11)	0.02	256 (10)	0.05
≥3	666 (35)	7519 (32)	0.06	819 (33)	0.04
Chronic kidney disease stage[d]					
0	202 (11)	3121 (13)	−0.09	337 (14)	−0.09
1	468 (25)	6024 (26)	−0.03	597 (24)	0.01
2	656 (35)	8348 (36)	−0.03	883 (35)	−0.03
3A	297 (15)	3064 (13)	0.04	316 (13)	0.05
3B	179 (9)	2088 (9)	0.01	237 (9)	−0.01
4	77 (4)	627 (3)	0.07	82 (3)	0.04
5 or dialysis	28 (1)	115 (1)	0.10	19 (1)	0.07
Elevated serum creatinine level, No[d,g]	266 (14)	2664 (11)	0.08	334 (13)	0.01
Chronic liver disease	103 (5)	1392 (6)	−0.02	141 (6)	−0.01
Depression	395 (20)	5266 (22)	−0.05	527 (21)	−0.01
Visual impairment or blindness	95 (5)	618 (3)	0.12	93 (4)	0.06
Health Care Use, No. (%)					
Emergency department visit for any cause in prior year	649 (34)	6822 (29)	0.10	780 (31)	0.05
Inpatient hospitalization for any cause in prior year	379 (20)	3069 (13)	0.18	421 (17)	0.07
No. of outpatient medical visits in prior 2 y by quartile					
0-6	423 (22)	5931 (25)	−0.08	613 (25)	−0.06
7-11	435 (23)	6148 (26)	−0.08	609 (24)	−0.04
12-19	480 (25)	5769 (24)	0.01	631 (25)	−0.01
≥20	590 (31)	5713 (24)	−0.14	647 (26)	0.11
Diabetic ketoacidosis in prior year	31 (2)	206 (1)	0.07	46 (2)	−0.02
Emergency department or inpatient hospitalization for hypoglycemia within prior year	16 (1)	115 (1)	0.04	22 (1)	−0.01
No. of hypoglycemic events resulting in emergency department or inpatient stay in prior year, median (IQR)	0 (0 to 2)	0 (0 to 3)	0.04	0 (0 to 3)	−0.0002
Kaiser Permanente of Northern California service area[d]					
A	114 (6)	1989 (8)	−0.10	196 (8)	−0.08
B	209 (11)	2392 (10)	0.02	224 (9)	0.06
C	123 (6)	1631 (7)	−0.02	121 (5)	0.07
D	144 (7)	740 (3)	0.19	172 (7)	0.02
E	128 (7)	1870 (8)	−0.05	164 (7)	0.004
F	71 (4)	1513 (6)	−0.13	123 (5)	−0.06
G	253 (13)	2080 (9)	−0.14	272 (11)	0.07
H	139 (7)	3810 (16)	−0.28	244 (10)	−0.09
I	97 (5)	1981 (8)	−0.14	166 (7)	−0.07
J	143 (7)	581 (2)	0.23	135 (5)	0.08
K	65 (3)	1831 (8)	−0.19	175 (7)	−0.16
L	139 (7)	1600 (7)	0.02	129 (5)	0.09
M	272 (14)	1513 (6)	0.26	354 (14)	−0.001

(continued)

Table 1. Baseline Characteristics of 25 489 Patients With Type 2 Diabetes (continued)

Characteristic	Before Frequency Matching			After Frequency Matching[a]	
	Insulin Analog (n = 1928)	NPH Insulin (n = 23 561)	Standardized Difference[b]	NPH Insulin (n = 2500)[c]	Standardized Difference[b]
Prescribing clinician specialty					
Primary care	1631 (85)	21 595 (92)	−0.22	2120 (85)	−0.002
Endocrinologist	74 (4)	667 (3)	0.05	90 (4)	0.01
Other specialist	223 (12)	1299 (6)	0.22	290 (12)	−0.01
Clinical Characteristics of Diabetes					
Duration of diabetes, mean (SD), y[d]	11.6 (7.9)	10.6 (6.4)	0.18	11.7 (7.4)	−0.01
Age at diabetes onset, mean (SD), y[d]	49.2 (11.2)	50.0 (10.8)	−0.08	49.0 (9.3)	0.03
Body mass index, mean (SD)[d]	32.2 (7.5)	33.3 (7.5)	−0.15	32.7 (7.2)	−0.06
Hemoglobin A_{1c} level, mean (SD), %[d]	9.41 (2.0)	9.40 (1.8)	0.01	9.39 (1.8)	0.02
Type of diabetes medication, No. (%)					
None	166 (9)	1142 (5)	0.15	172 (7)	0.06
Metformin	1330 (69)	17 915 (76)	−0.16	1805 (72)	−0.07
Sulfonylurea	1590 (82)	20 648 (88)	−0.15	2142 (86)	−0.09
Thiazolidinedione	540 (28)	5533 (23)	0.10	668 (27)	0.03
Dipeptidyl peptidase 4 inhibitors	38 (2)	248 (1)	0.08	40 (2)	0.03
Glucagon-like peptide 1 receptor agonists	23 (1)	71 (<1)	0.10	12 (1)	0.07
Other[h]	54 (3)	322 (1)	0.10	44 (2)	0.07
Types of cardiometabolic medications, No. (%)					
Statins	1409 (73)	18 553 (79)	−0.13	1922 (77)	−0.09
Angiotensin-converting enzyme inhibitors	912 (47)	11 185 (47)	−0.003	1192 (48)	−0.01
β-Blockers	828 (43)	9951 (42)	0.01	1056 (42)	0.01
Medication nonadherence, %[d,i]	432 (22)	5473 (23)	0.15	591 (24)	−0.03
Year of index insulin prescription, No. (%)					
2006	289 (15)	1683 (7)	0.25	313 (13)	0.07
2007	310 (16)	3277 (14)	0.06	354 (14)	0.06
2008	280 (15)	2357 (10)	0.14	373 (15)	−0.01
2009	243 (13)	1947 (8)	0.14	294 (12)	0.03
2010	104 (5)	2072 (9)	−0.13	176 (7)	−0.07
2011	169 (9)	2667 (11)	−0.09	212 (8)	0.01
2012	211 (11)	3120 (13)	−0.07	289 (12)	−0.02
2013	214 (11)	3227 (14)	−0.08	247 (10)	0.04
2014	108 (6)	3211 (14)	−0.27	242 (10)	−0.15
Patient co-pay for index insulin dispensed, median (IQR), $	20 (10 to 35)	10 (5 to 10)	0.67	15 (10 to 45)	0.05

Abbreviations: IQR, interquartile range; NPH, neutral protamine Hagedorn.

[a] Patients who initiated NPH insulin were frequency matched with patients initiating insulin analogs based on propensity score quintile.

[b] Compares characteristics for patients who initiated insulin analogs vs NPH insulin. An absolute value ≤0.1 indicates a negligible difference in the mean or prevalence of a covariate between groups.[21]

[c] The number of patients in each category for the bootstrapped analysis (1000 samples of 2500 each) calculated based on the distributions in the 2.5 million observations and then applied to the 2500. Numbers reflect average across the 1000 samples.

[d] Missing data: race/ethnicity (n = 280), neighborhood deprivation index (n = 242), chronic kidney disease stage (n = 213), elevated serum creatinine (n = 33), Kaiser Permanente of Northern California service area (n = 61), duration of diabetes (n = 6641), age at diabetes onset (n = 6641), body mass index (n = 1429), hemoglobin A_{1c} (n = 402), and medication nonadherence (n = 5474).

[e] Created by a principal components analysis of 8 census-derived variables at the census tract level (% of men in management and professional occupations, living in crowded housing, households in poverty, female-headed households with dependents, households receiving public assistance, households earning <$30 000/year, individuals with less than a high school education, and unemployment).[24,25] Negative scores = less deprivation.

[f] Based on the modified version of the Deyo Charlson Score.[26] Possible scores ranged from 0-17 and represent the number of selected comorbid conditions (other than diabetes) during the 2 years prior to baseline.

[g] Defined as >1.5 mg/dL in men and >1.4 mg/dL in women.

[h] Including α-glucosidase inhibitors, amylin, and meglitinides.

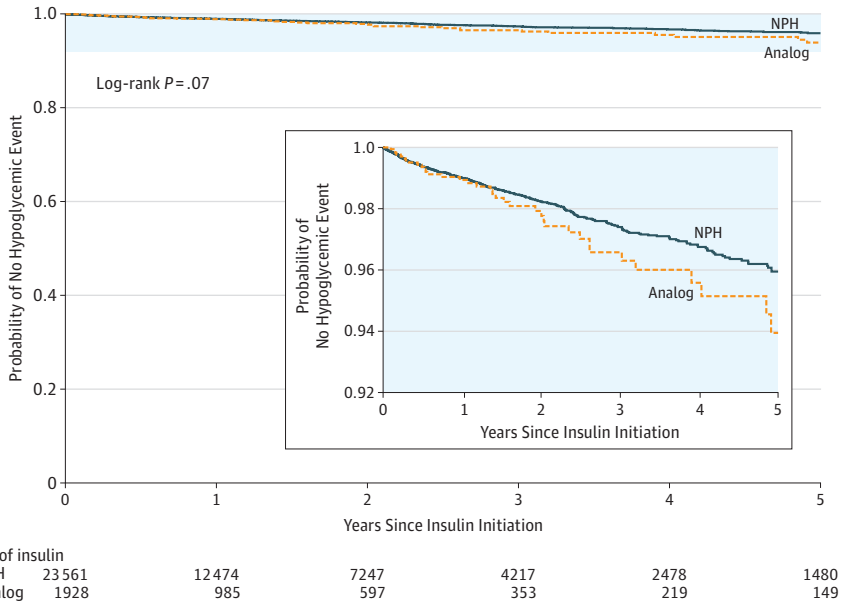
[i] Based on the continuous measure of medication gaps.[19,20] Possible values ranged from 0-100 and represent the percentage of time a patient did not have sufficient medication supply based on electronic pharmacy dispensing data. Medication nonadherence was defined as lacking medication >20% of the time within the year prior to baseline.

Sensitivity Analyses

For hypoglycemia-related ED visits or hospital admissions after initiation of insulin analogs vs NPH insulin, the HR was 1.22 (95% CI, 0.86 to 1.75) using traditional regression adjustment for covariates that were significantly different at baseline, for prior hypoglycemia-related ED visits or hospital admissions, and for time-dependent indicators of diabetes medication use (Table 2).

Within 1 year of insulin initiation, hemoglobin A_{1c} levels decreased by 1.27 percentage points (95% CI, 1.14 to 1.39 percentage points) among patients who started insulin analogs and by 1.43 percentage points (95% CI, 1.33 to 1.53 percentage points) among patients who started NPH insulin after excluding patients with changes in the use of diabetes medications (n = 5199). The difference-in-differences in hemoglobin A_{1c}

Figure 2. Time to First Hypoglycemia-Related Emergency Department Visit or Hospital Admission Among Patients With Type 2 Diabetes



The median follow-up was 1.03 years (interquartile range, 0.36-2.37 years) among patients who initiated an insulin analog and 1.09 years (interquartile range, 0.41-2.38 years) among patients who initiated neutral protamine Hagedorn (NPH) insulin.

Table 2. Survival Analysis

	Hazard Ratio (95% CI)[a]
Full Cohort (N = 25 489)	
Unadjusted	1.35 (0.97-1.88)
Model 1: adjusts for prior severe hypoglycemia-related ED visits or hospital admissions	1.33 (0.95-1.84)
Model 2: adjusts for prior severe hypoglycemia-related ED visits or hospital admissions and time-dependent indicators for oral diabetes therapy use	1.31 (0.94-1.82)
Model 3: adjusts for prior severe hypoglycemia-related ED visits or hospital admissions, time-dependent indicators for oral diabetes therapy use, and additional unbalanced baseline covariates[b]	1.22 (0.86-1.75)
Propensity Score–Matched Sample (n = 4428)	
Unadjusted	1.17 (0.73-1.75)
Model 1: adjusts for prior severe hypoglycemia-related ED visits or hospital admissions	1.18 (0.74-1.78)
Model 2: adjusts for prior severe hypoglycemia-related ED visits or hospital admissions and time-dependent indicators for oral diabetes therapy use	1.21 (0.75-1.84)
Model 3: adjusts for prior severe hypoglycemia-related ED visits or hospital admissions, time-dependent indicators for oral diabetes therapy use, and additional unbalanced baseline covariates[c]	1.16 (0.71-1.78)

Abbreviation: ED, emergency department.

[a] The hazard ratios in the full cohort used traditional regression adjustment. The hazard ratios in the frequency-matched sample used 1000 bootstrap regressions. Risk conferred by initiating long-acting insulin analog vs neutral protamine Hagedorn insulin. Hazard ratio >1 favors NP insulin.

[b] The covariates were baseline diabetes treatment regimen, statin use, visual impairment, hospital use, outpatient medical visits, duration of diabetes, body mass index, year of index prescription, patient insulin co-pay, Kaiser Permanente of Northern California (KPNC) service area, prescribing clinician specialty, and medication nonadherence.

[c] The covariates were outpatient medical visits, KPNC service area, and year of index prescription.

levels was −0.16% (95% CI, −0.005% to 0.34%), which was not a clinically significant change.

Discussion

In this observational study of patients with type 2 diabetes in a large integrated health care system, initiation of basal insulin analogs compared with NPH insulin was not associated with a lower rate of ED visits or hospital admissions related to hypoglycemia. Moreover, initiation of NPH insulin was associated with a slightly greater, but not clinically meaningful, decline in hemoglobin A_{1c} level from baseline. These results suggest that the use of basal insulin analogs among patients with type 2 diabetes in usual practice settings may not be associated with clinical advantages with respect to these outcomes compared with NPH insulin.

Randomized clinical trials suggest that long-acting insulin analogs may offer some advantages for patients with type 2 diabetes, but the benefits appear relatively modest.[5] In several meta-analyses,[5,27,28] benefits in terms of reduced hypoglycemia risk have been reported for both types of insulin

Table 3. Changes in Glycemic Control

	Hemoglobin A_{1c} Level, Mean (95% CI), %[a]	
	Insulin Analog	NPH Insulin
Baseline[b]	9.41 (9.34 to 9.50)	9.39 (9.32 to 9.47)
Postbaseline[c]	8.16 (8.09 to 8.24)	7.92 (7.85 to 7.99)
No. of days between baseline and postbaseline measure, mean (SD)	298 (103)	288 (98)
Pre-post change	1.26 (1.16 to 1.36)	1.48 (1.39 to 1.57)
Unadjusted difference-in-differences estimate[d]	−0.22 (−0.09 to −0.37)	
Adjusted difference-in-differences estimate[e]	−0.22 (−0.09 to −0.37)	

Abbreviation: NPH, neutral protamine Hagedorn.

[a] The results are from 1000 bootstrap samples of the frequency-matched cohort representing 21 422 of the 24 489 patients in the cohort who met the inclusion criteria for the hemoglobin A_{1c} analysis (prebaseline hemoglobin A_{1c} level collected within the 12 months prior to insulin initiation and at least 90 days of follow-up after insulin initiation).

[b] Indicates the last measure within the 12 months prior to insulin initiation.

[c] The last hemoglobin A_{1c} level was assessed prior to censoring and within 3 to 12 months after insulin initiation.

[d] Calculated as the pre-post change in hemoglobin A_{1c} level for the insulin analog group minus the pre-post change in hemoglobin A_{1c} level for the NPH insulin group.

[e] Adjusted for outpatient medical visits, Kaiser Permanente of Northern California service area, and year of index prescription.

analog (glargine and detemir) compared with NPH insulin, but only with respect to nocturnal hypoglycemia. Benefits with respect to severe hypoglycemia (defined as requiring assistance from another person to administer carbohydrates, glucagon, or other resuscitative treatment) were not significant.

One meta-analysis[29] found that glargine use in combination with oral agents was associated with a higher probability of reaching the target hemoglobin A_{1c} level without nocturnal hypoglycemia compared with the use of NPH insulin in combination with oral agents. This difference was largely driven by a reduction in nocturnal hypoglycemia with the use of glargine. In a patient-level meta-analysis,[30] the incidence of overall and nocturnal hypoglycemia was modestly lower in patients with type 2 diabetes treated with glargine compared with NPH insulin. Differences in glycemic control between NPH insulin and basal insulin analogs in the trials were minimal and there were not consistently greater decreases in hemoglobin A_{1c} levels associated with insulin analog use in patients with type 2 diabetes.[30]

In 1 meta-analysis,[28] compared with NPH insulin, the difference in hemoglobin A_{1c} level was −0.05% (95% CI, −0.13% to 0.04%) for insulin glargine and 0.13% (95% CI, 0.03% to 0.22%) for insulin detemir. Because allocation to insulin analogs vs NPH insulin was not concealed in most trials, the potential for ascertainment bias exists, especially for subjective outcomes such as patient-reported hypoglycemia. In addition, clinical trials typically include specific algorithms to achieve strict glycemic control targets and, as a result, trial participants achieve tighter glycemic control compared with patients encountered in clinical practice.

Prior observational studies have shown reduced hypoglycemia risk and improved glycemic control with the use of insulin analogs compared with NPH insulin, but they did not adequately account for confounding factors. For example, 2 large observational studies[31,32] using national registries in Finland showed a significantly increased risk of hospitalization related to severe hypoglycemia with the use of NPH insulin compared with either the insulin analog detemir or glargine, but the studies lacked information about hemoglobin A_{1c} level and major risk factors for hypoglycemia.

In a related study also conducted in Finland, NPH insulin use was associated with increased mortality compared with basal insulin analogs, but again, the study did not adjust for important confounders.[33] Similarly, other studies did not use the more rigorous techniques for balancing covariates, such as propensity score matching.[32,34]

One study from the US Department of Veterans Affairs compared insulin analogs with NPH insulin using clinician practice pattern as an instrumental variable to address confounding by indication.[35] This study examined hospitalizations for ambulatory care–sensitive conditions and mortality, and found no consistent difference in these outcomes when comparing use of long-acting insulin analogs and NPH insulin.[35]

The findings of the present study support the use of NPH insulin in many patients with type 2 diabetes to reduce the costs of care. Insulin prices in the United States have increased 3-fold between 2002 and 2013, particularly for insulin analogs.[8] In 2013, the estimated per-patient expenditures on insulin were greater than for all other diabetes medications combined.[8] A prior study found an increase in the use of insulin analogs for the management of type 2 diabetes with a resultant increase in inflation-adjusted out-of-pocket costs.[4]

The rising cost of insulin may directly affect the health outcomes of patients with diabetes because the associated increased cost share is known to contribute to nonadherence.[36-39] In contrast to insulin analogs, NPH insulin can be purchased for as little as $25 per vial, about one-tenth the price of either insulin analog glargine or detemir.[40] It is likely that only select patients with type 2 diabetes benefit from insulin analogs vs human insulin preparations. To contain health care costs, decisions to use more expensive insulin should be made by informed patients and clinicians, and driven by convincing data about the benefits, harms, and tradeoffs.

Limitations

This study has several limitations. First, this was an observational study and is thus subject to confounding. Specifically, patients with type 2 diabetes who initiated insulin analogs may

be different from those who started NPH insulin. Despite matching on propensity score quintiles, some substantive differences between the 2 groups remained (standardized difference >0.1).

However, the results did not change after additional adjustment for these unbalanced factors. Nonetheless, it is possible that the study did not completely account for confounding by indication due to unmeasured or missing confounders.

Second, the primary outcome was based on ED or hospital use related to hypoglycemia. Therefore, differences in nocturnal and self-reported hypoglycemia, or adverse events treated by emergency medical services but not transported to the ED could not be examined.

Third, the 95% CIs ranged from 0.71 to 1.78 for the HR for hypoglycemia-related ED visits or hospital admissions, which may include a clinically important difference. Therefore, this study may have been underpowered to detect a benefit or harm of that magnitude.

Fourth, these findings come from an integrated health care delivery system and may not necessarily be generalizable to other types of health care settings.

Fifth, the comparisons between NPH insulin and basal insulin analogs did not include convenience, number of injections required, or mode of delivery (vial vs pen). It is possible that basal insulin analogs may confer these and other advantages to patients with type 2 diabetes.

Conclusions

Among patients with type 2 diabetes, initiation of a basal insulin analog compared with NPH insulin was not associated with a reduced risk of hypoglycemia-related ED visits or hospital admissions or with improved glycemic control. These findings suggest that the use of basal insulin analogs in usual practice settings may not be associated with clinical advantages for these outcomes.

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Drafting of the manuscript: Lipska.
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