

Low-Cost Insulin for Socially At-Risk Patients: Evidence for Effectiveness

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Insulin analogues, which include rapid-acting insulins (ie, aspart, lispro) and long-acting basal insulins (ie, glargine, detemir), are the most commonly prescribed insulins in the United States.¹ However, their price has increased dramatically over the past decade, making them unaffordable for many patients.¹ As a result, many patients have been forced to ration their insulin or forgo the use of insulin products altogether.² One study estimated that approximately 1 in 4 patients with diabetes ration their insulin because of cost.³ By contrast, human synthetic insulins, such as regular insulin and isophane/neutral protamine Hagedorn (NPH), have been available for decades and are approximately 10 times less expensive than analogue insulins.² Additionally, these insulins are available without a prescription, which make them more accessible for patients with limited insurance coverage compared with insulin analogues, which all require a prescription.⁴

To address issues related to the cost of diabetes medication, the American Diabetes Association (ADA) published a new clinical decision-making framework in its 2019 *Standards of Medical Care in Diabetes*, which recommends that clinicians prescribe effective medications with the lowest acquisition cost for patients with financial constraints.⁵⁻⁷ Additionally, in 2019, the National Academy of Medicine recommended that providers alter clinical management strategies to accommodate for social and financial barriers, a practice known as adjustment or social risk-informed care.⁸ Qualitative and anecdotal data demonstrate that primary care providers incorporate cost concerns into their prescribing practices for patients with diabetes.^{9,10} However, these practices have not been examined on a large scale using nationally representative data. It is also unclear how the use of low-cost vs high-cost insulin may affect diabetes outcomes among patients with social risk factors, who are at higher risk for adverse diabetes outcomes¹¹⁻¹⁵ and who may use lower-cost insulin out of necessity rather than by choice.^{16,17} As providers and health systems across the nation respond to the call for patient-centered, social risk-informed management strategies, it is important to understand current national trends in prescribing practices for patients with financial risk and whether outcomes differ between patients who are prescribed more costly vs less costly insulin.

ABSTRACT

OBJECTIVES: The price of analogue insulin has increased dramatically, making it unaffordable for many patients and insurance carriers. By contrast, human synthetic insulins are available at a fraction of the cost. The objective of this study was to examine whether patients with financial constraints were more likely to use low-cost human insulins compared with higher-cost analogue insulins and to determine whether outcomes differ between users of each type of insulin.

STUDY DESIGN: Retrospective cohort study.

METHODS: Analysis of 4 cycles of the National Health and Nutrition Examination Survey was performed. Adults with diabetes who reported use of insulin were included. The primary outcome was use of human insulin or analogue insulin. The dependent variable was self-reported financial constraints, a composite variable. Secondary analysis examined the association between use of human vs analogue insulin and patient outcomes.

RESULTS: Of 22,263 eligible respondents, 698 (3.1%) reported use of insulin and the type of insulin used, representing 485,228 patients nationally. Patients with 1 or more financial risk factors were more likely to use human insulin compared with patients without any financial risk factors (88.5% vs 76.7%; $P = .014$). There was no association between use of human vs analogue insulin on diabetic or other patient outcomes among patients regardless of financial risk.

CONCLUSIONS: Patients with financial risk factors may be more likely to use low-cost human synthetic insulins compared with insulin analogues. Outcomes were similar, even when stratified by financial risk.

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TAKEAWAY POINTS

- ▶ Compared with patients with diabetes who do not have financial constraints, those with financial constraints were more likely to use human synthetic insulins compared with more expensive insulin analogues (88.5% vs 76.7%; $P = .014$).
- ▶ Patients with financial constraints had worse diabetes outcomes (adjusted odds ratio [AOR], 2.37; 95% CI, 1.16-4.84), but use of human insulin did not appear to contribute to these outcomes (AOR, 1.30; 95% CI, 0.58-2.89).
- ▶ Human insulin may offer low-cost, effective treatment for certain patients with diabetes and financial constraints.

Using the National Health and Nutrition Examination Survey (NHANES) database, a nationally representative cohort that includes data on medication use, health outcomes, and social determinants of health, we sought to (1) examine whether lower-cost human insulins were more commonly used among patients with significant financial risk factors compared with those without and (2) compare diabetes-specific and other health outcomes between patients with financial risk factors who use lower-cost human insulin compared with analogue insulin.

METHODS

Design

We used data from NHANES, a publicly available, cross-sectional data set compiled and maintained by the CDC's National Center for Health Statistics (NCHS). Interview questions span a wide domain of topics that include demographics, socioeconomic status, and health behaviors. The examination component of the survey includes medical, dental, and environmental laboratory tests. Sampling methodology is complex and representative. However, oversampling of underrepresented groups (such as persons 60 years and older and African American and Hispanic individuals) is used to ensure a more robust and nationally representative sample. Each survey cycle consists of 5000 participants located throughout the United States.

Participants/Main Measures

Our study included participants, 21 years and older, from 4 survey cycles (2007-2008, 2009-2010, 2011-2012, and 2013-2014) who reported use of insulin and the specific type of insulin used. Patients 21 years and older were selected based on methods from prior studies that sought to limit the number of young adults with type 1 diabetes, as they often differ in clinical and behavioral characteristics from older adults.¹⁵ The exposure of interest was financial risk, a composite variable that included the following variables: food insecurity (marginal, low, or very low food security), poverty (moderate to high poverty index), low educational attainment (high school diploma or lower), Medicaid insurance (Medicaid, dual Medicare/Medicaid), lack of prescription coverage in the past year, and report of insurance lapse in the past year. Respondents were considered to have financial risk if they reported 1 or more of these risk factors.

The primary outcome was use of any human insulin product. Human insulins were defined as NPH, NPH/insulin regular, insulin zinc, and zinc extended. Analogue insulins were defined as insulin aspart, insulin aspart protamine, glulisine, lispro, lispro protamine, detemir, and glargine.

The secondary outcome was presence of adverse outcomes, a composite measure that included diabetes metrics and overall health outcome metrics. The composite variable

included uncontrolled glycated hemoglobin A_{1c} (HbA_{1c}), diabetic retinopathy, proteinuria, and overnight hospitalizations. HbA_{1c} and proteinuria were both obtained from laboratory data. HbA_{1c} was dichotomized as "controlled" (< 9%) vs "uncontrolled" (≥ 9%) based on definitions used in prior studies examining diabetes control in low-income populations.¹² Proteinuria was categorized as urine protein/creatinine ratio of less than 30 mg/g (normal), 30 to 200 mg/g (moderate), and greater than 200 mg/g (severe). Self-reported outcomes included diabetic retinopathy and overnight hospitalization, both treated as binary variables. These individual variables were recoded to create a binary composite diabetic complication variable that captured any instance of a complication. Covariates associated with poor diabetes outcomes (age, sex, race/ethnicity, education level) were included, as were comorbidities (self-reported kidney failure, congestive heart failure, coronary heart disease, myocardial infarction, and stroke) and number of prescription medicines taken by each participant (calculated by NCHS).¹⁸ Responses of "don't know" and "refused" were recoded as missing.

Summary statistics were calculated for all variables. The χ^2 test was used to compare characteristics of respondents in each insulin category per NCHS guidelines. Multivariable logistic regression models were constructed using variables that met a P value threshold of .05 in bivariate analyses to assess the independent relationship between the presence of significant financial risk factors and the use of human vs analogue insulin. Multivariate models were also used to examine the relationship between use of human and analogue insulin and clinical outcomes, stratified by financial risk. For all models, human insulin was treated as the index group. Mobile Examination Center sample weights were calculated per NCHS guidelines. Analyses were performed using SAS version 9.4 (SAS Institute). The ChristianaCare Institutional Review Board approved this study.

RESULTS

Of 22,263 eligible respondents, 802 (3.6%) reported the use of insulin and 695 (3.1%) reported the type of insulin used, representing 485,228 patients when weighted national estimates were applied. The sample was 47% female (327 of 695) and 42% White race (292 of 695). Nearly one-fourth of respondents, 23.2% ($n = 195$), reported use of human insulin and 71.6% ($n = 500$) reported use of analogue. Overall,

72.5% (n = 503) of respondents reported at least 1 financial risk factor from our composite metric.

Respondents who reported the use of human insulin were less likely to be college graduates (10.0% vs 22.0%; $P = .011$) and were more likely to have had an insurance lapse in the past 12 months (8.3% vs 3.5%; $P = .04$). There were no significant differences in poverty level, insurance status, number of prescriptions, or prescription coverage between insulin categories. For the composite outcome of financial risk, patients who reported at least 1 financial risk factor were more likely to use human insulin compared with analogue (88.5% vs 76.7%; $P = .014$) (Table 1). On multivariate analysis, after adjusting for age and comorbidities (weak kidneys, history of heart attack, and coronary heart disease), there was no significant association between the composite variable of financial risk and use of human insulin compared with analogue insulin (adjusted odds ratio [AOR], 1.93; 95% CI, 0.96-3.88) (Table 2).

The clinical characteristics of respondents who used human insulin differed from the characteristics of those who used analogue insulin. The users of human insulin were more likely to report weak/failing kidneys (24% vs 14%; $P = .026$), coronary heart disease (20.8% vs 12.1%; $P = .006$), and history of a heart attack (18.9% vs 10.2%; $P = .04$) compared with analogue insulin users (Table 1). Regarding clinical outcomes, there was no significant difference between insulin groups regarding the proportion of patients who demonstrated poor vs adequate control of HbA_{1c} or the proportion of those who reported overnight hospitalizations, diabetic retinopathy or proteinuria, or the composite metric for adverse health outcomes (Table 1). After adjustment for age, financial risk, weak or failing kidneys, coronary heart disease, and myocardial infarction, use of human insulin was not associated with adverse outcomes compared with use of analogue insulin (AOR, 0.91; 95% CI, 0.47-1.75) (Table 3 and Figure). The analysis was repeated using an HbA_{1c} threshold of greater than 7% for poor control, based on ADA guidelines,¹⁹ and there remained no significant association (AOR, 1.05; 95% CI, 0.41-2.71). However, we found that financial risk and history of kidney disease were both independently associated with increased odds of adverse outcomes (financial risk: AOR, 2.37;

TABLE 1. Characteristics of Sample by Reported Insulin Type: NHANES 2007-2008, 2009-2010, 2011-2012, and 2013-2014^a

Characteristics	Human insulin ^b (n = 195)		Analogue insulin ^c (n = 500)		P ^d
	n (%)	Weighted frequency	n (%)	Weighted frequency	
Demographics					
Gender ^e					.953
Male	102 (53.6)	742,622	266 (53.9)	2,132,969	
Female	93 (46.4)	643,721	234 (46.1)	1,824,939	
Age category					.064
21-40 years	18 (14.2)	196,929	51 (11.4)	451,314	
41-64 years	84 (44.1)	611,699	232 (52.7)	2,084,817	
65-79 years	65 (26.9)	372,553	172 (29.4)	1,162,875	
≥ 80 years	28 (14.8)	205,162	45 (6.5)	258,904	
Race/ethnicity					.150
White (non-Hispanic)	75 (64.2)	889,812	217 (68.8)	2,722,626	
Black (non-Hispanic)	71 (21.9)	303,036	144 (15.1)	598,468	
Mexican American	19 (4.6)	63,680	70 (7.5)	295,994	
Other	30 (9.4)	129,815	69 (8.6)	340,820	
Insurance coverage (group)					.166
Private	41 (31.3)	379,656	138 (40.9)	1,484,274	
Medicaid	20 (9.6)	116,019	53 (11.0)	399,803	
Medicare	75 (41.3)	499,894	193 (38.3)	1,389,972	
Medicare/Medicaid (dual eligible)	23 (10.2)	123,933	46 (5.9)	214,853	
Other insurance	10 (7.6)	91,549	23 (4.0)	143,593	
Education level					.011
High school or less	70 (26.1)	360,556	170 (22.3)	882,357	
High school diploma or GED	49 (33.5)	463,179	109 (22.6)	893,977	
Some college	57 (30.4)	419,813	147 (33.1)	1,308,241	
College graduate or above	19 (10.0)	137,578	73 (22.0)	871,281	
Financial risk factors					
Food security					.156
Full food security	121 (65.2)	885,260	328 (74.5)	2,930,126	
Marginal food security	27 (12.6)	171,275	59 (8.8)	345,291	
Low/very low food security	45 (22.2)	300,633	111 (16.7)	656,605	
Family monthly poverty level category					.238
≤ 1.30	75 (34.7)	452,926	199 (31.5)	1,188,765	
> 1.30 and ≤ 1.85	39 (19.8)	259,181	77 (14.9)	563,593	
> 1.85	67 (45.5)	593,844	195 (53.5)	2,017,798	
Prescription coverage					.448
Yes	158 (95.0)	1,131,519	434 (96.6)	3,506,201	
No	11 (5.0)	59,465	18 (3.4)	123,160	
Insurance lapse ^f					.044
Yes	13 (8.3)	100,107	17 (3.5)	128,350	
No	157 (91.7)	1,112,964	436 (96.5)	3,504,150	
Composite financial risk ^g					.014
Yes	137 (88.5)	979,832	366 (76.7)	2,642,326	
No	14 (11.5)	127,875	56 (23.3)	800,936	

(continued)

CLINICAL

TABLE 1. (Continued) Characteristics of Sample by Reported Insulin Type: NHANES 2007-2008, 2009-2010, 2011-2012, and 2013-2014*

Characteristics	Human insulin ^b (n = 195)		Analogue insulin ^c (n = 500)		P ^d
	n (%)	Weighted frequency	n (%)	Weighted frequency	
Comorbidities					
Ever told they had weak/failing kidneys					.026
Yes	47 (24.2)	333,905	86 (14.0)	553,979	
No	147 (75.8)	1,045,853	414 (86.0)	3,403,929	
Congestive heart failure					.181
Yes	40 (22.0)	303,287	81 (14.7)	581,045	
No	153 (78.3)	1,077,661	418 (85.3)	3,372,423	
Coronary heart disease					.006
Yes	36 (20.8)	286,613	77 (12.1)	478,521	
No	157 (79.2)	1,089,564	422 (87.9)	3,474,624	
Myocardial infarction					.044
Yes	37 (18.9)	261,675	67 (10.2)	403,134	
No	157 (81.1)	1,122,472	432 (89.8)	3,551,431	
Stroke					.150
Yes	31 (17.4)	241,155	68 (11.7)	463,620	
No	164 (82.6)	1,145,188	432 (88.3)	3,494,288	
Mean (SEM) number of prescriptions	8.0 (0.458)		7.1 (0.231)		.096
Outcomes					
Overnight hospital patient in past year					.181
Yes	63 (33.1)	459,263	165 (26.9)	1,062,734	
No	132 (66.9)	927,080	334 (73.1)	2,890,945	
Diabetic retinopathy					.181
Yes	80 (42.3)	571,381	180 (34.4)	1,349,070	
No	109 (57.7)	778,370	313 (65.6)	2,577,613	
HbA _{1c} (category)					.179
Good control (≤ 9%)	139 (81.1)	1,055,762	339 (75.1)	2,856,056	
Poor/very poor control (> 9%)	40 (18.9)	245,989	342 (24.9)	947,744	
Urine protein-creatinine ratio					.084
< 30 mg/g (normal)	97 (57.4)	743,509	269 (61.4)	2,332,939	
30-200 mg/g (moderate)	42 (19.2)	248,514	114 (24.2)	917,788	
> 200 mg/g (severe)	46 (23.4)	304,155	94 (14.5)	549,507	
Composite adverse outcomes ^e					.466
Complications	134 (75.4)	913,426	348 (70.7)	2,567,552	
No complications	34 (24.6)	298,739	95 (29.3)	1,061,530	

GED, General Educational Development; HbA_{1c}, glycated hemoglobin A_{1c}; NCHS, National Center for Health Statistics; NHANES, National Health and Nutrition Examination Survey; NPH, neutral protamine Hagedorn; SEM, standard error of the mean.

*All values other than mean (SEM) number of prescriptions are reported as n (%), followed by weighted frequency.

^bHuman insulin: NPH, NPH/insulin regular, insulin zinc, and zinc extended.

^cAnalogue insulin: insulin aspart, insulin aspart protamine, glulisine, lispro, lispro protamine, detemir, and glargine.

^dCalculated per NCHS guidelines, using the Rao-Scott F-adjusted χ^2 statistic for categorical variables and t test for continuous data.

^ePopulation estimates based on NCHS survey weights.

^fOther insurance: single-service plan, state-sponsored health plan, Indian Health Service, military health care.

^gComposite risk metric compiled from the following variables: food insecurity (marginal, low, or very low), poverty index (moderate to high poverty), low educational attainment (high school diploma or lower), Medicaid insurance (Medicaid, dual Medicare/Medicaid), lack of prescription coverage in the past year, and insurance lapse in the past year.

^hComposite metric compiled from the following variables: uncontrolled diabetes (HbA_{1c} > 9%), weak/failing kidneys, self-reported hospitalization, presence of retinopathy, and proteinuria.

95% CI, 1.16-4.84; kidney disease: AOR, 4.24; 95% CI, 1.40-12.86).

Using the same multivariate adjustments (age, weak or failing kidneys, coronary heart disease, and myocardial infarction), we examined the odds of diabetic complications among a stratified group of respondents who reported financial risk compared with those who did not. We found that human insulin was not associated with risk of diabetic complications when compared with use of analogue insulin (AOR, 1.30; 95% CI, 0.58-2.89). However, respondents who reported weak or failing kidneys had significantly higher odds of complications (AOR, 3.42; 95% CI, 1.31-10.34) than those who did not report weak or failing kidneys. For respondents who did not report financial risk factors, human insulin was associated with a protective effect for adverse outcomes (AOR, 0.14; 95% CI, 0.02-0.81).

DISCUSSION

The ADA, Department of Veterans Affairs/ Department of Defense, National Academy of Medicine, and thought leaders in the field have advocated that medical providers consider social risk factors in their care management decisions for patients with diabetes.^{8,19-23} The cost of insulin analogues tripled from 2002 to 2013, making them unaffordable for many patients with diabetes.^{1,22} The cost of human insulins has also risen, but they have remained significantly less expensive.²² Over the past decade, the introduction of less expensive brands of human insulin has made them more affordable than in the past.¹⁶ To our knowledge, this is the first study in a nationally representative cohort of patients with diabetes to provide evidence that patients with financial risk are more likely to use lower-cost insulins compared with those without financial risk factors. Unlike previous studies that included only patients with active insurance coverage,^{24,25} our study examined a diverse patient sample that included patients without insurance coverage, who may have used less expensive human insulin as a matter of financial necessity rather than choice. We found that patients with financial risk factors were more than twice as likely to have adverse diabetes outcomes compared with those without financial risk factors. However, we found no significant differences in clinical outcomes

among patients who used human insulins compared with analogue insulin, when stratified by financial risk.

Our findings add to a current body of literature that supports the use of human synthetic insulins as a cost-effective approach to management of diabetes.²⁴⁻²⁷ The cost savings associated with use of human insulin compared with analogue insulin could be substantial. For managed care organizations, the use of human synthetic insulin compared with analogue insulin has led to significant reductions in insulin expenditures for both the insurer and the beneficiaries.²⁴ Certainly for uninsured patients or those with limited prescription coverage, human insulin, which has a retail value as low as \$25 per vial, is up to 10 times less expensive than a vial of analogue insulin.²⁸ Indeed, our findings demonstrated that those who reported a lapse in insurance in the prior year were more likely to use human synthetic insulins. Among patients with insurance coverage, beneficiaries may in some cases have lower co-pays for human insulin compared with analogue insulin, which could allow for substantial savings, although this is not universal.²⁴

Although our analysis and others demonstrate similar outcomes between users of human and analogue insulin, human insulin may not be the best choice for certain patients. According to the 2019 *Standards of Medical Care in Diabetes*, the ADA recommends that patients with type 1 diabetes use basal and rapid-acting insulin analogues rather than human insulin. Additionally, the ADA recommends that most patients with type 2 diabetes who require injectable medication be started on glucagon-like peptide-1 receptor agonists rather than insulin.¹⁹ These newer medications carry important benefits related to cardiovascular mortality, but they are much more costly than human synthetic insulin, averaging \$700 to \$1000 per month.¹⁹ Therefore, although our data demonstrate that human insulins may be effective, they are not considered as first-line agents for many patients with diabetes according to current practice guidelines and do not carry the cardiovascular benefits of newer diabetes medications.

Similar to prior work, our study demonstrates that patients with financial risk factors have a higher risk of adverse diabetes outcomes.¹¹⁻¹⁵ Although our findings do not indicate that use of human insulin is associated with poor outcomes, such insulins may not be the safest option for patients with an elevated baseline risk of diabetes complications. In particular, NPH, which carries an increased risk of nocturnal hypoglycemia,²⁹ may not be the best choice for patients with an elevated baseline risk of hypoglycemia, such as low-income patients, those with food insecurity,¹⁵ and the very elderly population.³⁰ There are conflicting recommendations regarding the safest insulin formulations for use in these patient groups. Although the ADA advocates for use of the lowest-cost insulin possible for patients with financial concerns,¹⁹ other experts advocate for use of long-acting insulin analogues rather than NPH to reduce the risk of hypoglycemia.⁵ Notably and importantly, we could not assess the incidence of hypoglycemia in our study because no data are available on this in the NHANES database. It is imperative that future studies evaluate the incidence of hypoglycemic events among users of NPH compared with basal insulin among low-income, at-risk patients.¹⁶

TABLE 2. Association Between Presence of Financial Risk Factors^a and Use of Human vs Analogue Insulin^b

Covariate	Adjusted odds ratio	95% CI
Financial risk vs no financial risk	1.93	0.96-3.88
Age	1.00	0.98-1.02
Weak or failing kidneys: yes vs no	1.80	0.95-3.43
Coronary heart disease: yes vs no	1.21	0.54-2.67
Myocardial infarction: yes vs no	1.40	0.49-3.96

^aModel adjusted for age, weak/failing kidneys, coronary heart disease, and myocardial infarction.

^bComposite financial risk metric compiled from the following variables: food insecurity (marginal, low, or very low), poverty index (moderate to high poverty), low educational attainment (high school diploma or lower), Medicaid insurance (Medicaid, dual Medicare/Medicaid), lack of prescription coverage in the past year, and insurance lapse in the past year.

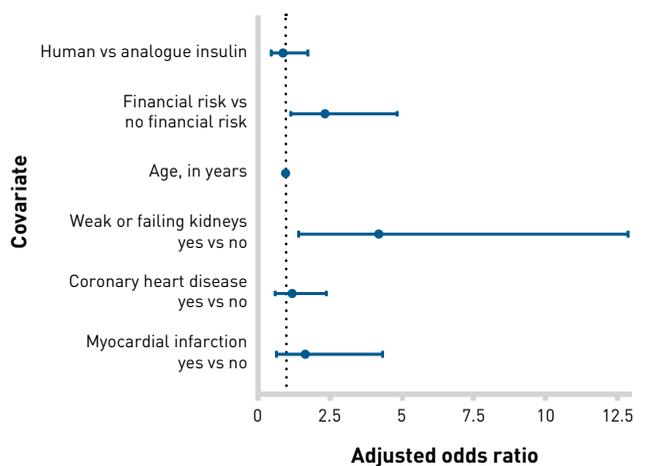
TABLE 3. Association Between Use of Human vs Analogue Insulin and Adverse Outcomes^{a,b}

Covariate	Adjusted odds ratio	95% CI
Human vs analogue insulin	0.91	0.47-1.75
Financial risk vs no financial risk	2.37	1.16-4.84
Age	1.00	0.98-1.02
Weak or failing kidneys: yes vs no	4.24	1.40-12.86
Coronary heart disease: yes vs no	1.20	0.61-2.36
Myocardial infarction: yes vs no	1.68	0.65-4.32

^aModel adjusted for financial risk, age, weak/failing kidneys, coronary heart disease, and myocardial infarction.

^bComposite metric compiled from the following variables: uncontrolled diabetes (glycated hemoglobin A_{1c} ≥ 9%), weak/failing kidneys, self-reported hospitalization, presence of retinopathy, and proteinuria.

FIGURE. Adjusted Odds^a of Adverse Health Outcomes^b



^aModel adjusted for financial risk, age, weak/failing kidneys, coronary heart disease, and myocardial infarction.

^bComposite metric compiled from the following variables: uncontrolled diabetes (glycated hemoglobin A_{1c} ≥ 9%), weak/failing kidneys, self-reported hospitalization, presence of retinopathy, and proteinuria.

Limitations

Our study has several important limitations. Although NHANES provides rich clinical and sociodemographic data, we were limited by our inability to adjust for unmeasured characteristics that influence diabetes outcomes, such as patient and provider preference. Although we were unable to assess hypoglycemia, we did assess days of hospitalization as an outcome, which may account for some severe hypoglycemic events requiring emergency medical attention. Lastly, our study was observational and retrospective in nature, which limits our ability to infer whether differential use of human vs analogue insulin was truly due to financial risk of patients compared with other factors.

CONCLUSIONS

We found that in a generalized, nationally representative sample of patients with diabetes, patients with 1 or more financial risk factors were significantly more likely to be prescribed human insulin compared with patients without any financial risk factors. Although patients with financial risk were more likely to have adverse outcomes, we found that there were no significant differences in outcomes between users of human and analogue insulin even when accounting for financial risk. Although human insulin is prescribed less frequently than analogue insulin, it may offer a cost-effective treatment option for certain patients with diabetes. Future research should further examine factors contributing to poor diabetes outcomes among patients with financial risk. ■

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