

Long-Term Outcomes of Analogue Insulin Compared With NPH for Patients With Type 2 Diabetes Mellitus

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The progressive nature of type 2 diabetes mellitus requires many patients to use insulin to maintain glycemic control.^{1,2} Neutral protamine Hagedorn (NPH) insulin was the most commonly used intermediate-to long-acting insulin until the introduction of the long-acting insulin analogues: insulin glargine in 2000^{2,3} and insulin detemir in 2005.⁴ The long-acting insulin analogues were designed with properties that prolonged absorption, and with a flattened activity peak that extended duration of effect and also resulted in a reduced risk of hypoglycemia.⁵⁻⁷

The significantly higher cost of analogue insulin compared with NPH^{8,9} led researchers and policy makers to compare the efficacy and cost of these medications. Several reviews found no significant difference between analogue insulin and NPH on glycemic control or severe hypoglycemia (ie, low glucose level requiring assistance from another person) but did show reduced likelihood of nocturnal hypoglycemia for patients using analogue insulin.^{6,7,10,11}

Despite these short-term differences, potential long-term benefits have been difficult to test due to the short time frame of studies comparing analogue insulin with NPH.^{2,7} Some cost-effectiveness studies were based on modeling that used clinical trial results as predictors of long-term treatment effects (eg, Center for Outcomes Research Diabetes Model).¹ Other cost-effectiveness studies used retrospective claims that may better reflect clinical settings outside of trials. Results from these studies are mixed, with some concluding analogue insulin was cost-effective^{1,5} and others concluding analogue insulin was not an efficient use of healthcare resources.^{12,13} However, an important limitation of these claims-based studies was the assumption that no systematic, unobserved differences existed between the groups being compared (eg, those that started on NPH compared with analogue insulin).

To bridge this gap in the evidence, we used national Veterans Health Administration (VA) records to systematically compare long-term outcomes for patients using NPH or ana-

ABSTRACT

Background: Long-acting insulin analogues (eg, insulin glargine and insulin detemir) are an alternative to neutral protamine Hagedorn (NPH) insulin for maintaining glycemic control in patients with diabetes. Clinical trials comparing analogue insulin and NPH have neither been adequately powered nor had sufficient follow-up to examine long-term health outcomes.

Objectives: To compare the effects of NPH and long-acting insulin analogues on long-term outcomes.

Study Design: This retrospective observational study relied on administrative data from the Veterans Health Administration and Medicare from 2000 to 2010. Local variations in analogue insulin prescribing rates were used in instrumental variable models to control for confounding. Outcomes were assessed using survival models.

Methods: The study population included US veterans dually enrolled in Medicare who received at least 1 prescription for oral diabetes medication and then initiated long-acting insulin between 2001 and 2009. Outcomes included ambulatory care-sensitive condition (ACSC) hospitalizations and mortality.

Results: There was no significant relationship between type of insulin and ACSC hospitalization or mortality. The hazard ratio for mortality of individuals starting a long-acting analogue insulin was 0.97 (95% CI, 0.85-1.11), and was 1.05 (95% CI, 0.95-1.16) for ACSC hospitalization. Differences in risk remained insignificant when predicting diabetes-specific ACSC hospitalizations, but starting on long-acting analogue insulin significantly increased the risk of a cardiovascular-specific ACSC hospitalization.

Conclusions: We found no consistent difference in long-term health outcomes when comparing use of long-acting insulin analogues and NPH insulin. The higher cost of analogue insulin without demonstrable clinical benefit raises questions of its cost-effectiveness in the treatment of patients with diabetes.

Am J Manag Care. 2015;21(3):e235-e243

Take-Away Points

The progressive nature of type 2 diabetes mellitus requires many patients to initiate insulin. This research compares the effects of the neutral protamine Hagedorn (NPH) and analogue insulin on long-term outcomes.

- Analogue insulin is significantly more expensive than NPH.
- Clinical trials comparing analogue insulin with NPH have not been adequately powered nor had sufficient follow-up to examine long-term health outcomes.
- There were no significant differences in the risk of ambulatory care-sensitive condition hospitalization or mortality for patients who initiated analogue insulin compared with NPH.
- The higher cost of analogue insulin without demonstrable clinical benefit raises questions of its cost-effectiveness in the treatment of patients with diabetes.

logue insulin. We used a novel approach to an established observational comparative effectiveness method, instrumental variables, to obtain unbiased estimates despite the possibility of unobserved differences between groups.

METHODS**Data Sources**

Patient-level national data from the VA were used and supplemented with data from Medicare to ensure completeness in the measures of outcomes, as VA patients often use non-VA facilities for hospital care.¹⁴ The study was reviewed and approved by the Institutional Review Board at the VA Boston Healthcare System.

Study Population

All prescription claims for metformin, sulfonylurea, thiazolidinedione, and long-acting insulin (ie, NPH, insulin glargine and insulin detemir, and mixtures of short- and long-acting insulins) between 2000 and 2007 were extracted from VA pharmacy files (Figure). Eligible individuals had a history of being prescribed at least 1 oral diabetes medication, and initiated long-acting insulin between February 1, 2001, and December 31, 2009. The initiation date for the long-acting insulin was the start of the study period (“index date”) for each patient and the prior 12 months was the baseline period. To ensure that all hospitalizations were recorded, we further limited the cohort to include only those enrolled in Medicare as well as the VA. The last index date permitted was at the end of 2009, to allow a minimum 12-month outcome period. This resulted in a cohort of 142,940 patients, including 118,878 who initiated NPH and 24,062 who initiated analogue insulin.

Insulin Treatment

The main objective of the study was to compare the long-term effects of NPH and analogue insulin. Patients

who initiated NPH or an NPH/regular insulin mixture were compared with patients who started glargine, detemir, or short-acting and long-acting mixtures that included analogue insulin. To improve comparability among patients, we attempted to isolate patients at a similar point in the progression of diabetes. Consequently, patients were required to have a prescription for an oral diabetes medication during the baseline period before initiating insulin. Eighty percent of the individuals remained on the same insulin they started (NPH or analogue insulin). Among those who started on analogue insulin, 99% received glargine.

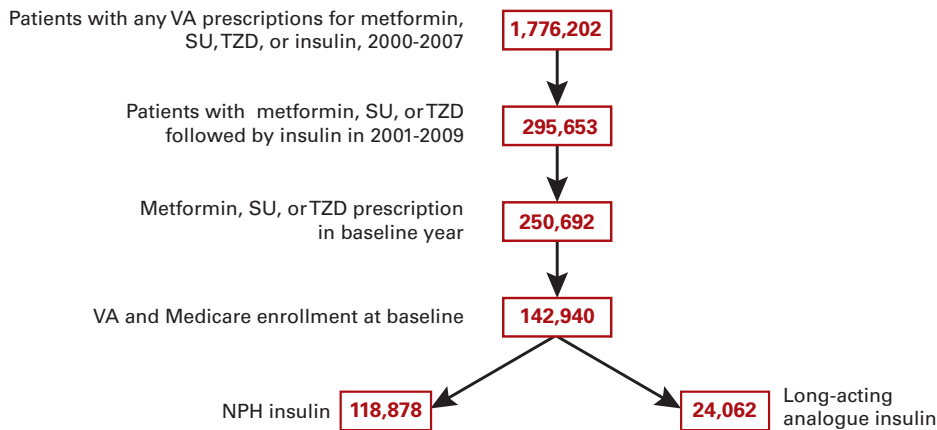
Provider Practice Pattern as Instrumental Variable

The principal threat to a simple comparison of outcomes is that the selection of treatment by patients and providers could be influenced by unmeasured differences in patient risk (selection bias or confounding by indication). To address this, we developed instrumental variables models, which identify a factor (the instrumental variable [IV]) that influences treatment but is effectively random with respect to patient risk and other potential confounders.^{15,16} The statistical model isolates the component of treatment variation attributable to the IV and measures the relationship between this component and outcomes.¹⁷ The success of the approach depends on the effective randomness of the IV (controlling for all the other variables in the model) as well as the strength of the IV’s influence on treatment status.^{16,18}

VA patients are assigned to their primary care physician by variable and often arbitrary methods, so in this study, the IV was the proportion of long-acting insulin prescriptions written for analogue insulin by each provider during an individual’s baseline period¹⁹—the 12 months before the index date on which analogue insulin was prescribed. The instrument assigned to each individual was the proportion of analogue insulin prescriptions written by the provider who prescribed the initial insulin prescription on the index date.

For example, if an individual started on long-acting insulin on January 1, 2003, their baseline period was January 1, 2002, to December 31, 2002 (see eAppendix Figure A1). We identified the provider that prescribed insulin on January 1, 2003, and calculated their proportion of analogue insulin prescriptions in that baseline period (January to December 2002). An individual’s insulin prescription does not contribute to their instrumental variable calcu-

■ **Figure 1.** Sample Selection



NPH indicates neutral protamine Hagedorn; SU, sulfonylurea; TZD, thiazolidinedione; VA, Veterans Health Administration.

lation, eliminating concerns about selection bias. Providers and patients were aligned based on the index date to minimize confounding that could occur if patients later switched providers.

If a provider prescribed insulin to less than 10 unique patients during the baseline period (53% of the time), the rate at the community-based outpatient clinic (CBOC) or VA medical center (VAMC) at which the provider practiced was used.

Provider Quality Controls

The IV will not be effective if correlated with other provider characteristics that might also affect outcomes, causing biased estimates of the treatment-outcome relationship. Therefore, we included 3 provider-level process quality variables: percent of glycated hemoglobin (A1C) labs $\geq 9\%$,^{20,21} percent of blood pressure readings $\geq 140/90$ mm Hg,²² and percent of low-density lipoprotein cholesterol labs >100 mg/dL.²² These variables were computed at the same provider, CBOC, or VAMC level, and time periods as the IV prescribing rate.

Covariates

Additional control variables computed at baseline included patient age, sex, race, A1C, serum creatinine, urine microalbumin, body mass index (see [Table 1](#) for categorizations), 29 indicator variables for comorbidities,²³ 8 indicator variables for the components of the Young diabetes severity index,²⁴ and indicator variables for calendar years corresponding to index dates. Individuals can be diagnosed with multiple comorbidities (eg, obesity and congestive heart failure [CHF]).

Outcomes

Outcomes included mortality and hospital admission (VA or Medicare) for any of 13 ambulatory care-sensitive conditions (ACSCs) as defined by the Agency for Healthcare Research and Quality.^{25,26} These hospitalizations are hypothesized to be preventable with high-quality outpatient care and include several diabetes and cardiovascular complications such as uncontrolled diabetes, short- and long-term complications of diabetes, CHF, and chronic obstructive pulmonary disease. Sensitivity analyses estimated models for specific ACSC hospitalization types most closely related to diabetes and cardiovascular disease. The VA Vital Status File, which determines the date of death from VA, Medicare, and Social Security Administration data, was used to determine mortality.²⁷ Patients were censored either at the end of 2010, or when they experienced either outcome (mortality or ACSC hospitalization), or the date they first switched between long-acting insulin types (NPH and analogue insulin). Consequently, the modeled outcome was the amount of time between the index date and each individual's censoring date.

Statistical Models

We used Stata version 10 (StataCorp LP, College Station, Texas) to estimate the effects of analogue insulin use on the risks of outcomes using Cox proportional hazards models. This model was chosen for 2 reasons: first, a time-to-event analysis has more statistical power than a logistic regression, because more information is used. In a logistic regression, estimates are based on differences between individuals who had events and those who did not. In a time-to-event model, estimates are

Table 1. Selected Descriptive Demographic, Comorbidity, and Outcome Statistics in Baseline (n = 142, 940)^a

	Mean or Percent
Demographics	
Age	69.3 ^b
Male	98
White	84
Diabetes management	
A1C missing	17
A1C <7	12
A1C ≥7 but <8	23
A1C ≥8 but <9	22
A1C ≥9	26
Retinopathy complications ^c	25
Nephropathy complications ^c	28
Neuropathy complications ^c	31
Cerebrovascular complications ^c	17
Cardiovascular complications (some) ^c	24
Cardiovascular complications (severe) ^c	37
Peripheral vascular complications ^c	23
Metabolic complications ^c	2
Metformin prescription	68
Sulfonylurea prescription	92
Thiazolidinedione prescription	31
Cardiovascular comorbidities	
BMI missing	21
BMI normal	11
BMI overweight	27
BMI obese	42
Congestive heart failure ^d	26
Cardiac arrhythmias ^d	28
Valvular disease ^d	13
Hypertension ^d	88
Pulmonary circulatory disorder ^d	3
Chronic obstructive pulmonary disease ^d	28
Outcomes	
ACSC hospitalization	30
Mortality	16

A1C indicates glycated hemoglobin; ACSC, ambulatory care–sensitive condition; BMI, body mass index.

^aFor complete descriptive statistics refer to **eAppendix Table A1**. Individuals can be diagnosed with multiple comorbidities (eg, obesity and congestive heart failure).

^bMean is reported for age. Percentages are reported for all other variables.

^cYoung Diabetes Complications Severity Index.

^dElixhauser comorbidity.

based on differences in time to event as well. The second reason to use a Cox model was to mimic a clinical trial study design. In this study, individuals started analogue or NPH insulin and we then predicted time until death or an ACSC hospitalization, using the provider's prescribing pattern as an instrumental variable to control for selection bias. This is analogous to individuals starting on the treatment or placebo in a randomized clinical trial.

The IV approach estimates a pair of simultaneous equations: one for the likelihood of receiving analogue insulin compared with NPH, and the second for the likelihood of the outcome. The treatment equation modeled the likelihood of receiving analogue insulin as a function of the provider-level prescribing rate and control variables. The outcome equations related treatment and control variables to probabilities of ACSC hospitalization and death. Because the outcome equations were nonlinear, we used the 2-stage residual inclusion technique²⁸ to estimate IV specifications. Two-stage models typically require computationally intensive bootstrapping to calculate accurate standard errors.²⁹ We bootstrapped standard errors for the mortality model and determined that the large samples and strong instruments involved resulted in bootstrapped values that were virtually identical to the asymptotic values generated automatically by the statistical software.

The Cox models assume that analogue insulin treatment increases or decreases outcome risk by a constant proportion over time. We tested this assumption using scaled Schoenfeld residuals from the mortality and hospitalization equations.³⁰

Finally, to control for facility quality differences, we included a facility-level fixed effect in the treatment equation and a facility-level random effect in the outcome equations. Including a fixed effect in the treatment equation and a random effect in the outcome equation improved identification between the 2 stages and strengthened computational efficiency of the estimation algorithms. In sensitivity analyses, we estimated models with fixed effects in both the first and second stage; results were qualitatively unchanged but computationally intensive so we chose to present the random effects version.

RESULTS

Patients in the sample were elderly (mean age = 69 years), about 84% white, and overwhelmingly male

Table 2. Selected Sample Means or Percentages for Patients Starting NPH and Analogue Insulin and Patients Assigned to Above- and Below-Median Analogue Prescribing Providers^a

	Individual Insulin Choice		Provider Insulin Prescribing	
	NPH n = 118,878	Analogue Insulin n = 24,062	Bottom 50% Analogue ^b n = 71,468	Top 50% Analogue ^b n = 71,472
Demographics				
Age	69.0 ^c	70.6	69.1	69.5
Male	98	98	99	98
White	84	86	85	84
Diabetes management				
A1C missing	17	20	17	17
A1C <7	11	15	11	12
A1C ≥7 but <8	22	25	21	24
A1C ≥8 but <9	22	20	22	22
A1C ≥9	27	21	28	25
Retinopathy complications ^d	25	25	26	25
Nephropathy complications ^d	27	31	26	29
Neuropathy complications ^d	30	34	30	31
Cerebrovascular complications ^d	17	19	18	17
Cardiovascular complications (some) ^d	24	25	24	24
Cardiovascular complications (severe) ^d	37	38	38	37
Peripheral vascular complications ^d	22	24	23	22
Metabolic complications ^d	2	2	2	2
Metformin prescription	69	66	68	68
Sulfonylurea prescription	93	87	93	91
Thiazolidinedione prescription	32	27	29	33
Cardiovascular comorbidities				
BMI missing	20	29	19	24
BMI normal	11	9	12	9
BMI overweight	27	24	28	25
BMI obese	42	39	41	42
Congestive heart failure ^e	26	26	27	25
Cardiac arrhythmias ^e	28	31	28	29
Valvular disease ^e	12	14	13	13
Hypertension ^e	87	89	86	89
Pulmonary circulatory disorder ^e	3	3	3	3
Chronic obstructive pulmonary disease ^e	28	28	28	28
Outcomes				
ACSC hospitalization	32	21	36	24
Mortality	17	11	19	13

A1C indicates glycated hemoglobin; ACSC, ambulatory care-sensitive condition; BMI, body mass index; NPH, neutral protamine Hagedorn.

^aFor complete comparisons on all variables included in model refer to **eAppendix Table A2**. Individuals can be diagnosed with multiple comorbidities (eg, obesity and congestive heart failure).

^bThese 2 columns show descriptive statistics of patients assigned to providers who prescribe analogue insulin below and above the sample median.

^cMeans are reported for age. Percentages are reported for all other variables.

^dYoung Diabetes Complications Severity Index.

^eElixhauser comorbidity.

(Table 1). Over a quarter of the patients had average A1C ≥9% and diabetes complications such as retinopathy or nephropathy during the baseline period. Patients also had high rates of cardiovascular comorbidities, with 42% diagnosed with obesity and 26% with CHF. Sixteen percent of

the sample died and 30% had an ACSC hospitalization in the outcome period.

The first 2 columns of **Table 2** compare means of selected demographics and risk adjustment variables focused on diabetes severity and cardiovascular comor-

Table 3. Selected Results from Second-Stage Cox Model: Risk of ACSC Hospitalization (n = 142,940)^a

	Hazard Ratio	P	95% CI
Treatment effects			
Start on analogue insulin	1.05	.339	0.95-1.16
Residual estimated from 1st stage	0.94	.295	0.85-1.05
Demographics			
Age	1.02	<0.001	1.02-1.02
Male	0.93	.073	0.86-1.01
White	0.93	<0.001	0.90-0.96
Diabetes management			
A1C missing (ref = A1C <7)	1.00	.884	0.96-1.05
A1C ≥7 but <8	0.97	.104	0.94-1.01
A1C ≥8 but <9	1.01	.543	0.98-1.05
A1C ≥9	1.17	<0.001	1.13-1.21
Retinopathy complications ^b	1.03	.002	1.01-1.06
Nephropathy complications ^b	1.08	<0.001	1.05-1.11
Neuropathy complications ^b	1.08	<0.001	1.06-1.11
Cerebrovascular complications ^b	1.04	.006	1.01-1.06
Cardiovascular complications (some) ^b	1.19	<0.001	1.15-1.22
Cardiovascular complications (severe) ^b	1.33	<0.001	1.28-1.37
Peripheral vascular complications ^b	1.27	<0.001	1.24-1.30
Metabolic complications ^b	1.04	.198	0.98-1.10
Metformin in baseline	0.89	<0.001	0.87-0.91
Sulfonylurea in baseline	1.01	.681	0.97-1.05
Thiazolidinedione in baseline	0.87	<0.001	0.86-0.89
Cardiovascular comorbidities			
BMI missing (ref = BMI normal)	0.86	<0.001	0.83-0.89
BMI overweight	0.89	<0.001	0.86-0.92
BMI obese	0.89	<0.001	0.86-0.92
Congestive heart failure ^c	1.63	<0.001	1.58-1.68
Cardiac arrhythmias ^c	1.21	<0.001	1.18-1.24
Valvular disease ^c	1.01	.650	0.98-1.03
Pulmonary circulatory disease ^c	1.34	<0.001	1.28-1.40
Hypertension ^c	0.96	.020	0.93-0.99
Chronic obstructive pulmonary disease ^c	1.64	<0.001	1.60-1.67

A1C indicates glycated hemoglobin; ACSC, ambulatory care–sensitive condition; BMI, body mass index; ref, reference.

^aModel also includes all Elixhauser comorbidities; microalbumin, serum creatinine; provider quality controls in baseline; year fixed effects; and Veterans Affairs Medical Center random effects. (Refer to **eAppendix Table A4** for complete results.)

^bYoung Diabetes Complications Severity Index.

^cElixhauser comorbidity.

(21% compared with 27%) but were more likely to be missing A1C and BMI measurements during the baseline period. Thirty-two percent of the individuals who started on NPH had an ACSC hospitalization compared with 21% of individuals who started on analogue insulin; the figures were 17% and 11%, respectively, for mortality.

To demonstrate the effectively random nature of the instrumental variable, we divided the patients into those linked to providers with above- or below-median analogue insulin prescribing rates and compared means in the last 2 columns of Table 2. Patients linked to the above-median group received analogue insulin on 30% of days in the baseline year compared with 4% for the patients in the below-median group (data not shown). Comparing changes from the first 2 columns to the last 2 columns, the individual-level demographic and comorbidity variables become closely balanced with the instrumental variable of provider analogue prescribing rates. For example, 30% of the individuals who started NPH had a neuropathy complication, compared with 34% of patients who started on analogue insulin. When the sample is compared based on provider analogue prescribing rates, 30% of patients assigned

to low analogue prescribing providers had a neuropathy complication compared with 31% of patient assigned to high analogue prescribing providers. This consistent pattern of narrowing the difference between the first 2 columns demonstrates the randomizing effect of the chosen instrument. Patients assigned to low analogue prescribing

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■ **Table 4.** Effect of Analogue Insulin on Mortality and Diabetes and Cardiovascular ACSC Hospitalization (n = 142,940)^a

	Hazard Ratio	P	95% CI
Mortality	0.97	.628	0.85-1.11
Diabetic ACSC hospitalization	1.03	.776	0.83-1.29
Cardiovascular ACSC hospitalization	1.16	.039	1.01-1.33

ACSC indicates ambulatory care-sensitive condition.
^aModels include baseline demographics, Elixhauser comorbidities, Young Diabetes Complications Severity Index, glycated hemoglobin, body mass index, microalbumin, serum creatinine, metformin use, sulfonylurea use, thiazolidinedione use, provider quality controls, year fixed effects, and Veterans Affairs Medical Center random effects. (Refer to **eAppendix Tables A5-A7** for complete results.)

providers had higher ACSC hospitalization and mortality rates compared with patients assigned to high analogue prescribing providers.

Receipt of analogue insulin was strongly predicted by provider analogue prescribing history in the first-stage equation. The coefficient on provider analogue prescribing history was 2.76 (95% CI, 2.68-2.83) and the *F* statistic of 5135 easily exceeds the standard threshold for instrumental variable strength ($F > 10$)¹⁶ (**eAppendix Table A3**).

There was no significant relationship between the type of insulin initiated and the 2 main outcomes. The estimated hazard ratio for the effect of starting analogue insulin compared with NPH was 1.05 (95% CI, 0.95-1.16) for ACSC hospitalization (**Table 3**). Older age, A1C values $\geq 9\%$, diabetes complications, and cardiovascular comorbidities significantly increased the likelihood of experiencing an ACSC hospitalization. Receiving metformin or a thiazolidinedione at baseline significantly decreased this likelihood. The estimated hazard ratio for the effect of starting analogue insulin compared with NPH was 0.97 for mortality (95% CI, 0.85-1.11) (**Table 4**). Older age, cerebrovascular, cardiovascular and peripheral vascular disease complications, and cardiovascular comorbidities such as congestive heart failure significantly increased the likelihood of death (**eAppendix Table A5**). There was no significant difference in treatment effects in sensitivity analyses that predicted diabetes-specific ACSC hospitalizations. Individuals who started on analogue insulin were at a significantly increased risk of experiencing a cardiovascular-specific ACSC hospitalization (**Table 4**).

DISCUSSION

Short-term studies of analogue insulin and NPH have focused on glycemic control outcomes but have not had sufficient power or length of follow-up to examine long-term outcomes.^{7,11} Using a national sample of veterans diagnosed with diabetes and up to 10 years of follow-up, we found no significant difference between analogue insulin and NPH on the long-term outcomes of mortality

and ACSC hospitalization. To our knowledge, no prior studies have examined the long-term differences in effectiveness of these 2 insulins.

The advantages and disadvantages of analogue insulin compared with NPH in the care of patients with diabetes have been subject to debate. Some hypothesized that the decreased nocturnal hypoglycemia of analogue insulin would encourage long-term patient adherence and intensification of insulin when needed,¹ resulting in fewer long-term complications. Others concluded that any benefits of analogue insulin were insufficient to offset the substantially higher cost.¹² Our study's finding of no benefit in long-term outcomes for patients prescribed analogue insulin instead of NPH suggests that long-acting analogue insulin may not be cost-effective as a routine treatment for diabetes.

The lack of improvement in outcomes is striking when considering the cost implications of prescribing analogue insulin. Gellad et al (2013) found that Medicare Part D beneficiaries were 3 times more likely to be prescribed analogue insulin than a comparable VA population. The researchers estimated that Medicare Part D could have saved \$189 million in 2008 if prescribing patterns of long-acting insulin in Part D matched VA prescribing patterns.⁸ These specific cost-effectiveness calculations may change if biosimilars (eg, generic versions of analogue insulin) become available as the patents for analogue insulin expire.³¹ To successfully enter the market, manufacturers of biosimilars must prove they are just as safe and effective as the reference product. This is a more cumbersome task for protein-based drugs such as insulin compared with small-molecule generics, since small changes in protocol can lead to significant differences in the final product.³² Consequently, biosimilars are estimated to be only 20% to 40% cheaper than current analogue insulin products,³² and NPH may continue to be the most cost-effective alternative.

This study helps to establish innovative comparative effectiveness methods featuring provider prescribing patterns as instrumental variables.³³⁻³⁶ These methods

are increasingly applicable with the growing adoption of electronic medical records. The use of instrumental variables minimizes the risk of confounding due to unmeasured differences in patient health. Applying these quasi-experimental methods to retrospective data allows providers and policy makers to make decisions about the most effective and cost-efficient treatments in a timely manner, improving outcomes and lowering costs.

The main limitation of this study is that data were not available to examine hypoglycemia and subsequent quality-of-life outcomes. Our study data indicate that most patients did not switch from NPH to analogue insulin during the study period, suggesting that any quality-of-life differences were likely small. However, accurately measuring the occurrence and frequency of hypoglycemia is difficult.³⁷ Surveys relying on self-report by patients find that severe and nocturnal hypoglycemia have a negative impact on health-related quality of life and work productivity,^{38,39} and future research should continue to systematically study the frequency and impact of these quality-of-life outcomes through self-monitoring (including continuous glucose monitoring) and patient self-report. Another limitation is that the study population was nearly all male and composed entirely of elderly veterans. Future research should compare the long-term outcomes of NPH and analogue insulin in populations not well represented in our sample.

CONCLUSIONS

Our study found no benefit in long-term health outcomes for patients who were prescribed analogue insulin compared with NPH. Given the higher cost of analogue insulin, these findings raise questions about the cost-effectiveness of this prescribing practice. The growing prevalence of diabetes along with the proliferation of new treatments emphasizes the need for such observational comparative effectiveness studies to help identify the most efficient uses of healthcare resources.

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Source of Funding: Health Services Research and Development Service of the US Department of Veterans Affairs (Grant No. IIR 10-136), AHRQ R01 HS019708, and NIH K24 DK63214.

Author Disclosures: The authors report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (JCP, TAL, WFG, SDP, DE, PRC); acquisition of data (JCP); analysis and interpretation of data (JCP, TAL, WFG, SDP, DE, PRC); drafting of the manuscript (JCP, PRC); critical revision of the manuscript for important intellectual content (JCP, WFG, SDP, DE, PRC); statistical analysis (JCP, TAL, SDP, DE); obtaining funding (SDP); administrative, technical, or logistic support (DE, WFG, TAL, JCP); and supervision (JCP, SDP).

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eAppendix

Figure A1. Example of Study Design Timing

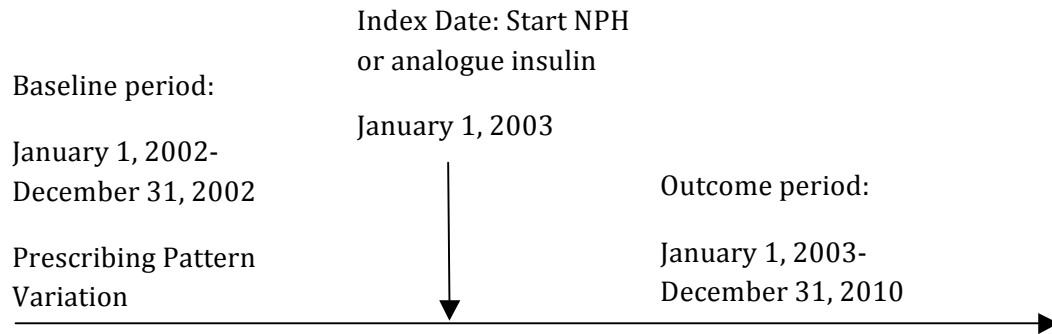


Table A1: Descriptive Demographic and Comorbidity Statistics in Baseline (n = 142,940)^a

	Mean or Percent
Demographics	
Age	69.3 ^b
Male	98
White	84
Black	12
Other	3
Diabetes management	
A1C missing	17
A1C <7	12
A1C ≥7 & A1C <8	23
A1C ≥8 & A1C <9	22
A1C ≥9	26
Retinopathy complications ^c	25
Nephropathy complications ^c	28
Neuropathy complications ^c	31
Cerebrovascular complications ^c	17
Cardiovascular complications (some) ^c	24
Cardiovascular complications (severe) ^c	37
Peripheral vascular complications ^c	23
Metabolic complications ^c	2
Metformin prescription	68
Sulfonylurea prescription	92
Thiazolidinedione prescription	31
Microalbumin missing	65
Microalbumin normal	28
Microalbumin high	7
Serum creatinine missing	17
Serum creatinine normal	66
Serum creatinine high	17
Cardiovascular comorbidities	
BMI missing	21
BMI normal	11
BMI overweight	27
BMI obese	42
Congestive heart failure ^d	26
Cardiac arrhythmias ^d	28
Valvular disease ^d	13
Hypertension ^d	88
Pulmonary circulatory disorder ^d	3
Chronic obstructive pulmonary disease ^d	28
Other comorbidities	
Paralysis ^d	2
Other neurological disorder ^d	7
Hypothyroidism ^d	10

Renal failure ^d	15
Liver disease ^d	4
Peptic ulcer excluding bleeding ^d	3
AIDS ^d	0
Lymphoma ^d	1
Metastatic cancer ^d	2
Solid tumor without metastasis ^d	20
Rheumatoid arthritis ^d	3
Coagulopathy ^d	5
Weight loss ^d	4
Fluid and electrolyte disorders ^d	18
Blood loss anemias ^d	2
Deficiency anemias ^d	23
Alcohol abuse ^d	4
Drug abuse ^d	2
Psychoses ^d	12
Depression ^d	16
Provider process quality variables	
Provider % A1C ≥ 9 in baseline period	21
Provider BP % ≥ 140 and ≥ 90 in baseline period	7
Provider LDL % > 100 in baseline period	37
Outcomes	
ACSC Hospitalization	30
Mortality	16

A1C indicates glycated hemoglobin; ACSC, ambulatory care–sensitive condition; BMI, body mass index.

^aIndividuals can be diagnosed with multiple comorbidities (eg, congestive heart failure, obesity).

^bMeans are reported for age. Percentages are reported for all other variables.

^cYoung Diabetes Complications Severity Index.

^dElixhauser comorbidity.

Table A2: Sample Means and Percentages for Patients Starting NPH and Analogue Insulin and Patients Assigned to Above And Below-Median Analogue Prescribing Providers

	Individual Insulin Choice		Provider Insulin Prescribing	
	NPH n = 118,878	Analogue insulin n = 24,062	Bottom 50% Analogue ^b n = 71,468	Top 50% Analogue ^a n = 71,472
Demographics				
Age	69.0 ^b	70.6	69.1	69.5
Male	98	98	99	98
White	84	86	85	84
Black	13	11	12	13
Other	4	3	4	3
Diabetes management				
A1C missing	17	20	17	17
A1C <7	11	15	11	12
A1C ≥7 & A1C <8	22	25	21	24
A1C ≥8 & A1C <9	22	20	22	22
A1C ≥9	27	21	28	25
Retinopathy complications ^c	25	25	26	25
Nephropathy complications ^c	27	31	26	29
Neuropathy complications ^c	30	34	30	31
Cerebrovascular complications ^c	17	19	18	17
Cardiovascular complications (some) ^c	24	25	24	24
Cardiovascular complications (severe) ^c	37	38	38	37
Peripheral vascular complications ^c	22	24	23	22
Metabolic complications ^c	2	2	2	2
Metformin prescription	69	66	68	68
Sulfonylurea prescription	93	87	93	91
Thiazolidinedione prescription	32	27	29	33
Microalbumin missing	66	60	68	62
Microalbumin normal	27	33	25	31
Microalbumin high	6	8	6	7
Serum creatinine missing	16	22	16	18
Serum creatinine normal	67	63	67	66
Serum creatinine high	17	15	17	16
Cardiovascular comorbidities				
BMI missing	20	29	19	24
BMI normal	11	9	12	9
BMI overweight	27	24	28	25
BMI obese	42	39	41	42
Congestive heart failure ^d	26	26	27	25
Cardiac arrhythmias ^d	28	31	28	29
Valvular disease ^d	12	14	13	13

Hypertension ^d	87	89	86	89
Pulmonary circulatory disorder ^d	3	3	3	3
Chronic obstructive pulmonary disease ^d	28	28	28	28
Other comorbidities				
Paralysis ^d	2	2	2	2
Other neurological disorder ^d	7	8	7	7
Hypothyroidism ^d	9	11	9	10
Renal failure ^d	15	17	14	16
Liver disease ^d	4	4	4	4
Peptic ulcer excluding bleeding ^d	3	3	3	3
AIDS ^d	0	0	0	0
Lymphoma ^d	1	1	1	1
Metastatic cancer ^d	2	2	2	2
Solid tumor without metastasis ^d	20	21	19	20
Rheumatoid arthritis ^d	3	3	3	3
Coagulopathy ^d	5	5	5	6
Weight loss ^d	3	4	3	4
Fluid and electrolyte disorders ^d	17	19	17	18
Blood loss anemias ^d	2	2	2	2
Deficiency anemias ^d	22	26	22	24
Alcohol abuse ^d	4	4	4	4
Drug abuse ^d	2	2	2	2
Psychoses ^d	12	12	12	12
Depression ^d	16	17	15	16
Provider process quality variables				
Provider % A1C ≥ 9 in baseline period	20	21	21	20
Provider BP % ≥ 140 and ≥ 90 in baseline period	7	6	7	6
Provider LDL % > 100 in baseline period	39	29	42	32
Outcomes				
ACSC hospitalization	32	21	36	24
Mortality	17	11	19	13

A1C indicates glycated hemoglobin; ACSC, ambulatory care–sensitive condition; BMI, body mass index.

^aThese two columns show descriptive statistics of patients assigned to providers who prescribe analogue insulin below and above the sample median.

^bMeans are reported for age. Percentages are reported for all other variables.

^cYoung Diabetes Complications Severity Index.

^dElixhauser comorbidity.

Table A3. First-Stage Probit: Receiving Analogue Prescription Compared to NPH (n = 142,940)^a

	Coefficient	P	95% CI	
Instrument				
Provider prescribing history	2.757	<0.001	2.681	2.832
Demographics				
Age	0.005	<0.001	0.004	0.007
Male	-0.081	0.040	-0.159	-0.004
White (ref = black)	0.102	<0.001	0.068	0.137
Other	0.087	0.011	0.020	0.155
Diabetes management				
A1C missing (ref = A1C <7)	-0.004	0.864	-0.047	0.039
A1C ≥7 & A1C <8	-0.144	<0.001	-0.178	-0.110
A1C ≥8 & A1C <9	-0.232	<0.001	-0.268	-0.197
A1C ≥9	-0.226	<0.001	-0.262	-0.191
Retinopathy complications ^b	0.053	<0.001	0.030	0.076
Nephropathy complications ^b	0.041	0.008	0.011	0.072
Neuropathy complications ^b	0.094	<0.001	0.072	0.116
Cerebrovascular complications ^b	0.016	0.242	-0.011	0.044
Cardiovascular complications (some) ^b	0.051	<0.001	0.024	0.078
Cardiovascular complications (severe) ^b	0.041	0.025	0.005	0.076
Peripheral vascular complications ^b	0.036	0.004	0.011	0.061
Metabolic complications ^b	0.142	<0.001	0.074	0.211
Metformin prescription	-0.134	<0.001	-0.157	-0.110
Sulfonylurea prescription	-0.472	<0.001	-0.505	-0.439
Thiazolidinedione prescription	-0.032	0.006	-0.054	-0.009
Microalbumin missing (ref = microalbumin normal)	0.035	0.007	0.010	0.060
Microalbumin high	0.026	0.235	-0.017	0.069
Serum creatinine missing (ref = serum creatinine normal)	0.077	<0.001	0.040	0.115
Serum creatinine high	-0.055	0.001	-0.087	-0.022
Cardiovascular comorbidities				
BMI missing (ref = BMI normal)	0.069	0.001	0.029	0.108
BMI overweight	0.008	0.682	-0.030	0.046
BMI obese	-0.016	0.388	-0.054	0.021
Congestive heart failure ^c	0.046	0.007	0.012	0.080
Cardiac arrhythmias ^c	0.010	0.477	-0.017	0.036
Valvular disease ^c	0.093	<0.001	0.062	0.124
Hypertension ^c	-0.003	0.869	-0.035	0.029
Pulmonary circulatory disorder ^c	-0.020	0.505	-0.078	0.038
Chronic obstructive pulmonary disease ^c	-0.030	0.011	-0.054	-0.007
Other comorbidities				
Paralysis ^c	0.015	0.668	-0.053	0.082

Other neurological disorder ^c	0.049	0.013	0.010	0.089
Hypothyroidism ^c	0.071	<0.001	0.039	0.103
Renal failure ^c	0.008	0.683	-0.029	0.044
Liver disease ^c	0.012	0.649	-0.041	0.066
Peptic ulcer excluding bleeding ^c	0.034	0.279	-0.028	0.096
AIDS ^c	0.044	0.651	-0.146	0.234
Lymphoma ^c	0.051	0.238	-0.034	0.137
Metastatic cancer ^c	-0.005	0.889	-0.076	0.066
Solid tumor without metastasis ^c	-0.011	0.422	-0.036	0.015
Rheumatoid arthritis ^c	0.031	0.289	-0.026	0.088
Coagulopathy ^c	-0.009	0.693	-0.054	0.036
Weight loss ^c	0.018	0.512	-0.035	0.070
Fluid and electrolyte disorders ^c	0.042	0.003	0.014	0.071
Blood loss anemias ^c	0.014	0.702	-0.057	0.085
Deficiency anemias ^c	0.022	0.101	-0.004	0.047
Alcohol abuse ^c	-0.033	0.262	-0.090	0.024
Drug abuse ^c	-0.067	0.093	-0.144	0.011
Psychoses ^c	0.044	0.008	0.012	0.077
Depression ^c	0.006	0.679	-0.022	0.034
Provider process quality variables				
Provider % A1C ≥ 9 in baseline period	0.058	0.281	-0.048	0.165
Provider BP % ≥ 140 and ≥ 90 in baseline period	0.408	0.008	0.108	0.708
Provider LDL% > 100 in baseline period	-0.056	0.212	-0.144	0.032

A1C indicates glycated hemoglobin; BMI, body mass index; ref, reference.

^aModel also includes Veterans Affairs Medical Center fixed effects and year effects that are not shown.

^bYoung Diabetes Complications Severity Index.

^cElixhauser comorbidity.

Table A4. Second-Stage Cox Model: Risk of ACSC hospitalization (n = 142, 940)^a

	Hazard Ratio	P	95% CI	
Treatment effects				
Start on analogue insulin	1.05	0.339	0.95	1.16
Residual estimated from 1 st stage	0.95	0.295	0.85	1.05
Demographics				
Age	1.02	<0.001	1.02	1.02
Male	0.93	0.073	0.86	1.01
White (ref = black)	0.93	<0.001	0.90	0.96
Other	0.92	0.010	0.86	0.98
Diabetes management				
A1C missing (ref = A1C <7)	1.00	0.884	0.96	1.05
A1C ≥7 & A1C <8	0.97	0.104	0.94	1.01
A1C ≥8 & A1C <9	1.01	0.543	0.98	1.05
A1C ≥9	1.17	<0.001	1.13	1.21
Retinopathy complications ^b	1.03	0.002	1.01	1.06
Nephropathy complications ^b	1.08	<0.001	1.05	1.11
Neuropathy complications ^b	1.08	<0.001	1.06	1.11
Cerebrovascular complications ^b	1.04	0.006	1.01	1.06
Cardiovascular complications (some) ^b	1.19	<0.001	1.15	1.22
Cardiovascular complications (severe) ^b	1.33	<0.001	1.28	1.37
Peripheral vascular complications ^b	1.27	<0.001	1.24	1.30
Metabolic complications ^b	1.04	0.198	0.98	1.10
Metformin prescription	0.89	<0.001	0.87	0.91
Sulfonylurea prescription	1.01	0.681	0.97	1.05
Thiazolidinedione prescription	0.87	<0.001	0.86	0.89
Microalbumin missing (ref = microalbumin normal)	1.17	<0.001	1.14	1.20
Microalbumin high	1.21	<0.001	1.16	1.27
Serum creatinine missing (ref = serum creatinine normal)	0.95	0.006	0.92	0.99
Serum creatinine high	1.13	0.000	1.10	1.17
Cardiovascular comorbidities				
BMI missing (ref = BMI normal)	0.86	<0.001	0.83	0.89
BMI overweight	0.89	<0.001	0.86	0.92
BMI obese	0.89	<0.001	0.86	0.92
Congestive heart failure ^c	1.63	<0.001	1.58	1.68
Cardiac arrhythmias ^c	1.21	<0.001	1.18	1.24
Valvular disease ^c	1.01	0.650	0.98	1.03
Hypertension ^c	0.96	0.020	0.93	0.99
Pulmonary circulatory disorder ^c	1.34	<0.001	1.28	1.40
Chronic obstructive pulmonary disease ^c	1.64	<0.001	1.60	1.67
Other comorbidities				
Paralysis ^c	1.24	<0.001	1.17	1.31
Other neurological disorder ^c	1.12	<0.001	1.08	1.16
Hypothyroidism ^c	0.98	0.270	0.95	1.01

Renal failure ^c	0.99	0.403	0.95	1.02
Liver disease ^c	1.00	0.997	0.95	1.05
Peptic ulcer excluding bleeding ^c	1.04	0.175	0.98	1.09
AIDS ^c	0.87	0.167	0.71	1.06
Lymphoma ^c	1.20	<0.001	1.11	1.30
Metastatic cancer ^c	1.33	<0.001	1.24	1.42
Solid tumor without metastasis ^c	1.02	0.067	1.00	1.05
Rheumatoid arthritis ^c	1.06	0.022	1.01	1.12
Coagulopathy ^c	1.02	0.286	0.98	1.06
Weight loss ^c	1.05	0.041	1.00	1.10
Fluid and electrolyte disorders ^c	1.21	<0.001	1.18	1.24
Blood loss anemias ^c	0.98	0.503	0.92	1.04
Deficiency anemias ^c	1.09	<0.001	1.06	1.12
Alcohol abuse ^c	1.11	<0.001	1.06	1.18
Drug abuse ^c	1.24	<0.001	1.15	1.33
Psychoses ^c	1.13	<0.001	1.09	1.16
Depression ^c	1.10	<0.001	1.07	1.13
Provider process quality variables				
Provider % A1C ≥ 9 in baseline period	1.05	0.431	0.93	1.18
Provider BP % ≥ 140 and ≥ 90 in baseline period	0.95	0.766	0.67	1.34
Provider LDL% >100 in baseline period	1.05	0.288	0.96	1.14

A1C indicates glycated hemoglobin; ACSC, ambulatory care-sensitive condition; BMI, body mass index; ref, reference

^aYear fixed effects not shown. Model also includes Veterans Affairs Medical Center random effects.

^bYoung Diabetes Complications Severity Index.

^cElixhauser comorbidity.

Table A5. Second-Stage Cox Model: Risk of Mortality (n = 142, 940)^a

	Hazard Ratio	P	95% CI	
Treatment effects				
Start on analogue insulin	0.97	0.628	0.85	1.11
Residual estimated from 1 st stage	1.01	0.892	0.87	1.16
Demographics				
Age	1.05	<0.001	1.04	1.05
Male	1.31	<0.001	1.15	1.50
White (ref = black)	1.16	<0.001	1.11	1.22
Other	1.02	0.660	0.94	1.11
Diabetes management				
A1C missing (ref = A1C <7)	0.95	0.061	0.90	1.00
A1C ≥7 & A1C <8	0.81	<0.001	0.78	0.85
A1C ≥8 & A1C <9	0.83	<0.001	0.80	0.87
A1C ≥9	0.95	0.036	0.91	1.00
Retinopathy complications ^b	0.92	<0.001	0.90	0.95
Nephropathy complications ^b	0.94	0.003	0.91	0.98
Neuropathy complications ^b	0.93	<0.001	0.91	0.96
Cerebrovascular complications ^b	1.08	<0.001	1.05	1.12
Cardiovascular complications (some) ^b	1.03	0.105	0.99	1.07
Cardiovascular complications (severe) ^b	1.18	<0.001	1.12	1.23
Peripheral vascular complications ^b	1.19	<0.001	1.15	1.22
Metabolic complications ^b	1.03	0.453	0.95	1.12
Metformin prescription	0.76	<0.001	0.74	0.78
Sulfonylurea prescription	0.93	0.006	0.89	0.98
Thiazolidinedione prescription	0.81	<0.001	0.79	0.84
Microalbumin missing (ref = microalbumin normal)	1.18	<0.001	1.14	1.22
Microalbumin high	1.24	<0.001	1.17	1.31
Serum creatinine missing (ref = serum creatinine normal)	0.99	0.674	0.94	1.04
Serum creatinine high	1.27	<0.001	1.23	1.32
Cardiovascular comorbidities				
BMI missing (ref = BMI normal)	0.73	<0.001	0.70	0.76
BMI overweight	0.70	<0.001	0.68	0.73
BMI obese	0.66	<0.001	0.64	0.69
Congestive heart failure ^c	1.26	<0.001	1.20	1.31
Cardiac arrhythmias ^c	1.01	0.539	0.98	1.04
Valvular disease ^c	0.94	0.001	0.90	0.98
Hypertension ^c	0.83	<0.001	0.80	0.87
Pulmonary circulatory disorder ^c	1.22	<0.001	1.14	1.31
Chronic obstructive pulmonary disease ^c	1.25	<0.001	1.21	1.28
Other Comorbidities				
Paralysis ^c	1.25	<0.001	1.15	1.35
Other neurological disorder ^c	1.26	<0.001	1.21	1.32

Hypothyroidism ^c	0.92	<0.001	0.88	0.96
Renal failure ^c	1.06	0.008	1.02	1.11
Liver disease ^c	1.62	<0.001	1.53	1.72
Peptic ulcer excluding bleeding ^c	0.91	0.014	0.84	0.98
AIDS ^c	1.22	0.088	0.97	1.53
Lymphoma ^c	1.40	<0.001	1.28	1.52
Metastatic cancer ^c	3.41	<0.001	3.22	3.62
Solid tumor without metastasis ^c	1.30	<0.001	1.26	1.34
Rheumatoid arthritis ^c	0.96	0.278	0.89	1.03
Coagulopathy ^c	1.21	<0.001	1.15	1.27
Weight loss ^c	1.33	<0.001	1.26	1.41
Fluid and electrolyte disorders ^c	1.21	<0.001	1.17	1.26
Blood loss anemias ^c	1.07	0.126	0.98	1.15
Deficiency anemias ^c	1.11	<0.001	1.08	1.15
Alcohol abuse ^c	1.31	<0.001	1.22	1.41
Drug abuse ^c	1.12	0.038	1.01	1.25
Psychoses ^c	1.19	<0.001	1.14	1.24
Depression ^c	1.08	<0.001	1.04	1.12
Provider process quality variables				
Provider % A1C ≥ 9 in baseline period	0.99	0.876	0.85	1.15
Provider BP % ≥ 140 and ≥ 90 in baseline period	1.68	0.031	1.05	2.68
Provider LDL% > 100 in baseline period	1.06	0.341	0.94	1.19

A1C indicates glycated hemoglobin; BMI, body mass index; ref, reference

^aYear fixed effects not shown. Model also includes Veterans Affairs Medical Center random effects.

^bYoung Diabetes Complications Severity Index.

^cElixhauser comorbidity.

Table A6. Second-Stage Cox Model: Risk of Diabetic ACSC Hospitalization (n = 142, 940)^a

	Hazard Ratio	P	95% CI	
Treatment effects				
Start on analogue insulin	1.03	0.776	0.83	1.29
Residual estimated from 1 st stage	1.00	0.997	0.79	1.27
Demographics				
Age	1.01	<.001	1.01	1.01
Male	0.90	0.235	0.76	1.07
White (ref = black)	0.77	<0.001	0.72	0.82
Other	0.84	0.006	0.74	0.95
Diabetes management				
A1C missing (ref = HbA1C <7)	1.24	<0.001	1.12	1.36
A1C ≥7 & HbA1C <8	1.04	0.361	0.96	1.13
A1C ≥8 & HbA1C <9	1.16	<0.001	1.07	1.26
A1C ≥9	1.59	<0.001	1.47	1.72
Retinopathy complications ^b	1.25	<0.001	1.20	1.31
Nephropathy complications ^b	1.06	0.102	0.99	1.13
Neuropathy complications ^b	1.36	<0.001	1.30	1.42
Cerebrovascular complications ^b	1.08	0.009	1.02	1.14
Cardiovascular complications (some) ^b	0.94	0.029	0.88	0.99
Cardiovascular complications (severe) ^b	1.10	0.013	1.02	1.18
Peripheral vascular complications ^b	1.97	<0.001	1.88	2.07
Metabolic complications ^b	1.38	<0.001	1.24	1.54
Metformin prescription	0.98	0.398	0.93	1.03
Sulfonylurea prescription	1.06	0.220	0.97	1.15
Thiazolidinedione prescription	0.93	0.004	0.89	0.98
Microalbumin missing (ref = microalbumin normal)	1.19	<0.001	1.13	1.26
Microalbumin high	1.23	<0.001	1.12	1.36
Serum creatinine missing (ref = serum creatinine normal)	0.93	0.060	0.86	1.00
Serum creatinine high	1.34	<0.001	1.26	1.43
Cardiovascular comorbidities				
BMI missing (ref = BMI normal)	0.72	<0.001	0.66	0.77
BMI overweight	0.77	<0.001	0.72	0.82
BMI obese	0.67	<0.001	0.62	0.71
Congestive heart failure ^c	1.06	0.088	0.99	1.14
Cardiac arrhythmias ^c	1.06	0.034	1.00	1.12
Valvular disease ^c	0.87	<0.001	0.81	0.93
Hypertension ^c	0.90	0.001	0.84	0.96
Pulmonary circulatory disorder ^c	0.99	0.929	0.86	1.14
Chronic obstructive pulmonary disease ^c	0.96	0.113	0.91	1.01
Other comorbidities				
Paralysis ^c	1.11	0.096	0.98	1.26
Other neurological disorder ^c	1.20	<0.001	1.11	1.29

Hypothyroidism ^c	0.89	0.002	0.82	0.96
Renal failure ^c	1.13	0.001	1.05	1.22
Liver disease ^c	1.08	0.185	0.97	1.20
Peptic ulcer excluding bleeding ^c	1.07	0.275	0.95	1.20
AIDS ^c	0.91	0.583	0.65	1.27
Lymphoma ^c	1.04	0.690	0.86	1.25
Metastatic cancer ^c	1.17	0.069	0.99	1.38
Solid tumor without metastasis ^c	0.92	0.007	0.87	0.98
Rheumatoid arthritis ^c	0.96	0.534	0.85	1.09
Coagulopathy ^c	1.04	0.358	0.95	1.14
Weight loss ^c	1.24	<0.001	1.12	1.37
Fluid and electrolyte disorders ^c	1.29	<0.001	1.22	1.37
Blood loss anemias ^c	0.86	0.043	0.74	1.00
Deficiency anemias ^c	1.25	<0.001	1.18	1.32
Alcohol abuse ^c	1.38	<0.001	1.25	1.53
Drug abuse ^c	1.37	<0.001	1.20	1.56
Psychoses ^c	1.22	<0.001	1.14	1.30
Depression ^c	1.08	0.018	1.01	1.14
Provider process quality variables				
Provider % A1C ≥ 9 in baseline period	0.92	0.528	0.71	1.19
Provider BP % ≥ 140 and ≥ 90 in baseline period	3.08	0.004	1.45	6.57
Provider LDL% > 100 in baseline period	0.97	0.763	0.80	1.18

A1C indicates glycated hemoglobin; ACSC, ambulatory care-sensitive condition; BMI, body mass index; ref, reference

^aYear fixed effects not shown. Model also includes Veterans Affairs Medical Center random effects.

^bYoung Diabetes Complications Severity Index.

^cElixhauser comorbidity.

Table A7. Second-Stage Cox Model: Risk of Cardiovascular ACSC Hospitalization (n = 142,940)^a

	Hazard Ratio	P	95% CI	
Treatment effects				
Start on analogue insulin	1.16	0.039	1.01	1.33
Residual estimated from 1 st stage	0.83	0.016	0.71	0.97
Demographics				
Age	1.01	<0.001	1.01	1.01
Male	1.01	0.913	0.89	1.14
White (ref = black)	0.95	0.034	0.91	1.00
Other	0.90	0.041	0.82	1.00
Diabetes management				
A1C missing (ref = A _{1c} <7)	1.00	0.988	0.94	1.06
A1C ≥7 & A1C <8	0.98	0.362	0.93	1.03
A1C ≥8 & A1C <9	1.02	0.372	0.97	1.07
A1C ≥9	1.17	<0.001	1.11	1.23
Retinopathy complications ^b	0.99	0.710	0.96	1.03
Nephropathy complications ^b	1.13	<0.001	1.09	1.18
Neuropathy complications ^b	0.95	0.001	0.92	0.98
Cerebrovascular complications ^b	0.98	0.321	0.95	1.02
Cardiovascular complications (some) ^b	1.58	<0.001	1.51	1.66
Cardiovascular complications (severe) ^b	1.79	<0.001	1.70	1.89
Peripheral vascular complications ^b	1.12	<0.001	1.08	1.15
Metabolic complications ^b	0.87	0.004	0.80	0.96
Metformin prescription	0.89	<0.001	0.86	0.92
Sulfonylurea prescription	1.00	0.910	0.95	1.06
Thiazolidinedione prescription	0.86	<0.001	0.83	0.89
Microalbumin missing (ref = microalbumin normal)	1.17	<0.001	1.13	1.22
Microalbumin high	1.30	<0.001	1.23	1.38
Serum creatinine missing (ref = serum creatinine normal)	0.98	0.547	0.93	1.04
Serum creatinine high	1.21	<0.001	1.16	1.26
Cardiovascular comorbidities				
BMI missing (ref = BMI normal)	0.92	0.006	0.87	0.98
BMI overweight	0.98	0.401	0.93	1.03
BMI obese	1.06	0.028	1.01	1.11
Congestive heart failure ^c	2.21	<0.001	2.12	2.31
Cardiac arrhythmias ^c	1.29	<0.001	1.25	1.33
Valvular disease ^c	1.12	<0.001	1.08	1.16
Hypertension ^c	1.01	0.577	0.97	1.06
Pulmonary circulatory disorder ^c	1.45	<0.001	1.37	1.54
Chronic obstructive pulmonary disease ^c	2.00	<0.001	1.94	2.06
Other comorbidities				
Paralysis ^c	0.94	0.182	0.85	1.03

Other neurological disorder ^c	0.95	0.047	0.90	1.00
Hypothyroidism ^c	0.98	0.326	0.94	1.02
Renal failure ^c	1.00	0.893	0.96	1.05
Liver disease ^c	0.87	0.001	0.80	0.95
Peptic ulcer excluding bleeding ^c	1.00	0.979	0.93	1.08
AIDS ^c	0.78	0.160	0.55	1.10
Lymphoma ^c	0.97	0.683	0.86	1.10
Metastatic cancer ^c	0.98	0.701	0.87	1.10
Solid tumor without metastasis ^c	0.95	0.010	0.92	0.99
Rheumatoid arthritis ^c	0.95	0.188	0.88	1.03
Coagulopathy ^c	1.00	0.879	0.94	1.05
Weight loss ^c	0.92	0.042	0.86	0.98
Fluid and electrolyte disorders ^c	1.14	<0.001	1.10	1.18
Blood loss anemias ^c	1.02	0.652	0.94	1.11
Deficiency anemias ^c	1.02	0.199	0.99	1.06
Alcohol abuse ^c	1.07	0.112	0.98	1.16
Drug abuse ^c	1.17	0.006	1.04	1.31
Psychoses ^c	0.94	0.009	0.89	0.98
Depression ^c	1.10	<0.001	1.06	1.14
Provider process quality variables				
Provider % A1C ≥ 9 in baseline period	1.09	0.304	0.92	1.29
Provider BP % ≥ 140 and ≥ 90 in baseline period	0.68	0.126	0.41	1.12
Provider LDL% >100 in baseline period	1.16	0.021	1.02	1.31

A1C indicates glycated hemoglobin; ACSC, ambulatory care–sensitive condition; BMI, body mass index; ref, reference

^aYear fixed effects not shown. Model also includes Veterans Affairs Medical Center random effects.

^bYoung Diabetes Complications Severity Index.

^cElixhauser comorbidity.