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Glycemic Control and Infections Among US Hemodialysis Patients With Diabetes Mellitus

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Introduction: Patients with diabetes mellitus (DM) on hemodialysis (HD) may be particularly vulnerable to infections.

Methods: We used merged data from the United States Renal Data System and electronic health records data from a large US dialysis provider to retrospectively examine the association between glycemic control and infections in these patients. Adult patients with DM aged ≥18 years who initiated in-center maintenance HD treatment from 2006 to 2011 and survived >90 days were included. Quarterly mean time-averaged hemoglobin A1c (HbA1c) values were categorized into <5.5%, 5.5 to <6.5%, 6.5 to <7.5%, 7.5 to <8.5%, and ≥8.5%. We used Medicare claims to ascertain infection-related outcomes and the ESRD Death Notification to identify death from infectious cause. We used Cox proportional hazards models to estimate multivariable-adjusted hazard ratios and 95% confidence intervals (CIs) for the associations between time-averaged HbA1c categories and infectious events.

Results: In a cohort of 33,753 eligible patients, those with higher HbA1c levels had higher rates of diabetic foot infections and skin and soft tissue infections, with patients with HbA1c ≥8.5% having 23% (95% CI, 5%, 45%) and 22% (95% CI, 5%, 42%) higher rates, respectively, compared with HbA1c 5.5 to <6.5%. Patients in the lower HbA1c categories had higher rates of infection-related and all-cause mortality (*P*-for-trend <0.001).

Conclusion: This study highlights the need for greater attention to foot evaluation and skin and soft tissue infections among patients on HD with less than optimal diabetes control.

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Patients with diabetes and end-stage renal disease (ESRD) have an excessive burden of infection, and this is especially true for patients undergoing hemodialysis. Hemodialysis vascular-access device–associated infection continues to be a major clinical predicament[1,2]; however, the majority of infections are not related to dialysis, and infections of the skin and soft tissue, foot, and lung contribute to the broad spectrum of infections that patients on dialysis experience throughout the course of their treatment.[1] Although meticulous preventive measures at the dialysis site can prevent a substantial number of dialysis-related infections such as hemodialysis vascular-access device–associated infections, currently there is no standard protocol for the prevention of infections that are not related to dialysis. Patients with kidney failure experience various immunologic abnormalities and neutrophil dysfunction that are exacerbated by their underlying disease and complications, use of immunosuppressive drugs, malnutrition, and trace element deficiencies, iron overload, hyperparathyroidism, and the specific dialysis procedure.[3] Hemodialysis patients in particular are predisposed to infection risk, and the majority of these patients require at least 1 hospitalization every year for infection.[3]

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Particularly in patients with diabetes, foot infections are the most common, and they can lead to other complications including osteomyelitis, amputation, and death.[4] These patients are also more likely to develop soft tissue infections, most notably necrotizing fasciitis,[5,6] which carries a mortality of approximately 40%.[4] Patients with diabetes are also more susceptible to respiratory infections caused by various microorganisms, such as *Staphylococcus aureus,* gram-negative organisms, and *Mycobacterium tuberculosis*, and are at excess risk for complications, morbidity, and mortality associated with these infections.[4] Although studies have shown that rare and sometimes more severe infections can occur more commonly in patients with diabetes compared to those without diabetes,[7] the body of evidence supporting the link between diabetes control and susceptibility to more common infections is surprisingly scarce and conflicting.[4,7]

The current evidence in the medical literature indicates that patients with diabetes, as well as those who are on dialysis, are particularly vulnerable to infections. However, there is a dearth of clinical data on the relationship between glycemic control and infections in patients on dialysis who have diabetes. Infection-related diabetes complications also disproportionately affect minority populations, but only a limited number of studies have examined racial and ethnic differences in the incidence of infections in the diabetic population.[8,9] Therefore, in this study, we aimed to examine the association between glycemic control and different types of infections in patients with diabetes undergoing hemodialysis, and whether these relationships are influenced by race and ethnicity.

METHODS

Study Design and Population

The study population included all adult patients (≥18 years of age) with incident ESRD between 2006 and 2011 and with diabetes reported as a comorbidity or cause of kidney disease in the ESRD Medical Evidence Report (form CMS-2728) with no missing data on sex, race, ethnicity, or census region (N = 122,735) (Figure 1). Using a retrospective cohort design, we restricted the cohort to those who received maintenance hemodialysis at a DaVita outpatient facility and did not change to a different type of ESRD treatment (e.g., peritoneal dialysis or kidney transplantation) for 90 days (n = 78,486). Because we relied on Medicare payment claims information to ascertain comorbid conditions and outcomes, we further restricted the cohort to patients with Medicare fee-for-service (Parts A and B) as their primary payer by 90 days after initiation of hemodialysis (n = 46,510). We further excluded 12,757 patients who did not have any data on HbA1c during the first 90 days, to ascertain baseline exposure level at the start of follow-up. The final cohort consisted of 33,753 patients. This study was approved by the institutional review board of Stanford University and was conducted in accordance with the Declaration of Helsinki guidelines.

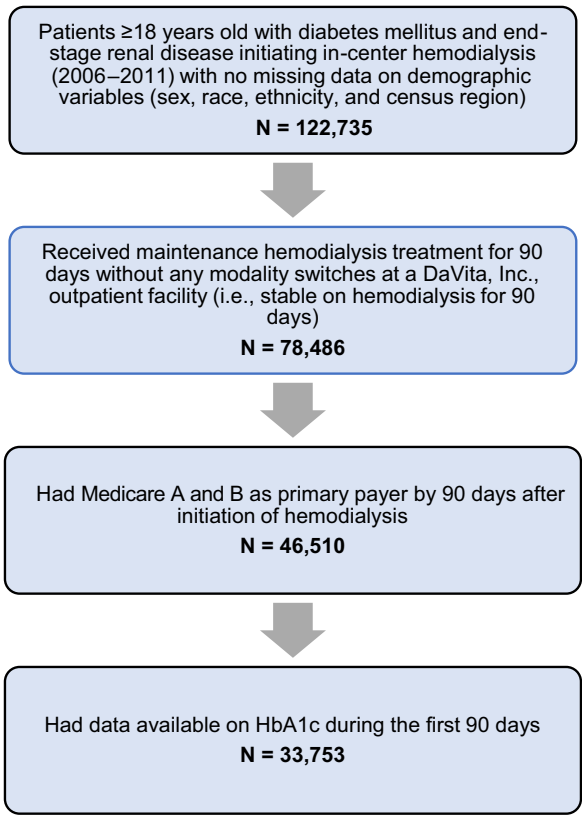

Figure 1. Study population derived from the United States Renal Data System and electronic health records of DaVita, Inc. HbA1c, hemoglobin A1c.

Exposure

The primary exposure was time-varying quarterly mean HbA1c level. We divided time since hemodialysis initiation into 90-day quarters. We abstracted HbA1c data from the DaVita Electronic Health Record (EHR) and averaged all available HbA1c values within each quarter. HbA1c values were categorized into 5 groups: <5.5% (<37 mmol/mol); 5.5 to <6.5% (37 to <48 mmol/mol); 6.5 to <7.5% (48 to <58 mmol/mol); 7.5 to <8.5% (58 to <69 mmol/mol); and ≥8.5% (≥69 mmol/mol).

Outcomes

Primary outcomes of interest were diabetic foot infections, pneumonia, skin and soft tissue infections, and infection due to a device such as catheter or graft, identified using International Classification of Diseases, Ninth Edition (ICD-9) procedure codes

(Supplementary Table S1). Secondary outcomes were all-cause mortality and infection-related mortality, which were ascertained using Medicare billing claims and the Death Notification form, as well as a composite outcome that was defined as infection-related mortality or hospitalization. We defined the index date as 90 days after hemodialysis initiation and followed the patients from the index date until an event of interest occurred. We censored at the end of the study period (December 31, 2011) or when patients switched from in-center hemodialysis treatment to a different modality, were lost to follow-up, or stopped receiving treatment at DaVita, lost Medicare Parts A and B coverage, underwent kidney transplantation, or died (when applicable).

Covariates

We obtained information on age, sex, reported race (white, black, other), and Hispanic ethnicity from the Medical Evidence Report. Description on how reported comorbidities and socioeconomic data were obtained has been reported previously.[10] Briefly, comorbidities were obtained from claims using the International Classification of Diseases, Ninth Revision, diagnosis and procedure codes from at least 1 inpatient or 2 or more outpatient encounters separated by at least 1 day. We combined information from both the Medical Evidence Report and claims data to define baseline comorbidities and used claims thereafter to create quarterly-updated comorbidities. We obtained area-level socioeconomic data from the US Census Bureau American Community Survey at the ZIP code level. We used the DaVita EHRs to abstract data on laboratory values, vital signs, central venous catheters, and body mass index (BMI). We averaged all laboratory variables within 90-day quarters and treated them as time-varying variables defined in the quarter preceding outcome ascertainment. Sociodemographic variables, estimated glomerular filtration rate (eGFR), and BMI were ascertained at time of hemodialysis initiation only.

Statistical Analysis

We compared patients' baseline characteristics across 5 different levels of baseline HbA1c using counts and proportions for categorical variables and mean (SD) or median (interquartile range) for continuous variables. We described variables using means and SDs for normally distributed continuous data, medians and 25th and 75th percentile values for non−normally distributed data, and counts and proportions for categorical data. We tested for linear trend across HbA1c categories using the Cochran−Armitage test for categorical variables and simple linear regression for continuous variables.

For each outcome, we calculated unadjusted incidence rates, defined as the number of events over person-time observed, across baseline HbA1c categories. We applied a cause-specific survival model as a function of time-varying exposure (extended Cox) to the HbA1c level categories to compute adjusted hazard ratios for each outcome, with HbA1c measured in the quarter immediately before the quarter during which the outcome was measured, with the second lowest category of mean HbA1c level (5.5 to <6.5% [37 to <48 mmol/mol]) as the referent. Hazard ratios were adjusted in 4 nested models: model 1, adjusted for year of incident ESRD; model 2, additionally adjusted for census division, sociodemographic variables, and Medicare/Medicaid dual eligibility; model 3, additionally adjusted for baseline BMI, eGFR, and time-updated comorbidities, central venous catheter use; and model 4, additionally adjusted for either baseline or time-varying laboratory variables. Standard errors were robustly estimated using sandwich estimators. We respectively tested the linear effect of the exposure using contrast and tested for effect modification by race (white, black, other) and ethnicity (Hispanic, non-Hispanic) by including a multiplicative interaction term in the model.

We also performed several sensitivity analyses using complete cases, as the main results for complete cases and multiple imputation were identical. Complete cases were defined as patients without missing data. In the first sensitivity analysis, we addressed other infections as a potential competing risk by (i) censoring follow-up time at time of infections other than the primary infection (outcome) of interest, and, separately, (ii) adding a time-varying covariate for other infections. Using this latter model, we also conducted a spline analysis to examine the association between HbA1c as a continuous exposure and infection-related outcomes, with restricted cubic splines for HbA1c at the 5th, 35th, 65th, and 95th percentiles and a fixed referent group of HbA1c 5.5 to <6.5%, comparing the hazard for infectious outcomes of interest between 2 hypothetical patients who are similar for all covariates at a time t but differ in their average HbA1c measurements.

In the second sensitivity analysis, we addressed the possibility that the facility in which the patient had dialysis had an effect on infection rates. In this case, we ran frailty models (random effects Cox model with facility as a cluster variable) using all the covariates on data censored for other infections. The facility included in the model was assumed to be the first one in which a patient started dialysis, as we found that 99% of the patients always dialyzed at the same location.

An additional sensitivity analysis was performed to account for competing risks for all outcomes except

Table 1. Baseline characteristics of 33,753 US adult patients with diabetes mellitus initiating maintenance hemodialysis at a DaVita outpatient facility, by baseline HbA1c category (in % [mmol/mol])

Patient characteristic	All patients (N = 33,753)	<5.5 (<37) (n = 5873)	5.5 to <6.5 (37 to <48) (n = 13,295)	6.5 to <7.5 (48 to <58) (n = 8637)	7.5 to <8.5 (58 to <69) (n = 3649)	≥8.5 (≥69) (n = 2299)	*P*-for-trend
HbA1c (%)	6.5 ± 1.2	5.1 ± 0.3	6.0 ± 0.3	6.9 ± 0.3	7.9 ± 0.3	9.5 ± 1.0	<0.001
Demographics							
Age, yr	64 ± 13	66 ± 13	66 ± 13	64 ± 13	60 ± 14	56 ± 13	<0.001
Male sex, n (%)	17,771 (52.7)	2943 (50.1)	7082 (53.3)	4649 (53.8)	1926 (52.8)	1171 (50.9)	0.16
Race, n (%)							
White	21,919 (64.9)	3785 (64.4)	8720 (65.6)	5690 (65.9)	2339 (64.1)	1385 (60.2)	0.005
Black	9762 (28.9)	1779 (30.3)	3765 (28.3)	2384 (27.6)	1070 (29.3)	764 (33.2)	0.15
Asian	1285 (3.8)	197 (3.4)	539 (4.1)	359 (4.1)	126 (3.5)	64 (2.8)	0.31
Native American	722 (2.1)	102 (1.7)	242 (1.8)	193 (2.2)	103 (2.8)	82 (3.6)	<0.001
Other/multiracial	65 (0.2)	10 (0.2)	29 (0.2)	11 (0.1)	11 (0.3)	4 (0.2)	0.79
Hispanic ethnicity, n (%)	6097 (18.1)	873 (14.9)	2329 (17.5)	1646 (19.1)	779 (21.3)	470 (20.4)	<0.001
Medicare/Medicaid dual eligibility	15,197 (45.0)	2551 (43.4)	5639 (42.4)	3929 (45.5)	1819 (49.8)	1259 (54.8)	<0.001
Socioeconomic variables							
Median rent ($)	869 ± 275	874 ± 278	881 ± 281	862 ± 271	859 ± 268	832 ± 259	<0.001
Missing, n (%)	544 (1.6)	84 (1.4)	218 (1.6)	131 (1.5)	66 (1.8)	45 (2.0)	
Median household income ($)	49,494 ± 19,477	50,015 ± 19.911	50,264 ± 20,151	49,132 ± 18,898	48,344 ± 18,286	46,890 ± 17,974	<0.001
Missing, n (%)	396 (1.2)	64 (1.1)	151 (1.1)	103 (1.2)	46 (1.3)	32 (1.4)	
% Living below poverty line	17.8 ± 10.0	17.6 ± 10.1	17.4 ± 10.0	17.7 ± 9.9	18.4 ± 10.1	19.1 ± 10.1	<0.001
Missing, n (%)	385 (1.1)	59 (1.0)	148 (1.1)	102 (1.2)	45 (1.2)	31 (1.3)	
% Unemployed	10.3 ± 4.7	10.3 ± 4.9	10.2 ± 4.7	10.3 ± 4.5	10.5 ± 4.7	10.7 ± 4.9	<0.001
Missing, n (%)	384 (1.1)	59 (1.0)	146 (1.1)	103 (1.2)	45 (1.2)	31 (1.3)	
% <High school education	19.1 ± 11.7	18.6 ± 11.3	18.7 ± 11.7	19.3 ± 11.8	19.9 ± 12.0	20.5 ± 12.0	<0.001
Missing, n (%)	383 (1.1)	58 (1.0)	147 (1.1)	101 (1.2)	44 (1.2)	31 (1.3)	
Census region, n (%)							
New England	890 (2.6)	151 (2.6)	383 (2.9)	230 (2.7)	80 (2.2)	46 (2.0)	0.03
Northeast Central	4741 (14.0)	807 (13.7)	1895 (14.3)	1214 (14.1)	511 (14.0)	314 (13.7)	0.88
Northwest Central	1783 (5.3)	365 (6.2)	712 (5.4)	4648 (5.4)	175 (4.8)	123 (5.4)	0.76
Southeast Central	2017 (6.0)	364 (6.2)	752 (5.7)	517 (6.0)	222 (6.1)	161 (7.0)	0.17
Southwest Central	5080 (15.1)	880 (15.0)	1979 (14.9)	1294 (15.0)	553 (15.2)	374 (16.3)	0.22
Mid-Atlantic	2784 (8.2)	507 (8.6)	1149 (8.6)	663 (7.7)	307 (8.4)	158 (6.9)	0.006
South Atlantic	8480 (25.1)	1588 (27.0)	3327 (25.0)	2154 (24.9)	861 (23.6)	550 (23.9)	<0.001
Mountain West	1819 (5.4)	301 (5.1)	642 (4.8)	492 (5.7)	225 (6.2)	159 (6.9)	<0.001
Pacific	6159 (18.2)	969 (16.5)	2456 (18.5)	1605 (18.6)	715 (19.6)	414 (18.0)	0.007
Reported comorbidities, n (%)							
Heart failure	13,617 (40.3)	2303 (39.2)	5458 (41.1)	3569 (41.3)	1423 (39.0)	864 (37.6)	0.17
Arrhythmias	8245 (24.4)	1483 (25.3)	3362 (25.3)	2052 (23.8)	861 (23.6)	487 (21.2)	<0.001
Coronary artery disease	15,168 (44.9)	2544 (43.3)	6135 (46.1)	3938 (45.6)	1617 (44.3)	934 (40.6)	0.06
Other cardiac disease	7694 (22.8)	1443 (24.6)	3163 (23.8)	1895 (21.9)	740 (20.3)	453 (19.7)	<0.001
Peripheral vascular disease	7676 (22.7)	1316 (22.4)	3083 (23.2)	1983 (23.2)	817 (22.4)	477 (20.7)	0.14
Hypertension	31,975 (94.7)	5534 (94.2)	12,613 (94.9)	8210 (95.1)	3454 (94.7)	2164 (94.1)	0.82
Chronic obstructive pulmonary disease	4880 (14.5)	1009 (17.2)	1977 (14.9)	1175 (13.6)	477 (13.1)	242 (10.5)	<.001
Current tobacco use	2911 (8.6)	495 (8.4)	1144 (8.6)	716 (8.3)	318 (8.7)	238 (10.4)	0.06
Cancer	14,657 (43.4)	2511 (42.8)	5955 (44.8)	3853 (44.6)	1508 (41.3)	830 (36.1)	<0.001
Alcohol dependence	562 (1.7)	159 (2.7)	197 (1.5)	122 (1.4)	57 (1.6)	27 (1.2)	<0.001
Liver disease	12,212 (36.2)	1951 (33.2)	4758 (35.8)	3292 (38.1)	1394 (38.2)	817 (35.5)	<0.001
Central venous catheter use	28,010 (83.0)	5014 (85.4)	11,053 (83.1)	7099 (82.2)	2998 (82.2)	1846 (80.3)	<0.001
Missing, n (%)	161 (0.5)	25 (0.4)	58 (0.4)	42 (0.5)	24 (0.7)	12 (0.5)	
Laboratory measurements							
Body mass index (kg/m^2)	30.4 ± 8.1	29.5 ± 7.8	30.3 ± 8.1	30.8 ± 8.2	31.2 ± 8.2	31.2 ± 8.5	<0.001
Missing, n (%)	338 (1.0)	56 (1.0)	138 (1.0)	80 (0.9)	39 (1.1)	25 (1.1)	
Platelet count (×10^3/μl), median (25th–75th percentile)	252 (202–310)	237 (187–295)	247 (199–305)	250 (207–314)	266 (217–327)	274 (223–333)	<0.001
Missing, n (%)	152 (0.5)	28 (0.5)	56 (0.4)	40 (0.5)	13 (0.4)	15 (0.7)	

(Continued on next page)

Table 1. (Continued) Baseline characteristics of 33,753 US adult patients with diabetes mellitus initiating maintenance hemodialysis at a DaVita outpatient facility, by baseline HbA1c category (in % [mmol/mol])

Patient characteristic	All patients (N = 33,753)	<5.5 (<37) (n = 5873)	5.5 to <6.5 (37 to <48) (n = 13,295)	6.5 to <7.5 (48 to <58) (n = 8637)	7.5 to <8.5 (58 to <69) (n = 3649)	≥8.5 (≥69) (n = 2299)	*P*-for-trend
White blood cell count (×1000/mm^3)	7.9 ± 2.6	7.6 ± 2.5	7.9 ± 2.6	8.1 ± 2.7	8.2 ± 2.4	8.1 ± 2.3	<0.001
Missing, n (%)	108 (0.3)	23 (0.4)	37 (0.3)	25 (0.3)	9 (0.2)	14 (0.6)	
Albumin (g/dl)	3.5 ± 0.4	3.4 ± 0.5	3.5 ± 0.4	3.5 ± 0.4	3.4 ± 0.4	3.4 ± 0.4	0.003
Missing, n (%)	27 (0.1)	6 (0.1)	11 (0.1)	8 (0.1)	0	2 (0.1)	
Ferritin (ng/ml)	360 ± 336	389 ± 353	375 ± 341	354 ± 350	314 ± 259	303 ± 298	<0.001
Missing, n (%)	265 (0.8)	52 (0.9)	113 (0.8)	62 (0.7)	21 (0.6)	17 (0.7)	
Estimated GFR (ml/min per 1.73 m^2)	13 ± 5	12 ± 5	12 ± 5	13 ± 5	13 ± 5	13 ± 5	<0.001
Missing, n (%)	793 (2.3)	148 (2.5)	327 (2.5)	180 (2.1)	82 (2.2)	56 (2.4)	

GFR, glomerular filtration rate; HbA1c, hemoglobin A1c.
Data are reported as means and SDs unless otherwise noted. Variables are described using means and SDs for normally distributed continuous data, medians and 25th and 75th percentile values for non–normally distributed data, and counts and proportions for categorical data. *P* values were computed using a 2-sided trend analysis.

all-cause mortality. We performed a subdistribution analysis, in which all-cause or non–infection-related mortality and kidney transplantation were treated as competing events. Both cause-specific and subdistribution hazard models allow for the comparison and quantification of the hazard of the event. Subdistribution hazard ratios can also be interpreted as having an effect (increasing or decreasing) on the cumulative incidence function. However, the subdistribution hazard ratio cannot be used to quantify the magnitude of that association.[11] We used the R package *KMI,* which performs Kaplan–Meier multiple imputation to recover missing potential censoring information for those patients with a competing risk and allows the use of standard Cox analysis using the new (imputed) times.[12,13]

Missing Data

Missing data were handled using multiple imputation methods with a fully conditional specification approach as implemented in R using the MICE package,[14] and 25 imputed data sets were obtained for each outcome. Under multiple imputation, we assumed that the data were missing at random, conditional on observed variables. Age >90 years was capped at 90 years because of Health Insurance Portability and Accountability Act (HIPAA) requirements for de-identifiability of the data.

RESULTS

We identified 33,753 patients who initiated and continued on hemodialysis for 90 days. Details of patient characteristics across categories of HbA1c are shown in Table 1. At baseline, the mean HbA1c was 6.5% (48 mmol/mol) (±1.2), and the mean age was 64 years (±13). Patients with higher baseline HbA1c levels tended to be younger, were of predominantly white race, and were of Hispanic ethnicity. They also tended to have fewer comorbidities and higher values of several laboratory measures except for albumin and ferritin.

The unadjusted incidence rates (per 100 person-years) for primary outcomes of interest were 4.0 for diabetic foot infections (1977 events, total person-time of 49,390), 6.7 for pneumonia (3231 events, total person-time of 48,071 years), 3.9 for skin and soft tissue infections (1924 events, total person-time of 49,394 years), and 10.3 for infections due to a device such as catheter or graft (4702 events, total person-time of 45,549 years). Although patients in higher baseline HbA1c categories had higher incidence rates for these primary infection outcomes of interest, those in the lowest HbA1c category had the highest incidence rates for both infection-related mortality and all-cause mortality, as well as the composite outcome of infection-related mortality or hospitalization (Table 2).

Focusing on models that adjusted for all recorded information, including time-varying laboratory measures, there was a significant trend toward higher rates of diabetic foot infections and other skin and soft tissue infections with higher HbA1c levels ($P < 0.001$) (Figure 2a). There was no significant trend toward an adjusted association across HbA1c levels and pneumonia. However, patients with low HbA1c (<5.5% [<37 mmol/mol]) had a 14% (95% CI, 2%, 27%) higher rate of pneumonia compared to patients in the HbA1c referent group of 5.5 to <6.5% (37 to <48 mmol/mol). There were no associations across HbA1c categories with rates of infection due to medical devices (e.g., catheter or graft). Detailed results from the Cox proportional hazards models for all study outcomes, and by level of covariate adjustment, are presented in Supplementary Table S2.

Higher HbA1c levels were associated with lower rates of infection-related mortality and all-cause

Table 2. Unadjusted incidence rates (per 100 person-years) of different types of infections according to HbA1c categories at baseline

	HbA1c, % (mmol/mol)																	
	<5.5 (<37)				5.5 to <6.5 (37 to <48)				6.5 to <7.5 (48 to <58)				7.5 to <8.5 (58 to <69)				≥8.5 (≥69)			
Type of infection	No. of events	Total PT[a]	Mean PT[a]	IR[b]	No. of events	Total PT[a]	Mean PT[a]	IR[b]	No. of events	Total PT[a]	Mean PT[a]	IR[b]	No. of events	Total PT[a]	Mean PT[a]	IR[b]	No. of events	Total PT[a]	Mean PT[a]	IR[b]
Diabetic foot infections	275	8960	1.5	3.1	770	19,220	1.4	4.0	553	12,585	1.5	4.4	239	5316	1.5	4.5	140	3309	1.4	4.2
Skin and soft tissue infections	298	8922	1.5	3.3	673	19,305	1.5	3.5	523	12,572	1.5	4.2	237	5312	1.5	4.5	193	3283	1.4	5.9
Pneumonia	577	8652	1.5	6.7	1228	18,748	1.4	6.6	832	12,272	1.4	6.8	358	5183	1.4	6.9	236	3216	1.4	7.3
Infection due to device (catheter/graft)	812	8244	1.4	9.8	1787	17,812	1.3	10.0	1205	11,621	1.3	10.4	557	4879	1.3	11.4	341	2993	1.3	11.4
Infection-related death	241	9252	1.6	2.6	444	20,012	1.5	2.2	297	13,168	1.5	2.3	105	5579	1.5	1.9	60	3477	1.5	1.7
All-cause mortality	1969	9252	1.6	21.3	4093	20,012	1.5	20.5	2541	13,168	1.5	19.3	982	5579	1.5	17.6	604	3477	1.5	17.4
Composite outcome[c]	1725	7414	1.3	23.3	3819	15,887	1.2	24.0	2602	10,211	1.2	25.5	1133	4258	1.2	26.6	740	2592	1.1	28.6

HbA1c, hemoglobin A1c; IR, incidence rate; PT, person-time.
[a]PT is given in years.
[b]IR is computed as number of events/total PT × 100.
[c]Infection-related death or hospitalization.

mortality (all *P*-for-trend <0.001) (Figure 2b). We did not find any significant associations between HbA1c levels and infection-related or all-cause mortality in any of the higher HbA1c categories. In models 1 to 4, patients with HbA1c <5.5% had higher infection-related and all-cause mortality rates compared with patients with HbA1c 5.5 to <6.5%. In model 4, we found that patients with HbA1c <5.5% (<37 mmol/mol) had 33% (95% CI, 13%, 56%) and 18% (95% CI, 11%, 25%) higher rates of infection-related and all-cause mortality respectively, compared with patients with HbA1c 5.5 to <6.5% (37 to <48 mmol/mol), but these associations became either no longer significant (infection-related mortality) or only marginally significant (all-cause mortality) after adjusting for time-varying but not baseline laboratory values (Supplementary Table S2). There were no associations across HbA1c categories with rates of the composite outcome consisting of infection-related mortality or hospitalization (all *P*-for-trend >0.05) (Supplementary Table S2).

We examined HbA1c as a continuous variable to better understand the association between HbA1c and the first 4 outcomes of interest (i.e., diabetic foot infections, skin and soft tissue infections, pneumonia, and infection due to device) (Figure 3). Comparing 2 HbA1c values that are 0.5% apart for which the comparator HbA1c is lower, an increase in HbA1c by 0.5% was associated with decreased rates of diabetic foot infections and pneumonia when HbA1c was ≤6.5%, whereas the rates did not change for HbA1c >6.5%. An opposite trend was observed for skin and soft tissue infections in that an increase in HbA1c by 0.5% was associated with slightly increased rates of infection, but the rates did not change for HbA1c >6.5%. The association was close to null for infections due to device.

Results from sensitivity analyses that used complete cases to address other infections as a potential competing risk by (i) censoring follow-up time at time of infections other than the primary infection (outcome) of interest, and, separately, (ii) adding a time-varying covariate for other infections were not materially different from the main findings (Supplementary Tables S3 and S4). Similarly, we did not observe any substantial differences in the main findings when using frailty models to address the possibility that the facility in which the patient dialyzed had an effect on infection rates (data not shown).

In subdistribution hazard models that treated all-cause mortality and transplantation as competing risks for the outcomes diabetic foot infections, pneumonia, skin and soft tissue infections, infection due to device (catheter/graft), and infection-related mortality

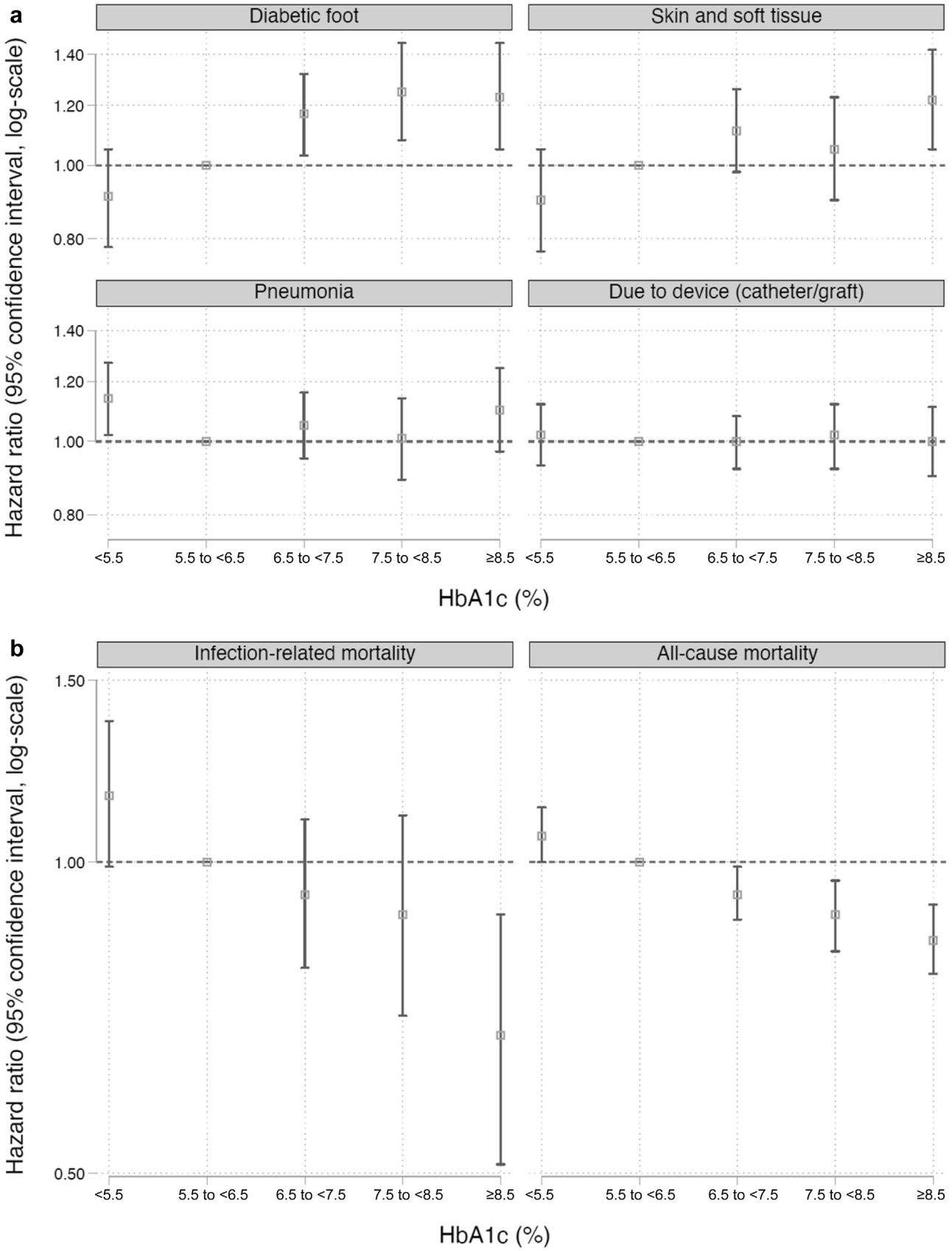

Figure 2. (a) Associations between hemoglobin A1c (HbA1c) categories and infection-related outcomes. Model adjusted for year of end-stage renal disease (ESRD) incidence; census division (a marker for location); demographic variables, such as age, sex, race/ethnicity, Medicare/Medicaid dual eligibility, and area-level geocoded socioeconomic status (SES) variables such as median rent, median household income, percentage living below the poverty line, percentage unemployed, and percentage with less than high school education; baseline (continued)

as well as in models that treated non−infection-related mortality and transplantation as competing risks for the composite outcome, we did not observe any substantial differences from the main findings estimating cause-specific hazard ratios (Supplementary Table S5).

There was no evidence of effect modification of the association between time-averaged HbA1c and any of the 4 infectious outcomes of interest, infection-related and all-cause mortality, and composite outcome by race and ethnicity (*P*-for-interaction >0.05 for all).

DISCUSSION

In this large prospective study of the association between glycemic control and infections in a cohort of incident US patients with diabetes on hemodialysis, we found that higher HbA1c levels were associated with higher rates of diabetic foot infections and skin and soft tissue infections. In lesser powered categorical analyses, high HbA1c levels ≥8.5% were directly associated with both outcomes, but the associations were not significant in all other individual categories. In contrast, although no significant trends were detected between HbA1c levels and the incidence of pneumonia, patients with HbA1c <5.5% (<37 mmol/mol) had a higher rate of pneumonia compared with patients with HbA1c 5.5 to <6.5% (37 to <48 mmol/mol) in categorical analyses. We found inverse associations between HbA1c levels and rates of infection-related and all-cause mortality, with patients in lower HbA1c categories having higher rates of mortality. There were no associations across HbA1c categories with rates of infection due to devices or the composite outcome consisting of infection-related mortality or hospitalization. We found no evidence of effect modification of any of these associations by race and ethnicity.

Patients with diabetes on hemodialysis have higher infection rates than the diabetic population at large, and almost all of the difference in these infection rates can be explained by foot and skin and soft tissue infections. In a study by Berman *et al*. of patients with ESRD on dialysis,[1] two-thirds of the episodes of infection occurred in catheter-access devices, skin and soft tissues, or the lung. Although we did not find any significant associations between glycemic control and rates of infection due to devices (catheter/graft), we found that poorer glycemic control was associated with higher rates of skin and soft tissue infections. This is consistent with previous studies that showed that patients with diabetes are more likely to develop skin and soft tissue infections, including folliculitis, furunculosis, and subcutaneous abscesses, often with more severe clinical presentations.[15,16]

Diabetic foot complications are among the most preventable long-term complications of diabetes, yet they are often mismanaged in patients with diabetes and chronic kidney disease because the focus of care is primarily on prevention and management of cardiovascular and kidney complications.[17,18] As a result, early risk factors for foot complications are easily overlooked in these high-risk patients, leading to lower limb amputation rates that are 10 times higher than in patients with diabetes alone.[18] Hence, it is imperative to identify risk factors for lower extremity amputations, such as poor glycemic control, in these high-risk patients. Chronic hyperglycemia disrupts wound healing in patients with diabetes,[19−21] and poor glycemic control has been shown to be associated with a higher risk of lower extremity ulcerations, with even moderate elevations in HbA1c raising the risk of amputation.[22,23] Similarly, we found a higher rate of diabetic foot infection with higher HbA1c levels in patients on hemodialysis. Glycemic control is also important for the management of diabetic foot ulcerations because the main pathogenesis of foot ulceration in patients with diabetes and ESRD is primarily through peripheral neuropathy, which can be delayed or prevented with good glycemic control.[24] A recent study showed that there was no clinically meaningful association between baseline or prospective HbA1c and wound healing in patients with diabetic foot ulcers.[25]

Pneumonia is a serious complication in the ESRD population that could result from host defense abnormalities. Rates of pneumonia have been shown to be 5 times higher in the dialysis population compared with the non-CKD population, and studies have shown that length of hospital stays for pneumonia in patients with

Figure 2. (continued) body mass index (BMI) and estimated glomerular filtration rate (eGFR); preexisting comorbidities including heart failure, arrythmias, coronary artery disease, other cardiac disease, peripheral vascular disease, hypertension, chronic obstructive pulmonary disease, current tobacco use, cancer, alcohol dependence, and liver disease; central venous catheter use; baseline laboratory variables such as albumin, platelet count, white blood cell count, and ferritin, as well as time-varying laboratory variables. (b) Associations between HbA1c categories and infection-related and all-cause mortality. Model adjusted for year of ESRD incidence; census division (a marker for location); demographic variables, such as age, sex, race/ethnicity, Medicare/Medicaid dual eligibility, and area-level geocoded SES variables such as median rent, median household income, percentage living below the poverty line, percentage unemployed, and percentage with less than high school education; baseline BMI and eGFR; preexisting comorbidities including heart failure, arrythmias, coronary artery disease, other cardiac disease, peripheral vascular disease, hypertension, chronic obstructive pulmonary disease, current tobacco use, cancer, alcohol dependence, and liver disease; central venous catheter use; baseline laboratory variables such as albumin, platelet count, white blood cell count, and ferritin, as well as time-varying laboratory variables.

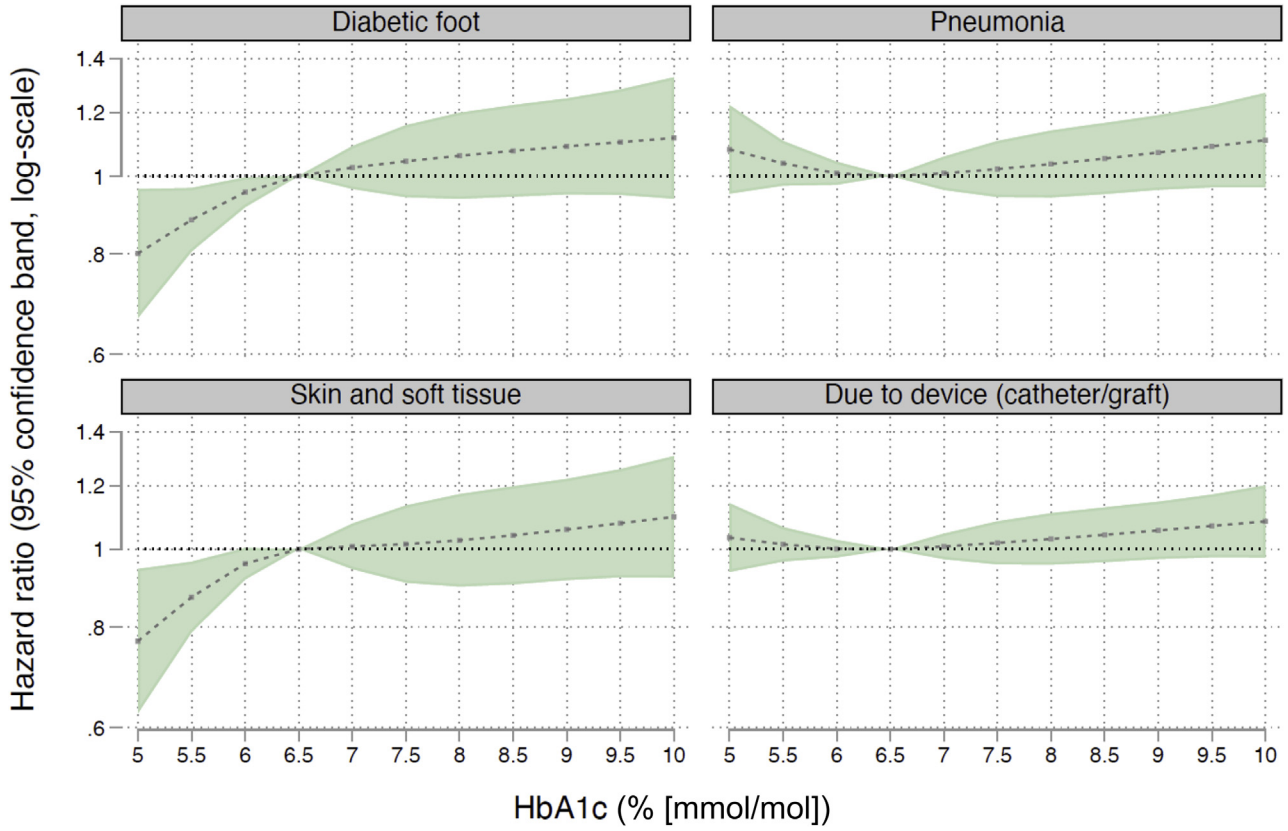

Figure 3. Associations between continuous hemoglobin A1c (HbA1c) and infection-related outcomes, including restricted cubic splines for HbA1c with knots at the 5th, 35th, 65th, and 95th percentiles. Models were from complete cases analyses and adjusted for year of end-stage renal disease incidence; census division (a marker for location); demographic variables, such as age, sex, race/ethnicity, Medicare/Medicaid dual eligibility, and area-level geocoded socioeconomic status variables such as median rent, median household income, percentage living below the poverty line, percentage unemployed, and percentage with less than high school education; baseline body mass index (BMI) and estimated glomerular filtration rate; preexisting comorbidities including heart failure, arrythmias, coronary artery disease, other cardiac disease, peripheral vascular disease, hypertension, chronic obstructive pulmonary disease, current tobacco use, cancer, alcohol dependence, and liver disease; central venous catheter use; baseline laboratory variables such as albumin, platelet count, white blood cell count, and ferritin, as well as time-varying laboratory variables; and time-varying covariate for other infections. Four separate plots were generated for each of the 4 infectious outcomes of interest, comparing the hazard for each of the outcomes between 2 hypothetical patients who are similar for all covariates at a time *t* but differ in their average HbA1c measurements, with a fixed referent group of HbA1c 5.5 to <6.5%.

chronic kidney disease or ESRD are 4 to 6 times longer than those in the non-CKD population.[26] Moreover, hyperglycemia can elicit harmful physiologic effects and immunologic abnormalities in patients with diabetes.[27] Some previous studies have shown that diabetes, increases in plasma glucose, and hyperglycemia or poor long-term glycemic control are associated with higher risks of pneumonia or pneumonia-related hospitalizations,[28,29] whereas other studies have failed to find an association between diabetes and pneumonia.[30,31] We did not find any significant associations between glycemic control and rates of pneumonia in patients with higher HbA1c levels compared with those with HbA1c 5.5% to <6.5% (37 to <48 mmol/mol), although the HbA1c ≥8.5% (≥69 mmol/mol) group had a 13% increased pneumonia risk in model 3 that was slightly attenuated and no longer significant after adjustment for other laboratory parameters. However, we found an 18% higher rate of pneumonia in patients with HbA1c <5.5% (<37 mmol/mol) compared with those in the referent category. Kornum *et al.*[29] found that even well-controlled diabetes, with an HbA1c level <7% (53 mmol/mol), was associated with a 22% increased risk of hospitalized pneumonia, suggesting that tight glycemic control may not be enough to reduce susceptibility to pneumonia, which may have a multifactorial disease pathogenesis and etiology that requires a multifaceted care approach.

Our findings contrast with those of previous studies conducted in patients with diabetes undergoing hemodialysis that showed either null or weak associations between HbA1c and mortality[32,33] or positive associations between HbA1c and mortality.[34] We found decreasing trends in the rates of infection-related and all-cause mortality across increasing levels of HbA1c, with approximately 25% to 35% reduced rates of these

outcomes in the highest HbA1c category of ≥8.5% (≥69 mmol/mol). In contrast, patients in the lowest HbA1c category of <5.5% (<37 mmol/mol) had approximately 20% to 30% increased rates of mortality outcomes when adjusted for baseline laboratory values, which were attenuated but remained borderline significant when adjusted for time-varying laboratory values. These findings remained largely unchanged in sensitivity analyses in which we accounted for competing risks for infection-related mortality, and were similar to findings from a large retrospective study that was conducted in a cohort of patients with diabetes and CKD in which a U-shaped association was observed between HbA1c and mortality, with increases in the risk of mortality at HbA1c levels <6.5% (<48 mmol/mol) and >8.0% (64 mmol/mol).[35] Patients with low HbA1c values have poor prognosis due to cachexia and may have "burned out" diabetes. Malnutrition−inflammation syndrome is highly prevalent among these patients, and low HbA1c levels may be indicative of other underlying adverse health conditions associated with malnutrition, inflammation, and anemia that are all associated with increased risk of mortality. Our multivariable-adjusted models have taken this into account by adjusting for markers of malnutrition and inflammation, but why higher levels of HbA1c were associated with lower rates of infection-related and all-cause mortality despite adjustment for these factors is not apparent. Kalantar-Zadeh *et al.*[34] found that higher HbA1c values were incrementally associated with increased risks of mortality, with the risk of all-cause mortality being 41% higher in the HbA1c ≥10% (≥86 mmol/mol) range compared with HbA1c in the 5% to 6% (31−42 mmol/mol) range after adjusting for a comprehensive set of confounders including factors related to anemia and nutrition. However, there was still an increased risk of mortality in the HbA1c range <5% (<31 mmol/mol) compared with HbA1c in the 5% to 6% range (31−42 mmol/mol).[34] Taken together, these findings suggest that intensive glycemic control below the level of 5% to 5.5% (31−37 mmol/mol) in patients with diabetes on hemodialysis may be harmful. A higher target HbA1c may be more appropriate in some patients with diabetes and ESRD, but this speculation should be confirmed in future randomized clinical trials.

Our study has a few limitations that should be noted. First, the findings herein may not be generalizable to other patient populations, such as those of commercially insured patients, due to the selective cohort of patients used in this study (i.e., patients with diabetes on hemodialysis who were insured by Medicare). Second, the reliability of HbA1c as an indicator of glycemic control in patients on hemodialysis should be considered. Patients on hemodialysis may have falsely low HbA1c levels due to shorter erythrocyte lifespan, lower erythrocyte concentrations seen in anemia, or predominance of younger erythrocytes, which occur in patients who are on iron replacement therapy or erythropoiesis-stimulating agents.[10,36] Third, because we abstracted the data on comorbidities from an administrative database, we were not able to adjust for the severity of these conditions. However, the under-ascertainment of comorbidities would have led to nondifferential bias, biasing the results toward the null and underestimating the true effect. Finally, we cannot completely exclude the possibility of residual confounding due to the observational nature of the study.

Despite these limitations, our study has some major strengths. We used and took advantage of 2 large and detailed data sources to examine associations between glycemic control and multiple infection-related outcomes, which enabled us to adjust for a wide array of demographic and socioeconomic factors as well as clinical parameters, including both baseline and prospective laboratory values, using a longitudinal, time-varying analytic design. Our study also had a relatively long follow-up and large sample size, and the findings were robust to sensitivity analyses. In addition, our findings shed light on the impact of glycemic control on infections in patients among whom this relation has been understudied, as patients with diabetes and ESRD are excluded from most trials of glycemic control due to reduced eGFR.

In conclusion, higher time-varying HbA1c was associated with increased rates of diabetic foot infections, skin, and soft tissue infections, and with lower rates of infection-related and all-cause mortality, but were not associated with rates of pneumonia or infection due to devices such as catheters or grafts. This study highlights the need for greater attention to foot evaluation and care among patients receiving HD with less-than-optimal diabetes control. This could, and should, be implemented in the dialysis unit, where these patients are usually seen at regular intervals, whereas attendance in renal, diabetes, or primary care clinics may be low in comparison due to a demanding dialysis schedule. This also opens up the opportunity for diabetes specialist nurses to work alongside the hemodialysis staff to ensure an ongoing diabetes support that includes glycemic control and timely intervention for urgent complications, including hypoglycemia, through coordinated care for patients on hemodialysis. To provide stronger evidence for clinical recommendations for optimal HbA1c target levels, further research is warranted to examine causal relations between HbA1c control and various types of

infections in this high-risk population of diabetic patients on hemodialysis.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. ICD-9 codes used to define primary outcomes.

Table S2. Hazard ratios (95% CI) of infection-related outcomes according to HbA1c categories (n = 33,753).

Table S3. Hazard ratios (95% CI) of infection-related outcomes according to HbA1c categories using complete cases defined as patients without any missing data (additionally censoring for other infections) (n = 31,866).

Table S4. Hazard ratios (95% CI) of infection-related outcomes according to HbA1c categories using complete cases defined as patients without any missing data (N = 31,866).

Table S5. Subdistribution hazard ratios (95% CI) of infection-related outcomes according to HbA1c categories (N = 33,753).

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