

UC Irvine

UC Irvine Previously Published Works

Title

Hypoglycemia-Related Hospitalizations and Mortality Among Patients With Diabetes Transitioning to Dialysis.

Permalink

<https://escholarship.org/uc/item/2mb4q2x0>

Journal

American journal of kidney diseases : the official journal of the National Kidney Foundation, 72(5)

ISSN

0272-6386

Authors

Rhee, Connie M
Kovesdy, Csaba P
You, Amy S
et al.

Publication Date

2018-11-01

DOI

10.1053/j.ajkd.2018.04.022

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

Hypoglycemia-Related Hospitalizations and Mortality Among Patients With Diabetes Transitioning to Dialysis



Connie M. Rhee, Csaba P. Kovcsdy, Amy S. You, John J. Sim, Melissa Soohoo, Elani Streja, Miklos Z. Molnar, Alpesh N. Amin, Kevin Abbott, Danh V. Nguyen, and Kamyar Kalantar-Zadeh

Rationale & Objective: Diabetic patients with declining kidney function are at heightened risk for hypoglycemia. We sought to determine whether hypoglycemia-related hospitalizations in the interval before dialysis therapy initiation are associated with post-end-stage renal disease (ESRD) mortality among incident patients with ESRD with diabetes.

Study Design: Observational cohort study.

Setting & Participants: US veterans from the national Veterans Affairs database with diabetes and chronic kidney disease transitioning to dialysis therapy from October 2007 to September 2011.

Exposure: Hypoglycemia-related hospitalizations during the pre-ESRD period and antidiabetic medication regimens.

Outcome: The outcome of post-ESRD all-cause mortality was evaluated relative to pre-ESRD hypoglycemia. The outcome of pre-ESRD hypoglycemia-related hospitalization was evaluated relative to antidiabetic medication regimens.

Analytic Approach: We examined whether the occurrence and frequency of pre-ESRD hypoglycemia-related hospitalizations are associated with post-ESRD mortality using Cox regression models adjusted for case-mix covariates. In a subcohort of patients prescribed 0 to 2 oral antidiabetic drugs and/or insulin, we examined the 12 most commonly prescribed

antidiabetic medication regimens and risk for pre-ESRD hypoglycemia-related hospitalization using logistic regression models adjusted for case-mix covariates.

Results: Among 30,156 patients who met eligibility criteria, the occurrence of pre-ESRD hypoglycemia-related hospitalization(s) was associated with higher post-ESRD mortality risk: adjusted HR (aHR), 1.25; 95% CI, 1.17-1.34 (reference group: no hypoglycemia hospitalization). Increasing frequency of hypoglycemia-related hospitalizations was independently associated with incrementally higher mortality risk: aHRs of 1.21 (95% CI, 1.12-1.30), 1.47 (95% CI, 1.19-1.82), and 2.07 (95% CI, 1.46-2.95) for 1, 2, and 3 or more hypoglycemia-related hospitalizations, respectively (reference group: no hypoglycemia hospitalization). Compared with patients who were prescribed neither oral antidiabetic drugs nor insulin, medication regimens that included sulfonylureas and/or insulin were associated with higher risk for hypoglycemia.

Limitations: Residual confounding cannot be excluded.

Conclusions: Among incident patients with ESRD with diabetes, a dose-dependent relationship between frequency of pre-ESRD hypoglycemia-related hospitalizations and post-ESRD mortality was observed. Further study of diabetic management strategies that prevent hypoglycemia as patients with chronic kidney disease transition to ESRD are warranted.

Complete author and article information provided before references.

Correspondence to
C.M. Rhee (crhee1@uci.edu)

Am J Kidney Dis. 72(5): 701-710. Published online July 20, 2018.

doi: 10.1053/j.ajkd.2018.04.022

© 2018 by the National Kidney Foundation, Inc. Published by Elsevier Inc. All rights reserved.

Chronic kidney disease (CKD) is one of the most prevalent complications of diabetes mellitus, affecting 30% to 40% of patients with type 1 and 2 diabetes.¹ Diabetic kidney disease accounts for 44% of incident end-stage renal disease (ESRD) cases in the United States, and the annual mortality rate of diabetic patients with ESRD exceeds those with other ESRD causes.² Hence, there is compelling need to identify modifiable risk factors for the exceedingly high death risk of the diabetic ESRD population, particularly in the early phases of transitioning from non-dialysis-dependent (NDD) CKD to ESRD treated by maintenance dialysis, when a mortality peak is observed.²⁻⁴

Optimal glycemic control is an ongoing area of uncertainty in the management of diabetic patients with CKD.⁵ Although early trials showed that intensive glycemic control lowers the risk for microvascular complications in diabetic patients with minimal end-organ damage,^{6,7}

contemporary trials have shown lack of benefit and adverse cardiovascular outcomes among patients with long-standing type 2 diabetes with underlying cardiovascular risk, individuals who are akin to diabetic patients with kidney disease.⁸⁻¹¹ Furthermore, the mentioned trials have shown that hypoglycemia may be a trade-off of the benefits of intensive glycemic control.^{8,9,11,12} Diabetic patients with NDD-CKD progressing to maintenance dialysis therapy may be vulnerable to hypoglycemia due to impaired renal gluconeogenesis, longer insulin half-life, reduced antidiabetic medication metabolism and clearance, and co-existing comorbid conditions (eg, malnutrition and gastroparesis).^{5,13,14} Observational data suggest that more than one-third of incident diabetic hemodialysis patients may experience spontaneous normalization of hyperglycemia and frequent hypoglycemic events necessitating discontinuation of antidiabetic medications.^{5,15}

In the general population, hypoglycemia is associated with heightened risk for hospitalization,^{16,17} mortality,^{12,18,19} and cost burden.²⁰ However, there has been sparse examination of risk factors and sequelae of hypoglycemia in diabetic patients with kidney disease, particularly among those progressing to ESRD. Prior studies are limited by lack of antidiabetic medication data²¹ or restriction to study populations at the extremes of CKD. With respect to the latter, these studies have exclusively focused on NDD-CKD²¹⁻²³ versus maintenance dialysis patients,²⁴ and it is unknown whether repeated hypoglycemic events more than 1 to 2 years before transitioning to ESRD have long-term sequelae during ESRD in patients who survive to dialysis therapy.

A substantial impediment to this end has been the paucity of pre-ESRD transition data across large post-ESRD databases.³ Thus, through linkage of pre-ESRD data from the national Veterans Affairs (VA) database with post-ESRD registries (US Renal Data System [USRDS]), we sought to examine the relationship between pre-ESRD hypoglycemia events during the predialysis transition period with post-ESRD mortality among US veterans with diabetes. We also investigated clinical characteristics associated with risk for hypoglycemia in the pre-ESRD transition period.

Methods

Source Cohort

We conducted a historical cohort study with longitudinal data from the Transition of Care in CKD (TC-CKD) study, a retrospective cohort study examining US veterans transitioning to ESRD from October 1, 2007, to September 30, 2011.^{3,25-28} Our source population consisted of 52,172 patients who were identified from the national VA database and linked to the USRDS registry. Patients were included provided that they were 18 years or older at the time of entry into the VA health care system, had a history of diabetes ascertained by International Classification of Diseases, Ninth Revision (ICD-9) codes (249.xx, 250.xx, 357.2, 362.0x, and 366.41) before dialysis therapy initiation and/or cause of ESRD due to diabetes, had no missing data for core variables needed to calculate estimated glomerular filtration rate (eGFR), and initiated dialysis therapy before study entry or after exiting the study (Fig S1).

Patients were categorized into various analytic cohorts according to their time of entry into the VA health care system, which defined their pre-ESRD observation intervals before transitioning to dialysis therapy: more than 6- to 12-month, more than 1- to 2-year, and more than 2- to 5-year prelude periods. Given that a core objective of the TC-CKD study is to determine the impact of pre-ESRD comorbid conditions on post-ESRD outcomes, we a priori defined the more than 1- to 2-year prelude period as our primary exposure window during which potential interventions informed by the present study can have greater impact on post-ESRD outcomes (ie, modification of comorbid conditions/events in earlier stages of CKD may

have greater impact on outcomes as compared with later stages). The study was approved by the institutional review boards of the University of California Irvine, Tibor Rubin VA, and Memphis VA. The study was exempt from informed written consent due to its nonintrusive nature and anonymity of patients.

Exposure Ascertainment

Given that hypoglycemia events ascertained by blood glucose levels may not be captured in the VA database (ie, low capillary blood glucose levels observed in the field), we focused on hypoglycemia events requiring medical attention by identifying hypoglycemia-related hospitalization(s) ascertained by ICD-9 codes using VA, Centers for Medicare & Medicaid Services (CMS), and USRDS sources (251.0-251.3, 962.3, 995.23, 996.57, E9323; and 250.80-250.83 but without 259.8, 272.7, 681.xx, 682.xx, 686.9x, 707.1-707.9, 709.3, 730-730.2, or 731.8).²⁹⁻³² In coprimary analyses, we first examined the association of any occurrence of hypoglycemia-related hospitalization(s) (presence vs absence) with mortality risk. We then examined the association between the frequency of hypoglycemia-related hospitalization(s) with mortality.

Sociodemographic, Comorbidity, Medication, and Laboratory Data

Data from VA and USRDS Patient and Medical Evidence files were used to determine patients' sociodemographic information at the time of dialysis therapy initiation. Cause of ESRD and dialysis modality information were obtained from USRDS sources. Comorbid condition data were extracted from the VA Inpatient and Outpatient Medical SAS data sets³³ and CMS data sets using ICD-9 diagnostic/procedure and Current Procedural Terminology codes.³⁴ Charlson Comorbidity Index (CCI) scores were estimated using the Deyo modification for administrative data sets without including kidney disease.³⁵ Medication data were obtained from CMS Part D and VA pharmacy dispensation records.³⁶ Hemoglobin A_{1c} (HbA_{1c}), random glucose, and other laboratory data except serum creatinine were obtained from the VA Decision Support System-National Data Extracts Laboratory Results files.³⁷ VA Corporate Data Warehouse LabChem data files were used to extract serum creatinine data.³⁸ The CKD-EPI (CKD Epidemiology Collaboration) creatinine equation was used to calculate eGFR.³⁹

Outcome Ascertainment

Our outcome of interest was all-cause mortality. Patients were censored at kidney transplantation, loss to follow-up, or the last date of available follow-up data (December 27, 2012), whichever occurred first. The at-risk period began the day after dialysis therapy initiation (ie, following the exposure window) and concluded upon experiencing the outcome of interest or a censoring event. All-cause mortality, censoring events, and associated dates were obtained from VA, CMS, and USRDS sources.

Statistical Analysis

We conducted logistic regression analyses examining the association of modifiable and nonmodifiable sociodemographic, comorbidity, dialysis treatment, laboratory, and antidiabetic medication characteristics with likelihood of experiencing hypoglycemia-related hospitalization(s) during the more than 1- to 2-year prelude period. In a subcohort of patients prescribed 0 to 2 oral antidiabetic drugs and/or insulin, we also examined the 12 most commonly prescribed antidiabetic medication regimens and risk for pre-ESRD hypoglycemia-related hospitalization(s).

We then estimated the association of any occurrence (separately) and frequency of hypoglycemia-related hospitalization(s) with mortality using Cox models. Logistic regression and Cox models were conducted using 5 hierarchical levels of covariate adjustment: (1) minimally adjusted model: adjusted for patient's calendar quarter of dialysis therapy initiation to account for secular changes in care over time; (2) case-mix model: adjusted for covariates in model 1, plus age at dialysis therapy initiation, sex, race, and ethnicity; (3) expanded case-mix model: adjusted for covariates in model 2, plus cause of ESRD, initial dialysis modality, residential region, congestive heart failure (CHF), cerebrovascular disease, and CCI score; (4) expanded case-mix plus laboratory model: adjusted for covariates in model 3, plus HbA_{1c}, serum albumin, eGFR averaged over the prelude period (ie, proxy of residual kidney function), and last eGFR obtained before dialysis therapy initiation (ie, proxy of dialysis practice patterns); and (5) expanded case-mix plus laboratory plus medication model: adjusted for covariates in model 4 plus insulin and oral antidiabetic drug use during the exposure period.

We a priori defined the case-mix model as our preferred model, which included core sociodemographic measures and other confounders of the association between hypoglycemia-related hospitalizations and mortality. Although there were no missing data for covariates in case-mix models, there were varying degrees of missing data for covariates in expanded case-mix, expanded case-mix plus laboratory, and expanded case-mix plus laboratory plus medication models, including cause of ESRD (4.8%), modality (10.9%), residential region (3.9%), HbA_{1c} level (42.6%), serum albumin level (41.7%), eGFR averaged over the prelude period (37.8%), and last eGFR obtained before dialysis therapy initiation (37.8%; proportions shown represent data from the more than 1- to 2-year prelude cohort). Hence, further adjustment for potential confounders in these latter models (which have the potential for inherent selection bias due to missing data) were conducted as sensitivity analyses. Models incrementally adjusted for pre-ESRD eGFR slope and proxies of diabetes severity (eg, number of oral antidiabetic drugs and insulin type) were also examined as sensitivity analyses.

To address missing covariate data, we implemented multiple imputation, which generates complete data sets (ie, replaces missing values in the data set) by borrowing information from other covariates and accounts for uncertainty associated with the estimation of missing values when estimating the regression parameters, logistic regression parameter, and discriminant function method parameter, according to variable type and using the PROC MI procedure in SAS (SAS Institute Inc).⁴⁰ We included the following variables in the imputation model using 7 imputed data sets: age, sex, race, ethnicity, residential region, CCI score, CHF, cerebrovascular disease, HbA_{1c} level, serum albumin level, eGFR, insulin, and oral antidiabetic drug use. The PROC MIANALYZE procedure was then used to combine results across imputations.

We also conducted subgroup analyses of any occurrence of hypoglycemia-related hospitalization(s) and mortality across clinically relevant subgroups. Proportional hazards assumptions were confirmed using graphical analysis. Analyses and figures were generated using SAS, version 9.4; Stata, version 13.1 (Stata Corp), and SigmaPlot, version 12.5 (Systat Software).

Results

Study Population

Among 30,156 patients who met eligibility criteria for the more than 1- to 2- year prelude period (Fig S1), 5.9% experienced 1 or more hypoglycemia-related hospitalization(s) before dialysis therapy initiation, with 94.1%, 5.1%, 0.6%, and 0.2% experiencing 0, 1, 2, and 3 or more hypoglycemia-related hospitalizations (Table S1). Among these patients, 0.1%, 98.3%, and 1.6% had type 1, type 2, and unknown diabetes type, respectively, and the overall mean and median eGFR slope was -10.5 ± 8.92 (standard deviation) and -8.2 (quartile 1 [Q1]-Q3, -13.0 to -5.1) mL/min/1.73 m² per year, respectively. Patients with the presence of any hypoglycemia-related hospitalization(s) tended to be younger, were less likely to be white, were more likely to be receiving in-center hemodialysis, had a higher CCI score and were more likely to have CHF or cerebrovascular disease, had higher HbA_{1c} and prelude-averaged eGFR and lower serum albumin values, and were more likely to be using insulin (including rapid-, short-, intermediate-, and long-acting types) and oral antidiabetic drugs (including sulfonylureas, thiazolidinediones, and metformin) compared with those with absence of hypoglycemia-related hospitalization(s) (Table 1).

Clinical Characteristics and Hypoglycemia-Related Hospitalization Risk

In case-mix logistic regression analyses, patients of Hispanic ethnicity, with CHF or cerebrovascular disease, with higher HbA_{1c} and prelude-averaged eGFR values,

Table 1. Baseline Characteristics Among Patients According to Presence Versus Absence of Hypoglycemia-Related Hospitalization in the More Than 1- to 2-Year Prelude Period

	Overall (N = 30,156)	Hospitalization		P
		Presence (n = 1,767; 5.9%)	Absence (n = 28,389; 94.1%)	
Age at dialysis initiation, y	72 ± 11	71 ± 10	72 ± 11	0.001
Female sex	5%	5%	5%	0.6
White race	74%	66%	74%	<0.001
Hispanic ethnicity	7%	8%	7%	0.2
Cause of ESRD				<0.001
Diabetes	60%	71%	59%	
Hypertension	22%	18%	23%	
Glomerulonephritis	3%	<1%	3%	
Cystic kidney disease	<1%	<1%	<1%	
Other urologic disorder	<1%	<1%	<1%	
Other cause	9%	6%	9%	
Unknown/missing	5%	4%	5%	
Modality				<0.001
In-center HD	84%	87%	84%	
Home HD/PD	5%	3%	5%	
Unknown	11%	10%	11%	
Residential region				0.4
Northeast	18%	18%	18%	
Midwest	23%	22%	23%	
South	42%	43%	42%	
West	18%	17%	18%	
Comorbid conditions				
Charlson Comorbidity Index score	6 ± 3	7 ± 3	6 ± 3	<0.001
Congestive heart failure	65%	75%	64%	<0.001
Cerebrovascular disease	35%	41%	35%	<0.001
Laboratory tests				
Hemoglobin A _{1c} , %	6.9% [6.2%-7.9%]	7.2% [6.3%-8.3%]	6.9% [6.2%-7.8%]	<0.001
Serum albumin, g/dL	3.6 [3.2-3.9]	3.4 [3.0-3.8]	3.6 [3.2-3.9]	<0.001
eGFR averaged over the prelude period, mL/min/1.73 m ²	21 [16-31]	23 [17-33]	21 [16-30]	<0.001
eGFR at dialysis initiation, mL/min/1.73 m ²	14 [10-22]	14 [10-23]	14 [10-22]	0.4
Medications				
Insulin	45%	60%	44%	<0.001
Oral antidiabetic medications	48%	61%	48%	<0.001
Alpha-glucosidase inhibitor	2%	3%	2%	<0.001
Sulfonylurea	39%	49%	39%	<0.001
Thiazolidinedione	17%	22%	17%	<0.001
Metformin	18%	25%	18%	<0.001
DPP-4 inhibitor	1%	1%	1%	0.9
Meglitinide	1%	2%	1%	<0.001
Rapid-acting insulin	16%	24%	15%	<0.001
Short-acting insulin	37%	51%	36%	<0.001
Intermediate-acting insulin	36%	48%	35%	<0.001
Long-acting insulin	16%	25%	15%	<0.001
Unknown type/inhaled insulin	<1%	<1%	<1%	0.7

Note: Values for continuous variables given as mean ± standard deviation or median [Q1-Q3].

Abbreviations: DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HD, hemodialysis; PD, peritoneal dialysis; Q, quartile.

and with use of rapid-, short-, intermediate-, and long-acting insulin had a higher likelihood of experiencing hypoglycemia-related hospitalization(s) (Table S2). Conversely, patients of white race and with higher

serum albumin levels were less likely to experience hypoglycemia-related hospitalization(s). These patterns of association largely persisted in analyses adjusted for additional covariates.

Antidiabetic Medications and Hypoglycemia-Related Hospitalization Risk

We examined a subcohort of 28,047 patients who were prescribed 0 to 2 oral antidiabetic drugs with or without insulin (Table S3). In case-mix analyses, patients who were prescribed an increasing number of oral antidiabetic drugs (without insulin) had an incrementally higher risk for hypoglycemia-related hospitalization(s) (the reference group comprised patients prescribed neither oral antidiabetic drugs nor insulin; Table 2). Using the same reference group, we also observed that patients prescribed insulin had higher risk for hypoglycemia-related hospitalization(s), with even higher risk among those concomitantly prescribed 1 or 2 oral antidiabetic drugs. This pattern of findings persisted in analyses adjusted for expanded case-mix and expanded case-mix plus laboratory covariates.

Among patients from this subcohort, we also examined 27,389 patients receiving the 12 most commonly prescribed antidiabetic medication regimens (Table 2). Compared with patients who were prescribed neither oral

antidiabetic drugs nor insulin, all antidiabetic medication regimens were associated with higher risk for hypoglycemia-related hospitalization except for thiazolidinedione and metformin monotherapy.

Hypoglycemia-Related Hospitalization and Mortality

Patients contributed a total of 57,673 patient-years of follow-up, during which time 12,480 all-cause deaths occurred (Table S4). Median at-risk time was 1.8 (Q1-Q3, 0.7-2.9) years. We first examined the occurrence of any hypoglycemia-related hospitalization over a more than 1- to 2-year prelude period and post-ESRD mortality (Fig 1; Tables S5 and S6). In case-mix models, the presence of any hypoglycemia-related hospitalization was associated with higher mortality (reference group: those with absence of hypoglycemia-related hospitalization). These findings were robust in analyses restricted to patients with type 2 diabetes (Table S7) and after incremental adjustment for expanded case-mix, laboratory, and medication covariates (Table S6), as well as eGFR

Table 2. Antidiabetic Medication Regimens Associated With Hypoglycemia-Related Hospitalizations in the More Than 1- to 2-Year Prelude Period

	Minimally Adjusted	Case-Mix Adjusted	Expanded Case-Mix Adjusted	Expanded Case-Mix + Laboratory Adjusted
Medication combinations (n = 28,047^a)				
No antidiabetic drugs + no insulin	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
No insulin + 1 antidiabetic drug	1.66 (1.38-2.00) ^b	1.68 (1.39-2.02) ^b	1.54 (1.27-1.86) ^b	1.50 (1.24-1.81) ^b
No insulin + 2 antidiabetic drugs	2.42 (1.99-2.96) ^b	2.47 (2.02-3.01) ^b	2.25 (1.84-2.75) ^b	2.09 (1.71-2.57) ^b
Insulin only	2.35 (2.02-2.74) ^b	2.39 (2.04-2.79) ^b	1.90 (1.61-2.23) ^b	1.70 (1.44-2.01) ^b
Insulin + 1 antidiabetic drug	2.87 (2.45-3.35) ^b	2.91 (2.48-3.42) ^b	2.28 (1.93-2.69) ^b	1.98 (1.66-2.35) ^b
Insulin + 2 antidiabetic drugs	2.70 (2.27-3.21) ^b	2.77 (2.32-3.31) ^b	2.20 (1.83-2.64) ^b	1.83 (1.52-2.22) ^b
Most common medication patterns (n = 27,389^c)				
No insulin				
No antidiabetic drug + no insulin	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Sulfonylurea only	1.81 (1.49-2.19) ^b	1.82 (1.49-2.21) ^b	1.64 (1.35-2.00) ^b	1.62 (1.33-1.97) ^b
Thiazolidinedione only	1.05 (0.52-2.15)	1.06 (0.52-2.16)	0.99 (0.49-2.03)	0.97 (0.47-1.98)
Metformin	0.98 (0.52-1.86)	1.04 (0.55-1.96)	1.06 (0.56-2.02)	0.96 (0.50-1.83)
Sulfonylurea + thiazolidinedione	2.17 (1.62-2.90) ^b	2.18 (1.62-2.92) ^b	1.95 (1.45-2.63) ^b	1.87 (1.39-2.52) ^b
Sulfonylurea + metformin	2.70 (2.09-3.50) ^b	2.79 (2.16-3.61) ^b	2.60 (2.00-3.37) ^b	2.34 (1.80-3.04) ^b
Insulin				
Insulin only	2.36 (2.02-2.74) ^b	2.39 (2.04-2.80) ^b	1.90 (1.62-2.24) ^b	1.70 (1.44-2.01) ^b
Sulfonylurea + insulin	2.76 (2.30-3.32) ^b	2.78 (2.31-3.35) ^b	2.19 (1.81-2.64) ^b	1.94 (1.59-2.36) ^b
Thiazolidinedione + insulin	2.76 (2.09-3.65) ^b	2.82 (2.13-3.73) ^b	2.20 (1.65-2.92) ^b	1.93 (1.44-1.58) ^b
Metformin + insulin	3.36 (2.56-4.41) ^b	3.48 (2.64-4.59) ^b	2.74 (2.07-3.63) ^b	2.15 (1.61-2.87) ^b
Sulfonylurea + thiazolidinedione + insulin	2.47 (1.91-3.18) ^b	2.52 (1.95-3.25) ^b	1.98 (1.53-2.57) ^b	1.74 (1.33-2.27) ^b
Sulfonylurea + metformin + insulin	2.57 (2.04-3.24) ^b	2.66 (2.10-3.36) ^b	2.14 (1.68-2.72) ^b	1.71 (1.34-2.19) ^b
Thiazolidinedione + metformin + insulin	2.93 (1.86-4.59) ^b	3.08 (1.95-4.85) ^b	2.49 (1.57-3.94) ^b	1.95 (1.22-3.11) ^b

Note: Values shown are odds ratio (95% confidence interval). Minimally adjusted model adjusted for patient's calendar quarter of dialysis therapy initiation. Case-mix-adjusted model adjusted for covariates in the minimally adjusted model and age at dialysis therapy initiation, sex, race, and ethnicity. Expanded case-mix model adjusted for covariates in the case-mix model and cause of end-stage kidney disease, initial dialysis modality, residential region, congestive heart failure, cerebrovascular disease, and Charlson Comorbidity Index score. Expanded case-mix + laboratory-adjusted model adjusted for covariates in the expanded case-mix model and hemoglobin A_{1c} level, serum albumin level, estimated glomerular filtration rate averaged over the prelude period, and last estimated glomerular filtration rate obtained before dialysis therapy initiation.

^aOnly included patients on treatment with 0, 1, or 2 oral antidiabetic drugs.

^bStatistically significant.

^cOnly includes patients prescribed the 12 most common medication combinations.

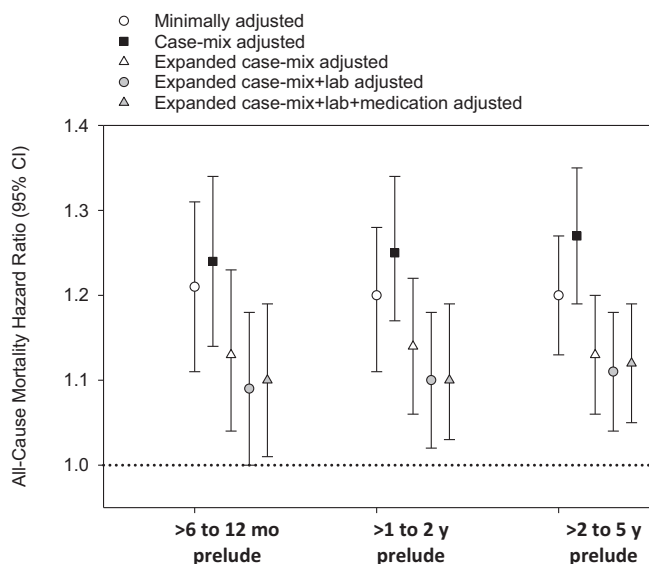


Figure 1. Association between presence of hypoglycemia-related hospitalization across various prelude periods and mortality (reference group: absence of hypoglycemia-related hospitalization). Minimally adjusted model adjusted for patient's calendar quarter of dialysis therapy initiation. Case-mix-adjusted model adjusted for covariates in the minimally adjusted model and age at dialysis therapy initiation, sex, race, and ethnicity. Expanded case-mix model adjusted for covariates in the case-mix model and cause of end-stage kidney disease, initial dialysis modality, residential region, congestive heart failure, cerebrovascular disease, and Charlson Comorbidity Index score. Expanded case-mix + laboratory (lab)-adjusted model adjusted for covariates in the expanded case-mix model and hemoglobin A_{1c} level, serum albumin level, estimated glomerular filtration rate averaged over the prelude period, and last estimated glomerular filtration rate obtained before dialysis therapy initiation. Expanded case-mix + laboratory + medication-adjusted model adjusted for covariates in the expanded case-mix + laboratory test model and insulin and oral antidiabetic drugs. Abbreviation: CI, confidence interval.

slope, number of oral antidiabetic drugs, and insulin type used (Table S8). Similar findings were also observed in sensitivity analyses examining any hypoglycemia-related hospitalization over more than 6- to 12-month and more than 2- to 5-year prelude periods (Fig 1; Tables S5 and S6).

In case-mix analyses, an increasing frequency of hypoglycemia-related hospitalizations over the more than 1- to 2-year prelude period was also associated with incrementally higher death risk (reference group: no hypoglycemia-related hospitalizations; Fig 2; Tables S5 and S9). Findings were robust in analyses restricted to patients with type 2 diabetes (Table S7), and similar trends were observed after incremental adjustment for expanded case-mix, laboratory, medication, eGFR slope, number of oral antidiabetic drugs, and insulin type covariates (Tables S8 and S9). When frequency of hypoglycemia-related hospitalizations was examined across more than 6- to 12-month and more than 2- to 5-year prelude intervals, a similar pattern of findings was observed (Fig 2; Tables S5 and S9).

Hypoglycemia-Related Hospitalization and Mortality Across Subgroups

We also examined the association between occurrence of any hypoglycemia-related hospitalization(s) over the more than 1- to 2-year prelude period and mortality across clinically relevant subgroups (Fig S2; Table S10). In case-mix analyses, we observed effect modification of the hypoglycemia-mortality association across subgroups of age, race, and insulin use: P values for interactions were <0.001, 0.04, and 0.05, respectively. We observed stronger associations between hypoglycemia-related hospitalization(s) and mortality among patients younger than 65 versus 65 years and older, nonwhite versus white race, and insulin users versus nonusers.

Discussion

In a large national incident ESRD cohort of US veterans with diabetes, ~6% of patients experienced a hypoglycemia-related hospitalization within 2 years before transitioning to dialysis therapy. We observed a dose-dependent relationship between increasing frequency of hypoglycemia-related hospitalizations and incrementally higher mortality after transitioning to dialysis therapy, such that experiencing 3 or more events in the pre-ESRD prelude period was associated with 2-fold higher post-ESRD death risk.

Increasing evidence suggests that hypoglycemia is a frequent occurrence in diabetic patients with NDD-CKD, with adverse implications on survival.^{21-23,41} In a secondary analysis of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial stratified by kidney function, hypoglycemia rates were nearly 2-fold higher in patients with mild to moderate CKD (stages 1-3 CKD) versus normal kidney function.²³ Although the association between hypoglycemia and mortality was not directly examined, intensive glucose lowering versus standard therapy was associated with 31% and 41% higher risk for all-cause and cardiovascular death, respectively, in those with CKD, but not in those without CKD. In another study of 8,767 type 2 diabetic patients from the Hong Kong Diabetes Registry, hypoglycemia-related hospitalizations and CKD were each independently associated with higher mortality, and patients with both hypoglycemia and CKD had nearly 4-fold higher death risk compared with those with neither risk factor.²² A large population-based study of 243,222 veterans showed that the incidence of hypoglycemia ascertained by blood glucose level in the ambulatory and inpatient setting was higher in patients with versus without CKD.²¹ Moreover, there was a graded association between severity of hypoglycemia and short-term (ie, 1-day) mortality that was stronger among patients without versus with CKD. However, inference from these findings was limited by the lack of medication data and noncapture of hypoglycemia events occurring outside the ambulatory and inpatient setting. Furthermore, although these studies, which exclusively focused on patients with NDD-CKD, inform the short-

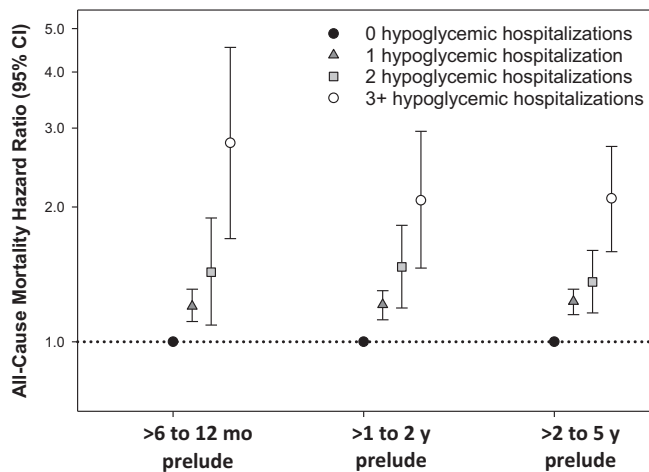


Figure 2. Association between frequency of hypoglycemia-related hospitalizations across various prelude periods and mortality (reference group: zero hypoglycemic hospitalizations). Analyses adjusted for case-mix covariates, which include patient's calendar quarter of dialysis therapy initiation, age at dialysis therapy initiation, sex, race, and ethnicity. Abbreviation: CI, confidence interval.

term complications of low glycemic status, little is known about the long-term sequelae of hypoglycemia and particularly the long-term complications of repeated pre-ESRD hypoglycemia episodes over time among patients with CKD who survive to maintenance dialysis therapy. Hence, our study provides insight into the long-term impact of hypoglycemia events requiring medical attention during later stages of CKD on postdialysis mortality risk of incident patients with ESRD.

Given their disproportionate representation in the broader CKD population and their heightened death risk compared with nondiabetic counterparts,² diabetic patients with NDD-CKD progressing to maintenance dialysis therapy are a critical target for determining risk factors contributing to this precarious postdialysis period. There are several pathways by which hypoglycemia may lead to short-term complications as observed in the mentioned studies. First, glucose is a critical source of fuel for the central nervous system,^{14,42} and hypoglycemia may directly lead to death due to encephalopathy, seizures, and coma, as well as indirectly by dizziness, disequilibrium, gait abnormalities, and subsequent falls. Second, by causing an abrupt increase in adrenergic activity, hypoglycemia may also precipitate coronary ischemia, ventricular arrhythmias, and sudden cardiac death.⁴³ With respect to long-term sequelae, recurrent hypoglycemia has been reported to diminish autonomic nervous system responses (eg, cardiac vagal baroreflex sensitivity),^{42,44} further exacerbating cardiovascular risk over time. It has been hypothesized that increased frequency of hypoglycemia may explain the higher risk for adverse cardiovascular outcomes observed in studies of intensive glycemic control,^{10,12} which may be the pathway by which pre-ESRD hypoglycemia events contributed to

post-ESRD mortality in the present study. It is also possible that coexisting factors increasing hypoglycemia susceptibility (ie, protein-energy wasting, decreased kidney function leading to impaired gluconeogenesis, and uremia⁵) may contribute to mortality in this population. Future studies examining specific mechanisms by which hypoglycemia contributes to higher mortality specifically in diabetic patients with CKD are needed.

Another novel contribution of our study was the examination of antidiabetic medication patterns as a modifiable risk factor for hypoglycemia-related hospitalizations in the pre-ESRD period. Although we observed a graded association between number of prescribed oral antidiabetic drugs and risk for hypoglycemia, prescription of insulin alone had a similar magnitude of risk as compared to prescription of 2 oral antidiabetic drugs, and the association between hypoglycemia-related hospitalization(s) and mortality risk was stronger in insulin versus non-insulin users in subgroup analyses. Examination of the 12 most commonly prescribed antidiabetic medication patterns by drug class showed that compared to no receipt of oral antidiabetic drugs or insulin, regimens that included sulfonylureas and/or insulin were associated with heightened risk for hypoglycemia, whereas thiazolidinedione and metformin monotherapy did not demonstrate higher risk. Although these collective data suggest that certain oral antidiabetic drugs may carry lower risk for hypoglycemia versus other antidiabetic agents, these findings should be tempered by the potential toxicities associated with metformin (metformin-associated lactic acidosis⁴⁵⁻⁵⁰) and thiazolidinediones (fluid retention, osteoporosis, and bladder cancer⁵¹⁻⁵³) and US regulatory bodies' recommendations against the prescription of metformin among patients with eGFRs < 30 mL/min/1.73 m².⁵⁴ Further studies are needed to determine the net safety and effectiveness of specific antidiabetic therapies in CKD.

The strengths of our study include its examination of a large nationally representative cohort of incident patients with ESRD with both pre- and post-ESRD information; comprehensive availability of comorbidity, medication, and laboratory data; and reduced confounding by differential health care access and nonuniform medical treatment by receiving care within the VA system.

However, several limitations of our study bear mention. First, we defined hypoglycemia events using hospitalization records, likely capturing moderate to severe events and potentially excluding mild episodes that did not require medical attention. Hence, the frequency of events observed may be an underestimation given reliance on ICD-9 codes for ascertainment and potential noninclusion of patients who died immediately after the hypoglycemia event before initiating maintenance dialysis therapy. However, we elected to use the former approach given the risk for ascertainment bias that may be introduced by reliance on blood glucose measurements (ie, noncapture of hypoglycemia detected using capillary blood glucose measurement at home). Second, our analyses examined

prevalent antidiabetic medication use, which does not account for patients who may have ceased medication use due to adverse events or death, and prescription data may not reflect actual intake of medications. Third, our examination of post-ESRD mortality does not assess the relationship between hypoglycemia and short-term death, and our analyses did not include those who maintained stable kidney function, experienced death, or underwent kidney transplantation before dialysis therapy initiation or those who declined dialysis therapy, who may be inherently different from those who progressed to dialysis therapy. However, because prior data have confirmed an association between hypoglycemia events and immediate mortality risk in CKD, our intention was to specifically examine the long-term impact of pre-ESRD hypoglycemia on post-ESRD mortality. Fourth, granular examination of patients' clinical characteristics showed that eGFRs at dialysis therapy initiation tended to be higher among patients with increasing frequency of hypoglycemia. Because higher eGFRs may be a proxy of PEW and reduced muscle mass, hypervolemia resulting in creatinine dilution, and/or providers' inclination toward earlier dialysis therapy initiation among unstable patients, it is possible that underlying ill health among patients with hypoglycemia may have contributed to their heightened mortality risk. Although multivariable analyses adjusted for proxies of protein-energy wasting (serum albumin), fluid overload (CHF), and comorbid condition burden (CCI score), we cannot exclude the possibility of residual confounding by nutritional status, hypervolemia, and illness. Fifth, given that our analyses were restricted to veterans who are largely male, with greater comorbid condition burden and lower socioeconomic status, our findings may have limited external validity to distinct study populations, and the observed hypoglycemia-mortality associations may be generalizable only to patients with CKD who experienced hypoglycemia in the more than 1 to 2 years prelude period before dialysis therapy initiation as our primary exposure window. Last, our findings do not indicate a causal association between hypoglycemia-related hospitalization(s) and mortality.

In conclusion, we observed that hypoglycemia-related hospitalization(s) during the pre-ESRD prelude period were associated with higher post-ESRD mortality among diabetic incident patients with ESRD, and this risk was incrementally stronger with increasing frequency of hypoglycemia. Further studies are needed of management strategies that prevent hypoglycemia episodes among diabetic patients with NDD-CKD transitioning to dialysis therapy to evaluate whether reducing such episodes reduces the exceedingly high death rate in ESRD.

Supplementary Material

Figure S1: Study cohort creation.

Figure S2: Association between presence of hypoglycemia-related hospitalization during the >1-2-year prelude period and mortality across clinically relevant subgroups.

Table S1: Baseline characteristics among patients according to frequency of hypoglycemia-related hospitalization in the >1-2-year prelude period.

Table S2: Clinical characteristics associated with hypoglycemia-related hospitalizations in the >1-2-year prelude period.

Table S3: Baseline characteristics of patients according to antidiabetic medication status over the >1-2-year prelude period.

Table S4: Crude estimates of all-cause death events, follow-up time, and hypoglycemia-related hospitalization event rates overall and by frequency of hospitalization in the >1-2-year prelude cohort.

Table S5: Summary of associations of hypoglycemia-related hospitalizations across various prelude periods and mortality in case-mix-adjusted models.

Table S6: Association between hypoglycemia-related hospitalizations across various prelude periods and mortality.

Table S7: Sensitivity analyses of the association between hypoglycemia-related hospitalizations and mortality in the >1-2-year prelude cohort restricted to patients with type 2 diabetes only.

Table S8: Sensitivity analyses of the association between hypoglycemia-related hospitalizations and mortality in the >1-2-year prelude cohort incrementally adjusted for eGFR slope, number of oral antidiabetic drugs used, and insulin type used.

Table S9: Association between frequency of hypoglycemia-related hospitalizations across various prelude periods and mortality.

Table S10: Association between hypoglycemia-related hospitalizations in the >1-2-year prelude period and mortality across clinically relevant subgroups.

Article Information

Authors' Full Names and Academic Degrees: Connie M. Rhee, MD, MSc, Csaba P. Kovesdy, MD, Amy S. You, MS, John J. Sim, MD, Melissa Soohoo, MPH, Elani Streja, MPH, PhD, Miklos Z. Molnar, MD, PhD, Alpesh N. Amin, MD, MBA, Kevin Abbott, MD, MPH, Danh V. Nguyen, MS, PhD, and Kamyar Kalantar-Zadeh, MD, MPH, PhD.

Authors' Affiliations: Harold Simmons Center for Chronic Disease Research and Epidemiology, University of California Irvine School of Medicine, Orange, CA (CMR, ASY, MS, ES, KK-Z); Division of Nephrology, University of Tennessee Health Science Center (CPK, MZM); Nephrology Section, Memphis Veterans Affairs Medical Center (CPK); Division of Transplant Surgery, Methodist University Hospital Transplant Institute (MZM); Division of Transplant Surgery, Department of Surgery, University of Tennessee Health Science Center, Memphis, TN (MZM); Kaiser Permanente of Southern California, Los Angeles (JJS); Tibor Rubin Veterans Affairs Medical Center, Long Beach, CA (ES, KK-Z); Department of Transplantation and Surgery, Semmelweis University, Budapest, Hungary (MZM); Department of Medicine, University of California Irvine School of Medicine, Orange, CA (ANA, DVN); and Division of Kidney, Urologic and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD (KA).

Address for Correspondence: Connie M. Rhee, MD, MSc, Harold Simmons Center for Chronic Disease Research and Epidemiology, University of California Irvine School of Medicine, 101 The City Dr S, City Tower, Ste 400, Orange, CA 92868. E-mail: crhee1@uci.edu

Authors' Contributions: Research idea and study design: CMR, CPK, KA, KK-Z; data acquisition: CPK, KK-Z; data interpretation: CMR, CPK, ASY, JJS, MS, ES, MZM, ANA, KA, DVN, KK-Z; statistical analysis: ASY; supervision or mentorship: CMR, CPK, KK-Z. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability

for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Support: The study was supported by the National Institutes of Health (NIH)/National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) U01DK102163 grant (Drs Kalantar-Zadeh and Kovesdy), University of California Irvine Department of Medicine Chairman's Award (Dr Rhee), and by resources from the US Department of VA. The authors are supported by research grants from the NIH/NIDDK: K23-DK102903 (Dr Rhee), K24-DK091419 (Dr Kalantar-Zadeh), R01-DK09568 (Dr Kalantar-Zadeh), R01-DK078106 (Dr Kalantar-Zadeh), U01-DK102163 (Drs Kalantar-Zadeh and Kovesdy), and R01-DK092232 (Dr Nguyen). Drs Kovesdy, Streja, and Kalantar-Zadeh are employees of the Department of VA. Dr Streja is supported by a career development award from the Office of Research and Development of the Department of VA (IK2- CX 001266-01). Support for VA/CMS data is provided by the Department of VA, Veterans Health Administration, Office of Research and Development, VA Information Resource Center (project numbers SDR 02-237 and 98-004). The sponsor participated in the study design, interpretation of data, and writing of the report, but did not participate in the data collection, analysis, or decision to submit the report for publication.

Financial Disclosure: The authors declare that they have no other relevant financial interests.

Disclaimer: The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as official policy or interpretation of the US Department of Veterans Affairs. The data reported here have been supplied by the USRDS. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US government.

Prior Presentation: Portions of these data were presented as an oral abstract at the 2016 American Society of Nephrology Kidney Week Meeting, November 3-8, 2016, Chicago, IL.

Peer Review: Received December 17, 2017. Evaluated by 2 external peer reviewers, with direct editorial input from a Statistics/Methods Editor, an Associate Editor, and the Editor-in-Chief. Accepted in revised form April 27, 2018.

References

- Alicic RZ, Tuttle KR. Management of the diabetic patient with advanced chronic kidney disease. *Semin Dial*. 2010;23(2):140-147.
- Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2016 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis*. 2017;69(3)(suppl 1):A7-A8.
- Kalantar-Zadeh K, Kovesdy CP, Streja E, et al. Transition of care from pre-dialysis prelude to renal replacement therapy: the blueprints of emerging research in advanced chronic kidney disease. *Nephrol Dial Transplant*. 2017;32(suppl 2):ii91-ii98.
- Lukowsky LR, Kheifets L, Arah OA, Nissenson AR, Kalantar-Zadeh K. Patterns and predictors of early mortality in incident hemodialysis patients: new insights. *Am J Nephrol*. 2012;35(6):548-558.
- Rhee CM, Leung AM, Kovesdy CP, Lynch KE, Brent GA, Kalantar-Zadeh K. Updates on the management of diabetes in dialysis patients. *Semin Dial*. 2014;27(2):135-145.
- Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, Lachin J, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329(14):977-986.
- United Kingdom Prospective Diabetes Study (UKPDS). 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. *BMJ*. 1995;310(6972):83-88.
- Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358(24):2545-2559.
- Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009;360(2):129-139.
- Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet*. 2010;376(9739):419-430.
- Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358(24):2560-2572.
- Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *BMJ*. 2010;340:b4909.
- Abe M, Kalantar-Zadeh K. Haemodialysis-induced hypoglycaemia and glycaemic disarrays. *Nat Rev Nephrol*. 2015;11(5):302-313.
- Gosmanov AR, Gosmanova EO, Kovesdy CP. Evaluation and management of diabetic and non-diabetic hypoglycemia in end-stage renal disease. *Nephrol Dial Transplant*. 2016;31(1):8-15.
- Ricks J, Molnar MZ, Kovesdy CP, et al. Glycemic control and cardiovascular mortality in hemodialysis patients with diabetes: a 6-year cohort study. *Diabetes*. 2012;61(3):708-715.
- Lipska KJ, Ross JS, Wang Y, et al. National trends in US hospital admissions for hyperglycemia and hypoglycemia among Medicare beneficiaries, 1999 to 2011. *JAMA Intern Med*. 2014;174(7):1116-1124.
- Zaccardi F, Davies MJ, Dhalwani NN, et al. Trends in hospital admissions for hypoglycaemia in England: a retrospective, observational study. *Lancet Diabetes Endocrinol*. 2016;4(8):677-685.
- McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA. Increased mortality of patients with diabetes reporting severe hypoglycemia. *Diabetes Care*. 2012;35(9):1897-1901.
- Zoungas S, Patel A, Chalmers J, et al. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med*. 2010;363(15):1410-1418.
- Zhao Y, Shi Q, Wang Y, Fonseca V, Shi L. Economic burden of hypoglycemia: utilization of emergency department and outpatient services in the United States (2005-2009). *J Med Econ*. 2016;19(9):852-857.
- Moen MF, Zhan M, Hsu VD, et al. Frequency of hypoglycemia and its significance in chronic kidney disease. *Clin J Am Soc Nephrol*. 2009;4(6):1121-1127.
- Kong AP, Yang X, Luk A, et al. Hypoglycaemia, chronic kidney disease and death in type 2 diabetes: the Hong Kong diabetes registry. *BMC Endocr Disord*. 2014;14:48.
- Papademetriou V, Lovato L, Doumas M, et al. Chronic kidney disease and intensive glycemic control increase cardiovascular risk in patients with type 2 diabetes. *Kidney Int*. 2015;87(3):649-659.
- Cho A, Noh JW, Kim JK, et al. Prevalence and prognosis of hypoglycaemia in patients receiving maintenance dialysis. *Intern Med J*. 2016;46(12):1380-1385.

25. Molnar MZ, Gosmanova EO, Sumida K, et al. Predialysis cardiovascular disease medication adherence and mortality after transition to dialysis. *Am J Kidney Dis.* 2016;68(4):609-618.
26. Sumida K, Molnar MZ, Potukuchi PK, et al. Association of slopes of estimated glomerular filtration rate with post-end-stage renal disease mortality in patients with advanced chronic kidney disease transitioning to dialysis. *Mayo Clin Proc.* 2016;91(2):196-207.
27. Sumida K, Molnar MZ, Potukuchi PK, et al. Prognostic significance of pre-end-stage renal disease serum alkaline phosphatase for post-end-stage renal disease mortality in late-stage chronic kidney disease patients transitioning to dialysis. *Nephrol Dial Transplant.* 2018;33(2):264-273.
28. Sumida K, Molnar MZ, Potukuchi PK, et al. Association between vascular access creation and deceleration of estimated glomerular filtration rate decline in late-stage chronic kidney disease patients transitioning to end-stage renal disease. *Nephrol Dial Transplant.* 2017;32(8):1330-1337.
29. Eby EL, Van Brunt K, Brusko C, Curtis B, Lage MJ. Dosing of U-100 insulin and associated outcomes among Medicare enrollees with type 1 or type 2 diabetes. *Clin Interv Aging.* 2015;10:991-1001.
30. Katon WJ, Young BA, Russo J, et al. Association of depression with increased risk of severe hypoglycemic episodes in patients with diabetes. *Ann Fam Med.* 2013;11(3):245-250.
31. Quilliam BJ, Simeone JC, Ozbay AB. Risk factors for hypoglycemia-related hospitalization in patients with type 2 diabetes: a nested case-control study. *Clin Ther.* 2011;33(11):1781-1791.
32. Romley JA, Gong C, Jena AB, Goldman DP, Williams B, Peters A. Association between use of warfarin with common sulfonylureas and serious hypoglycemic events: retrospective cohort analysis. *BMJ.* 2015;351:h6223.
33. US Department of Veterans Affairs; Health Services Research and Development Service; VA Information Resource Center. *VIReC Research User Guide: VHA Medical SAS Datasets FY2006-2007.* Hines, IL: VA Information Resource Center; 2007.
34. Ravel V, Ahmadi SF, Streja E, et al. Pain and kidney function decline and mortality: a cohort study of US veterans. *Am J Kidney Dis.* 2016;68(2):240-246.
35. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol.* 1992;45(6):613-619.
36. US Department of Veterans Affairs; Health Services Research and Development Service; VA Information Resource Center. *VIReC Research User Guide: VHA Pharmacy Prescription Data.* 2nd ed. Hines, IL: VA Information Resource Center; 2008.
37. Hung AM, Roumie CL, Greevy RA, et al. Kidney function decline in metformin versus sulfonylurea initiators: assessment of time-dependent contribution of weight, blood pressure, and glycemic control. *Pharmacoepidemiol Drug Saf.* 2013;22(6):623-631.
38. US Department of Veterans Affairs; Health Services Research and Development Service; VA Information Resource Center. *VIReC Resource Guide: VA Corporate Data Warehouse.* Hines, IL: VA Information Resource Center; 2012.
39. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604-612.
40. US Renal Data System. *USRDS Special Study Center on Transition of Care in CKD.* Bethesda, MD: USRDS; 2014.
41. Ginsberg JS, Zhan M, Diamantidis CJ, Woods C, Chen J, Fink JC. Patient-reported and actionable safety events in CKD. *J Am Soc Nephrol.* 2014;25(7):1564-1573.
42. Cryer PE. Hypoglycemia, functional brain failure, and brain death. *J Clin Invest.* 2007;117(4):868-870.
43. Robinson RT, Harris ND, Ireland RH, Lee S, Newman C, Heller SR. Mechanisms of abnormal cardiac repolarization during insulin-induced hypoglycemia. *Diabetes.* 2003;52(6):1469-1474.
44. De Ferrari GM, Sanzo A, Bertolotti A, Specchia G, Vanoli E, Schwartz PJ. Baroreflex sensitivity predicts long-term cardiovascular mortality after myocardial infarction even in patients with preserved left ventricular function. *J Am Coll Cardiol.* 2007;50(24):2285-2290.
45. Bakris GL, Molitch ME. Should restrictions be relaxed for metformin use in chronic kidney disease? Yes, they should be relaxed! What's the fuss? *Diabetes Care.* 2016;39(7):1287-1291.
46. Kalantar-Zadeh K. Case 23-2013: a 54-year-old woman with metformin toxicity. *N Engl J Med.* 2013;369(18):1769.
47. Kalantar-Zadeh K, Kovesdy CP. Should restrictions be relaxed for metformin use in chronic kidney disease? No, we should never again compromise safety! *Diabetes Care.* 2016;39(7):1281-1286.
48. Kalantar-Zadeh K, Rhee CM. Metformin in chronic kidney disease: more harm than help? *Lancet Diabetes Endocrinol.* 2015;3(8):579-581.
49. Rhee CM, Kalantar-Zadeh K. Restricting metformin in CKD: continued caution warranted. *Am J Kidney Dis.* 2015;66(6):1101-1102.
50. Rhee CM, Kovesdy CP, Kalantar-Zadeh K. Risks of metformin in type 2 diabetes and chronic kidney disease: lessons learned from Taiwanese data. *Nephron.* 2017;135(2):147-153.
51. Tuccori M, Filion KB, Yin H, Yu OH, Platt RW, Azoulay L. Pioglitazone use and risk of bladder cancer: population based cohort study. *BMJ.* 2016;352:i1541.
52. Nesto RW, Bell D, Bonow RO, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. October 7, 2003. *Circulation.* 2003;108(23):2941-2948.
53. Napoli N, Chandran M, Pierroz DD, Abrahamsen B, Schwartz AV, Ferrari SL; IOF Bone and Diabetes Working Group. Mechanisms of diabetes mellitus-induced bone fragility. *Nat Rev Endocrinol.* 2017;13(4):208-219.
54. FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. <http://www.fda.gov/Drugs/DrugSafety>. Accessed March 20, 2018.