Hypoglycemic and Hyperglycemic Crises Among U.S. Adults With Diabetes and End-stage Kidney Disease: Population-Based Study, 2013–2017

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OBJECTIVE
We characterized annual trends of severe hypoglycemic and hyperglycemic crises (diabetic ketoacidosis/hyperglycemic hyperosmolar state) in patients with diabetes and end-stage kidney disease (ESKD).

RESEARCH DESIGN AND METHODS
This was a nationwide, retrospective study of adults (≥18 years old) with diabetes/ESKD, from the United States Renal Data System registry, between 2013 and 2017. Primary outcome was annual rates of emergency department visits or hospitalizations for hypoglycemic and hyperglycemic crises, reported as number of events/1,000 person-years. Event rates and risk factors were adjusted for patient age, sex, race/ethnicity, dialysis modality, comorbidities, treatment regimen, and U.S. region.

RESULTS
Among 521,789 adults with diabetes/ESKD (median age 65 years [interquartile range 57–73], 56.1% male, and 46% White), overall adjusted rates of hypoglycemic and hyperglycemic crises were 53.64 and 18.24 per 1,000 person-years, respectively. For both hypoglycemia and hyperglycemia crises, respectively, the risks decreased with age and were lowest in older patients (≥75 vs. 18–44 years old: incidence rate ratio 0.35, 95% CI 0.33–0.37, and 0.03, 0.02–0.03), women (1.09, 1.06–1.12, and 1.44, 1.36–1.54), and those with smoking (1.36, 1.28–1.43, and 1.71, 1.53–1.91), substance abuse (1.27, 1.15–1.42, and 1.53, 1.23–1.9), retinopathy (1.10, 1.06–1.15, and 1.36, 1.26–1.47), and insulin therapy (vs. no therapy; 0.60, 0.59–0.63, and 0.44, 0.39–0.48). For hypoglycemia, specifically, additional risk was conferred by Black race (1.11, 1.08–1.15) and amputation history (1.20, 1.13–1.27).

CONCLUSIONS
In this nationwide study of patients with diabetes/ESKD, hypoglycemic crises were threefold more common than hyperglycemic crises, greatly exceeding national reports in nondialysis patients with chronic kidney disease. Young, Black, and female patients were disproportionately affected.

In 2017, more than 760,000 adults were living with end-stage kidney disease (ESKD) in the U.S., with a progressive increase of ∼20,000 cases per year since 2012 (1,2). Care for patients with kidney disease, particularly ESKD, is expensive due to the high prevalence of chronic diseases and the complications associated with kidney failure.
and resource intensive, with 7% of all Medicare spending directed toward patients with ESKD (1–3). Diabetes is the leading cause of ESKD, responsible for ~47% of all ESKD cases (1,4,5). Thus, improving the management of patients with diabetes and ESKD (diabetes/ESKD) is an urgent priority for patients, health systems, and society.

Patients with diabetes and advanced chronic kidney disease (CKD), especially those with ESKD on dialysis, are clinically complex and often frail and have a high burden of comorbidities and medications (3,6). Glycemic management in patients with ESRD is challenging because of defects in peripheral glucose disposal due to uremia; decreased insulin clearance, resulting in greater susceptibility to iatrogenic hypoglycemia; and the underlying mild inflammatory state, which may predispose patients to hyperglycemia (6). Suboptimal diabetes management can therefore result in wide glycemic fluctuations ultimately culminating in acute glycemic crises of severe hypoglycemia, diabetic ketoacidosis (DKA), and hyperglycemic hyperosmolar state (HHS). These acute complications lead to morbidity, increased health care use, and impaired quality of life and can be fatal (7–10). More importantly, they are preventable with optimized outpatient management and close monitoring. In recognizing that patients with ESKD often have a limited life expectancy and high burden of disease and polypharmacy and face a high risk of iatrogenic hypoglycemia, clinical practice guidelines explicitly recommend treating this population less intensively, focusing instead on preventing the symptoms and complications associated with severe hypoglycemia and hyperglycemia (3,11). Previous studies have demonstrated increased risk for iatrogenic hypoglycemia in patients with predialysis CKD; however, there are limited data on severe hypoglycemia in patients with ESRD. Moreover, while suboptimal glycemic management can also lead to hyperglycemic crises (i.e., DKA/HHS), there are no data on these events among patients with diabetes/ESKD (12–14). Nationally representative data on hypoglycemic and hyperglycemic crises among patients with diabetes/ESKD are therefore needed to close diabetes-focused monitoring and support. To address these critical knowledge gaps and inform practice and policy recommendations regarding optimal glycemic management of patients with diabetes/ESKD, we examined recent trends and risk factors for severe hypoglycemic and hyperglycemic crises using a population-based cohort of adults with diabetes included in the United States Renal Data System (USRDS) between 2013 and 2017.

RESEARCH DESIGN AND METHODS

Data Source

We performed a retrospective analysis of USRDS data (2) between 2013 and 2017. The USRDS, funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), is a national data registry with collection and linkage of comprehensive information about CKD and ESKD from multiple sources in the U.S. Emory University’s institutional review board deemed the study exempt, as it involved analysis of de-identified publicly available data. Study results are reported in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational cohort studies (15).

Study Population

We included adult patients (≥18 years old) on hemodialysis or peritoneal dialysis included in USRDS and meeting eligibility criteria between 1 January 2013 and 31 December 2017. Included patients were required to have at least 3 months of dialysis prior to the index date and an established diagnosis of diabetes as of the index date (listed as either the primary cause of ESKD or as a comorbidity). Thus, both prevalent and incident ESKD cases were included (Supplementary Fig. 1).

Covariates

All covariates were ascertained from Centers for Medicare and Medicaid Services (CMS) 2728 Medical Evidence Report at the time of the index date. These included age, sex, race, ethnicity, census region (Midwest, Northeast, South, West), comorbidities, modality of dialysis (hemodialysis vs. peritoneal dialysis), and category of antidiabetes therapy (insulin, noninsulin, no pharmacotherapy). We specifically examined comorbidities previously reported to be associated with increased risk of diabetes crises (14,16): substance abuse, amputation, atherosclerotic or ischemic heart disease (ASCVD), cancer, heart failure (HF), chronic obstructive pulmonary disease, cerebrovascular disease, hypertension, retinopathy, peripheral vascular disease, tobacco use, and frailty. Patients with missing values for sex were excluded, and patients with missing data on race and region were grouped with the “unknown” category. Diabetes type was not specified in the CMS 2728 Medical Evidence Report.

Study Outcomes

The primary outcomes were emergency department (ED) visits or hospitalizations with a primary (first) diagnosis of severe hypoglycemic or hyperglycemic crises. ICD-9 and ICD-10 codes used to ascertain hypoglycemic and hyperglycemic crises are summarized in Supplementary Table 1.

Statistical Analyses

Baseline characteristics of patients with diabetes/ESKD were summarized with means (SD), medians (interquartile range [IQR]), and frequencies (percentages), as appropriate. Crude and adjusted (see below) rates of hypoglycemic and hyperglycemic crises per 1,000 person-years were calculated (separately) for the overall population and for subgroups of age, sex, race/ethnicity, U.S. census region, glucose-lowering regimen type, and dialysis modality. Change in rates over time was assessed with a $\chi^2$ test between the adjusted rates in 2013 and 2017.

Multivariable negative binomial regression was used to calculate incidence rate ratios (IRRs), associated 95% CIs, and $P$ values for the predicted number of hypoglycemia and hyperglycemia events per 1,000 person-years, with adjustment for year, age, sex, race/ethnicity, region, dialysis modality, duration of dialysis prior to index date, category of the glucose-lowering regimen, and comorbid conditions, clustering by individual and using an offset to account for total person-years in the study. Adjusted rates were calculated for the overall population and subgroups specified above using the margins of responses from the negative binomial model for each specified variable.

Data management, descriptive statistics, and crude rates were calculated with SAS, version 9.4 (SAS Institute). The negative binomial model, adjusted rates, and trend figure were calculated.
RESULTS
Study Population
Among 866,034 patients with ESKD on dialysis in the U.S. between 2013 and 2017, 521,789 (60.3%) had diabetes and met study inclusion/exclusion criteria (Supplementary Fig. 1). The median duration of dialysis upon cohort entry was 3.0 months (IQR 3–27.9), and patients were observed for a median of 23.8 months (10.1–44.0) after this index date. Median age was 65 years (57–73) years, and 43.9% were women, 46% non-Hispanic White, 28.7% non-Hispanic Black, and 18.8% Hispanic. The plurality of patients was in the Southern region of the U.S. (43%). The vast majority (92.1%) were receiving hemodialysis; 7.9% were receiving peritoneal dialysis. The most prevalent comorbidities were hypertension (89.3%), HF (32.5%), ASCVD (18.2%), peripheral vascular disease (13.2%), and retinopathy (12.5%). The majority of patients (63.8%) were treated with insulin, 17.5% were treated with noninsulin medications, and 18.7% were receiving no glucose-lowering medications upon cohort entry (Table 1).

Incidence Rates of Hypoglycemic Crises
Over the study period, 7.9% (n = 41,298) of patients experienced at least one hypoglycemic crisis, with an overall adjusted incidence rate of 53.64 (95% CI 52.9–54.4) per 1,000 person-years. Adjusted incidence rates of hypoglycemic crises declined between 2013 and 2017 from 64.5 to 45.13 per 1,000 person-years (P_trend < 0.01) (Fig. 1). Rates of hypoglycemic crises varied by patient age, sex, race/ethnicity, modality of dialysis, and U.S. census region (Fig. 2A). Younger patients (18–44 years of age) had the highest adjusted incidence of hypoglycemic crises, with 120.07 events (95% CI 114.84–125.30) per 1,000 person-years, compared with 42.07 events per 1,000 person-years among patients ≥75 years old. Women had a higher adjusted incidence rate of hypoglycemia compared with men: 56.26 (55.22–57.31) per 1,000 person-years vs. 51.57 (50.62–52.52) per 1,000 person-years. Non-Hispanic Black patients had the highest adjusted incidence rate of hypoglycemia at 60.02 (58.62–61.42) per 1,000 person-years among patients ≥75 years old. Women had a higher adjusted incidence rate of hypoglycemia compared with men: 56.26 (55.22–57.31) per 1,000 person-years vs. 51.57 (50.62–52.52) per 1,000 person-years. Non-Hispanic Black patients had the highest adjusted incidence rate of hypoglycemia at 60.02 (58.62–61.42) per 1,000 person-years, compared with 54.01 (52.91–55.10) for non-Hispanic White patients and 46.32 (95% CI 44.90–47.73) for Hispanic patients.

Risk Factors for Hypoglycemic Crises
The risk of experiencing hypoglycemic crises was higher for younger, female, and Black patients; patients using insulin therapy; patients in the Southern geographic region; patients on hemodialysis; and patients with some comorbidities (Table 2). In comparisons with younger patients (age 18–44 years), the IRR of experiencing a hypoglycemic crisis among patients aged 45–64, 65–74, and ≥75 years was 55% (IRR 0.46, 95% CI 0.43–0.47), 64% (0.36, 0.34–0.38), and 65% (0.35, 0.33–0.37) lower, respectively. Women had 9% higher risk of hypoglycemic

### Table 1—Study population

| Patients with diabetes and ESKD on dialysis | Age, years, median (IQR) | 65.0 (57.0–73.0) |
|-------------------------------------------|--------------------------|------------------|
| Age, years, category | 18–44 | 34,761 (6.7) |
|                           | 45–64 | 203,022 (38.9) |
|                           | 65–74 | 167,810 (32.2) |
|                           | ≥75   | 116,196 (22.3) |
| Sex | Female | 229,210 (43.9) |
|                          | Male  | 292,579 (56.1) |
| Race/ethnicity | White | 239,821 (46.0) |
|               | Black | 149,643 (28.7) |
|               | Hispanic | 97,887 (18.8) |
|               | Asian | 20,077 (3.8) |
|               | American Indian or Alaska Native | 6,993 (1.3) |
|               | Native Hawaiian or Pacific Islander | 6,493 (1.2) |
| U.S. region | Midwest | 101,239 (19.4) |
|             | Northeast | 78,091 (15.0) |
|             | South | 224,293 (43.0) |
|             | West | 109,089 (20.9) |
|             | Unknown/missing | 9,077 (1.7) |
| Dialysis modality | Hemodialysis | 480,559 (92.1) |
|                 | Peritoneal Dialysis | 41,230 (7.9) |
| Comorbidities | Substance abuse | 7,125 (1.4) |
|               | Tobacco use | 27,005 (5.2) |
|               | Hypertension | 466,125 (89.3) |
|               | ASCVD | 94,709 (18.2) |
|               | HF | 169,762 (32.5) |
|               | Cerebrovascular disease | 49,680 (9.5) |
|               | Retinopathy | 65,433 (12.5) |
|               | Amputations | 22,718 (4.4) |
|               | Peripheral vascular disease | 68,674 (13.2) |
| Glucose-lowering agents | Insulin | 333,050 (63.8) |
|                         | Noninsulin agents | 91,090 (17.5) |
|                         | No pharmacological therapy | 97,649 (18.7) |
| Index year | 2013 | 271,875 (52.1) |
|             | 2014 | 59,123 (11.3) |
|             | 2015 | 61,953 (11.9) |
|             | 2016 | 64,176 (12.3) |
|             | 2017 | 64,662 (12.4) |

Data are presented as N (%) unless otherwise indicated.

and created with Stata, version 16.0 (StataCorp).
crisis (IRR 1.09, 95% CI 1.06–1.12) compared with men. Risk of hypoglycemia was 11% higher in non-Hispanic Black patients (1.11, 1.08–1.15) and 14% lower in Hispanic patients (0.86, 0.83–0.89), compared with non-Hispanic White patients. Compared with patients treated with insulin (selected as the reference group), as insulin is the traditional modality of glycemic control in the setting of ESKD, patients treated with non-insulin medications had 34% lower risk (0.66, 0.64–0.69), while patients treated with lifestyle therapy only had a 40% lower risk (0.60, 0.59–0.63). Tobacco use, substance abuse, history of amputation, retinopathy, peripheral vascular disease, and cerebrovascular disease were comorbidities associated with higher risk (Table 2).

Incidence Rates of Hyperglycemic Crises

During the study period, 1.8% (n = 9,501) of patients experienced at least one hyperglycemic crisis, with an overall adjusted incidence rate of 18.24 events per 1,000 person-years. Adjusted incidence rates of hyperglycemic crises declined between 2013 and 2017, from 21.87 to 15.93 events per 1,000 person-years (P_trend < 0.01) (Fig. 1).

Rates of hyperglycemic crises varied by patient age, sex, race/ethnicity, modality of dialysis, and U.S. region (Fig. 2B). Patients 18–44 years of age had the highest adjusted incidence of hyperglycemia crises: 102.38 events (95% CI 98.07–106.70) per 1,000 person-years compared with 2.6 events (2.3–2.9) per 1,000 person-years among patients ≥75 years old. The adjusted rate of hyperglycemia among women was 22.15 (95% CI 21.40–22.91) per 1,000 person-years, compared with 15.4 (14.9–15.9) in men. Non-Hispanic White patients had the highest adjusted incidence rate of hyperglycemia at 23.05 (22.2–23.9) events per 1,000 person-years compared with 19.8 (18.9–20.6) in non-Hispanic Black patients and 10.6 (9.9–11.3) in Hispanic patients.

The IRR of experiencing a hyperglycemic crisis was higher for younger, female, and White patients; those using insulin therapy; by regions; and patients with comorbidities (Table 2). In comparisons with younger patients (age 18–44 years), frequency of hyperglycemia crises was 82% (IRR 0.18, 95% CI 0.16–0.19), 95% (0.05, 0.04–0.05), and 97% (0.03, 0.02–0.03) lower among patients 45–64, 65–74, and ≥75 years old, respectively. Women had 44% higher (IRR 1.44, 95% CI 1.35–1.54) risk of developing hyperglycemia crises compared with males. Frequency of hyperglycemia crises was 14% lower (0.86, 0.80–0.92) among Black patients and 54% lower (0.46, 0.42–0.51) among Hispanic patients, compared with non-Hispanic White patients. Compared with patients treated with insulin, patients treated with noninsulin medications had 72% lower risk of hyperglycemic crises (IRR 0.28, 95% CI 0.25–0.32), while patients treated with lifestyle therapy had a 56% lower risk (0.46, 0.39–0.48). Tobacco use, substance abuse, and history of retinopathy were comorbidities associated with higher risk of hyperglycemic crises (Table 2).

CONCLUSIONS

In this nationwide study of patients with diabetes/ESKD in the U.S., severe hypoglycemic and hyperglycemic crises were both common, though rates of severe hypoglycemia were almost three-fold higher than rates of hyperglycemia. Even though these events are preventable, young, Black patients and women experienced a disproportionate burden of both crises. Additional risk factors for both glycemic crises were treatment with insulin, smoking, substance abuse, and retinopathy, reinforcing the need for timely identification of individuals at risk and preventing these potentially fatal events.

The reported rates of severe hypoglycemia are higher than previous reports for high-risk populations, including elderly patients (16), elderly patients with long-standing (~40 years) type 1 diabetes (17), patients with long-standing (~15 years) type 2 diabetes treated with complex insulin regimens (18), and patients with diabetes and nondialysis CKD (14). Advanced kidney disease is an established risk factor for severe hypoglycemia (6), but most studies have not differentiated susceptibility for severe hyperglycemia and hyperglycemia by severity of CKD. Additionally, the epidemiology of severe hypoglycemia and its risk factors...
Figure 2—Crude and adjusted rates of hypoglycemia (A) and hyperglycemia (B) crises among patients with diabetes and ESKD on dialysis, by race/ethnicity, sex, age, U.S. region, and dialysis modality.
Table 2—Risk factors for hypoglycemia and hyperglycemia crises among patients with diabetes and ESKD on dialysis: 2013–2017

| Race/ethnicity                        | Hypoglycemia IRR (95% CI) P | Hyperglycemia IRR (95% CI) P |
|---------------------------------------|-----------------------------|-----------------------------|
| White                                  | 1.00 (0.97–1.03) <0.001     | 0.88 (0.84–0.92) <0.001     |
| Black                                  | 1.09 (1.06–1.12) <0.001     | 1.44 (1.35–1.54) <0.001     |
| Hispanic                               | 1.09 (1.06–1.12) <0.001     | 1.46 (1.37–1.55) <0.001     |
| Asian                                  | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| American Indian or Alaska Native      | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| Native Hawaiian or Pacific Islander    | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| Hispanic                               | 1.09 (1.06–1.12) <0.001     | 1.44 (1.35–1.54) <0.001     |
| Asian                                  | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| American Indian or Alaska Native      | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| Native Hawaiian or Pacific Islander    | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| Hispanic                               | 1.09 (1.06–1.12) <0.001     | 1.44 (1.35–1.54) <0.001     |
| Asian                                  | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| American Indian or Alaska Native      | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| Native Hawaiian or Pacific Islander    | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| Hispanic                               | 1.09 (1.06–1.12) <0.001     | 1.44 (1.35–1.54) <0.001     |
| Asian                                  | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| American Indian or Alaska Native      | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| Native Hawaiian or Pacific Islander    | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| Hispanic                               | 1.09 (1.06–1.12) <0.001     | 1.44 (1.35–1.54) <0.001     |
| Asian                                  | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| American Indian or Alaska Native      | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| Native Hawaiian or Pacific Islander    | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| Hispanic                               | 1.09 (1.06–1.12) <0.001     | 1.44 (1.35–1.54) <0.001     |
| Asian                                  | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| American Indian or Alaska Native      | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| Native Hawaiian or Pacific Islander    | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| Hispanic                               | 1.09 (1.06–1.12) <0.001     | 1.44 (1.35–1.54) <0.001     |
| Asian                                  | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| American Indian or Alaska Native      | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| Native Hawaiian or Pacific Islander    | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| Hispanic                               | 1.09 (1.06–1.12) <0.001     | 1.44 (1.35–1.54) <0.001     |
| Asian                                  | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| American Indian or Alaska Native      | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| Native Hawaiian or Pacific Islander    | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| Hispanic                               | 1.09 (1.06–1.12) <0.001     | 1.44 (1.35–1.54) <0.001     |
| Asian                                  | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| American Indian or Alaska Native      | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |
| Native Hawaiian or Pacific Islander    | 1.10 (1.07–1.13) <0.001     | 1.47 (1.38–1.56) <0.001     |

Ref, referent. *Control group.

has been mostly derived from single-center studies (19,20). In a study of commercially insured and Medicare Advantage beneficiaries, ESKD was strongly associated with severe hypoglycemia, with patients with diabetes/ESKD experiencing 43.35 episodes/1,000 person-years vs. 9.06 in the general population. However, patients with ESKD represented only 1.5% of that study’s sample (14). Our study therefore adds nationally representative data for a diverse population of patients on maintenance dialysis, allowing us to both capture the full burden of hypoglycemic (and hyperglycemic) crises in this population and to identify key geographic, demographic, and clinical subgroups of patients at highest risk.

While rates were lower than hypoglycemic rates, DKA/HHS episodes were also common in patients with diabetes/ESKD. Prior to this work, there was limited evidence on hyperglycemic crises among patients with diabetes/ESKD. In a recent study of privately insured and Medicare Advantage beneficiaries with diabetes, of whom ~20% had nephropathy (ESKD not reported separately), the adjusted rate of DKA/HHS was 17.73 per 1,000 person-years among patients with type 2 diabetes.
diabetes requiring intensive insulin therapy (21). Consistent with our study, young and Black patients faced the higher risk of hyperglycemic crises (21). Awareness of patients’ susceptibility to hyperglycemic crises is important, as patients with diabetes on hemodialysis experiencing DKA/ HHS can present with minimal symptoms and volume overload, rather than volume depletion, since osmotic diuresis does not occur (7,8). While the cause for these high rates is likely multifactorial, one hypothesis is that the focus on preventing hypoglycemia has resulted in substandard glycemic control and, ultimately, severe hyperglycemia. Finally, medication—particularly insulin—nonadherence, whether intentionally skipped on dialysis days when oral intake can be minimal, due to cost-related rationing, or unintentional, can lead to preventable severe hyperglycemia.

We found that 63.8% of this national cohort of patients were treated with insulin, which was associated with an increased risk of hypoglycemic and hyperglycemic crises by 34% and 72%, respectively, compared with treatment with noninsulin agents. Increasing evidence indicates that some patients with diabetes/ESKD may be treated safely with non-insulin glucose-lowering agents with lower risk of hypoglycemia, including glucagon-like peptide 1 receptor agonists and select dipeptidyl peptidase 4 inhibitors (6). However, cost is a major barrier, even for insured patients. Older adults with Medicare Advantage plans are less likely to be treated with glucagon-like peptide 1 receptor agonists and dipeptidyl peptidase 4 inhibitors compared with those with private insurance, with greater disparities among low-income patients (22).

Optimized glycemic monitoring can prevent hypoglycemic and hyperglycemic crises requiring ED or hospital care. Continuous glucose monitoring (CGM) with predictive hypoglycemia and hyperglycemia alarms may be especially important in this population susceptible to wide glycemic fluctuations (3,6,23). Several studies have shown that CGM can improve glycemic control and decrease hypoglycemia and hyperglycemia (23–25). In a recent nationwide study in France, CGM use resulted in 40–50% decrease in hospitalization for acute glycemic crises in patients with type 1 and type 2 diabetes (26). However, the evidence with factory-calibrated sensors is very limited in the dialysis population (6,23). Unfortunately, CGM use among patients with type 2 diabetes remains limited and is often cost prohibitive. Since hemoglobin A1c is not a reliable indicator in patients on dialysis and self-monitored glucose monitoring is limited (3), it is important to validate newer CGMs in this population, in order to make timely treatment decisions and prevent severe hyperglycemia and hypoglycemia. Additionally, high-risk diabetes/ESKD patients would benefit from greater availability of Certified Diabetes Care and Education Specialists (CDCES), focusing on recognizing, treating, and preventing hypoglycemia and hyperglycemia and on restoring impaired hypoglycemia awareness. Dialysis centers may consider creating multidisciplinary clinics, modeled after transplant centers, that incorporate CDGES and/or clinical pharmacists to allow for timely treatment modification. Finally, it is important for insulin-treated patients with diabetes/ESKD to be able to use glucagon and be educated on sick day rules.

We found that younger adults had the highest rates of both hypoglycemic and hyperglycemic crises. This population is particularly vulnerable because they must manage their diabetes and ESKD in the context of other life demands, like family, education, and employment. In addition, they are most likely to have type 1 diabetes, end-stage diabetes—related complications, and/or childhood causes of ESKD, representing a group with high-complexity disease severity. Consistent with prior work in non-ESKD populations (14,27), Black patients had the highest rates of severe hypoglycemic crises, which is also consistent with prior studies demonstrating disparities in diabetes health outcomes that may be related to poor access to care and/or quality of medical services, food insecurity, and inability to access brand-name noninsulin or analog insulin medications that pose a lower risk of hypoglycemia (27–29). We also found no association between the modality of dialysis (i.e., hemodialysis or peritoneal dialysis) and severe hypoglycemic or hyperglycemic events. This may be the result of selection bias, whereby patients with highest risk for glycemic excursions are preferentially treated with hemodialysis; still, our findings suggest that peritoneal dialysis may not be inferior to hemodialysis for these patients.

Limitations
This study has some limitations. We relied on retrospective USRDS data, which does not include factors that may have precipitated crises such as illness, medication errors, food insecurity, hypoglycemia unawareness, and others. We did not have access to information on social determinants of health, which may explain the observed disparities by age, sex, race/ethnicity, and region. We also were not able to differentiate the diabetes type, as this information is not available in USRDS, and we were not able to capture severe hypoglycemic events that do not require ED care or hospitalization. Thus, our findings likely underestimate the incidence of severe hypoglycemia. In addition, we did not assess for differences between center and home dialysis modality but found no differences between hemodialysis (HD) and peritoneal dialysis (PD) more broadly.

In summary, in this nationwide study of patients with diabetes/ESKD, we identified higher rates of hypoglycemic and hyperglycemic crises than previously reported in other non-ESKD high-risk populations. Younger patients, women, and non-Hispanic Blacks experienced the highest rates of severe hypoglycemia, and young patients and women also bore a disproportionate share of severe hyperglycemic events. Our results confirmed that patients with diabetes/ESKD are vulnerable to large glycemic excursions and that the current standard of care for glycemic monitoring and treatment for this population is far from optimal. For patients already bearing high morbidity, mortality, and health care use burdens, these data represent a call for action for innovative and personalized strategies that can decrease these preventable—and in many cases iatrogenic—acute diabetes complications in this population. A multidisciplinary management team, including endocrinologists/diabetologists, pharmacists, and CDGES, and use of CGM should be incorporated in dialysis centers to help prevent these avoidable acute glycemic complications.

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