Incidence of Uncommon Clinical Events in USA Patients with Dialysis-Dependent and Nondialysis-Dependent Chronic Kidney Disease: Analysis of Electronic Health Records from TriNetX

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Keywords

Chronic kidney disease · Observational cohort study · Clinical outcomes · Nondialysis-dependent · Dialysis-dependent

Abstract

Introduction: Further understanding of adverse clinical events in patients with chronic kidney disease (CKD) is needed. This study aimed to describe characteristics of patients with nondialysis-dependent (NDD) and dialysis-dependent (DD) CKD and to assess incidence rates of uncommon adverse clinical events of interest in these patients. **Methods:** This retrospective study used electronic medical record data from USA CKD patients (≥ 18 years) with estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² between January 1, 2010, and December 31, 2018, obtained from the USA-based TriNetX database. NDD-CKD and DD-CKD were diagnosed and staged from ≥ 2 consecutive eGFR readings, recorded ≥ 90 days apart. Dialysis was identified using procedure codes for renal replacement therapy. Outcomes assessed were select uncommon adverse clinical events, defined by International Classification of Disease, 9th and 10th Revision codes. **Results:** Incidence rates of adverse clinical

events per 100 person-years (95% confidence interval) were generally higher in patients with DD-CKD versus NDD-CKD. Differences were particularly pronounced for hyperkalemia (26.9 [26.2–27.6] vs. 4.5 [4.5–4.6]), acidosis (15.1 [14.7–15.6] vs. 3.4 [3.4–3.4]), and sepsis (14.6 [14.2–15.1] vs. 3.3 [3.3–3.4]). Among DD-CKD patients, incidence rates of adverse events were particularly high during the first 3 months following dialysis initiation. Incidence of adverse clinical events generally increased with decreasing eGFR among patients with NDD-CKD and with hemoglobin < 10 g/dL in both NDD- and DD-CKD patients. **Conclusions:** Our results help establish baseline rates of uncommon adverse clinical events and provide additional evidence of increased morbidity for patients with DD-CKD versus NDD-CKD.

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Introduction

Chronic kidney disease (CKD) is defined by reduced kidney function and is prevalent in individuals with diabetes, hypertension, and obesity [1]. CKD is associated with an increased risk of cardiovascular disease (CVD) and all-cause mortality, as well as with decreased quality

of life, when compared with the general population [1–3]. Other complications associated with CKD include anemia and metabolic bone disease, which increase in prevalence as kidney function declines [2, 4, 5].

Although highly important for improving the care of patients with CKD, well-designed clinical trials in nephrology are less common versus other specialties [6]. Moreover, patients with severe CKD are often excluded from randomized controlled trials in related indications, perhaps due to the high rates of adverse events in this population [7]. An analysis of randomized trials of cardiovascular interventions showed that patients with CKD were excluded from 212 (57.1%) of 371 trials identified [7]. Even studies of unselected CKD cohorts tend to include mostly patients with moderate CKD [8], meaning that findings do not adequately represent patients with severe CKD (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m²).

The lack of understanding of adverse event rates in patients with CKD can limit the ability of dialysis organizations, government agencies, other institutions, and payers to fully assess quality of care, potentially hindering patient counseling and patient education and impairing the development and delivery of innovative therapies to patients. Further description, quantification, and contextualization of adverse event rates in patients with CKD are, therefore, urgently needed. This study used USA-based data obtained from the TriNetX global research network to (1) describe the characteristics of patients with CKD (nondialysis-dependent [NDD] and dialysis-dependent [DD]) and (2) assess the rates of adverse clinical events in USA patients with NDD- and DD-CKD, stratified by eGFR at baseline in patients with NDD-CKD.

Materials and Methods

Study Design

This was a retrospective, noninterventive cohort study of patients with CKD (eGFR <60 mL/min/1.73 m²). The study protocol was performed in accordance with the International Conference on Harmonization Good Clinical Practice and the Declaration of Helsinki and the applicable legislation on noninterventive studies and/or observational studies.

The data source used for this study was TriNetX [9, 10], a novel, global federated research network which integrates a wide array of data from over 130 major health-care institutions worldwide, including academic medical centers, specialty hospitals, specialty physician practices, and community hospitals, collectively referred to as Health-Care Organizations (HCOs). Available data span multiple geographic regions, age-groups, and income levels. TriNetX aggregates information directly from electronic medical record (EMR) systems on a continuous basis. Data available for anal-

ysis includes patient demographics, diagnosis history, medications administered and prescribed, procedures performed, laboratory measures, and vital signs. The present analysis utilized a dataset comprising approximately 38 million patients in 35 health-care organizations in the USA.

Patient Population

Key inclusion criteria were adults (≥18 years) with CKD defined by ≥2 consecutive (≥90 days apart) eGFR measurements of <60 mL/min/1.73 m² recorded between January 1, 2010 and December 31, 2018. eGFR values were calculated from serum creatinine values, using the CKD epidemiology collaboration equation [11]. Patients with a history of renal transplantation and those with a life expectancy of <6 months (death within the first 6 months of the index date) were excluded.

The index date was defined as the date of the second eGFR measurement that satisfied the inclusion criteria and succeeded the first eGFR measurement by ≥90 days. While the first eGFR measurement could occur before 2010, the index date must have fallen on or after January 1, 2010. The study end date was defined as the earliest of last recorded patient encounter, date of death, or end of data coverage period on or before December 31, 2018.

Patients were stratified according to dialysis status (at the index date or during follow-up), with DD-CKD patients defined as those with an initial Current Procedural Terminology (CPT) code for dialysis, either at the index date or during follow-up (see online suppl. Text 1; for all online suppl. material, see www.karger.com/doi/10.1159/000516280). Incident dialysis was defined as a code for dialysis at least 1 year after the index date. For those with incident dialysis, we assessed adverse events within the first 3–6 months following the dialysis date. Data extracted included all available demographic and medical history information for up to 5 years prior to the index date and the results of laboratory investigations in the 1 year prior to the index date. In the event of multiple/different entries, the entry closest to the index date was used.

Study Outcomes

The outcomes investigated in this study were adverse clinical events, most of which are uncommon and cannot be studied in randomized trials with a high degree of precision. Adverse clinical events were defined by the presence of at least one relevant International Classification of Disease, 9th and 10th Revision (ICD-9, ICD-10) code (online suppl. Table 1), in either inpatient or outpatient encounters. The following events of interest were assessed: sepsis (broad definition included sepsis, septicemia, and bacteremia), urinary tract infection, gastrointestinal hemorrhage, hypoglycemia, pancreatitis, acidosis, hyperkalemia, rhabdomyolysis (broad definition included rhabdomyolysis and myalgia), severe cutaneous adverse reactions, pure red cell aplasia, tachycardia, thyroid events, pneumonia and lower respiratory infection, hepatic events, seizure (broad definition included seizure and transient alteration of awareness), retinal events, and allergic and anaphylaxis events. Incidence of adverse clinical events was reported by baseline eGFR value (only for patients with NDD-CKD) and by CKD status (NDD- or DD-CKD). Specific tachycardia and thyroid events were also assessed as a supplementary analysis in patients with NDD-CKD and DD-CKD; ICD-9 and ICD-10 codes are provided in online suppl. Table 1.

Table 1. Baseline patient characteristics

Characteristics	NDD-CKD (n = 470,807)	DD-CKD ^a (n = 21,334)	DD-CKD ^b (n = 21,334)	Incident dialysis (n = 6,214)
Male, n (%)	200,990 (42.7)	12,057 (56.5)	12,057 (56.5)	3,392 (54.6)
Mean age, years (SD)	69.4 (11.7)	58.1 (14.4)	57.1 (14.3)	60.1 (14.0)
CKD stage, n (%)				
G3a/G3b (eGFR 30–59 mL/min/1.73 m ²)	398,310 (84.6)			
G4 (eGFR 15–29 mL/min/1.73 m ²)	46,177 (9.8)	N/A	N/A	N/A
G5 (eGFR <15 mL/min/1.73 m ²)	26,320 (5.6)			
eGFR, median (IQR), mL/min/1.73 m ²	48.0 (37.1–54.7)	N/A	N/A	N/A
BMI, median (IQR), kg/m ²	28.6 (25.0–32.6)	27.6 (23.7–32.1)	28.0 (24.0–32.5)	28.0 (24.0–33.0)
Systolic BP, median (IQR), mm Hg	130.0 (118.0–142.0)	130.0 (113.0–147.0)	135.0 (118.0–152.0)	130.0 (112.0–146.0)
Diastolic BP, median (IQR), mm Hg	72 (64.0–80.0)	69.0 (60.0–80.0)	73.0 (63.0–83.0)	68.0 (58.0–78.0)

Among the 492,141 patients in the study cohort, there were no missing data for sex, age, and eGFR. The proportion of missing data was 43.1, 34.0, and 34.1% for BMI, systolic BP, and diastolic BP, respectively. BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; DD, dialysis-dependent; eGFR, estimated glomerular filtration rate; G, grade; IQR, interquartile range; N/A, not applicable; NDD, nondialysis-dependent; SD, standard deviation. ^a Dialysis date as index date. ^b CKD diagnosis as index date.

Statistical Analyses

This was a descriptive analysis without formal hypothesis testing. Summary statistics included the number of patients, mean, standard deviation, median, and 25th and 75th percentile values. Results are presented for NDD-CKD and DD-CKD populations, as well as for prespecified patient subpopulations.

Incidence rates of adverse clinical events of interest were calculated as the number of patients with events occurring during patient follow-up time at risk (the time in years in the study until the first event or loss to follow-up, whichever came first), divided by the total follow-up time in person-years (P-Y). Incidence rates were reported per 100 P-Y. Patients who commenced dialysis after the index date contributed person-time to both NDD- and DD-CKD cohorts, using dialysis date to split person-time into NDD-CKD and DD-CKD cohorts. Patients with NDD-CKD were censored at the point at which they commenced dialysis. Analyses assumed that patients who initiated dialysis remained on it throughout the entire observation period. For patients with NDD-CKD, incidence rates were stratified by CKD stage at baseline regardless of subsequent eGFR value during follow-up.

Sensitivity analyses were conducted in select higher risk patient populations. These included:

1. Analysis of patients with incident dialysis (outcomes were assessed within 3 and 6 months of incident dialysis, with adjustments made for patient attrition between the 3- and 6-month timepoints), given the high mortality rate observed in patients within 6 months of commencing dialysis.
2. The analysis of patients with baseline (at index date) hemoglobin (Hb) <10 g/dL, the Hb level recommended as the threshold for consideration of treatment with erythropoiesis-stimulating agents (ESAs) by Kidney Disease: Improving Global Outcomes guidelines [2].
3. Analysis of patients with baseline Hb <10 g/dL by dialysis status.
4. A time-varying analysis of eGFR stage, in which patients were reclassified into lower/more severe eGFR categories if eGFR

worsened (confirmed by 2 eGFR values ≥ 3 months apart) in order to account for CKD progression over time. For this analysis, patients could contribute time at risk in more than one subgroup. All analyses for this study were performed using Stata version 15 (StataCorp LP, College Station, TX, USA).

Results

Baseline Characteristics

A patient selection flowchart is shown in Figure 1. In total, 492,141 patients with CKD were identified from the TriNetX database: 470,807 patients with NDD-CKD and 21,334 patients with DD-CKD at baseline or during follow-up. Among patients with DD-CKD, there were 6,214 incident dialysis patients. Median (interquartile range) duration of follow-up was 2.0 (0.7–4.0) years for NDD-CKD, 2.6 (1.0–4.4) years for DD-CKD, and 1.3 (0.4–2.6) years for incident dialysis patients.

Baseline characteristics are summarized by dialysis status in Table 1 and overall in online suppl. Table 1. Compared with patients with NDD-CKD, patients with DD-CKD were younger (mean [standard deviation] age: 57.1 [14.3] vs. 69.4 [11.7] years) and more likely to be male (percentage of males in cohort: 56.5 vs. 42.7%).

Baseline Comorbidities, Medication Use, and Laboratory Investigations

Baseline patient comorbidities are summarized by dialysis status in Table 2 and overall in online suppl. Table 2. In general, comorbidities were more common in pa-

Fig. 1. Flow diagram of patient selection from TriNetX database. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate. ^aMeasurements were not necessarily consecutive.

tients with DD-CKD, both at the point of dialysis and index date, than in those with NDD-CKD. The most prevalent comorbidities were hypertension (78.4 and 91.8% of patients with NDD-CKD and DD-CKD, respectively), dyslipidemia (61.7 and 51.7% of patients with

NDD-CKD and DD-CKD, respectively), and diabetes (mainly type 2; 39.0 and 59.9% of patients with NDD-CKD and DD-CKD, respectively).

Cardiovascular comorbidities, in addition to hypertension, included coronary artery disease (29.6 and 39.6%

Table 2. Baseline comorbidities by dialysis status

Comorbidity, <i>n</i> (%)	NDD-CKD (<i>n</i> = 470,807)	DD-CKD ^a (<i>n</i> = 21,334)	DD-CKD ^b (<i>n</i> = 21,334)	Incident dialysis (<i>n</i> = 6,214)
Hypertension	368,990 (78.4)	20,669 (96.9)	19,579 (91.8)	6,137 (98.8)
Dyslipidemia	290,373 (61.7)	13,062 (61.2)	11,028 (51.7)	4,660 (75.0)
Diabetes (type 1 and 2)	183,604 (39.0)	13,661 (64.0)	12,779 (59.9)	4,370 (70.3)
Coronary artery disease	139,386 (29.6)	10,629 (49.8)	8,438 (39.6)	3,518 (56.6)
Peripheral vascular disease	78,100 (16.6)	8,140 (38.2)	5,943 (27.9)	2,926 (47.1)
Atrial fibrillation/flutter	77,320 (16.4)	4,779 (22.4)	3,465 (16.2)	1,575 (25.4)
Cardiac valve disease	68,676 (14.6)	6,852 (32.1)	4,876 (22.9)	2,471 (39.8)
Diabetic kidney disease	48,282 (10.3)	10,577 (49.6)	7,852 (36.8)	3,722 (59.9)
Myocardial infarction	47,357 (10.1)	4,495 (21.1)	3,136 (14.7)	1,614 (26.0)
Stroke	26,628 (5.7)	2,375 (11.1)	1,691 (7.9)	913 (14.7)
Angina	19,326 (4.1)	1,480 (6.9)	1,009 (4.7)	634 (10.2)
Obstructive uropathy	18,721 (4.0)	1,532 (7.2)	1,021 (4.8)	675 (10.9)
Deep vein thrombosis	14,492 (3.1)	2,031 (9.5)	1,425 (6.7)	652 (10.5)
Transient ischemic attack	14,080 (3.0)	801 (3.8)	576 (2.7)	345 (5.6)
Cystic kidney disease	9,004 (1.9)	1,485 (7.0)	1,144 (5.4)	562 (9.0)
Pulmonary embolism	9,427 (2.0)	668 (3.1)	489 (2.3)	232 (3.7)
Tobacco use	9,217 (2.0)	727 (3.4)	407 (1.9)	308 (5.0)
Percutaneous coronary intervention	5,320 (1.1)	564 (2.6)	291 (1.4)	239 (3.9)
Arterial embolism	4,390 (0.9)	782 (3.7)	561 (2.6)	268 (4.3)
Lupus nephritis	424 (0.1)	210 (1.0)	133 (0.6)	69 (1.1)
Coronary artery bypass graft	284 (0.1)	171 (0.8)	91 (0.4)	61 (1.0)
Chronic interstitial nephritis	187 (0.0)	54 (0.3)	23 (0.1)	25 (0.4)
Glomerulosclerosis	141 (0.0)	54 (0.3)	29 (0.1)	27 (0.4)
Minimal change disease	98 (0.0)	21 (0.1)	20 (0.1)	^c
IgA nephropathy	^c	^c	^c	^c
Renal artery stenosis	^c	^c	^c	^c

Baseline defined as within 5 years before the index date (date of CKD diagnosis). Presence of comorbidities was inferred from the presence of ICD-9/10 codes in EMRs. CKD, chronic kidney disease; EMR, electronic medical record. ^a Dialysis date as index date. ^b CKD diagnosis as index date. ^c *n* < 11 patients; percentage approximately zero.

of patients with NDD-CKD and DD-CKD, respectively), peripheral vascular disease (16.6 and 27.9% of patients with NDD-CKD and DD-CKD, respectively), and atrial fibrillation/flutter (16.4 and 16.2% of patients with NDD-CKD and DD-CKD, respectively). The prevalence of most comorbidities was higher among patients with incident dialysis than in the NDD-CKD and DD-CKD populations.

Baseline laboratory measures (taken within 1 year before the index date) are shown by dialysis status in Table 3. Patients with DD-CKD, particularly those with incident dialysis, had lower median levels of serum markers than those in patients with NDD-CKD: serum albumin (3.4, 3.1, and 3.8 g/dL in DD-CKD, incident dialysis, and NDD-CKD, respectively) and Hb (10.5, 9.1, and 12.5 g/dL, respectively); and higher serum ferritin (310.0, 270.5, and 126.0 ng/dL, respectively) and C-reactive protein val-

ues (2.5, 2.5, and 2.0 mg/dL, respectively). Baseline medication use, defined as medication use within 90 days before the patient index date, is summarized by dialysis status in online suppl. Table 3.

Adverse Clinical Events

Incidence Rates of Adverse Clinical Events Overall and by Dialysis Status

Overall incidence rates of the adverse clinical events assessed are summarized by dialysis status in Figure 2 and overall in online suppl. Figure 1. Compared with NDD-CKD, patients with DD-CKD had a higher incidence of most adverse clinical events. Incidence rates per 100 P-Y (95% confidence interval [CI]) of notable adverse clinical events include hyperkalemia (26.9 [26.2–27.6] in DD-CKD vs. 4.5 [4.5–4.6] in NDD-CKD), acidosis (15.1 [14.7–15.6] vs. 3.4 [3.4–3.4]), and sepsis (broad) (14.6

Table 3. Baseline laboratory investigations

Laboratory parameter	NDD-CKD (<i>n</i> = 470,807)			DD-CKD ^a (<i>n</i> = 21,334)			DD-CKD ^b (<i>n</i> = 21,334)			Incident dialysis (<i>n</i> = 6,214)		
	<i>n</i> (%)	median	(IQR)	<i>n</i> (%)	median	(IQR)	<i>n</i> (%)	median	(IQR)	<i>n</i> (%)	median	(IQR)
Serum creatinine, mg/dL	470,803 (100.0)	1.3 (1.1–1.6)		21,193 (99.3)	5.3 (3.4–7.8)		21,334 (100.0)	4.4 (2.2–7.2)		6,073 (97.7)	5.0 (3.5–7.2)	
Hemoglobin, g/dL	406,165 (86.3)	12.5 (11.0–13.9)		20,918 (98.1)	9.6 (8.4–11.0)		20,438 (95.8)	10.5 (9.2–11.8)		6,045 (97.3)	9.1 (8.2–10.4)	
Serum bicarbonate, mmol/L	380,807 (80.9)	26.0 (23.0–28.0)		19,688 (92.3)	25.0 (22.0–27.2)		19,589 (91.8)	25.0 (22.0–27.5)		5,658 (91.1)	24.0 (21.9–27.0)	
Serum potassium, mmol/L	386,302 (82.1)	4.2 (3.9–4.6)		19,724 (92.5)	4.3 (3.9–4.7)		19,634 (92.0)	4.3 (3.9–4.8)		5,680 (91.4)	4.2 (3.8–4.6)	
Serum albumin, g/dL	290,393 (61.7)	3.8 (3.4–4.1)		17,012 (79.7)	3.2 (2.6–3.7)		16,096 (75.5)	3.4 (2.9–3.8)		5,020 (80.8)	3.1 (2.6–3.5)	
LDL-C, mg/dL	207,664 (44.1)	91.0 (70.0–118.0)		6,967 (32.7)	78.0 (57.0–107.0)		6,604 (31.0)	85.0 (62.0–114.0)		2,436 (39.2)	79.7 (57.0–107.2)	
Cholesterol, mg/dL	192,705 (40.9)	168.0 (140.0–199.0)		8,655 (40.6)	149.0 (119.0–185.0)		8,252 (38.7)	157.0 (126.0–195.0)		2,794 (45.0)	151.0 (120.0–187.0)	
Serum triglyceride, mg/dL	182,312 (38.7)	129.0 (93.0–184.0)		8,074 (37.9)	124.0 (88.0–183.0)		7,645 (35.8)	129.0 (91.0–192.0)		2,658 (42.8)	128.0 (89.0–185.0)	
HDL-C, mg/dL	174,228 (37.0)	45.0 (36.5–56.0)		7,866 (36.9)	39.0 (30.0–49.0)		7,402 (34.7)	39.0 (31.0–50.0)		2,601 (41.9)	40.0 (32.0–50.0)	
HbA1c, %	169,474 (36.0)	6.4 (5.8–7.5)		11,261 (52.8)	6.2 (5.4–7.4)		10,114 (47.4)	6.4 (5.5–7.8)		3,682 (59.3)	6.3 (5.5–7.5)	
Serum phosphate, mg/dL	109,968 (23.4)	3.4 (2.9–4.0)		16,815 (78.8)	4.4 (3.4–5.6)		13,760 (64.5)	4.2 (3.4–5.3)		5,149 (82.9)	4.4 (3.4–5.5)	
Serum ferritin, ng/dL	46,407 (9.9)	126.0 (50.0–307.8)		8,722 (40.9)	337.0 (148.0–706.0)		6,328 (29.7)	310.0 (126.0–682.9)		3,116 (50.1)	270.5 (123.0–557.2)	
Serum iron, µg/dL	45,212 (9.6)	55.0 (34.0–80.0)		9,606 (45.0)	47.0 (31.0–70.0)		7,011 (32.9)	49.0 (32.0–72.0)		3,360 (54.1)	48.0 (31.0–70.0)	
Serum iron binding, µg/dL	41,606 (8.8)	295.0 (233.0–361.0)		7,668 (35.9)	220.0 (176.0–269.0)		5,635 (26.4)	226.0 (180.0–279.0)		2,648 (42.6)	232.0 (188.0–281.0)	
Serum urate, mg/dL	27,794 (5.9)	6.7 (5.4–8.2)		3,260 (15.3)	6.9 (5.2–8.8)		2,464 (11.6)	6.8 (5.1–8.7)		1,176 (18.9)	7.5 (5.8–9.0)	
Serum transferrin, mg/dL	20,152 (4.3)	220.0 (174.0–265.0)		5,592 (26.2)	165.0 (132.0–200.0)		3,683 (17.3)	168.0 (133.0–206.0)		2,027 (32.6)	172.0 (141.0–208.0)	
Serum C-reactive protein, mg/dL	22,073 (4.7)	2.0 (0.7–5.2)		1,748 (8.2)	2.7 (1.0–5.7)		1,430 (6.7)	2.5 (1.0–5.6)		596 (9.6)	2.5 (0.8–5.2)	

Baseline investigations within 1 year before the index date. Values recorded within 7 days after the index date are also included. Parathyroid hormones and urine albumin-to-creatinine ratio were not recorded. Among the 492,141 patients in the study cohort, the proportions of missing data for individual parameters were serum creatinine, 0%; hemoglobin, 13.3%; serum bicarbonate, 18.6%; serum potassium, 17.5%; serum albumin, 37.7%; LDL-C, 56.5%; cholesterol, 59.2%; serum triglyceride, 61.4%; HDL-C, 63.1%; HbA1c, 63.1%; serum phosphate, 74.9%; serum ferritin, 89.3%; serum iron, 89.4%; serum iron binding, 90.4%; serum urate, 93.9%; serum transferrin, 95.2%; and serum C-reactive protein, 95.2%. CKD, chronic kidney disease; DD, dialysis-dependent; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; NDD, nondialysis-dependent. ^a Dialysis date as index date. ^b CKD diagnosis as index date.

Fig. 2. Incidence rate of clinical adverse events per 100 P-Y by dialysis status. CI, confidence interval; CKD, chronic kidney disease; DD, dialysis-dependent; GI, gastrointestinal; NDD, nondialysis-dependent; P-Y, patient-years; UTI, urinary tract infection.

[14.2–15.1] vs. 3.3 [3.3–3.4]; Fig. 2). Incidence of specific tachycardia and thyroid events are summarized by dialysis status in online suppl. Table 4.

Incidence Rates of Adverse Clinical Events by Baseline eGFR

Among patients with NDD-CKD, the incidence of adverse clinical events generally increased with decreasing eGFR (Fig. 3). When comparing patients with eGFR 30–59 mL/min/1.73 m² and eGFR <15 mL/min/1.73 m², the difference in incidence per 100 P-Y (95% CI) was particularly evident for hyperkalemia (3.4 [3.3–3.4] vs. 18.7 [18.2–19.1]), acidosis (2.5 [2.4–2.5] vs. 13.0 [12.7–13.4]), and sepsis (broad) (2.7 [2.7–2.8] vs. 9.5 [9.2–9.8]).

Sensitivity Analyses

Incidence Rates of Adverse Clinical Events in Incident Dialysis Patients

In the incident dialysis population, adverse event incidence rates per 100 P-Y (95% CI) during the first 3 months were generally higher than during the first 6 months following dialysis initiation. There were notable increases in hyperkalemia (60.5 [57.0–64.3] and 51.2 [48.9–53.6]), acidosis (42.2 [39.4–45.2] and 31.9 [30.2–33.7]), sepsis (broad) (35.1 [32.8–37.5] and 29.6 [28.1–31.1]), and sep-

sis (specific) (29.1 [27.1–31.4] and 24.1 [22.8–25.4]) at 3 months compared with 6 months (Fig. 4).

Incidence Rates of Adverse Clinical Events in Patients with Hb <10 g/dL

In total, 62,029 (12.6%) patients had Hb <10 g/dL at the index date: 54,100 (11.5%) and 7,929 (37.2%) patients with NDD-CKD and DD-CKD, respectively. Among patients with NDD-CKD, the incidence rates per 100 P-Y (95% CI) of hyperkalemia, acidosis, and sepsis (broad) were higher among those with Hb <10 g/dL than those with Hb ≥10 g/dL (13.5 [13.2–13.7] vs. 3.8 [3.8–3.9], 11.3 [11.1–11.5] vs. 2.8 [2.8–2.8], and 10.7 [10.5–10.9] vs. 2.7 [2.7–2.8], respectively) (Fig. 5a).

Among patients with DD-CKD, the incidence rates of hyperkalemia, acidosis, and sepsis (broad) were also higher among those with Hb <10 g/dL than in those with Hb ≥10 g/dL (32.4 [31.1–33.7] vs. 24.0 [23.2–24.8], 18.3 [17.4–19.1] vs. 13.5 [13.0–14.1], and 18.1 [17.3–19.0] vs. 12.9 [12.4–13.4], respectively) (Fig. 5b). Among patients with incident dialysis, the incidence rates of hyperkalemia, acidosis, and sepsis (broad) were comparable between patients with Hb <10 g/dL and patients with Hb ≥10 g/dL (22.9 [19.9–26.4] vs. 23.1 [21.5–24.9], 16.0 [13.6–18.7] vs. 14.4 [13.2–15.6], and 13.6 [11.8–15.6] vs. 13.7 [12.7–14.7], respectively) (Fig. 5c).

Fig. 3. Incidence rate of clinical adverse events per 100 P-Y by CKD stage in patients with NDD-CKD. CI, confidence interval; CKD, chronic kidney disease; DD, dialysis-dependent; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; NDD, nondialysis-dependent; P-Y, patient-years; UTI, urinary tract infection.

Fig. 4. Incidence rate of clinical adverse events per 100 P-Y in the incident dialysis population. CI, confidence interval; GI, gastrointestinal; P-Y, patient-years; UTI, urinary tract infection.

Fig. 5. Incidence rate of clinical adverse events per 100 P-Y (Hb <10 vs. Hb $\geq$ 10 g/dL) in patients with NDD-CKD (a), DD-CKD (b), and incident dialysis (c). CI, confidence interval; CKD, chronic kidney disease; DD, dialysis-dependent; GI, gastrointestinal; Hb, hemoglobin; NDD, nondialysis-dependent; P-Y, patient-years; UTI, urinary tract infection.

Reclassifying Patients into Lower/More Severe CKD Stages

In the analysis where patients with NDD-CKD were reclassified into lower/more severe eGFR categories upon eGFR worsening, the overall rates of adverse clinical events per 100 P-Y (95% CI) were comparable with those from the original analysis of incidence rates by CKD stage (data not shown).

Discussion

In this retrospective, noninterventional analysis, baseline comorbidities, and incidence of uncommon adverse clinical events (difficult to assess precisely in randomized trials) in patients with NDD-CKD and DD-CKD were examined. Rates of adverse clinical events were generally higher in patients with DD-CKD, particularly among those with incident dialysis, compared with NDD-CKD and higher during the first 3 months following dialysis initiation than during the first 6 months. Adverse clinical event rates generally increased with decreasing eGFR among patients with NDD-CKD and with Hb <10 g/dL in both NDD- and DD-CKD. To the best of our knowledge, this is the largest database study to date assessing adverse clinical events in the CKD population.

Characteristics of the patients with CKD in this study were generally consistent with those reported in the previous studies, which have included patients from general practitioner surgeries in the Renal Risk in Derby study ($N = 1,741$) [12]; a large population-based cohort of adults in Alberta, Canada ($N = 47,228$) [8]; patients in outpatient clinics in South Taiwan ($N = 1,463$) [13]; and patients in indigenous communities in northwest Ontario ($N = 16,170$) [14]. The most common comorbidities at baseline of patients with CKD in these studies were hypertension, dyslipidemia, and diabetes. Many comorbidities, including hypertension, diabetes, and coronary artery disease, were more common in patients with DD-CKD than in patients with NDD-CKD (91.8 vs. 78.4%, 59.9 vs. 39.0%, and 39.6 vs. 29.6%, respectively). The prevalence of hypertension, diabetes, and coronary artery disease was particularly high in patients with incident dialysis compared with the overall DD-CKD population (98.8, 70.3, and 56.6%, respectively, in patients with incident dialysis). Notably, an analysis from the Dialysis Outcomes and Practice Patterns Study further suggested that the presence of certain comorbidities, particularly coronary artery disease and diabetes, but not hypertension, were predictive of increased mortality risk in hemodialysis patients [15].

Overall medication use reflected the prevalence of comorbidities and higher prevalence of Hb <10 g/dL in patients with DD-CKD, with higher use of antihypertensive agents, insulin, and ESAs in patients with DD-CKD versus NDD-CKD. It should be noted that medication use at baseline may have been underreported in this study, as only medications prescribed in HCOs are captured in EMR records. Therefore, EMR medication data are likely to be skewed toward capturing medications administered to patients while under direct care. Use of ESAs is particularly likely to be underreported, due to these medications being ordered and administered by dialysis units outside of HCOs.

Compared with patients with NDD-CKD, the overall incidence of adverse clinical events was higher in patients with DD-CKD; this difference was notably marked for hyperkalemia, sepsis, and acidosis, where the incidence rates were at least four-fold higher in patients with DD-CKD versus NDD-CKD. This increased incidence of clinical outcomes again reflects the more severe disease and higher comorbidity burden of DD-CKD versus NDD-CKD. In particular, hyperkalemia and bacterial infections have been reported as being common in patients with DD-CKD [16, 17]; and metabolic acidosis is also common in patients with renal failure [18]. It should be noted that patients with DD-CKD are likely to undergo more frequent laboratory monitoring than those with NDD-CKD, which may increase the likelihood of detecting abnormalities in these patients.

We also observed a general increase in adverse clinical events with decreasing eGFR in patients with NDD-CKD. This finding concurs with data from a population-based study of 440,526 patients with CKD from UK Biobank [19]. Among the patients in this study, lower eGFR was associated with higher risk of CVD, all-cause mortality, fatal CVD, and development of end-stage kidney disease [19]. Other studies have noted similar associations between declining eGFR and increased incidence of adverse outcomes [3, 20], although most of the available data comprise event rates of mortality and major adverse CKD and CVD outcomes.

In both NDD- and DD-CKD patients, Hb <10 g/dL was generally associated with increased adverse clinical event rates, compared with the overall populations. The presence of anemia in CKD has been associated with an increased risk of adverse clinical outcomes previously, particularly with heart failure and mortality [21, 22]. However, data on less common adverse events, such as those assessed in the present study, have not been widely reported. These data cannot be used to conclude that anemia is the cause of the increased rates of adverse events in patients with Hb <10 g/dL relative to those with Hb $\geq$ 10 g/dL. The increased adverse event rates seen may reflect

differences in care provided, differences in severity of underlying disease or comorbidity, or other factors.

This study has several strengths, which include the large and geographically diverse USA CKD patient population, meaning that data are generalizable to USA patients. Advantages inherent to the TriNetX database include comprehensive reporting of laboratory-tested and clinical events and the granularity of the coding. Data in the TriNetX network are not limited to patients receiving health coverage from a private or public insurer, reducing the likelihood of participants being lost to follow-up if their insurer changes. There is also the possibility for TriNetX data to be linked with other data sources, although the data used in this study were not linked to any other source.

A limitation of this study, as with all retrospective studies using routinely collected data, is the dependency on the quality and completeness of the data recorded and how it was recorded in the database. In this respect, the TriNetX data were not collected specifically for research purposes, and data are limited to EMRs collected as per routine clinical practice with no additional chart review data available. As a result, there is potential for miscoding of diagnoses and clinical events, and ICD codes may, at times, lack the sensitivity necessary to detect all adverse events of interest.

The TriNetX network captures data based on the dates during which patients are receiving medical care, regardless of whether they are enrolled in a health insurance plan. Start and end dates were derived based on the first and last encounter with the patient (e.g., diagnosis, lab testing, or prescriptions) likely resulting in an underestimate of time at risk. This could potentially bias results such that the sample includes more patients with high comorbidity burden or patients with advanced disease. A further limitation is that TriNetX captures patient data only when the patient receives care at the participating HCOs. Care received in other settings would not be available for inclusion in this analysis. Loss to follow-up could potentially skew covariate distributions and occurrence of outcomes. It should also be noted that the HCOs contributing to TriNetX are mainly large academic centers, where patients may have different characteristics compared with other settings.

Additional study limitations include the assumption, with respect to some covariates, that no evidence of a disease meant that a patient did not have that disease, which may not be accurate. Some known risk factors may not be recorded in the data or are not recent. Medication use was generally underrecorded, and there was an inability to verify whether the prescribed medication was taken by the patient. The presence of CKD was defined using standard eGFR-based criteria for CKD diagnosis and staging,

including requirement for ≥ 2 eGFR values < 60 mL/min/1.73 m², ≥ 90 days apart. These criteria were developed to minimize misclassification of acute kidney injury (AKI) events as CKD. Although it is theoretically possible that some patients could have been included in the cohort due to recurrent AKI events, it is considered unlikely that this was the case for a meaningful number of patients.

Mortality was also poorly captured in the database, as only deaths occurring at the point of care within the network were captured. Therefore, mortality was not included as an outcome in this study. Finally, as the presence of dialysis was defined based on patients having at least one relevant CPT code, the possibility that some DD-CKD patients may have received acute rather than chronic dialysis during the study cannot be excluded. Efforts were made to minimize this possibility through careful selection of CPT codes that were expected to be used only in the setting of chronic dialysis; however, it is possible that some patients receiving acute dialysis (e.g., to treat AKI) were miscoded to procedure codes consistent with chronic dialysis.

Conclusions

This study utilized a large EMR database to provide insight into the occurrence of uncommon adverse clinical events in patients with NDD-CKD and DD-CKD. Incidence rates of adverse clinical events were generally higher in patients with DD-CKD than in NDD-CKD and increased with decreasing eGFR in those with NDD-CKD. Event rates were higher in patients with Hb < 10 g/dL than in the overall CKD population, in patients with both NDD- and DD-CKD. In incident dialysis patients, rates of adverse clinical events were higher during the first 3 months after dialysis initiation than during the first 6 months. Our results help establish baseline rates of specific adverse clinical events and provide additional evidence of increased morbidity for dialysis versus nondialysis patients, as well as for patients with Hb < 10 g/dL versus the overall CKD population.

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Statement of Ethics

The study protocol was performed in accordance with International Conference on Harmonization Good Clinical Practice and the Declaration of Helsinki and the applicable legislation on non-interventional studies and/or observational studies. TriNetX data are deidentified, and platform users never receive any information on patient identifiers. Therefore, no patient consent was required for this study.

Conflict of Interest Statement

A.A.S., G.J., X.W., K.H., M.H., S.A.H., and D.L. are employees and stockholders of AstraZeneca. S.K. is an employee and stockholder of TriNetX.

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Author Contributions

A.A.S., G.J., X.W., S.K., K.H., M.H., S.A.H., and D.L. contributed to the design of the study. A.A.S. and X.W. conducted the data analysis and all the authors contributed to data interpretation and manuscript preparation and review. All the authors approved the final version of the manuscript and accept accountability for the overall work.

Data Availability Statement

Data underlying the findings described in this manuscript may be obtained in accordance with the data licensing agreement between AstraZeneca and TriNetX.