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ORIGINAL ARTICLE

Contemporary outcomes of anemia in US patients with chronic kidney disease

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ABSTRACT

Background. Long-term clinical outcome data from patients with non-dialysis-dependent (NDD) chronic kidney disease (CKD) are lacking. We characterized patients with NDD-CKD and anemia using real-world data from the USA.

Methods. This retrospective longitudinal observational study evaluated integrated Limited Claims and Electronic Health Record Data (IBM Health, Armonk, NY), including patients ≥18 years with two or more estimated glomerular filtration rate (eGFR) measures <60 mL/min/1.73 m^2 ≥90 days apart. Anemia was defined as the first observed hemoglobin <10 g/dL within 6-month pre- and post-CKD index date. Data were analyzed from January 2012 to June 2018. Patients with documented iron-deficiency anemia at baseline were excluded.

Results. Comprising 22 720 patients (57.4% female, 63.9% CKD stage 3, median hemoglobin 12.5 g/dL), median (interquartile range) follow-up for patients with and without anemia were 2.9 (1.5–4.4) and 3.8 (2.2–4.8) years, respectively. The most prevalent comorbidities were dyslipidemia (57.6%), type 2 diabetes mellitus (38.8%) and uncontrolled hypertension (20.0%). Overall, 23.3% of patients had anemia, of whom 1.9% and <0.1% received erythropoiesis-stimulating agents (ESAs) or intravenous iron, respectively. Anemia prevalence increased with CKD stage from 18.2% (stage 3a) to 72.8% (stage 5). Patients with anemia had a higher incidence rate of hospitalizations for heart failure (1.6 versus 0.8 per 100 patient-years), CKD stage advancement (43.5 versus 27.5 per 100 patient-years), and a 40% eGFR decrease (18.1 versus 7.3 per 100 patient-years) versus those without anemia.

Conclusions. Anemia, frequently observed in NDD-CKD and associated with adverse clinical outcomes, is rarely treated with ESAs and intravenous iron. These data suggest that opportunities exist for improved anemia management in patients with NDD-CKD.

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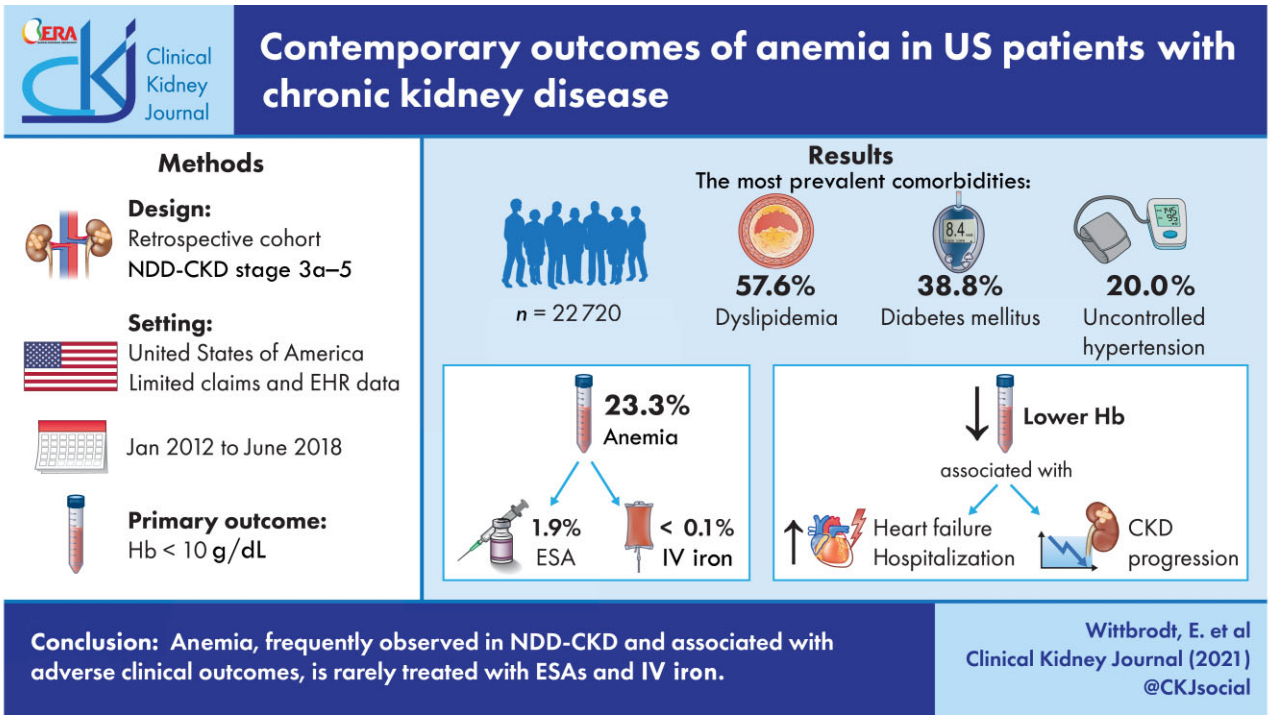
GRAPHICAL ABSTRACT



Keywords: anemia, CKD, epidemiology, hemoglobin, retrospective

INTRODUCTION

Contemporary, longitudinal real-world insight into the burden of anemia in patients with non-dialysis-dependent (NDD) chronic kidney disease (CKD) is lacking. Although associated with CKD disease progression, cardiovascular disease, reduced health-related quality of life (HRQoL) and increased mortality [1, 2], overall understanding of clinical outcomes associated with anemia in patients with NDD-CKD, which may improve diagnosis, prevention and management, is limited [3]. Such information should come from representative CKD populations receiving high-quality care in real-world practice.

Anemia treatment guidelines primarily focus on use of oral and intravenous (IV) iron and erythropoiesis-stimulating agents [ESAs; where (hemoglobin Hb) <10 g/dL] in patients with NDD-CKD [4]. Although ESAs are recommended for patients with Hb <10 g/dL, to decrease the risk of red blood cell (RBC) transfusions, anemia treatment is uncommon [5–7]. Indeed, in the USA, RBC transfusions appear to be more common than ESA treatment in patients with anemia in NDD-CKD [8].

Reluctance to treat anemia with Hb <10 g/dL in patients with CKD may stem from clinical trial outcomes of ESAs in NDD-CKD demonstrating an increased risk of mortality and thrombotic and cardiovascular events [9, 10], leading the US Food and Drug Administration to update ESA labeling with a boxed warning of the risks of targeting Hb levels >11.0 g/dL in patients with CKD [11]. Kidney Disease: Improving Global Outcomes (KDIGO) guidelines were also updated and advise against using ESAs in NDD-CKD patients with Hb levels ≥10.0 g/dL, stating that the initiation of ESA treatment in those with Hb levels <10 g/dL should be individualized [12]. These changes have led to decreased ESA use and increased RBC transfusions in NDD-CKD patients over the last decade [13].

Better understanding of anemia burden, management and outcomes in NDD-CKD patients is needed to identify opportunities to improve the care of patients with anemia of CKD in real-world clinical practice. This study aimed to understand patterns in anemia prevalence and clinical outcomes in patients with stage 3a–5 NDD-CKD, using data from a large US electronic medical records (EMR) database. Our key objective was to characterize the prevalence and incidence of anemia in patients with NDD-CKD and selected adverse clinical outcomes in real-world practice over 5 years.

MATERIALS AND METHODS

Study design

This retrospective, longitudinal, observational study used data from a large US EMR database (Explorys®) linked to commercial insurance claims (MarketScan®) from >55 million patients, covering multiple healthcare systems and healthcare providers. MarketScan® datasets contain information on >43.6 million insured individuals. We used data from two MarketScan® databases, Commercial and Medicare Supplemental databases, comprising medical and drug data from employers and health plans, and healthcare experience of retirees with Medicare supplemental insurance paid by employers, respectively. MarketScan® and Explorys® data are

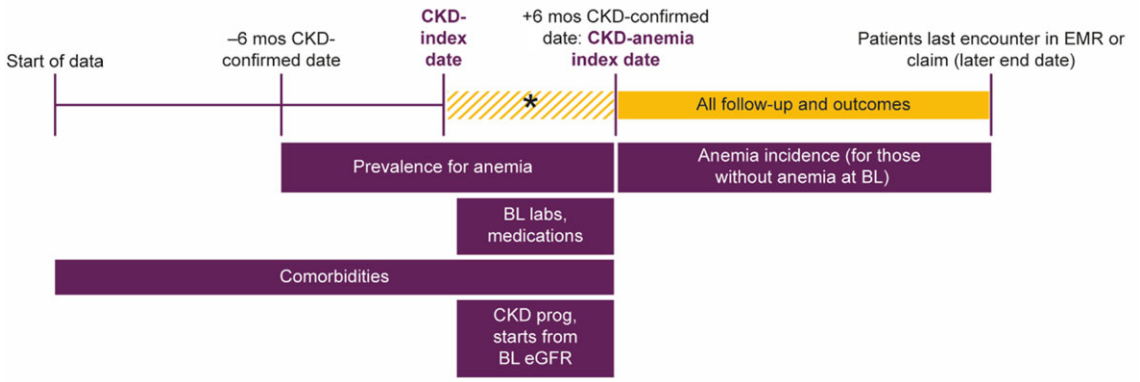


FIGURE 1: Study design. *Possible to find BL laboratory value-dependent outcomes, such as eGFR doubling or serum creatinine doubling here, as the BL laboratory value will be between 0 and 180 days of CKD index. BL, baseline; mos, months; prog, progression.

linked at the individual patient level using a deterministic algorithm and the linked dataset is de-identified as required under Health Insurance Portability and Accountability Act provisions. IBM® Watson Health™ collated the 5-year Limited Claims and Electronic Health Records Database (LCED). The static dataset consists of ∼4.4 million patients covering the period from 1 January 2012 to 30 June 2018, and 1 January 2012 to 30 September 2018 for claims and EMR data, respectively.

Patient population

The study population included inpatients and outpatients (≥18 years) with moderate-to-severe CKD (stages 3a–5) based on documented estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 between 1 January 2012 and 30 June 2018 (CKD index), with a second confirmatory eGFR ≥90 days later and with ≥1 Hb test >6 months after CKD index. Key exclusion criteria included dialysis (defined by Current Procedural Terminology, 4th Edition procedure codes) at baseline, active bleeding [defined by International Classification of Diseases (ICD) 9th and 10th edition diagnostic codes] and documented iron-deficiency anemia (defined by serum ferritin ≤30 ng/mL, or 31–99 ng/mL with either total iron-binding capacity >450 µg/dL or transferrin saturation <20% in patients with laboratory values available, or by ICD diagnostic code) as defined by KDIGO guidelines [14], during the baseline period.

Outcome measures

Patients were followed from the CKD index date until 30 September 2018; baseline was defined as the 6-month post-index date period (Figure 1). Patient characteristics and selected comorbidities (except cardiovascular conditions; defined as any history of these conditions prior to CKD index and through 6-month post-index), laboratory values and medications were collected during the baseline period. Uncontrolled hypertension was defined as a blood pressure measurement of ≥130/80 mmHg [15].

The primary objective was to characterize prevalence of anemia, defined as Hb <10 g/dL during one or more visit, to identify patients with severe anemia eligible for active treatment [12]—a stricter definition of anemia than the World Health Organization criteria (females <12 g/dL; males <13 g/dL) [16]. Patients with a Hb measurement <10 g/dL ± 6 months of CKD index were defined as having prevalent anemia; the first Hb measure post-index was considered the baseline value. All Hb tests were considered, regardless of patient setting.

Incidence of anemia during the study period was stratified by Hb ranges at baseline (<8, 8–9.9, 10–12, >12 g/dL) and CKD stage during the baseline period, from index to 5 years. Anemia incidence was calculated for patients at risk of anemia but without anemia at baseline.

Secondary outcome measures included anemia prevalence during the baseline period; anemia persistence, defined as any instance of two Hb measurements <10 g/dL ≥8 weeks apart (where all Hb readings between those two measurements are also <10 g/dL), regardless of treatment and expressed as rate per 100 patient-years (P-Y); and anemia recurrence, defined as two or more serial Hb <10 g/dL separated by one or more Hb ≥10 g/dL. Hb cycling was assessed by estimating the magnitude and frequency of changes in sequential Hb measurements between discrete Hb strata.

Exploratory outcomes included incidence rates (IRs) of selected cardiovascular events [hospitalization for acute coronary syndrome (ACS; including acute myocardial infarction and troponin-positive unstable angina), hospitalization for heart failure (HF) and hospitalization or emergency department visit for stroke] and CKD progression. CKD progression was determined by the presence of one or more of the following: decline in eGFR slope over the study period (as determined by simple linear regression), development of end-stage kidney disease [ESKD, defined as initiation of renal replacement therapy (i.e. hemodialysis, peritoneal dialysis) for >30 days or renal transplant; CKD stage 5 or eGFR <15 mL/min/1.73 m^2], a 40% decrease in eGFR, and doubling of serum creatinine. A composite IR of the following CKD progression endpoints was analyzed: ESKD development, 40% decrease in eGFR, and doubling of serum creatinine. Advancements in CKD stage beyond CKD stage at baseline defined by reported eGFR were also captured.

Statistical analyses

Assessed analyses are descriptive only. No comparative analyses were performed. Summary statistics for continuous variables included number of patients and mean and median values. Categorical variables included frequencies and percentages. For time-to-event endpoints, which were censored after the first event or study end, whichever occurred first, Kaplan–Meier estimates, IRs and all-event rates (per 100 P-Y)

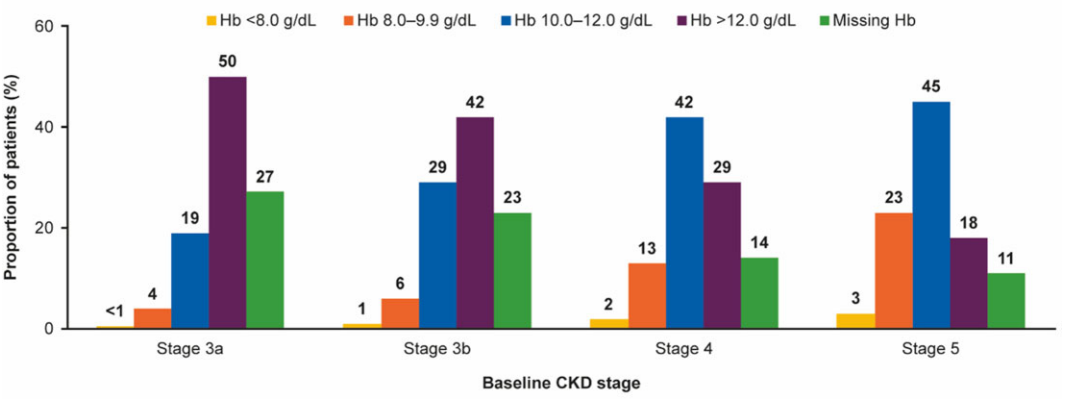


FIGURE 2: Baseline distribution (%) of Hb across CKD stage.

were calculated as appropriate. Missing data and distribution of follow-up duration were included. Hb cycling over time in the overall cohort was visualized using a Sankey diagram, generated on the Instant Health Data (IHD) Platform (Boston Health Economics, LLC).

IR ratios were calculated using the IHD platform to estimate the relative risk of anemia for cardiovascular or renal outcomes. Estimates were accompanied by 95% confidence intervals (CI) as appropriate.

RESULTS

Baseline characteristics

The study population comprised 22720 patients with a median [interquartile range (IQR)] follow-up of 3.6 (2.0–4.8) years (Supplementary data, Figure S1; Table 1) and a mean [standard deviation (SD)] age of 70.4 (12.7) years. Most patients were female (57.4%), 63.9% had CKD stage 3a, and the median (IQR) Hb level was 12.5 g/dL (11.3–13.7 g/dL) (Table 1). Patients with a more advanced CKD stage had lower Hb levels than patients with less advanced CKD (Figure 2).

Median (IQR) follow-up times for patients with and without anemia were 2.9 (1.5–4.4) years and 3.8 (2.2–4.8) years, respectively. Mean (SD) age in each group was 70.1 (13.6) years and 70.5 (12.3) years, respectively. A higher proportion of patients without anemia had CKD stage 3a (68.1%) compared with patients with anemia (50.0%), and median (IQR) Hb level was higher in patients without anemia [13.0 (12.0–14.0) g/dL] than with anemia [10.8 (9.8–12.0) g/dL].

The most frequently observed comorbidities were dyslipidemia (57.6%), type 2 diabetes mellitus (38.8%) and cardiovascular comorbidities [e.g. uncontrolled hypertension (20.0%), presence of HF (19.7%) and stroke (18.2%)] (Table 1). Prevalence of these comorbidities was reflected in the rates of glucose-lowering (25.1%) and cardiovascular medication (79.3%) use.

Prevalence and incidence of anemia

Baseline severe anemia prevalence (Hb <10 g/dL) in the overall cohort was 23.3%. Of patients with Hb tests in inpatient ($n = 9419$) and outpatient ($n = 16498$) settings, 32.6% ($n = 3074$) and 21.2% ($n = 3493$), respectively, had Hb <10 g/dL during the baseline period. Prevalence of anemia increased with CKD stage: of patients with stage 3a, 3b, 4 and 5, 18.2%, 24.8%, 41.2% and 72.8% had severe anemia at baseline, respectively. Notably, only 1.9% of patients with anemia ($n = 102$) used ESAs and <0.1% of patients with anemia ($n = 2$) received IV iron (Table 1). Except for stage 5, ESA medication use increased with advancing CKD stage in patients with anemia: of patients with stage 3a, 3b, 4 and 5, 0.7%, 2.6%, 5.2% and 1.3% used ESAs, respectively.

The IR for developing anemia post-baseline was 8.92 (95% CI 8.7–9.2) per 100 P-Y. Time-to-any event analysis of patients without anemia during the baseline period showed a linear increase in anemia risk over time (Supplementary data, Figure S2). Higher anemia IRs were observed for patients with advanced CKD (Supplementary data, Table S1).

Persistence and recurrence of anemia

IRs for anemia persistence and recurrence in patients with anemia were 10.8 and 2.1 per 100 P-Y, respectively (Supplementary data, Table S2). These rates were highest in patients with advanced CKD (Supplementary data, Table S2). Mean cumulative recurrence of anemia over time is shown in Supplementary Data, Figure S3.

Anemia progression

Patient Hb values fluctuated between the Hb strata above and below their recorded value during the baseline period. These fluctuations were visualized in a Sankey diagram, indicating the movement of patients through Hb strata (as assessed by routine laboratory measurements) after the CKD index date (Figure 3). Over time, the number of patients with Hb levels <8 g/dL increased (from 181 to 680 patients) (Figure 3). Mean change in Hb levels from baseline for the total population was −0.4 (1.9) g/dL and 0.1 (2.2) g/dL versus −0.6 (1.7) g/dL for those with versus without anemia during the baseline period, respectively. Fluctuations in Hb levels of ≥1 g/dL were experienced by 52.6% of the total population, 63.1% of patients with anemia and 48.4% without anemia during the baseline period.

Cardiovascular outcomes

During follow-up, 953 (4.2%) patients were hospitalized for HF, 514 (2.3%) for ACS and 675 (3.0%) were hospitalized or visited the emergency department for stroke. IRs (per 100 P-Y) of hospitalizations for HF (0.98) were greater than hospitalizations or emergency department visits for stroke (0.68) and hospitalizations for ACS (0.68) (Supplementary data, Table S3). A higher proportion

Table 1. Patient characteristics and comorbidities during the baseline period

Characteristics	Overall ($N = 22\,720$)	Patients without anemia ($n = 17\,437$)	Patients with anemia ($n = 5283$)
Female sex, *n* (%)	13 033 (57.4)	9845 (56.5)	3188 (60.3)
Mean age, years (SD)	70.4 (12.7)	70.5 (12.3)	70.1 (13.6)
Mean BMI, kg/m^2 (SD)	30.4 (7.2)	30.8 (7.1)	29.3 (7.4)
CKD stage, *n* (%)			
3a (eGFR 45–59 mL/min/1.73 m^2)	14 518 (63.9)	11 879 (68.1)	2639 (50.0)
3b (eGFR 30–44 mL/min/1.73 m^2)	5661 (24.9)	4260 (24.4)	1401 (26.5)
4 (eGFR 15–29 mL/min/1.73 m^2)	1923 (8.5)	1130 (6.5)	793 (15.0)
5 (eGFR <15 mL/min/1.73 m^2)	618 (2.7)	168 (1.0)	450 (8.5)
Laboratory values, median (IQR)			
eGFR,[a] mL/min/1.73 m^2	49.1 (39.7–55.0)	50.0 (42.0–56.0)	44.7 (31.0–53.0)
Serum creatinine,[b] mg/dL	1.3 (1.1–1.6)	1.3 (1.1–1.5)	1.4 (1.2–2.1)
Serum iron,[c] µg/dL	67.0 (52.8–90.0)	71.5 (57.0–90.8)	63.0 (42.3–85.8)
Serum ferritin,[d] ng/mL	133.0 (71.0–256.0)	110.3 (64.8–212.5)	164.4 (79.5–305.8)
TIBC,[e] µg/dL	295.0 (251.0–342.0)	313.0 (275.5–347.5)	268.0 (234.0–328.0)
Serum potassium,[f] mmol/L	4.2 (3.8–4.5)	4.2 (3.9–4.6)	4.1 (3.7–4.5)
Median Hb,[g] g/dL (IQR)	12.5 (11.3–13.7)	13.0 (12.0–14.0)	10.8 (9.8–12.0)
Hb category,[g] *n* (%)			
<8.0	181 (0.8)	0	181 (3.4)
8.0–9.9	1252 (5.5)	0	1252 (23.7)
10.0–12.0	5427 (23.9)	3172 (18.2)	2255 (42.7)
>12.0	10 245 (45.1)	9099 (52.2)	1146 (21.7)
Missing	5615 (24.7)	5166 (29.6)	449 (8.5)
Median follow-up time, years (IQR)	3.6 (2.0–4.8)	3.8 (2.2–4.8)	2.9 (1.5–4.4)
Comorbidities, *n* (%)			
Dyslipidemia	13 086 (57.6)	10 309 (59.1)	2777 (52.6)
Type 2 diabetes mellitus	8819 (38.8)	6601 (37.9)	2218 (42.0)
Uncontrolled hypertension	3094 (20.0)	2356 (20.4)	738 (18.7)
Heart failure	4464 (19.7)	2805 (16.1)	1659 (31.4)
Stroke	4127 (18.2)	2917 (16.7)	1210 (22.9)
Peripheral artery disease	2982 (13.1)	1998 (11.5)	984 (18.6)
Gout	1875 (8.3)	1409 (8.1)	466 (8.8)
Transient ischemic attack	1555 (6.8)	1114 (6.4)	441 (8.4)
Myocardial infarction	959 (4.2)	550 (3.2)	409 (7.7)
Unstable angina	794 (3.5)	517 (3.0)	277 (5.2)
Coronary revascularization	429 (1.9)	215 (1.2)	214 (4.1)
Pancreatitis	294 (1.3)	174 (1.0)	120 (2.3)
Systemic lupus erythematosus	193 (0.9)	120 (0.7)	73 (1.4)
Raynaud's syndrome	118 (0.5)	84 (0.5)	34 (0.6)
Prescription medications,[h] *n* (%)			
Statin	8177 (36.0)	6490 (37.2)	1687 (31.9)
RAASi	7211 (31.7)	5704 (32.7)	1507 (28.5)
ACEi[i]	4208 (18.5)	3328 (19.1)	880 (16.7)
ARB	2715 (12.0)	2181 (12.5)	534 (10.1)
MRA	1064 (4.7)	787 (4.5)	277 (5.2)
Non-insulin glucose-lowering medication	3744 (16.5)	3003 (17.2)	741 (14.0)
Sulfonylurea[i]	1889 (8.3)	1497 (8.6)	392 (7.4)
Insulin	1967 (8.7)	1432 (8.2)	535 (10.1)
Long-acting insulin[i]	1685 (7.4)	1222 (7.0)	463 (8.8)
Anticoagulant	2234 (9.8)	1593 (9.1)	641 (12.1)
Hemorrheologic agent			
Pentoxifylline[i]	40 (0.2)	29 (0.2)	11 (0.2)
ESA	162 (0.7)	60 (0.3)	102 (1.9)
IV iron	3 (<0.1)	1 (<0.1)	2 (<0.1)
Potassium binder	143 (0.6)	77 (0.4)	66 (1.3)
Sodium polystyrene sulfonate[i]	142 (0.6)	76 (0.4)	66 (1.3)

[a] $n = 22\,720$.
[b] $n = 1579$.
[c] $n = 200$.
[d] $n = 2519$.
[e] $n = 176$.
[f] $n = 1733$.
[g] As ascertained during the 6-month period between the CKD index date and the CKD-anemia index date.
[h] Data on oral iron medication are limited.
[i] Most commonly reported class/agent within medication group.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; BMI, body mass index; IQR, interquartile ratio; MRA, mineralocorticoid receptor antagonists; RAASi, renin-angiotensin-aldosterone system inhibitors; TIBC, total iron-binding capacity.

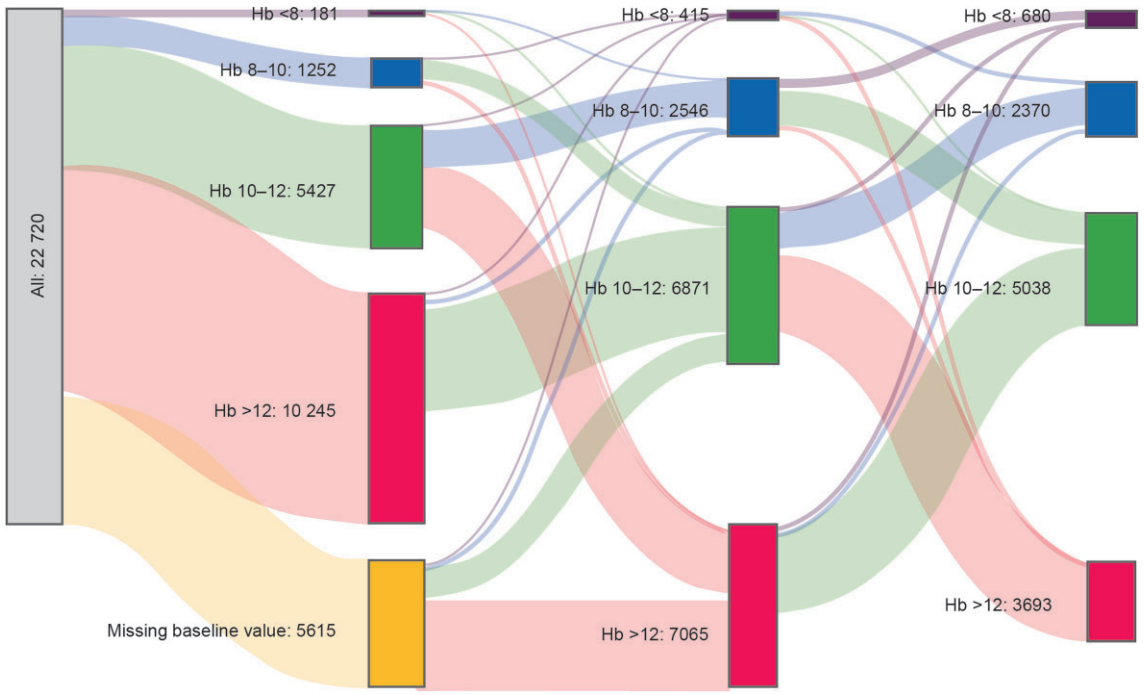


FIGURE 3: Sankey diagram of anemia progression in the overall patient cohort. The width of the lines indicates the proportion of patients in each stratum. The timing between Hb values was not considered; timing can vary between patients. The first three movements between strata after the baseline period are displayed; patients who did not move to a different link can be assumed to remain in the same node (strata, in this case).

of patients with anemia were hospitalized for HF compared with those without anemia (5.9% versus 3.7%, respectively; Figure 4A). The IR (per 100 P-Y) of hospitalizations for HF was higher in patients with baseline anemia than those without (Table 2); minimal increases in IRs of hospitalizations for ACS were observed in patients with increasing baseline CKD stage (Table 2).

Renal outcomes

In the overall population, CKD stage advanced in 13 872 (61.1%) patients and a 40% decline in eGFR was observed in 6706 patients (29.5%). ESKD developed post-baseline in 401 patients (1.8%); 7415 patients (32.64%) had either ESKD or a 40% eGFR decline, and 7427 (32.69%) had either ESKD or a 40% eGFR decline or doubling of serum creatinine from the baseline period. CKD stage advancement was the most frequently observed renal event associated with CKD progression (Supplementary data, Table S3).

A higher proportion of patients with versus without anemia had observed worsening of CKD, demonstrated by defined renal endpoints, particularly eGFR declines of 40% (44.1% versus 25.1% in patients without anemia) (Figure 4B). IRs (per 100 P-Y) for renal events associated with CKD progression were higher in patients with versus without baseline anemia (Table 2). Increases in IR for development of ESKD, the composite endpoint of ESKD and 40% decline in eGFR were proportional to increasing CKD stage (Supplementary data, Table S4).

Annual eGFR decline doubled for patients with versus without baseline anemia; median (IQR) annual change was −0.6 (−3.8 to 1.9) versus −0.3 (−2.5 to 1.3) mL/min/1.73 m^2, respectively.

DISCUSSION

This retrospective observational study examined the prevalence and incidence of anemia, as well as selected cardiovascular and renal outcomes, among adults with NDD-CKD using data from a large US cohort. A major strength of this study is the access to data of a large US population with NDD-CKD, including linkage to claims data, with the 5-year follow-up period enabling assessment of longitudinal clinical outcomes.

During the baseline period, 23.3% of patients had severe anemia (Hb <10 g/dL). Baseline anemia prevalence correlated with increasing CKD severity, consistent with previous reports [17], as would be expected from an increased loss of erythropoietin production due to decreased oxygen-sensing as renal function declines [1]. Incidence of anemia increased linearly over 5 years and was associated with advancing CKD stage. Over time, the number of patients with Hb levels <8 g/dL increased, possibly due to CKD progression. As expected, patients with anemia at baseline had a higher anemia persistence and recurrence compared with patients without anemia.

Only 1.9% of patients with baseline anemia received ESAs. ESA prescription was generally associated with severe CKD but remained low overall. The proportion of patients with anemia and CKD stage 5 receiving ESAs was particularly low, possibly due to these NDD-CKD patients receiving better specialist care and being more likely to receive close monitoring or receiving RBC transfusions to correct anemia, instead of ESAs, although these findings have not been captured here. Low use of ESAs and IV iron in our study, despite high prevalence, incidence and persistence of anemia in CKD, could be due to under-reporting or may reflect cardiovascular safety concerns over ESA use in patients with CKD, particularly those with underlying cardiovascular morbidities. In addition, potential lack of access to therapies, difficulties in administering parenteral therapies and/or RBC transfusions, may contribute to low use of anemia therapies. In a previous study, 22.8% of patients reported receiving anemia treatment [17]. However, risk of adverse effects from increased ESA dosage must be balanced against possible

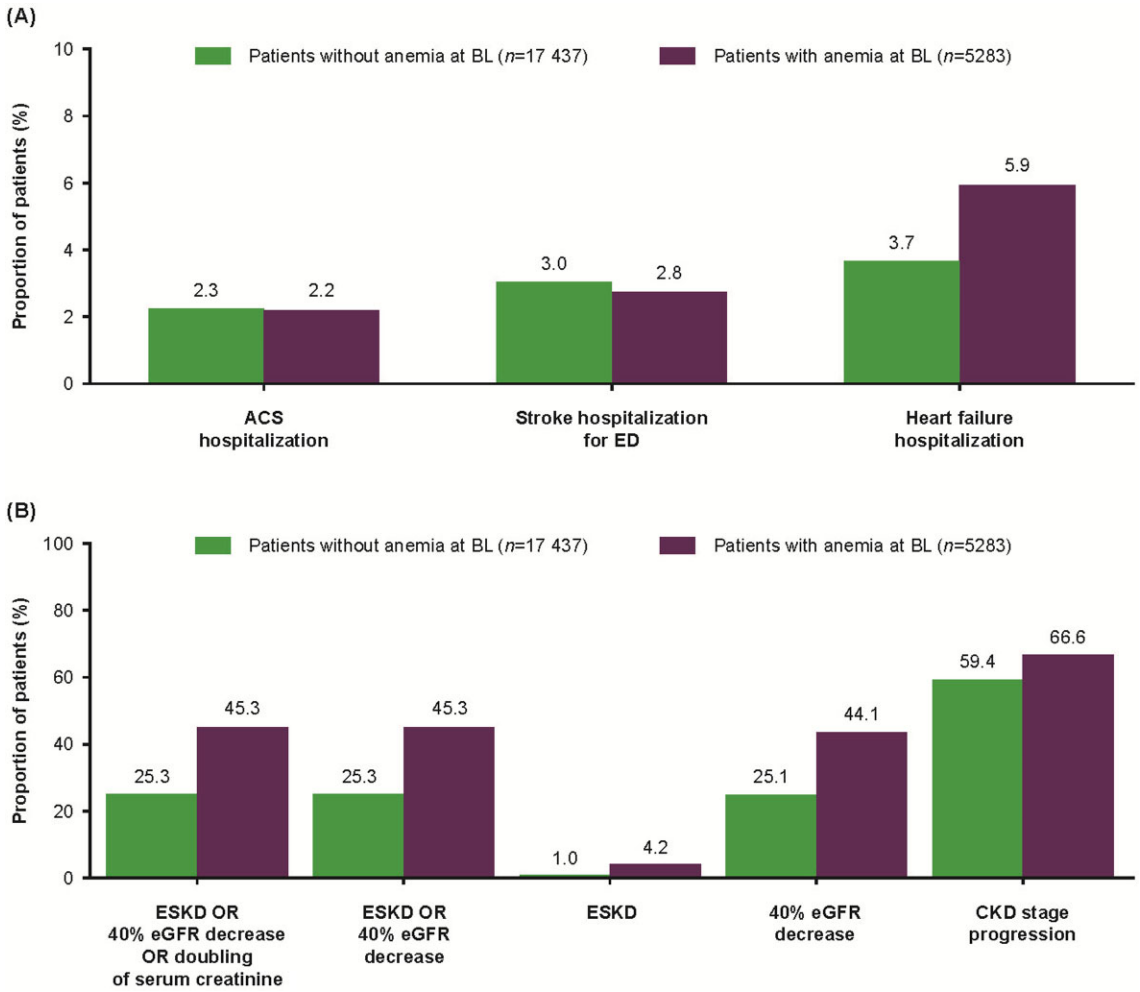


FIGURE 4: Proportion of patients with and without baseline anemia experiencing CV (**A**) and renal (**B**) events during follow-up. BL, baseline; CV, cardiovascular; ED, emergency department.

Table 2. IRs per 100 P-Y of selected CV and renal events stratified by presence of baseline anemia

	No presence of anemia at baseline ($n = 17\,437$)	Presence of anemia at baseline ($n = 5283$)	IRR[a] (95% CI)
CV events, IR per 100 P-Y (95% CI)			
ACS hospitalization	0.7 (0.6–0.7)	0.8 (0.6–0.9)	1.2 (0.9–1.4)
Stroke hospitalization or ED	0.7 (0.6–0.7)	0.7 (0.6–0.8)	1.0 (0.9–1.3)
Heart failure hospitalization	0.8 (0.8–0.9)	1.6 (1.4–1.7)	1.9 (1.6–2.1)
Renal events IR per 100 P-Y (95% CI)			
ESKD or 40% eGFR decrease or doubling of serum creatinine	9.7 (8.6–10.8)	25.0 (22.0–28.3)	2.6 (2.2–3.1)
ESKD or 40% eGFR decrease	8.3 (8.0–8.5)	21.4 (20.5–22.3)	2.6 (2.5–2.7)
ESKD	0.3 (0.3–0.3)	1.5 (1.3–1.6)	4.9 (4.0–6.0)
40% eGFR decrease	7.3 (7.1–7.5)	18.1 (17.4–18.8)	2.5 (2.4–2.6)
Doubling of serum creatinine	2.9 (2.4–3.5)	5.7 (4.7–7.1)	2.0 (1.5–2.6)
CKD stage progression	27.5 (26.9–28.0)	43.5 (42.0–44.9)	1.6 (1.5–1.6)

[a]IRR is a ratio of IR in anemia versus non-anemia.
CV, cardiovascular; ED, emergency department; IRR, incidence rate ratio.

benefits, such as improved HRQoL and RBC transfusion sparing effects [18–20]. Appropriate anemia treatment is recommended for CKD management [21]. However, necessity of follow-up visits to healthcare professionals and parenteral administration of some anemia treatments (ESAs, iron) may be significant obstacles to many patients not on dialysis.

Hb levels fluctuated over time and between Hb strata during the baseline period. While minor fluctuations in Hb levels

are normal [22], positive associations have been observed between Hb level variability and anemia severity [23]. However, evidence of recurrent anemia and Hb changes ≥1 g/dL over the 5-year period suggests that some patients experienced Hb cycling. This was more prevalent among patients with baseline anemia and those with advanced CKD and could be related to low baseline ESA use (and thus less stability in Hb levels). Similar to results from previous studies [24–27], presence of anemia was associated with a decline in kidney function, as demonstrated by patients with anemia having an eGFR decrease of more than double that of patients without anemia.

CKD stage and related comorbidities, specifically cardiovascular comorbidities and diabetes, can contribute to Hb fluctuations over time [22, 23]. As these fluctuations may result in an increased risk of hospitalization and mortality, reducing this variability and maintaining Hb targets could be key to improving clinical outcomes [22]. We found a higher incidence of hospitalization for HF in patients with versus without baseline anemia. Our study population had a high prevalence of cardiovascular and diabetes comorbidities and associated medication use, typical for patients with CKD [28–30]. Loss of renal function and declining eGFR associated with CKD have been reported to predict mortality and accelerate progression of cardiovascular disease and HF [31]. Reduced Hb levels and oxygen-carrying ability also results in impaired myocardial oxygen delivery, potentially causing or exacerbating cardiac abnormalities and HF [1]. This highlights the association between anemia and increased cardiovascular events such as HF hospitalization and ACS in patients already at risk due to CKD and other comorbidities such as diabetes [32]. The observed IRs of cardiovascular events were relatively low given the advanced mean age and multimorbid nature of the study cohort, perhaps owing to the requirement for commercial insurance coverage and routine healthcare visits to be included in the study database.

Limitations of this study include: (i) Anemia was defined as any Hb measurement of <10 g/dL within ± 6 months of the index CKD date. Other definitions of anemia requiring confirmation or persistence of Hb values below these thresholds would likely have led to lower anemia prevalence. Indeed, median Hb values for patients with anemia were >10 g/dL and rates of anemia recurrence and persistence were low. These factors may have contributed to the relatively low use of ESAs among patients with anemia. (ii) Reliance on data not collected for research purposes (administrative data are subject to potential coding error and are not collected for research); therefore, not all data may be available for each patient. (iii) Findings are based on a single database from multiple healthcare systems, but may not be generalizable to the entire US population. (iv) Not all relevant baseline period data, such as iron saturation levels and use of oral iron, were available. (v) Different insurance plans may have different criteria for payment of ESA and IV iron treatments, which may have contributed to their low usage as they are not generally reimbursed as first-line therapy in NDD anemia. (vi) Although iron deficiency anemia and active bleeding were excluded, the cause of anemia could not be definitively linked to CKD. (vii) Active malignancy was not an exclusion criterion due to difficulty in coding for this condition. (viii) Analyses were descriptive only and no adjustments were made for baseline covariates, meaning that there was no analysis of comparative effectiveness due to low anemia treatment utilization. (ix) LCED mortality data were not available. (x) Although laboratory values linked to inpatient hospital stays were excluded in a sensitivity analysis, no significant decrease in prevalence was observed; these data may be collected in future studies.

CONCLUSION

Severe anemia was frequently observed in a large US population of patients with NDD-CKD and was associated with increased HF hospitalizations and CKD progression. A high proportion of patients with anemia who were eligible for treatment were untreated with ESAs or IV iron. These data emphasize a continued unmet need for accessible, well-tolerated, effective and easily administered anemia therapies in patients with NDD-CKD in the USA.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study were collected from LCED (Limited Claims and Electronic Health Records Database), which is an integrated Truven and Explorys® database. Data underlying the findings described in this manuscript may be requested in accordance with AstraZeneca's data sharing policy described at https://astrazenecagroup-dt.pharmacm.com/DT/Home through www.vivli.org.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

All authors were involved in the drafting and critical revision of the manuscript. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

E.T.W., G.J., S.K., H.v.H., H.C. and J.A.S. are employees and stockholders of AstraZeneca. K.K.-Z. reports personal fees from Abbott, AbbVie, Alexion, Amgen, AstraZeneca, Aveo, Chugai, DaVita, Fresenius Medical Services, Genentech, Haymarket, Hospira, Kabi, Keryx, Novartis, Pfizer, Relypsa, Resverlogix, Sandoz, Sanofi, Shire, Vifor, ZS-Pharma, UpToDate, Baxter, Dr Schär, PCORI, and Amag Pharma, and grants and personal fees from National Institutes of Health outside the submitted work.

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