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ORIGINAL ARTICLE

High unmet treatment needs in patients with chronic kidney disease and type 2 diabetes: real-world evidence from a US claims database

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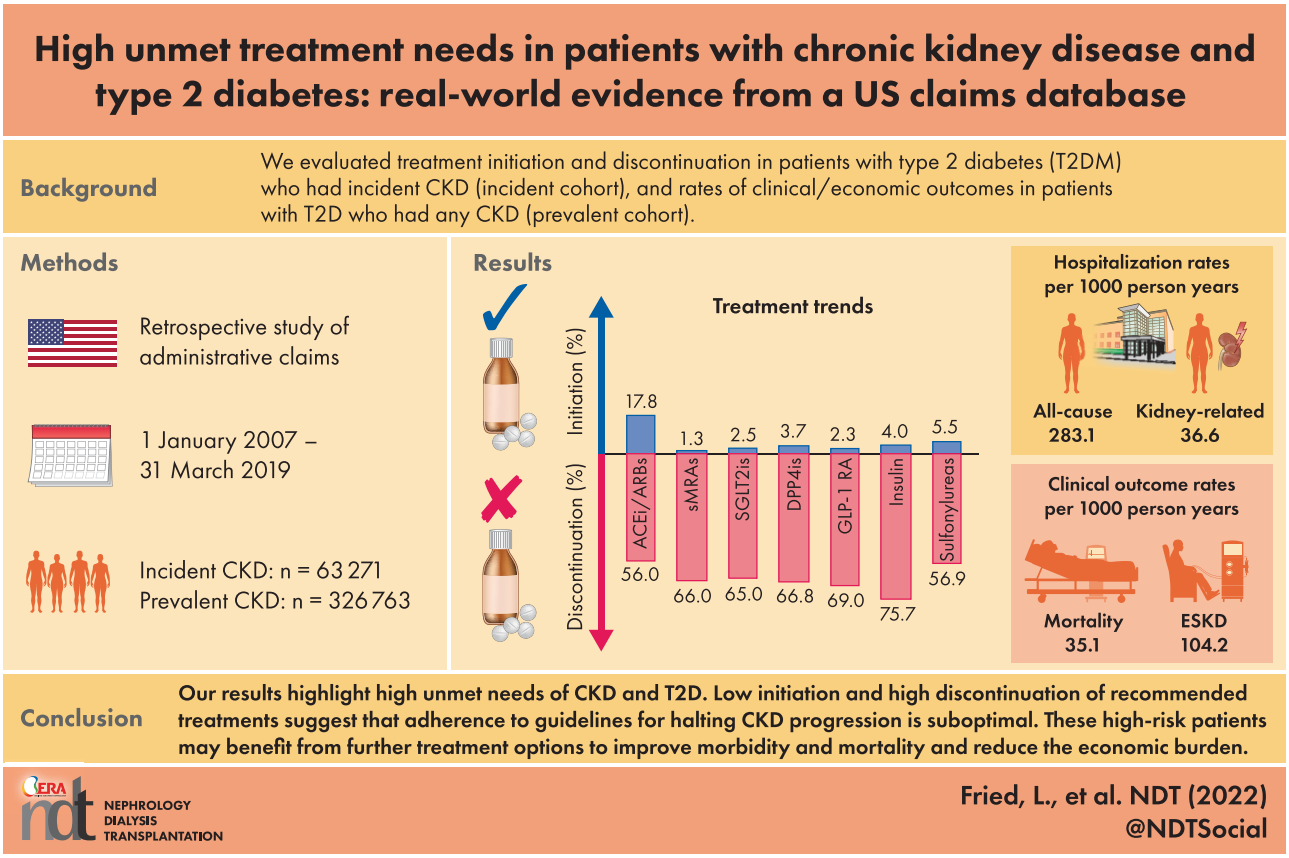
GRAPHICAL ABSTRACT



ABSTRACT

Background. Chronic kidney disease (CKD), a serious complication of type 2 diabetes (T2D) increases the comorbid risk of cardiovascular disease (CVD) and end-stage kidney disease (ESKD). Treatment guidelines recommend renin–angiotensin blockade and antihyperglycemic treatment with metformin and sodium-glucose cotransporter 2 inhibitors (SGLT2is) as first-line treatment. We evaluated treatment initiation and

KEY LEARNING POINTS

What is already known about this subject?

- CKD, a common yet serious complication of T2D, occurs in 20–40% of diabetic patients.
- Patients with CKD and T2D are at increased risk for morbidity often attributable to higher rates of CVD and ESKD, resulting in a significant burden on patient health and the healthcare system.
- The extent to which treatment guidelines are implemented in the real-world setting and in patients with different clinical characteristics is not well described.

What this study adds?

- There is a high overall unmet need in patients regarding clinical outcomes and costs as well as in predefined subgroups and in patients treated with the standard of care (SOC) for CKD and T2D.
- There were low initiation rates of SOC (ACEis/ARBs) overall and SGLT2is and sMRAs have very low initiation rates across subgroups, indicating that these were not used for CKD treatment during the study period.
- There were high discontinuation rates for all treatments, especially for SGLT2is and sMRAs versus ACEis/ARBs, requiring further investigation.

What impact this may have on practice or policy?

- New treatment options in CKD and T2D are warranted to improve clinical outcomes and reduce costs, especially in subgroups of patients with advanced CKD, a high risk of rapid progression and underlying CVD.

discontinuation overall and in subgroups of T2D patients with incident CKD (incident cohort) and rates of clinical and economic outcomes in patients with T2D and any CKD (prevalent cohort).

Methods. In this retrospective study of administrative claims in the USA between 1 January 2007 and 31 March 2019, we evaluated the proportion of patients with concomitant, newly initiated and discontinued use of antihypertensive [angiotensin-converting enzyme inhibitor (ACEi)/angiotensin II receptor blockers (ARBs), steroidal mineralocorticoid receptor antagonists (sMRAs)] and antidiabetic [SGLT2is, dipeptidyl peptidase-4 inhibitors (DPP4is), glucagon-like peptide-1 receptor agonists (GLP-1 RAs), insulin and sulfonylureas] medications, rates of clinical outcomes per 1000 person-years and mean total healthcare costs.

Results. We identified 63 127 and 326 763 patients in the incident and prevalent CKD cohorts, respectively. Low initiation and high discontinuation rates were observed with 17.8% and 56.0% for ACEi/ARBs, 1.3% and 66.0% for sMRAs, 2.5% and 65.0% for SGLT2is, 3.7% and 66.8% for DPP4is, 2.31% and 69.0% for GLP-1 RAs, 4% and 75.7% for insulin and 5.5% and 56.9% for sulfonylureas. Similar results were seen by subgroups. Rates of clinical outcomes ranged from 35.07 per 1000 person-years for all-cause mortality to 104.19 for ESKD, with rates of hospitalization ranging from 36.61 for kidney hospitalizations to 283.14 for all-cause hospitalizations. Among patients with comorbidities, higher clinical and economic outcomes were found.

Conclusion. Our results highlight high unmet needs of CKD and T2D, particularly subgroups of patients with multimorbid CVD, high-risk CKD (low estimated glomerular filtration rate or high urinary albumin:creatinine ratio) or rapidly progressing CKD. Low initiation and high discontinuation of recommended treatments suggest that adherence to guidelines for halting CKD progression is suboptimal. These high-risk patients may benefit from further treatment options to improve morbidity and mortality and reduce the economic burden.

Keywords: chronic kidney disease, clinical outcomes, diabetic kidney disease, real-world data, type 2 diabetes, unmet needs

INTRODUCTION

Chronic kidney disease (CKD), a common yet serious complication of type 2 diabetes (T2D), occurs in 20–40% of diabetic patients [1]. Patients with CKD and T2D are at increased risk for morbidity often attributable to higher rates of cardiovascular disease (CVD) and end-stage kidney disease (ESKD), resulting in a significant burden on patient health and the healthcare system [2–4]. It is well characterized that patients with CKD, T2D and certain comorbidities experience worse clinical and economic outcomes than with either condition alone [5–7]. This clinically varied subgroup of high-risk patients is complex, encompassing multimorbid patients with CVD or anemia, patients with rapidly progressing or severe CKD and patients with uncontrolled diabetes [6, 8, 9].

Given the complexity of these patients, treatment guidelines recommend comprehensive patient care targeting reductions in glycemic levels, CKD progression and CVD. Currently the Kidney Disease: Improving Global Outcomes (KDIGO) treatment guidelines suggest pharmacological treatment with renin–angiotensin system (RAS) blockade for hypertension, mainly monotherapy with angiotensin-converting enzyme inhibitors (ACEis) or angiotensin II receptor blockers (ARBs). The KDIGO clinical guidelines also suggest steroidal mineralocorticoid receptor antagonists (sMRAs) to treat refractory hypertension. Glycemic control with metformin (biguanides) and sodium-glucose cotransporter 2 inhibitors (SGLT2is) is initially recommended as an option for first-line antihyperglycemic treatment [10]. However, if glycemic targets are not achieved, patient factors and preference may inform subsequent combination therapy with other glucose-lowering drugs, such as glucagon-like peptide receptor agonists (GLP-1 RAs), dipeptidyl peptidase-4 inhibitors (DPP4is), sulfonylureas or

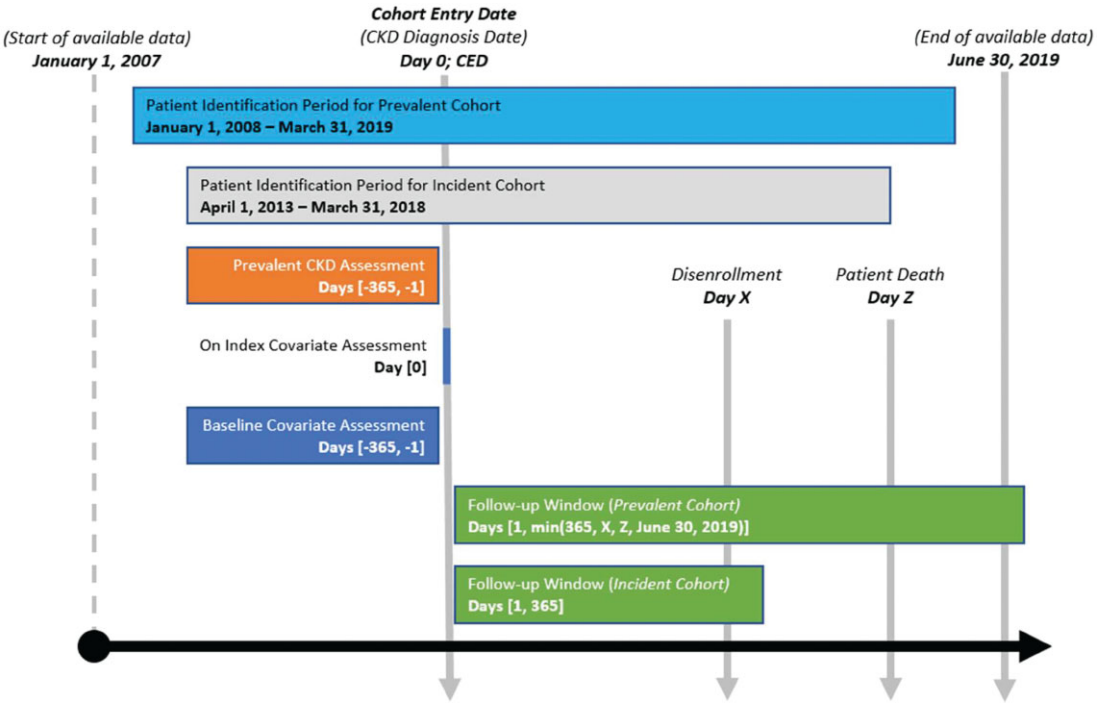


FIGURE 1: Study timelines for the IC and PC.

insulin [4, 11]. The extent to which these guidelines are implemented in the real-world setting and in patients with different clinical characteristics is not well described.

To better understand the burden of disease among patients with CKD and T2D, we sought to characterize the unmet treatment needs of this growing and potentially costly high-risk population using US-based real-world data. Specifically, we evaluated treatment patterns with antihypertensive and antidiabetic medication and sMRA initiation and discontinuation among T2D patients with newly diagnosed CKD, in addition to clinically important predefined subgroups. We also describe the rates of clinical outcomes, including mortality, kidney-related events and cardiovascular-related events, and total healthcare costs among patients with T2D and prevalent CKD.

MATERIALS AND METHODS

Data source

This retrospective observational study was conducted using Optum Clinformatics Data Mart (CDM) between 1 January 2007 and 30 June 2019. The data source is an administrative health claims database with longitudinal data of patients enrolled in commercial or Medicare Advantage health plans in the USA. The data contain demographic, medical encounters from inpatient and outpatient settings, pharmacy dispensing and laboratory results for a subset of patients. The source data include ~63 million unique members and are considered representative of the commercially insured US population.

Study population

The study population consisted of all patients ≥18 years of age with laboratory values confirming CKD [two estimated glomerular filtratin rate (eGFR) laboratory values <60 mL/min/1.73 m^2 and/or two urinary albumin:creatininte ratio (UACR) laboratory values ≥30 mg/g 90–365 days apart]. The date of the second laboratory value confirming CKD was considered the index date. Patients were required to have a T2D diagnosis in the 365 days prior to this index date, defined by at least one inpatient or at least two outpatient claims with International Classification of Diseases, 9th revision (ICD-9) or ICD-10 diagnosis codes for T2D between 30 and 365 days apart or any use of a second-line glucose-lowering agent. Our definition of T2D has high sensitivity (73.7%) and specificity (98.1%) compared with self-reports [12–14]. Patients were required to have at least 365 days of continuous enrollment prior to the index date and were excluded if they had evidence of CKD due to nondiabetic causes [15, 16].

Two different cohorts were used to evaluate treatment patterns and clinical outcomes separately (Fig. 1).

A cohort of T2D patients and newly diagnosed CKD patients (incident CKD only) between 1 April 2013 and 31 March 2018 was used to assess treatment patterns [incident cohort (IC)]. Patients in this cohort were required to have 365 days of continuous enrollment after the index date, during which treatment patterns were assessed to ensure the observability of patients during follow-up. Newly diagnosed CKD was defined as no evidence of kidney disease in the year prior to T2D diagnosis. The date 1 April 2013 was chosen based on the approval of SGLT2is in the USA and to ensure that all antiglycemic agents of interest were evaluated over the same time period and to minimize calendar time bias. This timeframe also reflected any changes in the use of medications that were on the market pre-SGLT2i approval, to take into account the availability of newer medications.

A second cohort of T2D patients with CKD (either prevalent or incident CKD) between 1 January 2008 and 31 March 2019 was created to assess the clinical outcomes and baseline treatment patterns [prevalent cohort (PC)]. Patients in this cohort were followed from the index date through the earliest of the occurrence of the respective outcome, disenrollment, death, the end of data (30 June 2019) or 365 days after the index date.

Variables and outcomes

Patient baseline characteristics, including sociodemographics, comorbidities and medication use, were assessed during the 365-day baseline period prior to the index date.

Treatment patterns, assessed in the IC, included individual and combinations of antihypertensive agents (ACEis, ARBs and sMRAs) and antiglycemic agents (SGLT2is, DPP4is, GLP-1 RAs, sulfonylureas and insulin). Treatment patterns were described in terms of initiation, among patients without prior use of the treatment and discontinuation among patients who initiated during follow-up. Discontinuation during the 365-day follow-up period was defined using a grace period of 30 days between prescriptions before being counted as discontinuation, to allow leeway for missed refills of the medication or splitting of pills [17].

Clinical outcomes and total healthcare costs assessed in the PC included hospitalizations (all-cause, cardiovascular- or kidney-related hospitalization), kidney outcomes (kidney transplant and ESKD) and mortality. Total healthcare costs included the sum of inpatient and outpatient services, outpatient facility and professional services and outpatient pharmacy costs.

Subgroup analysis

All outcomes were analyzed in predefined subgroups based on the patient's clinical status and their prescribed treatments (defined during the baseline period unless otherwise noted). Subgroups defined by the patient's clinical status included comorbidities (CVD and anemia), the underlying T2D or CKD status [last observed hemoglobin A1c (HbA1c) value, CKD rapid progression (defined by an eGFR decline $\geq$5 mL/year) and CKD severity stages identified by an eGFR categories according to KDIGO and UACR categories]. In addition, clinical and cost outcomes were examined in treatment subgroups, including diabetes treatment and antihypertensives treatment in monotherapy (insulin, ACEi/ARB and sMRA), combination therapy (insulin with SGLT2i and ACEi/ARB with sMRA) and in comprehensive care combination therapy with or without sMRA (ACEi/ARB with any SGLT2i, DPP4i or GLP-1 RA).

Statistical analysis

Baseline patient characteristics were reported as the number and proportion of patients. Treatment patterns were estimated as the number and proportion of patients who initiated a specific treatment having no prior use. Among those who initiated treatment in follow-up, the number and proportion of patients who discontinued a treatment were reported (maximum allowed gap of 30 days). Clinical outcomes were reported as rates of each outcome per 1000 person-years [95% confidence intervals (CIs)] and were estimated using Poisson regression with normal approximation and a robust variance estimator. Total healthcare costs were reported as the mean [standard deviation (SD)] for total healthcare costs per person per year. All analyses were conducted using the Aetion Evidence Platform (2021), which has been validated for a range of studies [18].

Full definitions of the patient cohorts, variables, outcomes and subgroup selection criteria are listed in Supplementary data, Table S1.

RESULTS

We identified 63 127 patients with T2D and newly diagnosed CKD (IC) between 1 April 2013 and 31 March 2018 and 326 763 patients with T2D and any CKD (PC) between 1 January 2008 and 31 March 2019 (Fig. 2).

Patient characteristics

Among the IC and PC, the median age was 72 years in both cohorts and 56.0% and 53.6% were female, respectively. Approximately half of all patients were at CKD stage G3a at index (53.0% and 47.8% for the IC and PC, respectively). The prevalence of UACR stage A2 at index was 31.0% and 25.0%, respectively; more than half of all patients were missing UACR information. Based on the KDIGO risk stratification, the majority of patients in the two cohorts were at moderate–high CKD risk (i.e. eGFR stage $\geq$3a and UACR stage $\geq$A1) at index (starting from 83.8% and 72.2% in the IC and PC, respectively). The most prevalent comorbidities were hypertension (87.8% and 91.9% for the IC and PC, respectively), hyperlipidemia (80.8% and 83.8%), resistant hypertension (77.7% and 81.7%) and pain disorders (67.6% and 73.3%) (Supplementary data, Tables S2 and S3).

Concomitant medication use

Among the PC, the most common concomitant class of antihypertensives was ACEis (46.8%) followed by ARBs (27.3%) and sMRAs (5.8%). Metformin was the most common glucose-lowering agent (38.2%), while the least common was GLP-1 RA (1.3%) and few patients were prescribed SGLT2i (2.2%). Among subgroups, all hypertensive agents were common for patients with CVD. For patients with rapid progression of CKD (i.e. eGFR decline $\geq$5 mL/year), the use of all concomitant antihypertensive and glucose-lowering agents was slightly higher when compared with their counterparts (Table 1).

Treatment patterns

In general, low initiation rates were observed among patients without prior use. Overall, 18 407 (29.2%) patients had

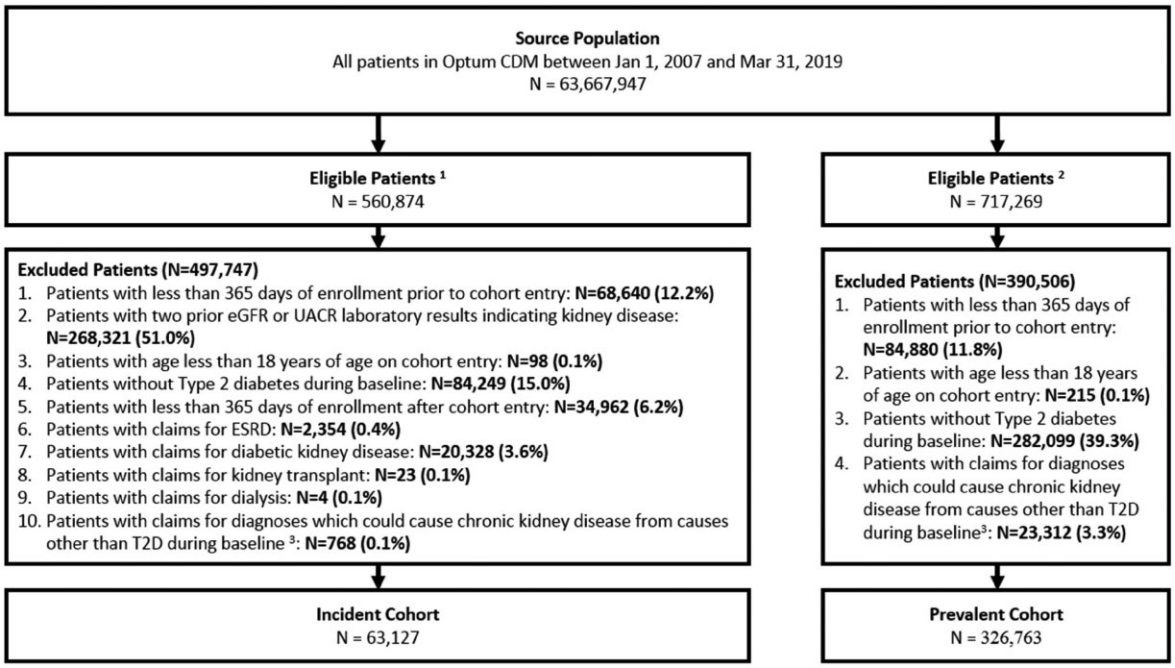


FIGURE 2: Flowchart of patient selection among patients with CKD and T2D (IC and PC).

no prior use of ACEis/ARBs, among which 17.8% of patients initiated ACEi/ARB therapy within 1 year. Approximately 1% of patients without prior use of sMRA initiated sMRA during follow-up. Few patients initiated antiglycemic treatments; 2.5% and 3.7% of patients initiated SGLT2i and DPP4i, respectively. Combination treatment with two antiglycemic agents was infrequent (<1%). In addition, within 1 year 4% and 5.5% of patients initiated inulin and sulfonylurea treatments, respectively.

In the subgroup analysis, we observed higher initiation of treatments in subgroups of patients with comorbid conditions than in subgroups without them. For example, treatment initiation in the subgroup of patients with CVD was higher than in the subgroup without CVD for all treatments except for ACEi/ARB (17.5% and 17.9%, respectively). The initiation rates were higher for all treatments assessed in the subgroup of patients with rapid progression of CKD (i.e. eGFR decline ≥5 mL/year), with nearly three times higher initiation of sMRA (2.9% and 0.9%, respectively) and sMRA in combination with ACEi/ARB (2.1% and 0.8%), despite being initiated relatively infrequently overall. Among the UACR subgroups, the initiation rate increased with increasing severity from A2 to A3 for ACEi/ARB (24.8% and 30.6%, respectively), sMRA (1.3% and 2.5%, respectively) and sMRA in combination with ACEi/ARB (1.1% and 2.2%, respectively), which is consistent with recent studies [19]. Initiation rates for all treatments among participants with UACR data were higher compared with those with missing UACR data.

The initiation rates for antidiabetic drugs were approximately the same in the UACR A2 and A3 subgroups. Among the eGFR subgroups, G5 had the lowest initiation rates relative to the other eGFR subgroup-specific results for ACEi/ARB, no initiation of sMRA in combination with ACEi/ARB and the highest initiation rate of DPP4i (4.7%), followed by GLP-1 RA (3.6%), SGLT2i (2.1%) and sulfonylureas (10.8%). Initiation rates for all treatments were nominally higher among participants without eGFR data compared with those with eGFR data (Table 3).

A majority of patients subsequently discontinued their newly initiated pharmacological treatments, ranging from 56.0% (ACEi/ARB) to 91.7% (combination therapy with DPP4i and GLP-1 RA). Approximately 66% of new users of sMRA discontinued treatment. The initiation of antidiabetic medications and sMRAs was infrequent and the majority of new users of SGLT2is discontinued their use (65.0%).

In subgroup-specific analyses, the observed discontinuation rates were higher within subgroups of patients with CVD than subgroups without CVD, with the highest discontinuation observed for DPP4i combinations (with SGLT2i, 83.6%; with GLP-1 RA, 91.1%, respectively). Among patients in the UACR subgroups, discontinuation rates were highest in the UACR A3 subgroup, except for sMRA in combination with ACEi/ARB, SGL2i and sulfonylureas (Tables 2 and 3).

Clinical outcomes and costs

Among all patients with CKD and T2D, high event rates of clinical outcomes per 1000 person-years were observed, ranging from 51.95 (95% CI 51.11–52.78) to 78.32 (95% CI 77.29–79.35) for CV-related hospitalization and as high as 104.19 (95% CI 102.98–105.39) for ESKD. The rate for all-cause hospitalization was 283.14 per 100 person-years (95% CI 281.09–285.20). In addition, all-cause mortality rates were 35.07 per 1000 person-years (95% CI 34.39–35.75) (Tables 4–6).

Table 1. Patient concomitant treatment characteristics in the PC assessed during a 365-day baseline period and by clinical status subgroups

		Comorbidities				Diabetes		CKD progression	
Concomitant medications use	All patients	Anemia	No anemia	CVD	No CVD	HbA1c <8%	HbA1c ≥8%	eGFR <5 mL/ year	eGFR ≥5 mL/ year
Patients, ***n***	326 763	95 912	230 851	75 834	250 929	190 874	65 482	168 621	41 720
Antihypertensive agents, *n* (%)									
ACEis	152 822 (46.8)	42 200 (44.0)	110 622 (47.9)	35 873 (47.3)	116 949 (46.6)	89 419 (46.8)	32 754 (50.0)	79 137 (46.9)	20 510 (49.2)
ARBs	89 313 (27.3)	27 306 (28.5)	62 007 (26.9)	21 328 (28.1)	67 985 (27.1)	52 338 (27.4)	19 292 (29.5)	43 544 (25.8)	11 556 (27.7)
sMRAs	18 941 (5.8)	7515 (7.8)	11 426 (4.9)	10 463 (13.8)	8478 (3.4)	9932 (5.2)	3688 (5.6)	9824 (5.8)	2816 (6.7)
Glucose-lowering agents, *n* (%)									
Biguanides	124 838 (38.2)	28 799 (30.0)	96 039 (41.6)	22 508 (29.7)	102 330 (40.8)	77 081 (40.4)	29 855 (45.6)	59 272 (35.2)	15 457 (37.0)
DPP4is	40 500 (12.4)	11 777 (12.3)	28 723 (12.4)	8 499 (11.2)	32 001 (12.8)	21 969 (11.5)	12 286 (18.8)	19 336 (11.5)	5280 (12.7)
SGLT2is	7324 (2.2)	1279 (1.3)	6045 (2.6)	1040 (1.4)	6284 (2.5)	3171 (1.7)	3293 (5.0)	2552 (1.5)	627 (1.5)
GLP-1 RAs	13 438 (4.1)	3 266 (3.4)	10 172 (4.4)	2 434 (3.2)	11 004 (4.4)	6361 (3.3)	4918 (7.5)	5619 (3.3)	1635 (3.9)
Insulin	83 900 (25.7)	28 099 (29.3)	55 801 (24.2)	25 096 (33.1)	58 804 (23.4)	33 581 (17.6)	34 491 (52.7)	39 082 (23.2)	12 153 (29.1)
Sulfonylureas	92 736 (28.4)	26 245 (27.4)	66 491 (28.8)	20 994 (27.7)	71 742 (28.6)	51 560 (27.0)	25 917 (39.6)	46 514 (27.6)	12 562 (30.1)

Table 2. Initiation and discontinuation of ACEi/ARB, sMRA or antidiabetic medication during 1-year follow-up among the IC and by clinical status subgroups

		Comorbidities				Diabetes		CKD progression	
Treatment patterns	All patients	Anemia	No anemia	CVD	No CVD	HbA1c <8%	HbA1c ≥8%	eGFR <5 mL/ year	eGFR ≥5 mL/ year
ACEi/ARB or sMRA, *n* (%)									
No prior use of ACEi/ARB	18 407	3520	14 887	5885	12 522	11 585	3903	9953	2127
Initiation of ACEi/ARB	3269 (17.76)	517 (14.69)	2752 (18.49)	1 032 (17.5)	2237 (17.9)	1901 (16.4)	924 (23.7)	1625 (16.33)	461 (21.67)
Discontinuation of ACEi/ARB	1831 (56.0)	298 (57.6)	1533 (55.7)	583 (56.5)	1248 (55.8)	1 009 (53.1)	586 (63.4)	899 (55.32)	259 (56.18)
No prior use of sMRA	60 513	10 657	49 856	20 127	40 386	37 232	14 219	31 649	7448
Initiation of sMRA	795 (1.31)	198 (1.86)	597 (1.20)	362 (1.8)	433 (1.1)	443 (1.2)	226 (1.6)	307 (0.97)	216 (2.90)
Discontinuation of sMRA	528 (66.4)	133 (67.2)	395 (66.2)	240 (66.3)	288 (66.5)	282 (63.7)	164 (72.6)	205 (66.78)	153 (70.83)
No prior use of both ACEi/ARBs + sMRAs	60 775	11 030	49 745	20 406	40 909	37 696	14 386	32 113	7554
Initiation of sMRAs + ACEi/ARBs	632 (1.04)	141 (1.28)	491 (0.99)	297 (1.5)	335 (0.8)	360 (1.0)	171 (1.2)	248 (0.77)	159 (2.10)
Discontinuation of ACEi/ARBs + sMRAs	543 (85.9)	125 (88.7)	418 (85.1)	258 (86.9)	285 (85.1)	303 (84.2)	152 (88.9)	223 (89.92)	133 (83.65)
Antidiabetic medication, *n* (%)									
No prior use of SGLT2i	54 637	9809	44 828	20 075	40 700	37 724	13 758	32 021	7575
Initiation of SGLT2i	1366 (2.50)	185 (1.89)	1181 (2.63)	510 (2.5)	856 (2.1)	517 (1.4)	687 (5.0)	629 (1.96)	224 (2.96)
Discontinuation of SGLT2i	888 (65.0)	121 (65.4)	767 (64.9)	359 (70.4)	529 (61.8)	327 (63.2)	457 (66.5)	412 (65.50)	144 (64.29)
No prior use of DPP4i	60 401	10 891	49 510	18 106	36 531	34 245	11 895	28 807	6698
Initiation of DPP4i	2260 (3.74)	376 (3.45)	1884 (3.81)	821 (4.5)	1439 (3.9)	1144 (3.3)	809 (6.8)	1136 (3.94)	370 (5.52)
Discontinuation of DPP4i	1510 (66.8)	247 (65.7)	1263 (67.0)	557 (67.8)	953 (66.2)	725 (63.4)	576 (71.2)	775 (68.22)	244 (65.95)
No prior use of GLP-1 RA	61 315	10 866	50 449	20 025	40 376	37 530	13 680	31 813	7433
Initiation of GLP-1 RA	1308 (2.13)	199 (1.83)	1 109 (2.20)	586 (2.9)	722 (1.8)	465 (1.2)	651 (4.8)	621 (1.95)	178 (2.39)
Discontinuation of GLP-1 RA	901 (68.9)	135 (67.8)	766 (69.1)	406 (69.3)	495 (68.6)	304 (65.4)	465 (71.4)	420 (67.63)	122 (68.54)
No prior use of both SGLT2i + DPP4i	62 522	11 225	51 297	20 934	41 588	38 480	14 526	32 821	7743
Initiation of SGLT2i + DPP4i	384 (0.61)	66 (0.59)	318 (0.62)	152 (0.7)	232 (0.6)	164 (0.4)	172 (1.2)	169 (0.51)	70 (0.90)
Discontinuation of SGLT2i + DPP4i	324 (84.4)	60 (90.9)	264 (83.0)	127 (83.6)	197 (84.9)	139 (84.8)	147 (85.5)	145 (85.80)	57 (81.43)
No prior use of both SGLT2i + GLP-1 RA	62 764	11 267	51 497	21 010	41 754	38 591	14 632	32 957	7764
Initiation of SGLT2i + GLP-1 RA	309 (0.49)	45 (0.40)	264 (0.51)	127 (0.6)	182 (0.4)	104 (0.3)	165 (1.1)	147 (0.45)	47 (0.61)
Discontinuation of SGLT2i + GLP-1 RA	260 (84.1)	37 (82.2)	223 (84.5)	110 (86.6)	150 (82.4)	86 (82.7)	141 (85.5)	125 (85.03)	43 (91.49)
No prior use of both DPP4i + GLP-1 RA	62 827	11 258	51 569	21 090	41 737	38 641	14 639	32 998	7750
Initiation of DPP4i + GLP-1 RA	228 (0.36)	33 (0.29)	195 (0.38)	101 (0.5)	127 (0.3)	85 (0.2)	113 (0.8)	100 (0.30)	42 (0.54)
Discontinuation of DPP4i + GLP-1 RA	209 (91.7)	32 (97.0)	177 (90.8)	92 (91.1)	117 (92.1)	78 (91.8)	104 (92.0)	94 (94.00)	38 (90.48)
No prior use of both insulin	48 915	8815	40 100	14 655	34 260	33 444	8016	26 084	5770
Initiation of insulin	1935 (4.0)	339 (3.8)	1 596 (4.0)	798 (5.4)	1137 (3.3)	741 (2.2)	884 (11.0)	943 (3.6)	320 (5.5)
Discontinuation of insulin	1464 (75.7)	257 (75.8)	1207 (75.6)	607 (76.1)	857 (75.4)	558 (75.3)	665 (75.2)	702 (74.4)	262 (81.9)
No prior use of both SU	44 915	8305	36 610	14 645	30 270	28 890	8900	23 781	5424
Initiation of SU	2478 (5.5)	429 (5.2)	2065 (5.6)	829 (5.7)	1665 (5.7)	1408 (4.9)	748 (8.4)	1290 (5.4)	402 (7.4)
Discontinuation of SU	1411 (56.9)	228 (53.1)	1191 (57.7)	467 (56.3)	952 (57.2)	752 (53.4)	469 (62.7)	751 (58.2)	225 (56.0)

Table 3. Initiation and discontinuation of ACEi/ARB, sMRA or antidiabetic medication during 1-year follow-up among the IC and by KDIGO stages

	eGFR					UACR				
Treatment patterns	G3 (moderate–severe)	G4 (severe)	G5 (kidney failure)	Missing	Nonmissing	A1 (<30 mg/g)	A2 (30 –<300 mg/g)	A3 (>300 mg/g)	Missing	Nonmissing
ACEi/ARB or sMRA, *n* (%)										
No prior use of ACEi/ARB	2262	256	46	2109	16 298	2279	5630	940	9558	8849
Initiation of ACEi/ARB	355 (15.7)	44 (17.2)	6 (13.0)	503 (23.9)	2766 (17.0)	325 (14.3)	1399 (24.8)	288 (30.6)	1257 (13.2)	2012 (22.7)
Discontinuation of ACEi/ARB	198 (55.8)	27 (61.4)	4 (66.7)	283 (56.3)	1548 (56.0)	166 (51.1)	806 (57.6)	176 (61.1)	683 (54.3)	1148 (57.1)
No prior use of sMRA	7359	832	142	7750	52 763	796	20 547	4 003	28 167	32 346
Initiation of sMRA	119 (1.6)	12 (1.4)	2 (1.4)	115 (1.5)	680 (1.3)	59 (0.8)	270 (1.3)	100 (2.5)	366 (1.3)	667 (2.1)
Discontinuation of sMRA	77 (64.7)	7 (58.3)	1 (50.0)	76 (66.1)	452 (66.5)	37 (62.7)	168 (62.2)	66 (66.0)	257 (70.2)	442 (66.3)
No prior use of both ACEi/ARB + sMRA	7522	849	142	7794	53 521	7908	20 677	4055	28 675	32 640
Initiation of ACEi/ARB + sMRA	105 (1.4)	10 (1.2)	0 (0)	88 (1.1)	544 (1.0)	48 (0.6)	218 (1.1)	88 (2.2)	278 (1)	354 (1.1)
Discontinuation of ACEi/ARB + sMRA	93 (88.6)	7 (70.0)	– (–)	73 (83.0)	470 (86.4)	44 (91.7)	179 (82.1)	72 (81.8)	248 (89.2)	295 (83.3)
Antidiabetic medication, *n* (%)										
No prior use of SGLT2i	7707	887	140	7531	53 244	7911	19 912	3979	28 973	31 802
Initiation of SGLT2i	61 (0.8)	7 (0.8)	3 (2.1)	235 (3.1)	1 131 (2.1)	133 (1.7)	723 (3.6)	142 (3.6)	368 (1.3)	998 (3.1)
Discontinuation of SGLT2i	47 (77.0)	4 (57.1)	3 (100.0)	139 (59.1)	749 (66.2)	99 (74.4)	439 (60.7)	101 (71.1)	249 (67.7)	639 (64.0)
No prior use of DPP4i	6843	780	129	6645	47 992	7120	17 794	3513	26 210	28 427
Initiation of DPP4i	323 (4.7)	29 (3.7)	6 (4.7)	305 (4.6)	1955 (4.1)	251 (3.5)	835 (4.7)	179 (5.1)	995 (3.8)	1265 (4.4)
Discontinuation of DPP4i	203 (62.8)	21 (72.4)	4 (66.7)	197 (64.6)	1313 (67.2)	154 (61.4)	556 (66.6)	121 (67.6)	679 (68.2)	831 (65.7)
No prior use of GLP-1 RA	7634	871	140	7525	52 876	7818	19 831	3913	28 839	31 562
Initiation of GLP-1 RA	142 (1.9)	20 (2.3)	5 (3.6)	193 (2.6)	1115 (2.1)	153 (2.0)	593 (3.0)	122 (3.1)	440 (1.5)	868 (2.8)
Discontinuation of GLP-1 RA	97 (68.3)	11 (55.0)	3 (60.0)	133 (68.9)	768 (68.9)	99 (64.7)	407 (68.6)	92 (75.4)	303 (68.9)	598 (68.9)
No prior use of both SGLT2i + DPP4i	7835	902	143	7817	54 705	8102	20 773	4109	29 538	32 984
Initiation of SGLT2i + DPP4i	20 (0.3)	7 (0.8)	0 (0)	67 (0.9)	317 (0.6)	30 (0.4)	194 (0.9)	32 (0.8)	128 (0.4)	256 (0.8)
Discontinuation of SGLT2i + DPP4i	18 (90.0)	6 (85.7)	– (–)	53 (79.1)	271 (85.5)	23 (76.7)	163 (84.0)	30 (93.8)	108 (84.4)	216 (84.4)
No prior use of both SGLT2i + GLP-1 RA	7873	903	144	7867	54 897	8131	20 857	4130	29 646	33 118
Initiation of SGLT2i + GLP-1 RA	15 (0.2)	2 (0.2)	1 (0.7)	53 (0.7)	256 (0.5)	34 (0.4)	173 (0.8)	26 (0.6)	76 (0.3)	233 (0.7)
Discontinuation of SGLT2i + GLP-1 RA	14 (93.3)	1 (50.0)	1 (100.0)	46 (86.8)	214 (83.6)	30 (88.2)	144 (83.2)	24 (92.3)	62 (81.6)	198 (85.0)
No prior use of both DPP4i + GLP-1 RA	7864	902	144	7868	54 959	8147	20 923	4119	29 638	33 189
Initiation of DPP4i + GLP-1 RA	29 (0.4)	6 (0.7)	1 (0.7)	32 (0.4)	196 (0.4)	28 (0.3)	95 (0.5)	18 (0.4)	0 (0)	141 (0.4)
Discontinuation of DPP4i + GLP-1 RA	27 (93.1)	5 (83.3)	1 (100.0)	30 (93.8)	179 (91.3)	26 (92.9)	85 (89.5)	17 (94.4)	– (–)	128 (90.8)
No prior use of both insulin	6067	639	115	5881	43 034	6587	15 407	2573	24 348	24 567
Initiation of insulin	311 (5.1)	57 (8.9)	7 (6.1)	259 (4.4)	1 676 (3.9)	210 (3.2)	727 (4.7)	190 (7.4)	808 (3.3)	1127 (4.6)
Discontinuation of insulin	226 (72.7)	43 (75.4)	5 (71.4)	192 (74.1)	1 272 (75.9)	157 (74.8)	556 (76.5)	150 (78.9)	601 (74.4)	863 (76.6)
No prior use of both SU	5481	619	102	5271	39 644	5865	14 344	2798	21 908	23 007
Initiation of SU	353 (6.4)	64 (10.3)	11 (10.8)	311 (5.9)	2183 (5.5)	329 (5.6)	804 (5.6)	228 (8.1)	1133 (5.2)	1361 (5.9)
Discontinuation of SU	193 (54.7)	37 (57.8)	7 (63.6)	180 (57.9)	1239 (56.8)	176 (53.5)	493 (61.3)	129 (56.6)	621 (54.8)	798 (58.6)

Table 4. Rates per 1000 person-years (95% CI) for hospitalizations, kidney outcomes and mortality and total healthcare costs among the PC and by clinical status subgroups

		Comorbidities				Diabetes		CKD progression	
Clinical outcomes and costs	All patients	Anemia	No anemia	CVD	No CVD	HbA1c <8%	HbA1c ≥8%	eGFR <5 mL/ year	eGFR ≥5 mL/ year
Patients, *n*	326 763	95 912	230 851	75 834	250 929	190 874	65 482	168 621	41 720
Hospitalizations									
All-cause hospitalization	283.14 (281.09–285.20)	439.17 (434.25–444.10)	225.29 (223.14–227.44)	558.13 (551.71–564.55)	213.53 (211.53–215.53)	253.87 (251.35–256.39)	289.60 (284.91–294.29)	243.75 (241.2–246.3)	351.36 (345.04–357.68)
CV-related hospitalizations[a]	78.32 (77.29–79.35)	124.79 (122.35–127.24)	59.90 (58.84–60.97)	213.37 (209.69–217.05)	41.61 (40.76–42.46)	66.40 (65.17–67.63)	88.42 (85.94–90.89)	59.46 (58.26–60.67)	112.33 (108.95–115.71)
HF-related hospitalizations	51.95 (51.11–52.78)	91.46 (89.38–93.53)	36.24 (35.41–37.06)	168.37 (165.13–171.60)	20.01 (19.43–20.60)	42.97 (41.98–43.96)	56.66 (54.69–58.62)	38.49 (37.53–39.45)	81.86 (78.99–84.73)
Kidney hospitalization	36.61 (35.91–37.31)	76.09 (74.20–77.97)	20.92 (20.29–21.54)	91.34 (89.00–93.68)	21.05 (20.45–21.65)	29.64 (28.82–30.45)	40.56 (38.90–42.22)	27.75 (26.94–28.57)	53.46 (51.16–55.76)
Kidney outcomes									
Kidney transplant	2.17 (2.00–2.34)	3.29 (2.90–3.68)	1.72 (1.54–1.90)	1.99 (1.65–2.33)	2.23 (2.03–2.42)	1.98 (1.77–2.19)	2.20 (1.81–2.58)	1.67 (1.47–1.87)	3.86 (3.25–4.47)
ESKD	104.19 (102.98–105.39)	213.21 (209.90–216.51)	63.56 (62.46–64.66)	196.50 (192.95–200.06)	78.74 (77.56–79.93)	89.13 (87.68–90.57)	97.22 (94.61–99.83)	96.16 (94.61–97.72)	145.17 (141.28–149.06)
Mortality									
All-cause mortality (post-2011 time period[b])	35.07 (34.39–35.75)	58.67 (57.04–60.30)	25.45 (24.77–26.14)	80.42 (78.27–82.58)	21.77 (21.17–22.38)	31.53 (30.69–32.37)	30.38 (28.96–31.80)	14.03 (13.45–14.6)	32.02 (30.26–33.78)
Total healthcare costs									
Mean (SD)	29 377.11 (63 788.94)	46 125.42 (92 528.99)	22 418.67 (45 139.27)	37 464.73 (73 329.91)	24 270.85 (56 353.31)	26 272.92 (57 889.39)	30 386.64 (65 847.75)	28 557.53 (61 567.68)	35 521.61 (69 169.79)
Median (minimum–maximum)	10 637.62 (0–5 510 172.95)	16 929.92 (0–5 510 172.95)	8 971.78 (0–2 720 822.86)	14 582.13 (0–2 776 130.79)	8 820.05 (0–5 510 172.95)	9 500.23 (0–3 264 757.48)	11 826.69 (0–5 510 172.95)	10 900.63 (0–3 264 757.48)	14 294.7 (0–5 510 172.95)

[a]As defined by myocardial infarction, stroke, heart failure, peripheral artery disease or revascularization.

[b]Some states stopped reporting death for privacy concerns in 2011. Approximately 30% fewer deaths are captured after this date in the CDM data and death rates are assumed to be underestimated.

Table 5. Rates per 1000 person-years (95% CI) for hospitalizations, kidney outcomes and mortality and total healthcare costs among by KDIGO stages in the PC

	eGFR			UACR		
Clinical outcomes and costs	G3 (moderate–severe)	G4 (severe)	G5 (kidney failure)	A1 (<30 mg/g)	A2 (30 – <300 mg/g)	A3 (>300 mg/g)
Patients, *n*	71 548	21 471	5109	36 488	81 768	25 495
Hospitalizations						
All-cause hospitalization	351.11 (346.18–356.05)	562.84 (550.77–574.92)	968.32 (932.55–1004.09)	201.87 (196.85–206.89)	210.26 (206.74–213.78)	326.00 (317.91–334.10)
CV-related hospitalizations[a]	103.53 (101.00–106.06)	187.21 (180.80–193.62)	213.37 (199.13–227.60)	43.93 (41.68–46.19)	57.64 (55.86–59.42)	108.88 (104.42–113.34)
HF-related hospitalizations	73.45 (71.33–75.57)	142.90 (137.34–148.45)	144.19 (132.64–155.74)	26.40 (24.66–28.14)	34.88 (33.50–36.26)	70.15 (66.60–73.70)
Kidney hospitalization	47.12 (45.44–48.81)	161.15 (155.23–167.07)	456.72 (434.67–478.76)	15.94 (14.59–17.29)	18.56 (17.56–19.56)	62.48 (59.14–65.82)
Kidney outcomes						
Kidney transplant	1.91 (1.57–2.25)	4.55 (3.59–5.51)	18.59 (14.57–22.61)	0.95 (0.62–1.27)	2.11 (1.77–2.44)	3.18 (2.43–3.92)
ESKD	131.28 (128.39–134.16)	462.07 (451.17–472.97)	4604.21 (4467.87–4740.55)	53.01 (50.52–55.50)	45.81 (44.22–47.39)	149.29 (143.97–154.61)
Mortality						
All-cause mortality (stratified by post-2011 time period[b])	46.76 (45.10–48.43)	84.24 (80.10–88.37)	118.66 (108.54–128.78)	23.00 (21.39–24.62)	24.47 (23.32–25.61)	39.14 (36.53–41.75)
Total healthcare costs						
Mean (SD)	30 769.60 (54 311.97)	50 581.46 (92 888.41)	184 159.01 (221 957.95)	21 575.30 (41 509.91)	21 506.66 (44 629.85)	32 652.04 (71 471.76)
Median (minimum–maximum)	12 771 (0–1 824 401)	19 859.91 (0–2 563 708.68)	184 159.01 (0–2 776 130.79)	9 219.57 (0–2 004 015)	8 723.65 (0–2 168 003.05)	11 914.59 (0–2 687 156.68)

[a] As defined by myocardial infarction, stroke, HF, peripheral artery disease or revascularization.

[b] Some states stopped reporting death for privacy concerns in 2011. Approximately 30% fewer deaths are captured after this date in the CDM data and death rates are assumed to be underestimated.

Table 6. Rates per 1000 person-years (95% CI) for hospitalizations, kidney outcomes and mortality and total healthcare costs by treatment subgroups in the PC

	Monotherapy			Combination therapy		Comprehensive care combination therapy (without sMRA)			Comprehensive care combination therapy (with sMRA)		
Clinical outcomes and costs	Insulin	ACEi/ARB	sMRA	Insulin with SGLT2i	ACEi/ARB with sMRA	SGLT2i with ACEi/ARB	DPP4i with ACEi/ARB	GLP-1 RA with ACEi/ARB	SGLT2i with ACEi/ARB and sMRA	DPP4i with ACEi/ARB and sMRA	GLP-1 RA with ACEi/ARB and sMRA
Patients, *n*	83 900	27 166	2417	2896	6343	6703	15 780	8857	300	1130	556
Hospitalizations											
All-cause hospitalization	372.36 (367.56–377.15)	373.62 (363.40–383.84)	930.82 (862.16–999.48)	215.05 (195.79–234.31)	734.24 (697.73–770.74)	153.00 (137.91–168.08)	283.72 (270.08–297.36)	206.17 (190.10–222.25)	243.36 (146.00–340.72)	526.36 (449.04–603.69)	385.33 (292.36–478.29)
CV-related hospitalizations[a]	113.13 (110.65–115.62)	103.60 (98.44–108.77)	357.11 (317.16–397.06)	54.02 (44.73–63.31)	293.66 (271.52–315.79)	29.77 (23.21–36.34)	76.45 (69.52–83.38)	53.07 (45.05–61.10)	68.46 (27.53–141.06)	239.67 (188.72–290.62)	128.74 (76.13–181.36)
HF-related hospitalizations	77.10 (75.06–79.14)	63.45 (59.43–67.47)	319.16 (281.51–356.81)	33.75 (26.45–41.06)	245.24 (225.09–265.39)	15.39 (10.68–20.10)	51.21 (45.56–56.87)	29.26 (23.31–35.20)	48.77 (15.84–113.81)	190.37 (145.12–235.62)	105.23 (57.91–152.55)
Kidney hospitalization	61.29 (59.48–63.10)	65.10 (61.02–69.18)	192.51 (163.66–221.37)	27.53 (20.94–34.12)	137.88 (122.93–152.82)	62 (5.10–12.14)	41.20 (36.13–46.26)	31.77 (25.58–37.97)	19.43 (2.35–70.19)	115.44 (80.52–150.35)	71.82 (32.78–110.86)
Kidney outcomes											
Kidney transplant	2.66 (2.29–3.03)	2.68 (1.86–3.50)	2.16 (0.26–7.81)	0.81 (0.10–2.93)	2.88 (1.16–5.94)	1.50 (0.41–3.83)	3.22 (1.81–4.63)	2.82 (1.29–5.34)	0.00 (0.00–35.77)	0.00 (0.00–9.97)	0.00 (0.00–20.12)
ESKD	162.11 (159.07–165.15)	184.28 (177.23–191.33)	300.06 (263.37–336.74)	43.93 (35.57–52.29)	221.10 (201.90–240.31)	27.46 (21.16–33.76)	106.03 (97.81–114.24)	72.04 (62.65–81.44)	39.16 (10.67–100.27)	191.50 (145.98–237.02)	128.43 (75.95–180.92)
Mortality											
All-cause mortality (stratified by post-2011 time period[b])	40.49 (39.04–41.94)	41.73 (38.50–44.97)	153.43 (128.19–178.66)	13.39 (8.82–17.95)	63.80 (53.76–73.85)	5.24 (2.49–7.98)	18.34 (14.97–21.70)	6.25 (3.51–9.00)	0.00 (0.00–35.77)	40.55 (20.03–61.08)	5.45 (0.14–30.39)
Total healthcare costs											
Mean (SD)	41 957.00 (82 826.40)	23 088.87 (57 886.54)	24 693.23 (43 126.11)	34 083.62 (60 917.35)	20 611.00 (39 397.57)	11 764.23 (21 008.75)	13 169.28 (29 103.39)	13 503.48 (25 975.71)	17 287.95 (34 456.83)	15 799.88 (26 912.35)	18 616.93 (37 782.70)
Median (minimum–maximum)	17 787.44 (0–5 510 172.95)	6 005.85 (0–2 098 634.45)	8106.49 (0–609 100.49)	19 657.70 (0–1 679 058.98)	6867.71 (0.87–677 838.79)	5191.99 (0–660 891.4)	4 747.23 (0–832 501.21)	6003.67 (0–672 890.75)	6439.83 (228.98–389 872.32)	6247.79 (55.74–300 728.83	7927.76 (27.14–610 133.44)

[a]As defined by myocardial infarction, stroke, HF, peripheral artery disease or revascularization.
[b]Some states stopped reporting death for privacy concerns in 2011. Approximately 30% fewer deaths are captured after this date in the CDM data and death rates are assumed to be underestimated.

Among patients in the predefined clinical subgroups, all-cause hospitalizations, cardiovascular-related hospitalizations, kidney outcomes and mortality were frequent among patients with CKD and T2D with selected multimorbidities (anemia or CVD). In addition, patients with rapid progression of CKD (i.e. eGFR decline ≥5 mL/year) experienced elevated rates of CV-related hospitalization [112.33 per 1000 person-years (95% CI 108.95–115.71)] and heart failure (HF)-related hospitalization [81.86 per 1000 person-years (95% CI 78.99–84.73)]. Patients with rapid progression of CKD also had nearly three-times higher rates of all-cause mortality, while the mortality rates approximately doubled from UACR stage A1 to stage A3.

In the treatment subgroup analysis we observed high rates of CV-related hospitalizations among patient subgroups prescribed solely antihypertensive medications (i.e. ACEi/ARB monotherapy or sMRA monotherapy). We also observed high rates of ESKD among patient subgroups prescribed solely antihypertensive medications, with a rate of 184.28 (95% CI 177.23–191.33) and 300.06 (95% CI 263.37–336.74) for ACEi/ARB monotherapy and for sMRA monotherapy, respectively.

Overall, the mean total healthcare costs were $29 377.11 per year (SD $63 788.94) in the PC. Total healthcare costs were higher among subgroups of patients with comorbid CVD or anemia ($37 464.73 and $46 125.42, respectively) compared with their counterparts. Patients with rapidly progressing CKD (eGFR decline ≥5 mL/year) incurred similar high costs. Additionally, patients in later stages of CKD (lower levels of eGFR or higher levels of UACR) had higher total healthcare costs, ranging from $30 770 for patients with CKD stage G3B to $184 159 for patients with CKD stage G5.

DISCUSSION

In this US-based cohort study evaluating treatment patterns and the disease burden of CKD and T2D, we observed a high unmet need in the treatment of patients with CKD and T2D within various comorbidity and treatment subgroups.

Overall, in the year prior to CKD diagnosis, ACEis, ARBs, insulin, sulfonylureas and metformin were the most common drugs prescribed in approximately a third of T2D patients with prevalent or incident CKD. In this population, only a few patients were prescribed SGLT2i and GLP-1 RA during the year prior to CKD diagnosis, while all antihypertensives were used more in patients with prior CVD. Among newly diagnosed CKD patients without prior medication use, low initiation rates of antihypertensives following CKD diagnosis were observed; even lower rates were observed for antidiabetic agents, while antidiabetic combinations were the most infrequent. However, in accordance with treatment guidelines during the study time period, the recommended RAS inhibitors had the highest initiation rates, while treatments advised against, such as the combination of DPP4i and GLP-1 RA, were almost never initiated and frequently discontinued [10]. Despite the low initiation rates, among subgroups we observed slightly higher rates among the multimorbid subgroups in the study population (i.e. CVD or CKD progression). Antihypertensive initiation rates were higher in patients with higher UACR stages, and the same trend was observed for SGLT2i and GLP-1 RA (individually and in combination) in more advanced eGFR stages. However, we found high discontinuation rates for SGLT2i (individually and in combination) among these subgroups, although the time period predates publication of the Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy study, showing benefit on the progression of kidney disease in those with a reduced eGFR [20, 21]. Similarly, we observed slightly higher initiation rates for sMRAs in less advanced eGFR stages; sMRA treatment during the study time period was recommended for patients with resistant hypertension and eGFR values >45 mL/min/1.73 m^2 [10]. Among patients who initiated antihypertensive medications after CKD diagnosis, the majority discontinued these treatments with higher rates in the CVD subgroup and the higher UACR subgroup. We also observed higher rates of all-cause hospitalization, cardiovascular-related hospitalization, kidney outcomes and all-cause mortality. The rates were high, particularly in patients with rapid progression of CKD (i.e. eGFR decline ≥5 mL/year) and later stages of CKD (lower levels of eGFR or higher levels of UACR), reflecting higher total healthcare costs. The clinical outcome rates were also higher among patients prescribed angiotensin–aldosterone inhibitors (i.e. sMRA monotherapy or with ACEi/ARB), which remained within a high range despite the slight decrease after the addition of SGLT2i and GLP-1 RA, suggesting that patients treated with these emerging therapies in CKD still have a high unmet therapeutic need. To evaluate the potential for selection bias by sampling those with laboratory results, we examined initiation and discontinuation treatment patterns among participants selected based only on eGFR or UACR, as well as with and without laboratory data, and found that there were no notable differences between the different groups.

Clinical guidelines recommend ACEi/ARB therapies to slow CKD progression. Furthermore, ACEi or ARB therapy is recommended as first-line treatment for patients with CKD and T2D who have hypertension and UACR ≥30 mg/g creatinine in order to delay CKD progression [10]. Additionally, evidence from meta-analyses demonstrate that coadministration of sMRA and ACEi/ARB show a UACR reduction but no clear eGFR preservation [11]. Indeed, randomized trials have shown evidence of increased risk of hyperkalemia and acute kidney injury when these treatments are combined; thus such combination treatment might not be used [19]. We observed low initiation rates and frequent discontinuation in our study for combinations of RAS inhibitors and sMRAs. This may be explained by adverse events similar to those observed in these trials. Additionally, it may be that these medications are simply indicated for resistant hypertension and heart failure, rather than CKD, in this study population. Nonetheless, the lack of medication persistence may be contributing to the elevated rates of clinical outcomes found in our study or the other indications for which these medications are prescribed. Further investigation is warranted on the reasons for discontinuation and their impacts [21, 22].

Intensive personalized glycemic control is recommended to treat patients with T2D [22, 23]. In addition, several cardiovascular safety trials evaluating antiglycemic drug classes among T2D patients using SGLT2is or GLP-1 RAs demonstrated a lower risk of cardiorenal events [23–26]. However, a clinical trial found that intensive glycemic control among patients with diabetes and baseline kidney disease resulted in higher rates of adverse events [26, 27]. Given that GLP-1 RAs and SGLT2is were first approved by the US Food and Drug Administration in 2005 and 2013, respectively, the use of these medications was low in our study population. Moreover, where used, these antiglycemic drugs, with evidence of their renoprotective effects coming even later, were discontinued in the majority of the study population and in almost all patients prescribed combinations of these drugs in the year following incident CKD diagnosis. While these new classes of antiglycemic therapy are increasingly becoming a part of the treatment regimen for patients with CKD and T2D, a better understanding of factors contributing to their low initiation and high discontinuation rates is needed and may warrant further investigation of physician and patient barriers to appropriate care.

Limitations

First, administrative claims data have the potential for misclassification of patients' diagnoses, since the presence of a claim with a diagnosis code may not indicate the presence of a disease but a rule-out code. Similarly, the limited duration of baseline enrollment may not allow capturing some patients with the disease, resulting in potential misclassification. To address this limitation in identifying patients with CKD and T2D, we used a validated algorithm for T2D as well as results from laboratory tests (eGFR and UACR) indicating sustained kidney disease for >3 months. Limited follow-up time in administrative claims may have also contributed to underestimation of rates of events. We found a high lack of screening for UACR, potentially impacting the representativeness of the CKD population. Nevertheless, treatment patterns analyses showed a similar trend overall between participants with and without UACR and eGFR lab values. Research into initiation and discontinuation rates among T2D patients and CKD patients separately could further evaluate the impact of disease over prescription. Third, requiring 1 year of continuous enrollment after the index date in the IC may have introduced selection bias. By requiring patients to remain continuously enrolled in their health plan for a fixed period of time following the index date, the resultant population may have biased the selection of healthier patients, as those who do not survive or are not enrolled for a minimum period of follow-up were excluded from the cohort. However, applying this requirement allowed for the uninterrupted evaluation of treatment patterns following the index event and reduced the bias due to competing risks. Fourth, using an 'as-treated' censoring approach after treatment initiation, meaning censoring patient follow-up after the treatment initiation due to reasons such as disenrollment or death, may have led to underestimates in the treatment discontinuation rate, highlighting an even greater unmet need. Fifth, the maximum allowed gap used in our study when evaluating drug discontinuation was 30 days, which may have overestimated discontinuation rates. However, this threshold was based on published literature by Bjarnadóttir *et al.* [17] showing that 68.7% of patients would have no gap in treatment coverage using this cut-off. Longer gaps might therefore reduce the observed discontinuation for a subset of patients. Sixth, while the CDM is representative of the commercially insured population of the USA, it may not be generalizable to individuals without commercial insurance.

CONCLUSIONS

Our results demonstrate a high unmet need among patients with CKD and T2D, particularly subgroups of patients with multimorbid CVD, advanced CKD (low eGFR or high UACR) or rapidly progressing CKD. Low initiation and high discontinuation of recommended therapies among these patients suggest that adherence to treatment guidelines for halting CKD progression is suboptimal. These high-risk patients may benefit from further treatment options to improve mortality and morbidity and reduce the economic burden.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

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CONFLICT OF INTEREST STATEMENT

L.F. is a consultant for Bayer Fibrogen and Akebia and a Data Safety Monitoring Board member for Novo Nordisk and CSL Behring. C.K. is a consultant for Abbott, Akebia, AstraZeneca, Bayer, Boehringer Ingelheim, Cara Therapeutics, CSL Behring, Rockwell and Vifor. K.F. is an employee of Bayer. K.B. was an employee of Bayer Plc and all of his work for this study was done under Bayer Plc affiliation. N.S. was an employee of Bayer AG and is now an employee of Boehringer Ingelheim. All of his work for this study was done under Bayer AG affiliation. H.R., M.B. and A.F. have no conflicts of interest to report. The results presented in this paper have not been published previously in whole or part, except in abstract form.

AUTHORS' CONTRIBUTIONS

L.F., N.S., K.F., K.B. and C.K. contributed to both the design of the study and interpretation of data, revision of the article and provided intellectual content of critical importance to the work described. H.R., M.B. and A.F. contributed to the analysis and interpretation of data, drafting and revision of the article, and provided intellectual content of critical importance to the work described. All authors had final approval of the version for publication.

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