Adv Ther
https://doi.org/10.1007/s12325-024-03028-z

ORIGINAL RESEARCH

Baseline Characteristics of the DISCOVER CKD Prospective Cohort

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Received: April 5, 2024 / Accepted: October 9, 2024

ABSTRACT

***Introduction*:** Real-world data from patients with chronic kidney disease (CKD) are limited, particularly regarding clinical management, treatment patterns and health-related quality of life (HRQoL) in the context of new therapies and updated standard of care guidelines.
***Methods*:** DISCOVER CKD is an observational cohort study enrolling adult patients with CKD, defined by an International Classification of Diseases, 10th Revision code, or with two estimated glomerular filtration rate measures < 75 ml/min/1.73 m^2 recorded 91–730 days apart. We describe the demographics, baseline characteristics and patient-reported outcomes of patients enrolled in the prospective phase.
***Results*:** Of 1052 patients (mean age 62.5 years; 36.9% female) enrolled from the USA, UK, Spain, Italy, Sweden and Japan, 727 (69.1%) had stage 2–3b CKD and 325 (30.9%) had stage 4–5 CKD. Overall, 72.4%, 43.0% and 37.5% of patients had histories of hypertension, diabetes and hyperlipidaemia, respectively. In total, 58.7% and 14.0% were receiving renin–angiotensin–aldosterone system inhibitors (RAASi)

Prior Presentation: Presented at the World Congress of Nephrology, March 30–April 2, 2023, Bangkok, Thailand.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-024-03028-z.

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Published online: 29 November 2024

and sodium-glucose co-transporter 2 inhibitors (SGLT2i), respectively. Compared with patients with stage 2–3b CKD, patients with stage 4–5 CKD reported numerically greater symptom burden across all 11 symptoms measured, numerically worse HRQoL across all eight categories measured using the 36-item Short Form (SF-36) questionnaire, and numerically greater impairment at work across all four categories measured using the Work Productivity and Activity Impairment chronic kidney disease (WPAI-CKD) questionnaire. Compared with patients with stage 2–3b CKD, a higher proportion of patients with stage 4–5 CKD had anaemia, hyperkalaemia and oedema (49.8% vs. 16.9%, 21.8% vs. 8.4% and 17.5% vs. 9.5%, respectively).

***Conclusions*:** These contemporary real-world data from six countries highlight the substantial symptom, medication and psychosocial burden associated with CKD, and continued gaps in treatment.

Graphical abstract available for this article.

***Trial registration*:** ClinicalTrials.gov identifier, NCT04034992.

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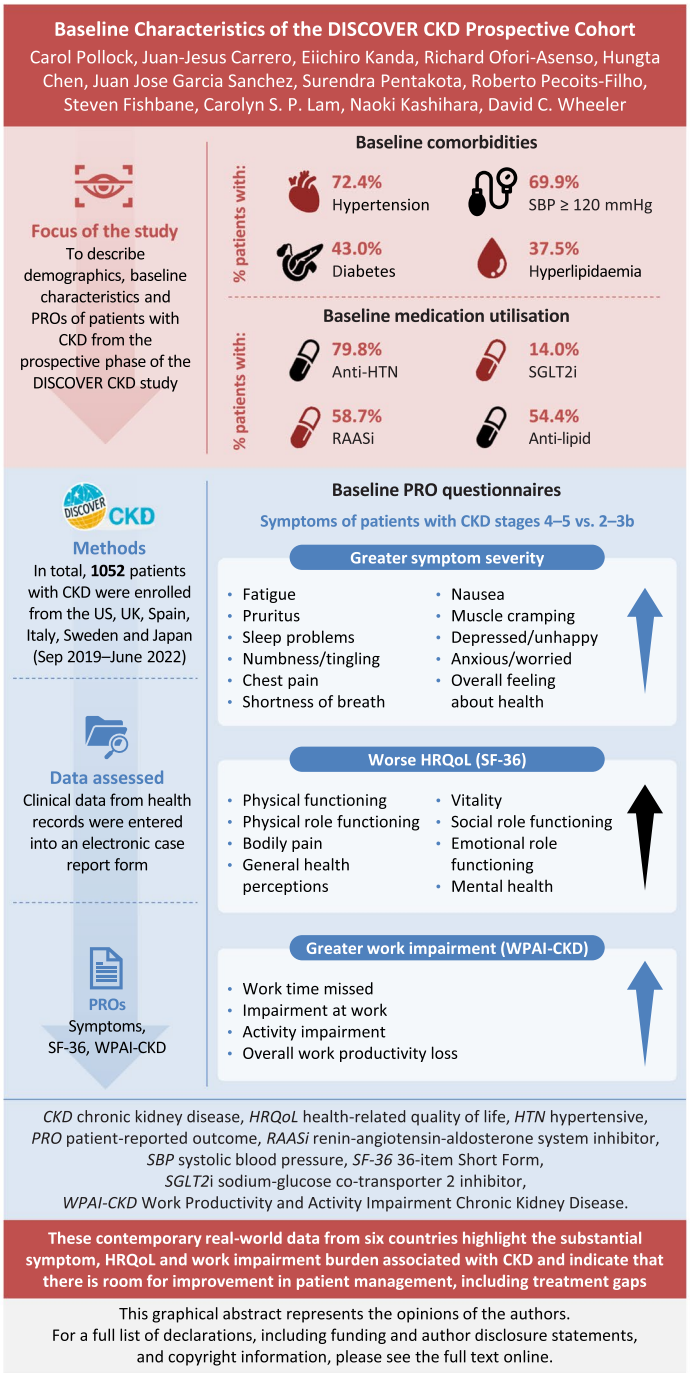
Graphical Abstract:



Keywords: Chronic kidney disease; DISCOVER CKD; Epidemiology; Patient-reported outcomes; Baseline characteristics

Key Summary Points

Why carry out this study?

Real-world data describing the clinical management of chronic kidney disease (CKD), treatment patterns and patient health-related quality of life (HRQoL) are limited in the context of new therapies and updated standard of care guidelines.

The prospective phase of the DISCOVER CKD observational study sought to improve our understanding of real-world CKD management and the patient experience by combining clinical and patient-reported data from a diverse patient cohort within different healthcare settings.

What was learned from the study?

Patients with CKD had a substantial comorbidity burden (hypertension, 72.4%; diabetes, 43.0%; hyperlipidaemia, 37.5%) and reported a high symptom burden, diminished work productivity and suboptimal HRQoL.

Use of guideline-directed therapies, including antihypertensive medications and renin–angiotensin–aldosterone system inhibitors, was suboptimal.

The results of this study confirm the negative impact of a diagnosis of CKD, regardless of disease stage, and indicate that patient management, including the use of guideline-directed therapies, can be improved.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.27195795.

INTRODUCTION

Chronic kidney disease (CKD) is highly prevalent and associated with substantial morbidity, mortality, and healthcare costs [1, 2]. There are more than 800 million people living with CKD, representing approximately 10% of the global population [3]. Patients with CKD have a high symptom burden and reduced health-related quality of life (HRQoL), regardless of CKD stage [4, 5], suggesting that there are opportunities for improved care for patients with CKD.

Using patient-reported outcomes (PROs) to guide treatment decisions enhances care by engaging patients in their own health assessment, improving the relationship with their treating physician, and helping to identify symptoms that may typically be neglected or under-recognised [6], thus allowing treatments to be tailored to individual needs. One study in patients with advanced cancer found that including symptom reporting alongside routine chemotherapy in patient care resulted in better HRQoL and survival rates than routine chemotherapy alone [7].

Real-world data from patients with CKD—particularly regarding clinical management, treatment patterns and HRQoL in the context of new therapies and updated standard of care guidelines—are limited [8]. DISCOVER CKD [8] (ClinicalTrials.gov identifier NCT04034992) is a multi-country, non-interventional cohort study that aims to characterise the epidemiology of CKD and describe clinical outcomes, including disease progression, pharmacological interventions and important clinical events across the patient journey. DISCOVER CKD aimed to recruit a diverse patient cohort, with representation from different countries and healthcare settings. The study includes retrospective [9, 10] and prospective cohorts; the retrospective phase comprises secondary data from more than 1.8 million patients (beginning 1 January 2008) and the prospective phase complements the retrospective phase by providing contemporary clinical and patient-reported data [8].

By using data from routine care, results from the prospective study may improve our understanding of real-world CKD management, as

well as the patient experience, and may facilitate improvements in CKD management and prognosis [8]. The prospective study will amalgamate clinical and patient-reported data to create a rich, up-to-date database that will be used to improve our understanding of CKD progression and the factors associated with PROs, with the ultimate aim of improving HRQoL and patient outcomes for patients with CKD. Here, we describe patient demographics, baseline characteristics and PROs of patients enrolled in the prospective phase of the DISCOVER CKD study.

METHODS

The DISCOVER CKD study rationale and methodology have been described previously [8] and are summarised below.

Patient Population

Patients with CKD were enrolled during September 2019–June 2022 from 45 sites across the USA ($n = 11$), the UK ($n = 7$), Spain ($n = 9$), Italy ($n = 5$), Sweden ($n = 4$) and Japan ($n = 9$). Investigators at each site supervised patient enrollment and data collection. Patients were followed up prospectively for a minimum of 1 year (potential maximum of approximately 3 years). All patients currently enrolled in DISCOVER CKD were included in this analysis; eligible patients were aged ≥ 18 years (≥ 20 years in Japan) with a confirmed diagnosis of CKD, defined by an International Classification of Diseases, 10th Revision (ICD-10) code for CKD (Supplementary materials), or with two estimated glomerular filtration rate (eGFR) measures of < 75 ml/min/1.73 m^2 recorded 91–730 days apart, or with an ICD-10 code for kidney failure with replacement therapy. eGFR was used for the definition of stage 2 CKD. The index date was the date of enrolment.

Data Capture

Secondary clinical data were extracted from patients' existing health records and entered into an electronic case report form. PROs were collected through questionnaires completed via a customised digital app at baseline and then every 6 months thereafter, except for symptoms, which were surveyed weekly. Completion of PRO questionnaires was voluntary, and patients did not receive payments or reimbursements.

PROs

HRQoL was measured via the 36-item Short Form (SF-36) questionnaire (4-week recall version) [11, 12] and scored using the Optum® PRO CoRE 1.5 Smart Measurement® System (2019) [13]. The SF-36 questionnaire consists of eight equally weighted sections, which are scored out of a maximum of 100; a score of 0 is equivalent to maximum disability and a score of 100 is equivalent to no disability. Outcomes are presented as mean scores. Physical activity measurements were based on the Rapid Assessment of Physical Activity (RAPA) questionnaire, which includes measures of aerobic activity (Part 1) and measures of strength and flexibility (Part 2) [14]. Proportions of patients within each activity level grouping are reported. Work productivity was measured via the Work Productivity and Activity Impairment chronic kidney disease (WPAI-CKD) questionnaire; five of six questions were based on a 7-day recall period [15]. Only employed patients were asked to complete the work productivity section of the WPAI-CKD questionnaire. Scores are expressed as mean percentage impairment; a score of 100% indicates the maximum impairment and lowest productivity.

Additional relevant symptoms were measured weekly with a 7-day recall period and rated out of 10, with higher scores indicating the greatest symptom severity (Supplementary materials). Additionally, patients rated their overall feeling about health (right now). The list of symptoms assessed was developed by AstraZeneca, based on a literature review and feedback from a patient advisory board. Mean scores are reported for individual symptoms. Diet was assessed via a simple 7-day food diary recorded by the patient at baseline.

Statistical Analysis

The present data are based on an interim study database analysis performed in November 2022. Patient characteristics were summarised descriptively. The overall cohort comprised all enrolled patients. Descriptive analyses were performed for the overall cohort and stratified by stage 2–3b CKD and stage 4–5 CKD (including patients on dialysis and with kidney transplantation), PRO completers and non-completers, and country. Each patient was clinically staged at baseline by the enrolling physician. CKD stage was defined by ICD-10 code, eGFR (stage 2, 60–75 ml/min/1.73 m^2; stage 3a, 45–59 ml/min/1.73 m^2; stage 3b, 30–44 ml/min/1.73 m^2; stage 4, 15–29 ml/min/1.73 m^2; stage 5, <15 ml/min/1.73 m^2) or other relevant laboratory and clinical assessments as determined by the enrolling physician. PRO scores were summarised descriptively. An exploratory analysis compared baseline PRO (symptom survey, SF-36 and WPAI-CKD) scores between patients with stage 2–3b and stage 4–5 CKD (inclusive of dialysis), and between patients with stage 3a–3b and stage 4–5 CKD without dialysis, based on an analysis of covariance (ANCOVA) model with adjustments for: age, sex, medication (renin–angiotensin–aldosterone system inhibitors [RAASi]) use and comorbidities. $P<0.05$ was considered statistically significant.

Ethical Approval

This study was performed in accordance with ethical principles consistent with the Declaration of Helsinki, International Conference on Harmonisation, Good Clinical Practice, and the applicable legislation on noninterventional studies and observational studies. The study received central (approval numbers, Italy: 711/19; UK, REC No. 19/YH/0357; Sweden, DNR 2019-05355; Spain 2021/342; and USA, Pro00036594) and local (Japan) institutional review board ethics approval. The names of the central ethics committees that approved the study are Italy: Comitato Etico Indipendente Istituto Clinico Humanitas; Spain: Ethics Committee for Research with Drugs of Galicia; Sweden: Swedish Ethical Review Authority; UK: Health Research Authority; and USA: Advarra. A full list of study sites and their respective ethics committees is provided in Supplementary Table S1. All patients provided written informed consent.

RESULTS

Patient Demographics and Baseline Characteristics

Of 1052 patients enrolled, 727 (69.1%) had stage 2–3b CKD and 325 (30.9%) had stage 4–5 CKD (including patients on dialysis and those with kidney transplantation). Patient demographics and baseline characteristics are shown in Table 1. The majority (79.5%) were enrolled by a nephrologist. The mean (standard deviation [SD]) age of the patient cohort was 62.5 (13.6) years, 36.9% were female, and mean (SD) time since CKD diagnosis was 6.7 (7.8) years (range 0–58.3 years). In all, 8.8% of patients had ongoing dialysis. Patients with stage 2–3b and stage 4–5 CKD had generally similar baseline demographics (Table 1). The most commonly reported CKD aetiologies (as indicated by treating physician) were type 2 diabetic kidney disease, ischaemic or hypertensive nephropathy, and glomerulonephritis (including chronic glomerulonephritis and immunoglobulin A and membranous nephropathy). Only 18.2% of patients' diagnoses were based on kidney biopsy.

Around 11% of patients reported being current smokers, and 16.4% reported a family history of CKD. About 60% of patients were married, 33.7% were employed/self-employed and a small proportion (6.9%) had no health insurance. More than 46% of patients were either overweight or obese and comorbidities were highly prevalent: 72.4%, 43.0% and 37.5% of patients had a history of hypertension, diabetes and hyperlipidaemia, respectively. Compared with patients with stage 2–3b CKD, a higher proportion of patients with stage 4–5 CKD had hyperkalaemia (21.8% vs. 8.4%) and oedema

Table 1 Patient demographics and baseline characteristics

Characteristic	Overall (*N* = 1052)	Stage 2–3b CKD (*N* = 727)	Stage 4–5 CKD[a] (*N* = 325)
Age, years, mean (SD)	62.5 (13.6)	63.4 (13.4)	60.5 (13.9)
Sex, female, *n* (%)[b]	388 (36.9)	274 (37.7)	114 (35.1)
Geographical location, *n* (%)[b]			
UK	185 (17.6)	91 (12.5)	94 (28.9)
Italy	104 (9.9)	63 (8.7)	41 (12.6)
Japan	223 (21.2)	155 (21.3)	68 (20.9)
Spain	129 (12.3)	111 (15.3)	18 (5.5)
Sweden	90 (8.6)	63 (8.7)	27 (8.3)
USA	321 (30.5)	244 (33.6)	77 (23.7)
Race, *n* (%)[b]			
White	644 (61.2)	462 (63.5)	182 (56.0)
Asian	235 (22.3)	161 (22.1)	74 (22.8)
Black/African American	79 (7.5)	44 (6.1)	35 (10.8)
Other	4 (0.4)	3 (0.4)	1 (0.3)
Missing/not reported	90 (8.6)	57 (7.8)	33 (10.2)
BMI, kg/m^2			
n	659	491	168
Mean (SD)	30.0 (7.4)	30.4 (7.5)	30.0 (7.1)
< 18.5, *n* (%)[b]	16 (1.5)	12 (1.7)	4 (1.2)
18.5 to < 25, *n* (%)[b]	155 (14.7)	110 (15.1)	45 (13.8)
25 to < 30, *n* (%)[b]	187 (17.8)	135 (18.6)	52 (16.0)
≥ 30, *n* (%)[b]	301 (28.6)	234 (32.2)	67 (20.6)
Missing, *n* (%)[b]	393 (37.4)	236 (32.5)	157 (48.3)
Alcohol usage			
Current	626 (59.5)	442 (60.8)	184 (56.6)
Former	105 (10.0)	66 (9.1)	39 (12.0)
Never	321 (30.5)	219 (30.1)	102 (31.4)
Nicotine usage, *n* (%)[b]			
Currently smokes	118 (11.2)	81 (11.1)	37 (11.4)
Formerly smoked	335 (31.8)	252 (34.7)	83 (25.5)

Table 1 continued

Characteristic	Overall (*N* = 1052)	Stage 2–3b CKD (*N* = 727)	Stage 4–5 CKD[a] (*N* = 325)
Never smoked	558 (53.0)	370 (50.9)	188 (57.8)
Missing	41 (3.9)	24 (3.3)	17 (5.2)
CKD stage, *n* (%)[b]			
2[c]	87 (8.3)	87 (12.0)	0 (0.0)
3a	332 (31.6)	332 (45.7)	0 (0.0)
3b	308 (29.3)	308 (42.4)	0 (0.0)
4	184 (17.5)	0 (0.0)	184 (56.6)
5	141 (13.4)	0 (0.0)	141 (43.4)
CKD aetiology,[d] *n* (%)[b]			
T2 diabetic kidney disease	246 (23.4)	174 (23.9)	72 (22.2)
Ischaemic/hypertensive nephropathy	201 (19.1)	153 (21.0)	48 (14.8)
Glomerulonephritis[e]	112 (10.6)	76 (10.5)	36 (11.1)
Polycystic kidney disease	51 (4.8)	28 (3.9)	23 (7.1)
T1 diabetic nephropathy	24 (2.3)	16 (2.2)	8 (2.5)
Lupus nephritis	13 (1.2)	8 (1.1)	75 (1.5)
Tubulointerstitial nephritis	10 (1.0)	3 (0.4)	7 (2.2)
Unknown	187 (17.8)	135 (18.6)	52 (16.0)
Other[f]	208 (19.8)	134 (18.4)	74 (22.8)
Speciality of enrolling physician, *n* (%)[b]			
Cardiology	25 (2.4)	22 (3.0)	3 (0.9)
Nephrology	836 (79.5)	530 (72.9)	305 (93.8)
General practice	63 (6.0)	62 (8.5)	1 (0.3)
Other[g]	128 (12.2)	113 (15.5)	15 (4.6)
Employment status, *n* (%)[b]			
Employed	307 (29.2)	207 (28.5)	100 (30.8)
Unemployed	137 (13.0)	80 (11.0)	57 (17.5)
Retired	414 (39.4)	314 (43.2)	100 (30.8)
Self-employed	47 (4.5)	32 (4.4)	15 (4.6)
Other	147 (14.0)	94 (12.9)	53 (16.3)

Table 1 continued

Characteristic	Overall (*N* = 1052)	Stage 2–3b CKD (*N* = 727)	Stage 4–5 CKD[a] (*N* = 325)
Marital status, *n* (%)[b]			
Married	632 (60.1)	459 (63.1)	173 (53.2)
Divorced	64 (6.1)	46 (6.3)	18 (5.5)
Widowed	56 (5.3)	39 (5.4)	17 (5.2)
Never married	148 (14.1)	90 (12.4)	58 (17.8)
Other	152 (14.4)	93 (12.8)	59 (18.2)
Health insurance coverage, *n* (%)[b]			
Private	88 (8.4)	66 (9.1)	22 (6.8)
Public/governmental	861 (81.8)	600 (82.5)	262 (80.6)
Mixed	12 (1.1)	10 (1.4)	2 (0.6)
No insurance	73 (6.9)	37 (5.1)	36 (11.1)
Unknown/missing	17 (1.6)	14 (1.9)	3 (0.9)
Family history, *n* (%)[b]			
CKD	173 (16.4)	110 (15.1)	63 (19.4)
Unknown	354 (33.7)	252 (34.7)	102 (31.4)
Dialysis	94 (8.9)	62 (8.5)	32 (9.8)
Unknown	362 (34.4)	251 (34.5)	111 (34.2)
Diabetes	285 (27.1)	217 (29.8)	68 (20.9)
Unknown	358 (34.0)	239 (32.9)	118 (36.3)
Medical history,[h] *n* (%)[b]			
Hypertension	762 (72.4)	534 (73.5)	228 (70.2)
Diabetes	452 (43.0)	324 (44.6)	128 (39.4)
Hyperlipidaemia	394 (37.5)	288 (39.6)	106 (32.6)
Myocardial infarction	126 (12.0)	69 (9.5)	57 (17.5)
Heart failure	74 (7.0)	45 (6.2)	29 (8.9)
Atrial fibrillation/flutter	56 (5.3)	40 (5.5)	16 (4.9)
Respiratory disease	134 (12.7)	93 (12.8)	41 (12.6)
Hyperkalaemia	132 (12.5)	61 (8.4)	71 (21.8)
Infection (past 12 months)	110 (10.5)	73 (10.0)	37 (11.4)
Oedema	126 (12.0)	69 (9.5)	57 (17.5)
Gout	105 (10.0)	62 (8.5)	43 (13.2)

Table 1 continued

Characteristic	Overall ($N=1052$)	Stage 2–3b CKD ($N=727$)	Stage 4–5 CKD[a] ($N=325$)
Cancer	102 (9.7)	67 (9.2)	35 (10.8)
Retinopathy	82 (7.8)	53 (7.3)	29 (8.9)
Stroke	64 (6.1)	38 (5.2)	26 (8.0)

BMI body mass index, *CKD* chronic kidney disease, *SD* standard deviation, *T1* type 1, *T2* type 2

[a]Stage 4–5 CKD includes patients on dialysis and with kidney transplantation

[b]Percentages are based on the total number of patients within each cohort: overall ($N=1052$); with stage 2–3b CKD ($N=727$); or with stage 4–5 CKD ($N=325$)

[c]Of the 87 patients with CKD stage 2, 18 had documented albuminuria

[d]Most likely aetiology of CKD, as recorded in the patient's medical records

[e]Includes chronic glomerulonephritis and immunoglobulin A and membranous nephropathy

[f]Includes focal segmental glomerulosclerosis, chronic interstitial nephritis, chronic pyelonephritis (infectious), other primary or secondary glomerulonephritis, obstructive nephropathy, cystic kidney disease (other), cystic kidney disease (medullary kidney disease), minimal change, renal artery stenosis, cystic kidney disease (medullary sponge kidney), and other (unspecified)

[g]Includes any specialty other than nephrology, cardiology or general practitioner

[h]History of medical conditions with prevalence ≥ 5% at baseline

(17.5% vs. 9.5%); proportions of patients with other comorbidities were generally balanced between the two groups.

Clinical and Biochemical Measures

Median values for chemical and biochemical measures are shown in Table 2. Median systolic blood pressure (SBP) was 134.0 mmHg and median diastolic blood pressure (DBP) was 77.0 mmHg. Compared with patients with stage 2–3b CKD, a slightly smaller proportion of patients with stage 4–5 CKD had an SBP of < 120 mmHg (14.2% vs. 17.1%) and DBP of < 80 mmHg (45.5% vs. 49.9%).

Median (Q_1, Q_3) haemoglobin (Hb) was 12.9 g/dL (11.6, 14.3; $n=894$) in the overall cohort. A higher proportion of patients with stage 4–5 CKD had any-grade anaemia (Hb < 12 g/dL) than patients with stage 2–3b CKD (49.8% vs. 16.9%).

Baseline HbA1c data by CKD stage in the overall cohort and in patients with diabetes are presented in Table 2.

Median (Q_1, Q_3) urinary albumin–creatinine ratio (UACR) was 11.8 mg/mmol (1.9, 61.4; $n=267$) in the overall cohort. Of patients with stage 2 CKD, 21% ($n=18/87$) had evidence of albuminuria as documented in their records or based on UACR values.

Medication Utilisation

Over half (58.7%) of the cohort were receiving RAASis; 64.4% of patients with stage 2–3b CKD and 46.2% of patients with stage 4–5 CKD (Fig. 1).

Overall, 79.8% of patients were receiving antihypertensive therapies (including RAASis). The proportions of patients overall who were receiving 1, 2, 3 and ≥ 4 antihypertensive therapies were 23.2%, 25.0%, 17.5% and 14.2%, respectively. Use of lipid-lowering and glucose-lowering therapies was also common, being received by 54.4% and 36.1% of patients, respectively (Fig. 1). Overall, 14.0% of patients were receiving sodium-glucose co-transporter 2 inhibitors

Table 2 Clinical and biochemical measures

Measure	Overall ($N = 1052$)	Stage 2–3b CKD ($N = 727$)	Stage 4–5[a] CKD ($N = 325$)
Systolic blood pressure, mmHg			
n	905	635	270
Median (Q_1, Q_3)	134.0 (121.0, 147.0)	132.0 (120.0, 145.0)	136.0 (122.0, 149.0)
< 120, *n* (%)[b]	170 (16.2)	124 (17.1)	46 (14.2)
≥ 120, *n* (%)[b]	735 (69.9)	510 (70.2)	225 (69.2)
Missing, *n* (%)[b]	147 (14.0)	93 (12.8)	54 (16.6)
Diastolic blood pressure, mmHg			
n	903	634	269
Median (Q_1, Q_3)	77.0 (70.0, 85.0)	77.0 (70.0, 85.0)	78.0 (70.0, 85.0)
< 80, *n* (%)[b]	511 (48.6)	363 (49.9)	148 (45.5)
≥ 80, *n* (%)[b]	392 (37.3)	270 (37.1)	122 (37.5)
Missing, *n* (%)[b]	149 (14.2)	94 (12.9)	55 (16.9)
eGFR, ml/min/1.73 m^2			
n	965	689	276
Median (Q_1, Q_3)	39.3 (25.3, 51.6)	45.9 (37.1, 54.9)	17.4 (9.5, 24.6)
Missing, *n* (%)[b]	87 (8.3)	38 (5.2)	49 (15.1)
Hb, g/dL			
n	894	627	267
Median (Q_1, Q_3)	12.9 (11.6, 14.3)	13.4 (12.2, 14.7)	11.6 (10.7, 12.8)
Hb < 8, *n* (%)[b]	7 (0.7)	4 (0.6)	3 (0.9)
Hb ≥ 8 to < 10, *n* (%)[b]	34 (3.2)	12 (1.7)	22 (6.8)
Hb ≥ 10 to < 12, *n* (%)[b]	244 (23.2)	107 (14.7)	137 (42.2)
Hb ≥ 12, *n* (%)[b]	609 (57.9)	504 (69.3)	105 (32.3)
Missing, *n* (%)[b]	158 (15.0)	100 (13.8)	58 (17.8)
Urinary albumin–creatinine ratio, mg/mmol			
n	267	217	50
Median (Q_1, Q_3)	11.8 (1.9, 61.4)	8.8 (1.6, 38.2)	53.8 (8.9, 113.8)
< 30, *n* (%)[b]	179 (17.0)	157 (21.6)	22 (6.8)
30–300, *n* (%)[b]	75 (7.1)	52 (7.2)	23 (7.1)
> 300, *n* (%)[b]	13 (1.2)	8 (1.1)	5 (1.5)
Missing, *n* (%)[b]	785 (74.6)	510 (70.2)	275 (84.6)

Table 2 continued

Measure	Overall ($N = 1052$)	Stage 2–3b CKD ($N = 727$)	Stage 4–5[a] CKD ($N = 325$)
LDL, mmol/L			
n	501	383	118
Median (Q_1, Q_3)	2.4 (1.8, 3.1)	2.4 (1.8, 3.1)	2.4 (1.8, 3.1)
Missing, *n* (%)[b]	551 (52.4)	344 (47.3)	207 (63.7)
Potassium, mmol/L			
n	909	641	268
Median (Q_1, Q_3)	4.4 (4.1, 4.8)	4.4 (4.1, 4.7)	4.6 (4.3, 5.0)
Missing, *n* (%)[b]	143 (13.6)	86 (11.8)	57 (17.5)
Bicarbonate, mmol/L			
n	263	168	95
Median (Q_1, Q_3)	25.0 (23.0, 27.0)	25.0 (23.0, 27.1)	24.0 (22.3, 27.0)
Missing, *n* (%)[b]	789 (75.0)	559 (76.9)	230 (70.8)
Sodium, mmol/L			
n	886	623	264
Median (Q_1, Q_3)	140.0 (138.0, 142.0)	140.0 (138.0, 142.0)	139.0 (138.0, 141.0)
Missing, *n* (%)[b]	165 (15.7)	104 (14.3)	61 (18.8)
Total cohort: HbA1c, mmol/mol			
n	439	355	84
Median (Q_1, Q_3)	46.5 (39.9, 57.5)	46.5 (39.9, 58.5)	46.5 (38.8, 54.2)
Missing, *n* (%)[b]	613 (58.3)	372 (51.2)	241 (74.2)
Patients with diabetes: HbA1c, mmol/mol			
n	271	217	54
Median (Q_1, Q_3)	51.0 (44.0, 62.0)	52.0 (45.0, 62.0)	48.0 (41.0, 56.0)
Missing, *n* (%)	181 (40.0)	107 (33.0)	74 (57.8)
Phosphate, mmol/L			
n	543	355	188
Median (Q_1, Q_3)	1.2 (1.0, 1.3)	1.1 (1.0, 1.3)	1.3 (1.1, 1.6)
Missing, *n* (%)[b]	509 (48.4)	372 (51.2)	137 (42.2)
Urate, μmol/L			
n	398	273	125
Median (Q_1, Q_3)	368.8 (309.3, 422.2)	356.9 (303.3, 416.4)	374.5 (321.2, 439.2)
Missing, *n* (%)[b]	654 (62.2)	454 (62.4)	200 (61.5)

Table 2 continued

Measure	Overall ($N=1052$)	Stage 2–3b CKD ($N=727$)	Stage 4–5[a] CKD ($N=325$)
C-reactive protein, mg/L			
n	286	174	111
Median (Q_1, Q_3)	1.4 (0.7, 4.9)	1.2 (0.6, 4.0)	2.0 (0.8, 7.3)
Missing, *n* (%)[b]	766 (72.8)	553 (76.1)	213 (65.5)

CKD chronic kidney disease, *eGFR* estimated glomerular filtration rate, *Hb* haemoglobin, *HbA1c* haemoglobin A1c (glycated haemoglobin), *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, Q_1 quartile 1, Q_3 quartile 3

[a]Stage 4–5 CKD includes patients on dialysis and with kidney transplantation

[b]Percentages are based on the total number of patients within each cohort: overall ($N=1052$); with stage 2–3b CKD ($N=727$); or with stage 4–5 CKD ($N=325$)

(SGLT2is) and 10.6% of patients were receiving erythropoiesis-stimulating agents (ESA), including 1.9% of patients with stage 2–3b CKD and 30.2% of patients with stage 4–5 CKD. Around one-third (30.9%) of the overall cohort were receiving proton pump inhibitors (PPIs); the proportions were similar in patients with stage 2–3b and stage 4–5 CKD (31.1% and 30.5%, respectively).

Food Diary Outcomes

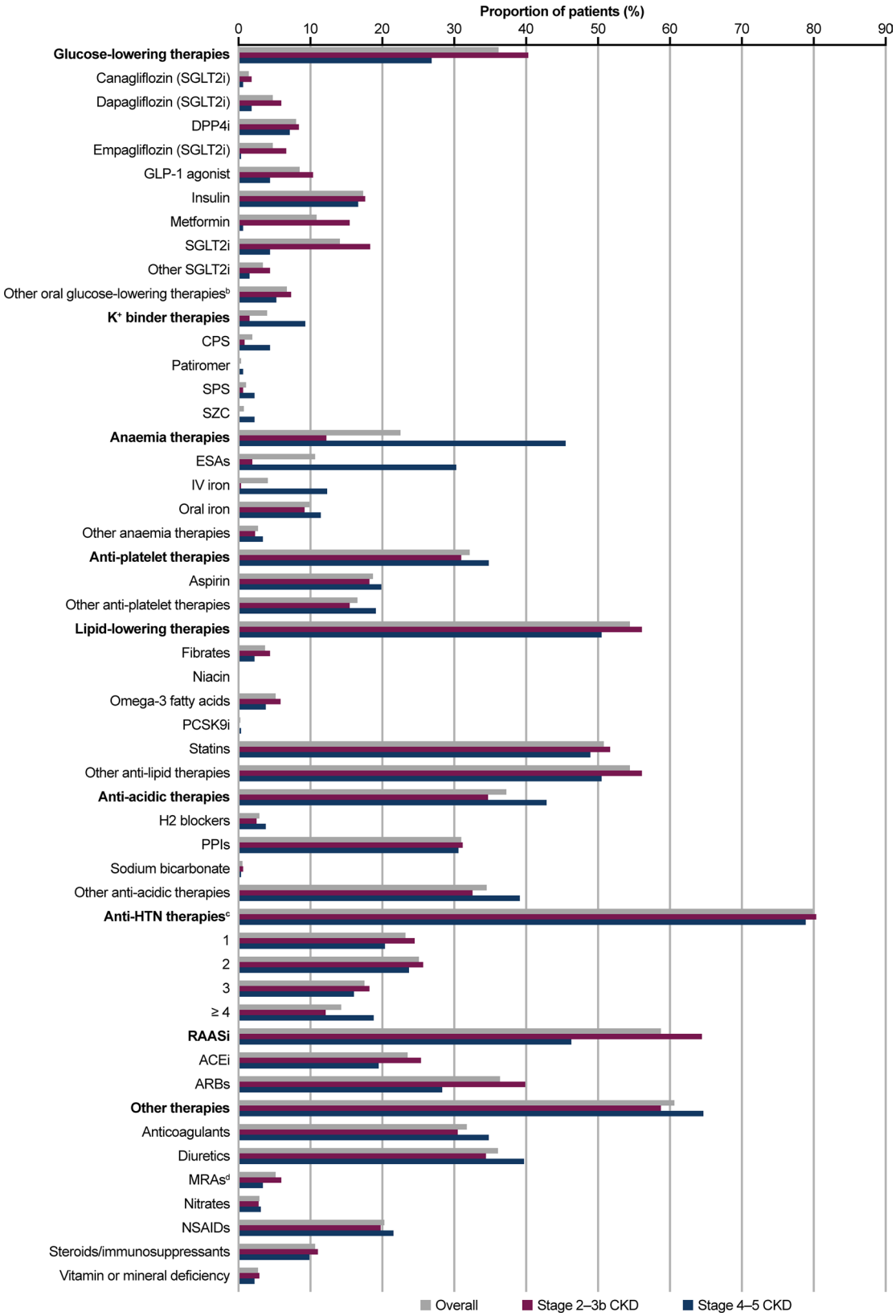
Overall, patients consumed a median (Q_1, Q_3) of 303.0 (171.0, 453.0), 363.0 (247.0, 597.0), 340.5 (194.0, 651.0) and 147.5 (11.5, 455.5) calories through breakfast, lunch, dinner and snacks, respectively; patients with stage 2–3b and stage 4–5 CKD had a similar calorie consumption across mealtimes (Table 3). The median grams of protein consumed through breakfast, lunch and dinner were 9.3 (4.3, 17.7), 15.7 (7.8, 32.6) and 19.1 (7.5, 32.5), respectively (Table 3).

PRO Questionnaires

At baseline, 42.3%, 42.0%, 40.6%, 41.1% and 41.6% of patients completed the symptoms, SF-36, WPAI-CKD, RAPA aerobic and RAPA strength and flexibility questionnaires, respectively. Compared with PROnon-completers, PRO completers were slightly younger (mean age 60.9 vs. 65.3 years) and included a higher proportion of non-white individuals (46.7% vs. 25.3%) (Supplementary Table S2).

Patients generally reported substantial symptom burden and impaired HRQoL and work productivity (Fig. 2). As assessed by the symptom survey, fatigue was reported as the symptom with the highest severity among the patients with CKD (Fig. 2a). Patients with stage 4–5 CKD reported a numerically greater symptom severity for each of 11 symptoms measured compared with patients with stage 2–3b CKD. Patients with stage 4–5 CKD also reported numerically worse HRQoL than patients with stage 2–3b CKD for each of eight SF-36 domains (Fig. 2b). The numerical differences were highest in the areas of physical functioning, physical role functioning and general health perception. Results from the WPAI-CKD questionnaire showed that patients with stage 4–5 CKD reported numerically greater work impairment than patients with stage 2–3b CKD for each of four categories measured (Fig. 2c). The mean percentage work time missed was 2.7% and 8.0% for patients with stage 2–3b CKD and stage 4–5 CKD, respectively. Of patients with stage 4 or 5 CKD, 40% were employed (including self-employment) versus 18% of patients with stage 5 CKD with dialysis.

When adjusting for age, sex, RAASi use, and relevant comorbidities, patients with stage 4–5 CKD (inclusive of dialysis) had significantly greater work impairment and worse HRQoL than those with earlier-stage CKD (stage 2–3b) (Supplementary Table S3). Comparison of patients


Proportion of patients (%)
0
10
20
30
40
50
60
70
80
90
Glucose-lowering therapies
Canagliflozin (SGLT2i)
Dapagliflozin (SGLT2i)
DPP4i
Empagliflozin (SGLT2i)
GLP-1 agonist
Insulin
Metformin
SGLT2i
Other SGLT2i
Other oral glucose-lowering therapies[b]
K+ binder therapies
CPS
Patiromer
SPS
SZC
Anaemia therapies
ESAs
IV iron
Oral iron
Other anaemia therapies
Anti-platelet therapies
Aspirin
Other anti-platelet therapies
Lipid-lowering therapies
Fibrates
Niacin
Omega-3 fatty acids
PCSK9i
Statins
Other anti-lipid therapies
Anti-acidic therapies
H2 blockers
PPIs
Sodium bicarbonate
Other anti-acidic therapies
Anti-HTN therapies[c]
1
2
3
≥ 4
RAASi
ACEi
ARBs
Other therapies
Anticoagulants
Diuretics
MRAs[d]
Nitrates
NSAIDs
Steroids/immunosuppressants
Vitamin or mineral deficiency
Overall
Stage 2–3b CKD
Stage 4–5 CKD

◂**Fig. 1** Current medications overall and by stage 2–3b and stage 4–5 CKD[a]. Data included in this figure do not take into account patient comorbidities or differing availability of drugs in different geographical locations or at different timepoints during the study. *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, Ca^+ calcium, *CKD* chronic kidney disease, *CPS* calcium polystyrene sulfonate, *DPP4i* dipeptidyl peptidase 4 inhibitor, *ESA* erythropoiesis-stimulating agent, *GLP-1* glucagon-like peptide-1, *H2* histamine 2, *HTN* hypertensive, *IV* intravenous, K^+ potassium, *MRA* mineralocorticoid receptor antagonist, *NSAID* nonsteroidal anti-inflammatory drug, *Patiromer* calcium patiromer sorbitex, *PCSK9* proprotein convertase subtilisin/kexin type 9, *PPI* proton pump inhibitor, *RAASi* renin–angiotensin–aldosterone system inhibitor, *SGLT2i* sodium-glucose cotransporter 2 inhibitor, *SPS* sodium polystyrene sulfonate, *SZC* sodium zirconium cyclosilicate. [a]CKD stage 4–5 includes patients on dialysis and with kidney transplantation. [b]Other oral glucose-lowering therapies include sulfonylureas, thiazolidinediones, biguanides and alpha-glucosidase inhibitors. [c]Anti-HTN therapies include ACEi, ARBs, diuretics, alpha blockers, beta blockers, combined alpha and beta blockers, Ca^+ channel blockers, alpha-2 receptor agonists and vasodilators. [d]MRAs include spironolactone and eplerenone

with stage 3 versus stage 4–5 CKD (without dialysis) showed significantly greater work impairment and worse HRQoL in the latter (Supplementary Table S3).

Overall, most patients partook in regular weekly aerobic activity but did not partake in any regular strength or flexibility activities, as assessed by the RAPA questionnaire (Fig. 2d). Compared with stage 2–3b CKD, a higher proportion of patients with stage 4–5 CKD reported an aerobic activity level of under-active light (32.2% vs. 23.2%, respectively) and a smaller proportion of patients reported an aerobic activity level of active (37.1% vs. 49.8%, respectively).

Across six different countries, patients generally reported a similar symptom severity and impairment to HRQoL, with slight variation in work productivity and physical activity levels (Supplementary Fig. S1).

DISCUSSION

Cohort Characteristics

The prospective DISCOVER CKD cohort is representative of multiple races, geographical locations and clinical backgrounds. Patient characteristics are generally similar to other published CKD cohorts; however, the DISCOVER CKD cohort is more geographically diverse (Table 4) [16–21].

Comorbidity and Medication Burden

This study demonstrates a significant burden of comorbidities among patients with CKD, which is consistent with previous findings [16–21]. The proportion of patients with hypertension was slightly lower (72.4%) in the DISCOVER CKD prospective cohort compared with other published CKD cohorts (range 77.8–96.1%) [16–21]. The proportion of patients with diabetes (type 1 or 2) in this study (43.0%) was similar to cohort studies from Germany, France, the USA and Spain (range 40.8–48.4%) and greater than cohort studies from Korea and China (33.7% and 22.3%, respectively) (Table 4) [16–21]. Compared with patients with stage 2–3b CKD, more patients with stage 4–5 CKD had anaemia, hyperkalaemia or oedema, indicating that comorbidity burden worsens with disease progression. Of note, there was a relatively low proportion of patients in the CKD stage 4 and 5 group with heart failure, which is surprising given that heart failure prevalence increases with declining renal function, reaching approximately 20% in patients undergoing haemodialysis [22, 23]. It is possible that the lower burden of some of the comorbidities, including heart failure, observed may reflect the inadvertent selection of a healthier CKD population than the overall CKD population. However, this was not investigated.

Medication utilisation in the study cohort was high, which is unsurprising given the high comorbidity burden in the population; however, the findings suggest that utilisation may not have been optimal. Indeed, given that over

Table 3 Food diary outcomes

Meal, median (Q_1, Q_3)	Overall ($N = 1052$)	Stage 2–3b CKD ($N = 727$)	Stage 4–5[a] CKD ($N = 325$)
Breakfast, *n*	165	122	43
Calories, kcal	303.0 (171.0, 453.0)	295.5 (168.0, 444.0)	311.0 (200.0, 626.0)
Protein, g	9.3 (4.3, 17.7)	9.3 (3.8, 17.4)	9.3 (4.9, 21.2)
Potassium, mg	335.0 (150.0, 556.5)	342.0 (165.0, 551.0)	290.0 (117.0, 735.0)
Sodium, mg	346.0 (104.0, 671.0)	348.0 (98.0, 671.0)	325.0 (125.0, 679.0)
Fat, g	5.8 (2.6, 15.2)	5.7 (1.9, 13.6)	7.6 (3.4, 21.4)
Lunch, *n*	119	89	30
Calories, kcal	363.0 (247.0, 597.0)	400.0 (267.0, 595.0)	331.0 (241.0, 604.0)
Protein, g	15.7 (7.8, 32.6)	19.4 (7.9, 33.2)	11.8 (7.2, 24.5)
Potassium, mg	437.5 (158.0, 990.0)	483.0 (180.5, 1005.0)	256.0 (72.0, 606.0)
Sodium, mg	369.0 (51.0, 669.0)	362.0 (51.0, 669.0)	407.0 (60.0, 628.0)
Fat, g	7.8 (1.2, 20.9)	8.8 (1.6, 23.2)	4.3 (1.0, 12.2)
Dinner, *n*	94	67	27
Calories, kcal	340.5 (194.0, 651.0)	313.0 (194.0, 651.0)	376.0 (179.0, 732.0)
Protein, g	19.1 (7.5, 32.5)	19.1 (7.0, 32.8)	19.1 (8.9, 32.1)
Potassium, mg	467.0 (220.0, 902.0)	468.0 (220.0, 912.0)	466.0 (205.0, 770.0)
Sodium, mg	459.5 (107.0, 1161.0)	485.0 (77.0, 977.0)	442.0 (107.0, 1353.0)
Fat, g	10.4 (2.7, 21.6)	10.7 (3.0, 21.6)	9.3 (1.9, 21.2)
Snacks, *n*	40	25	15
Calories, kcal	147.5 (11.5, 455.5)	158.0 (6.0, 453.0)	146.0 (27.0, 590.0)
Protein, g	2.4 (0.4, 12.1)	1.2 (0.3, 10.4)	3.3 (0.5, 15.6)
Potassium, mg	159.0 (8.0, 973.5)	153.0 (7.0, 689.0)	190.0 (48.0, 2676.0)
Sodium, mg	15.0 (3.0, 104.0)	15.0 (3.0, 104.0)	28.0 (2.0, 104.0)
Fat, g	2.5 (0.1, 13.4)[b]	1.7 (0.1, 18.2)	2.9 (0.1, 6.2)

CKD chronic kidney disease, Q_1 quartile 1, Q_3 quartile 3

[a]Stage 4–5 CKD includes patients on dialysis and with kidney transplantation

[b]Data available for $n = 39$

two-thirds of the overall cohort did not meet the Kidney Disease Improving Global Outcomes (KDIGO) and European Society of Cardiology SBP target of < 120 mmHg [24], the proportions of patients receiving antihypertensive and RAASi therapies were suboptimal. Overall, 25.0% and 17.5% of patients were receiving two and three antihypertensive therapies, respectively, which is lower than expected, considering that KDIGO recommends that patients with CKD who have an SBP of ≥ 20 mmHg above the target will need combinations of at least two antihypertensive drugs [25]. Fewer patients were receiving RAASi therapy in this study (58.7%) than in similar

cohort studies (range 68.3%–88.1%) (Table 4) [16–20]. These findings highlight a discord between the KDIGO blood pressure management guidelines for patients with CKD and clinical practice. However, national recommendations for blood pressure control in patients with CKD vary. For example, UK guidelines recommend a clinical blood pressure target of < 140/90 mmHg (SBP/DBP) in patients with CKD and an albumin to creatinine ratio of < 70 mg/mmol, and < 130/80 mmHg (SBP/DBP) in patients with CKD and an albumin to creatinine ratio of ≥ 70 mg/mmol [26]. Furthermore, some physicians may be reluctant to intensively target an SBP of < 120 mmHg if their patients have type 2 diabetes because of the significantly higher reported risk of serious adverse events attributed to antihypertensive medications and of eGFR reductions to < 30 ml/min/1.73 m^2 [27].

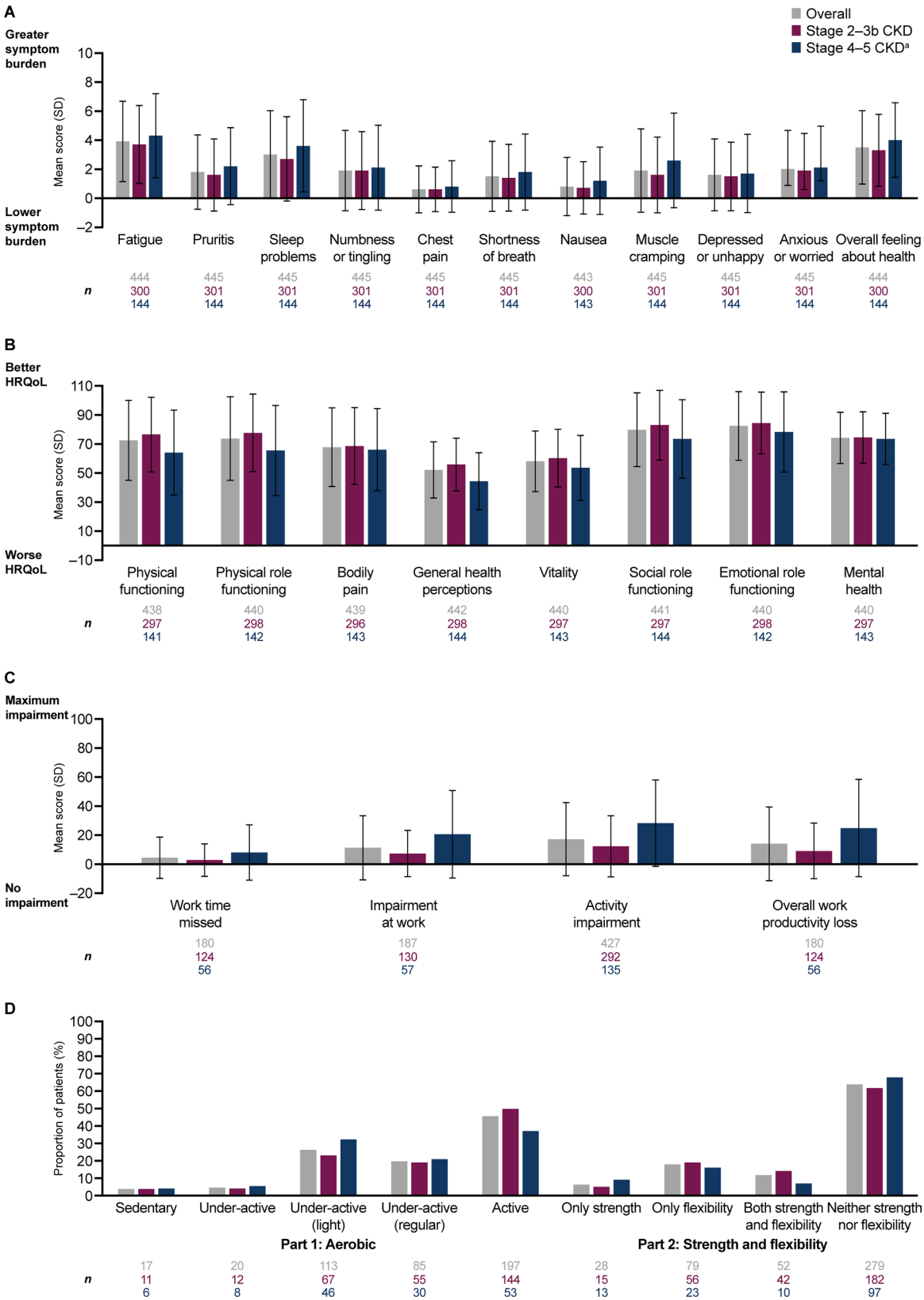
Our findings show room for improvement with metformin and SGLT2i utilisation, given that they are the recommended first-line therapies for patients with CKD [28] and type 2 diabetes, and that nearly half of all enrolled patients had diabetes. Metformin prescriptions are not expected in patients with stage 4–5 CKD, given that KDIGO and the American Diabetes Association recommend metformin only for patients with eGFR ≥ 30 ml/min/1.73 m^2 [29, 30]. However, in patients with stage 2–3 CKD, metformin was under-prescribed; 44.6% of these patients had type 1 or 2 diabetes but only 15.4% were receiving metformin. By contrast, metformin should be discontinued in the 0.6% of patients with stage 4–5 CKD. Recommendations to treat patients with CKD and type 2 diabetes with SGLT2is were more strongly reinforced in the KDIGO 2022 update than they had been previously [28]. As this study enrolled patients between September 2019 and June 2022, an increase in SGLT2i use in practice may not be reflected in our findings. The proportion of patients receiving PPIs in this study was similar to that in another published prospective CKD cohort study (30.9% vs. 32.5%, respectively) [31]. However, long-term PPI use in patients with CKD has been linked to both acute kidney injury and disease progression, and it is possible that they are being over-prescribed and used inappropriately [31]. The utilisation of RAASi and SGLT2i and impact on cardiorenal outcomes will be further explored in a forthcoming DISCOVER CKD publication.

Overall, the high comorbidity and medication burden of patients with CKD indicates a requirement for more comprehensive CKD management, including regular monitoring of health and treatments.

PRO Questionnaires

Patients in the DISCOVER CKD prospective cohort reported a high symptom burden, with fatigue being the symptom reported with highest severity, and suboptimal HRQoL, which aligns with findings of a meta-analysis [32]. For every SF-36 variable assessed in this study, mean scores were comparable with individuals reporting long-standing illnesses, and below those of healthy working adults reporting no long-standing illness [33]. This provides further evidence for the negative impact on HRQoL in patients with CKD and indicates that there is room for improvement in patient management, particularly with the mitigation of symptoms such as fatigue.

Patients with advanced CKD reported lower scores on the PRO questionnaires compared with patients with stage 2–3b CKD, highlighting the considerable increase in disease burden associated with CKD progression. In particular, this study found a numerically greater symptom severity for all assessed symptoms and worse HRQoL scores for all categories of the SF-36 questionnaire. According to the WPAI-CKD questionnaire, patients with advanced CKD reported numerically worse scores for all four categories of work time missed, impairment at work, activity impairment and overall work productivity loss. The lower scores in more advanced disease are unlikely to be due to differences in age or CKD aetiology, given that patients with stage 2–3b CKD had an older mean age than patients with stage 4–5 CKD (63.4 years vs. 60.5 years) and that there were no meaningful differences in CKD aetiology between groups. The decline in patient well-being with disease progression seen in this study may have implications for healthcare services as well as for


A
Overall
Stage 2–3b CKD
Stage 4–5 CKD[a]
Greater symptom burden
Lower symptom burden
Mean score (SD)
10
8
6
4
2
0
−2
Fatigue
Pruritis
Sleep problems
Numbness or tingling
Chest pain
Shortness of breath
Nausea
Muscle cramping
Depressed or unhappy
Anxious or worried
Overall feeling about health
n
444 445 445 445 445 445 443 445 445 445 444
300 301 301 301 301 301 300 301 301 301 300
144 144 144 144 144 144 143 144 144 144 144
B
Better HRQoL
Worse HRQoL
Mean score (SD)
110
90
70
50
30
10
−10
Physical functioning
Physical role functioning
Bodily pain
General health perceptions
Vitality
Social role functioning
Emotional role functioning
Mental health
n
438 440 439 442 440 441 440 440
297 298 296 298 297 297 298 297
141 142 143 144 143 144 142 143
C
Maximum impairment
No impairment
Mean score (SD)
100
80
60
40
20
0
−20
Work time missed
Impairment at work
Activity impairment
Overall work productivity loss
n
180 187 427 180
124 130 292 124
56 57 135 56
D
Proportion of patients (%)
100
90
80
70
60
50
40
30
20
10
0
Sedentary
Under-active
Under-active (light)
Under-active (regular)
Active
Only strength
Only flexibility
Both strength and flexibility
Neither strength nor flexibility
Part 1: Aerobic
Part 2: Strength and flexibility
n
17 20 113 85 197 28 79 52 279
11 12 67 55 144 15 56 42 182
6 8 46 30 53 13 23 10 97

◂**Fig. 2** Baseline patient-reported outcomes overall and by stage 2–3b and stage 4–5 CKD: Symptoms (**a**); SF-36 (**b**); WPAI-CKD (**c**); RAPA (**d**). **a** Scores describe patients' experience of symptoms in the last 7 days. Individual scores are out of a maximum of 10; the overall HRQoL score is a combined score out of a maximum of 110. Higher symptom/overall scores indicate greater symptom burden. **b** Weighted scores from each of eight sections of the SF-36 questionnaire are converted onto a 0–100 scale, with lower scores indicating worse HRQoL. **c** WPAI-CKD outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity. Work time missed = percent work time missed due to problem; impairment at work = percent impairment while working due to problem; activity impairment = percent activity impairment due to problem; overall work impairment = percent overall work impairment due to problem. **d** Aerobic RAPA categories are scored as follows: sedentary = no/rare physical activity; under-active = some light/moderate physical activity but not on a weekly basis; under-active (light activity) = weekly light physical activity; under-active regular = < 30 min/day or < 5 days/week of moderate physical activity or < 20 min/day or < 3 days/week of vigorous physical activity; active = ≥ 30 min/day or ≥ 5 days/week of moderate physical activity or ≥ 20 min/day or ≥ 3 days/week of vigorous physical activity. *CKD* chronic kidney disease, *HRQoL* health-related quality of life, *RAPA* Rapid Assessment of Physical Activity, *SD* standard deviation, *SF-36* 36-item Short Form *WPAI-CKD* Work Productivity and Activity Impairment chronic kidney disease. [a]CKD stage 4–5 includes patients on dialysis and with kidney transplantation

patients, such as increases in healthcare costs and societal costs (due to productivity loss) [34]. These findings suggest that to preserve patient HRQoL, prevention of CKD progression should be a priority in CKD management standard-of-care practices and that physicians should monitor patients closely to detect signs of worsening disease.

Future Analyses

The frequency of clinical events, such as heart failure, myocardial infarction, dialysis need and death, as well as complications, particularly those associated with the cardiovascular system and diabetes, will be assessed in future analyses and compared with their baseline frequency. It would be of interest to monitor the utilisation of SGLT2i, glucagon-like peptide-1 receptor agonists and non-steroidal mineralocorticoid receptor antagonists as awareness of new recommendations and accessibility to these classes of drugs increase. The longitudinal collection of a wide range of variables from a diverse patient population—both geographically and clinically—will provide a rich dataset to enhance the current understanding of the epidemiology, clinical management, treatment patterns and disease trajectory of patients with CKD.

Limitations

Strengths of this study include the racial, geographical and clinical diversity of the patient population, and the broad range of clinical variables collected, which will provide a rich dataset for future analyses and increase generalisability of our findings to patients with CKD worldwide. As is common with real-world studies, there were missing baseline data for some assessed variables in this analysis, in particular UACR (74.6%) and body mass index (37.4%), which limits the interpretation of CKD diagnosis and the generalisability of the results. Baseline eGFR data were missing at random for 87 (8.3%) patients, for whom CKD staging was based largely on ICD-10 codes; however, as the majority (79.3%) had CKD stages 3b–5 (Supplementary Table S4), the use of ICD-10 codes to define CKD stage in the absence of eGFR data may be deemed sufficient, in line with previous reports [35].

The high volume of missing data for some variables may reflect their infrequent or challenging measurement in clinical practice, or lack of documentation or access to the data. However, collecting data from electronic databases and health records is recognised as a key challenge in observational studies, for diverse reasons including potential for data fragmentation and heterogeneity [36].

The symptoms and food diary questionnaires were developed specifically for this study and are not yet validated; therefore, their reliability has not been fully ascertained, and the results should be considered exploratory in nature.

Table 4 Characteristics of the DISCOVER CKD prospective study population compared with published prospective observational CKD cohort studies in International Society of Nephrology International Network of Chronic Kidney Disease

Study	DISCOVER CKD	CKDopps [20]	CKD-REIN [19]	KNOW-CKD [16]	C-STRIDE [21]	CRIC [18]	MERENA [17]
Publication year	2023	2020	2018	2017	2017	2015	2011
Region	USA, UK, Spain, Italy, Sweden, Japan	Germany	France	Korea	China	USA	Spain
N	1052	1834	3033	2238	3168	3939	1129
Age, years, mean (SD)	62.5 (13.6)	75 (67–80)[a]	66.2 (12.9)	53.7 (12.2)	48.2 (13.7)	58.2 (11.0)	68 (13.0)
Sex, %							
Male	63.1	58	65.4	61.2	59.2	54.9	64.0
Female	36.9	42	34.6	38.8	40.8	45.1	36.0
BMI, kg/m^2 (%)	30.0 (7.4)	29 (6.0)	29 (6.0)	24.6 (3.4)	24.5 (3.6)	32.1 (7.8)	28.4 (4.9)
< 18.5, %	1.0	–	–	2.4[b]	46.6[c]	16.0[d]	22.7[d]
18.5–24.9, %	15.7	–	–	55.4[e]			
25–29.9, %	17.6	–	–	35.2	53.4[f]	28.6	45.7
≥ 30, %	28.4	–	35	6.4		55.2	31.7
Comorbidities, %							
Hypertension	72.4	85	91	96.1	77.8	86.1	92.7
Diabetes	43.0	42	43	33.7	22.3	48.4	40.8
Smoking status, %							
Currently smokes	11.4	–	12	15.7	38.2	13.1	9.6
Formerly smoked	32.0	–	47	30.4	–	–	36.2
Never smoked	52.6	–	–	53.9	–	–	54.2
CKD stage, %							

Table 4 continued

Study	DISCOVER CKD	CKDopps [20]	CKD-REIN [19]	KNOW-CKD [16]	C-STRIDE [21]	CRIC [18]	MERENA [17]
1	–	26.5[g]	–	11.8	30.8[h]	17.8[i]	–
2	8.3		–	18.7			–
3a	31.6		59[j]	18.0	15.7[k]	61.7[l]	38.4[j]
3b	29.3	73.5[n]		21.6	24.3[m]		
4	17.5		41	23.3	29.3[o]	20.5[n]	61.6
5	13.3		–	6.5	–		–
eGFR, ml/min/1.73 m^2	39.3 (25.3, 51.6)[a]	25 (21–31)[a]	33 (12)[p]	50.5 (30.3)[p]	50.7 (30.0)	44.9 (16.9)[q]	28 (8)[p]
Systolic blood pressure, mmHg	134.0 (121.0–147.0)[a]	139 (19)	142 (20)	127.8 (16.2)	129.3 (17.5)	128.5 (22.2)	141 (19)
Diastolic blood pressure, mmHg	77.0 (70.0–85.0)[a]	76 (11)	78 (12)	77.0 (11.1)	80.9 (11.7)	71.6 (12.8)	76 (11)
RAASi use, (%)	58.7[r]	79	76	85.4	–	68.3	88.1[r]
Stage 4–5 CKD and UACR < 30 mmol/mg, %	6.8	16	14	–	–	–	–

Data presented are mean (SD) values unless otherwise specified

BMI body mass index, *CKD* chronic kidney disease, *CKDopps* Chronic Kidney Disease Outcomes and Practice Patterns Study, *CKD-REIN* Chronic Kidney Disease Renal Epidemiology and Information Network, *CRIC* Chronic Renal Insufficiency Cohort Study, *C-STRIDE* Chinese Cohort of Chronic Kidney Disease, *eGFR* estimated glomerular filtration rate, *IQR* interquartile range, *KNOW-CKD* KoreaN cohort study for Outcome in patients With Chronic Kidney Disease, *MDRD* Modification of Diet in Renal Disease, *MERENA* Morbimortalidad en Enfermedad REnal en pacieNtes diAbéticos y no diabéticos, *RAASi* renin–angiotensin–aldosterone system inhibitor, *SD* standard deviation, *UACR* urinary albumin–creatinine ratio

[a]Median (IQR)

[b]BMI < 18.5 kg/m^2

[c]BMI < 24 kg/m^2

[d]BMI < 25 kg/m^2

[e]BMI 18.5–24.9 kg/m^2

Table 4 continued

[f]BMI ≥ 24 kg/m^2

[g]eGFR ≥ 30 ml/min/1.73 m^2

[h]eGFR > 60 ml/min/1.73 m^2

[i]eGFR ≥ 60 ml/min/1.73 m^2

[j]Stage 3a and 3b

[k]eGFR 45–60 ml/min/1.73 m^2

[l]eGFR 30 to < 60 ml/min/1.73 m^2

[m]eGFR 30–45 ml/min/1.73 m^2

[n]eGFR < 30 ml/min/1.73 m^2

[o]eGFR 15–30 mL/min/1.73 m^2

[p]Estimated using the MDRD, CKD Epidemiology Collaboration and Cockroft-Gault equations

[q]Estimated using the CRIC equation

[r]Including patients on angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (1% in DISCOVER CKD and 10.8% in MERENA)

Future studies would explore validation of these questionnaires to determine their internal consistency and validity. Although nearly two in five patients did not complete PRO questionnaires in this study, achieving high response rates to survey materials is generally recognised as challenging for a variety of factors [37]. Differences in baseline demographics and disease characteristics between PRO completers and non-completers mean that baseline PRO findings may differ among non-completers; this warrants further evaluation.

CONCLUSIONS

Patients enrolled in the DISCOVER CKD prospective cohort study were racially and clinically diverse, with representation across CKD stages, varied disease aetiologies, and a broad range of comorbidities and medication prescriptions. There is a need to improve prescribing patterns to ensure that patients with CKD and related comorbidities are receiving optimal, guideline-directed treatment.

ACKNOWLEDGEMENTS

We thank the participants of the study.

Medical Writing/Editorial Assistance. Medical writing support was provided by Katie Webster, BSc, Matthew Young, DPhil, and James Everington, MSc, and editorial support was provided by Jess Fawcett, BSc, all of Core (a division of Prime, London, UK), supported by AstraZeneca according to Good Publication Practice guidelines (https://doi.org/10.7326/M22-1460). The Sponsor was involved in the study design, collection, analysis and interpretation of data. However, ultimate responsibility for opinions, conclusions and data interpretation lies with the authors.

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Pecoits-Filho, Steven Fishbane, Carolyn S. P. Lam, Naoki Kashihara and David C. Wheeler. Data collection: Richard Ofori-Asenso, Hungta Chen, Juan Jose Garcia Sanchez, Surendra Pentakota. Data analysis: Hungta Chen, Richard Ofori-Asenso. Data interpretation: Carol Pollock, Juan-Jesus Carrero, Eiichiro Kanda, Richard Ofori-Asenso, Hungta Chen, Juan Jose Garcia Sanchez, Surendra Pentakota, Roberto Pecoits-Filho, Steven Fishbane, Carolyn S. P. Lam, Naoki Kashihara and David C. Wheeler. Drafting and reviewing the manuscript: Carol Pollock, Juan-Jesus Carrero, Eiichiro Kanda, Richard Ofori-Asenso, Hungta Chen, Juan Jose Garcia Sanchez, Surendra Pentakota, Roberto Pecoits-Filho, Steven Fishbane, Carolyn S. P. Lam, Naoki Kashihara and David C. Wheeler.

Funding. This analysis and all publication costs for this work, including the creation and publication of the graphical abstract, were funded by AstraZeneca.

Data Availability. The datasets generated during and/or analysed during the current study are available upon reasonable request in accordance with AstraZeneca's data sharing policy described at https://astrazenecagroup-dt.pharmacm.com/DT/Home.

Declarations

Conflict of Interest. Carol Pollock reports advisory board membership for AstraZeneca, Boehringer Ingelheim, Eli Lilly and Vifor Pharma; and speaker fees for AstraZeneca, Janssen-Cilag, Novartis, Otsuka and Vifor Pharma. Juan-Jesus Carrero reports institutional grants from Astellas, AstraZeneca and Vifor Pharma; speaker fees from AstraZeneca, Abbott and Nutricia; and consultancy for AstraZeneca and Bayer. Eiichiro Kanda is a consultant for AstraZeneca. Richard Ofori-Aseno, Hungta Chen, Juan Jose Garcia Sanchez and Surendra Pentakota are employees of and hold or may hold stock in AstraZeneca. Roberto Pecoits-Filho is an employee of Arbor Research Collaborative for Health, which receives global support for the ongoing Dialysis Outcomes and Practice Patterns Study Programs (provided without restriction on publications by a variety of funders; for details see https://www.dopps.org/AboutUs/Support.aspx). Roberto Pecoits-Filho also reports: research grants from Fresenius Medical Care; nonfinancial support from Akebia, AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk and FibroGen; personal fees from Travere Therapeutics; and consulting fees from George Clinical outside the submitted work. Steven Fishbane reports research support and consulting fees from AstraZeneca; and research support from Akebia Inc., MegaPro Biomedical Co., Ltd., Ardelyx, Corvidia Therapeutics, Inc. and Cara Therapeutics. Carolyn S. P. Lam is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Novo-Nordisk and Roche Diagnostics; has served as a consultant or is on the advisory board/steering committee/executive committee for Alleviant Medical, Allysta Pharma, Amgen, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, CardioRenal, Cytokinetics, Darma Inc., EchoNous Inc., Eli Lilly, Impulse Dynamics, Intellia Therapeutics, Ionis Pharmaceutical, Inc., Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, NovoNordisk, Prosciento Inc., Quidel Corporation, Radcliffe Group Ltd., Recardio Inc., ReCor Medical, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics and Us2.ai; and serves as co-founder and non-executive director of Us2.ai. Naoki Kashihara is a consultant for AstraZeneca, Boehringer Ingelheim, and Kyowa Hakko Kirin; and receives honoraria from Kyowa Hakko Kirin and Daiichi Sankyo. David C. Wheeler reports personal fees and nonfinancial support from AstraZeneca; and personal fees from Astellas, Bayer, Boehringer Ingelheim, GSK, Janssen, Mundipharma, Napp, Reata Pharmaceuticals, Tricida and Vifor Fresenius.

Ethical Approval. This study was performed in accordance with ethical principles consistent with the Declaration of Helsinki, International Conference on Harmonisation, Good Clinical Practice, and the applicable

legislation on noninterventional studies and observational studies. The study received central (approval numbers, Italy: 711/19; UK, REC No. 19/YH/0357; Sweden, DNR 2019–05355; Spain 2021/342; and USA, Pro00036594) and local (Japan) institutional review board ethics approval. The names of the central ethics committees that approved the study are Italy: Comitato Etico Indipendente Istituto Clinico Humanitas; Spain: Ethics Committee for Research with Drugs of Galicia; Sweden: Swedish Ethical Review Authority; UK: Health Research Authority; and USA: Advarra. A full list of study sites and their respective ethics committees is provided in Supplementary Table S1. All patients provided written informed consent.

REFERENCES

1. Sundstrom J, Bodegard J, Bollmann A, et al. Prevalence, outcomes, and cost of chronic kidney disease in a contemporary population of 2.4 million patients from 11 countries: the CaReMe CKD study. Lancet Reg Health Eur. 2022;20:100438. https://doi.org/10.1016/j.lanepe.2022.100438.

2. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020;395(10225):709–33. https://doi.org/10.1016/S0140-6736(20)30045-3.

3. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. Kidney Int Suppl. 2022;12(1):7–11. https://doi.org/10.1016/j.kisu.2021.11.003.

4. Brown SA, Tyrer FC, Clarke AL, et al. Symptom burden in patients with chronic kidney disease not requiring renal replacement therapy. Clin Kidney J. 2017;10(6):788–96. https://doi.org/10.1093/ckj/sfx057.

5. Cruz MC, Andrade C, Urrutia M, et al. Quality of life in patients with chronic kidney disease. Clinics. 2011;66(6):991–5. https://doi.org/10.1590/s1807-59322011000600012.

6. Tang E, Bansal A, Novak M, Mucsi I. Patient-reported outcomes in patients with chronic kidney disease and kidney transplant-part 1. Front Med (Lausanne). 2017;4:254. https://doi.org/10.3389/fmed.2017.00254.

7. Basch E, Deal AM, Kris MG, et al. Symptom monitoring with patient-reported outcomes during routine cancer treatment: a randomized controlled trial. J Clin Oncol. 2016;34(6):557–65. https://doi.org/10.1200/JCO.2015.63.0830.

8. Pecoits-Filho R, James G, Carrero JJ, et al. Methods and rationale of the DISCOVER CKD Global Observational Study. Clin Kidney J. 2021;14:1570–8. https://doi.org/10.1093/ckj/sfab046.

9. Pollock C, James G, Garcia Sanchez JJ, et al. Cost of end-of-life inpatient encounters in patients with chronic kidney disease in the United States: a report from the DISCOVER CKD retrospective cohort. Adv Ther. 2022;39(3):1432–45. https://doi.org/10.1007/s12325-021-02010-3.

10. James G, Garcia Sanchez JJ, Carrero JJ, et al. Low adherence to kidney disease: improving global outcomes 2012 CKD clinical practice guidelines despite clear evidence of utility. Kidney Int Rep. 2022;7(9):P2059–70. https://doi.org/10.1016/j.ekir.2022.05.033.

11. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473–83.

12. Optum, Inc. An excerpt from the User's Manual for the SF-36v2 Health Survey, Second Edition, Chapter 3, pages 29–37. https://www.optum.com/content/dam/optum/resources/Manual%20Excerpts/Which-Survey-To-Use.pdf. Accessed May 22, 2023.

13. Optum, Inc. Optum PRO CoRE 1.5 Smart Measurement System Version 1.5. 2019.

14. Topolski TD, LoGerfo J, Patrick DL, et al. The rapid assessment of physical activity (RAPA) among older adults. Prev Chronic Dis. 2006;3(4):A118.

15. Zhang W, Bansback N, Boonen A, et al. Validity of the work productivity and activity impairment questionnaire–general health version in patients with rheumatoid arthritis. Arthritis Res Ther. 2010;12(5):R177. https://doi.org/10.1186/ar3141.

16. Kang E, Han M, Kim H, et al. Baseline general characteristics of the Korean chronic kidney disease: report from the KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease (KNOW-CKD). J Korean Med Sci. 2017;32(2):221–30. https://doi.org/10.3346/jkms.2017.32.2.221.

17. Martinez-Castelao A, Gorriz JL, Portoles JM, et al. Baseline characteristics of patients with chronic kidney disease stage 3 and stage 4 in Spain: the MERENA observational cohort study. BMC Nephrol. 2011;12:53. https://doi.org/10.1186/1471-2369-12-53.

18. Denker M, Boyle S, Anderson AH, et al. Chronic Renal Insufficiency Cohort Study (CRIC): overview and summary of selected findings. Clin J Am Soc Nephrol CJASN. 2015;10(11):2073–83. https://doi.org/10.2215/CJN.04260415.

19. Stengel B, Metzger M, Combe C, et al. Risk profile, quality of life and care of patients with moderate and advanced CKD: the French CKD-REIN cohort study. Nephrol Dialy Transplant. 2019;34(2):277–86. https://doi.org/10.1093/ndt/gfy058.

20. Reichel H, Zee J, Tu C, et al. Chronic kidney disease progression and mortality risk profiles in Germany: results from the chronic kidney disease outcomes and practice patterns study. Nephrol Dialy Transplant. 2020;35(5):803–10. https://doi.org/10.1093/ndt/gfz260.

21. Yuan J, Zou XR, Han SP, et al. Prevalence and risk factors for cardiovascular disease among chronic kidney disease patients: results from the Chinese cohort study of chronic kidney disease (C-STRIDE). BMC Nephrol. 2017;18(1):23. https://doi.org/10.1186/s12882-017-0441-9.

22. Roehm B, Gulati G, Weiner DE. Heart failure management in dialysis patients: many treatment options with no clear evidence. Semin Dial. 2020;33(3):198–208. https://doi.org/10.1111/sdi.12878

23. Al-Naher A, Wright D, Devonald MAJ, Pirmohamed M. Renal function monitoring in heart failure – what is the optimal frequency? A narrative review. Br J Clin Pharmacol. 2018;84:5–17. https://doi.org/10.1111/bcp.13434

24. Kidney Disease Improving Global Outcomes. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International. 2024;105(4S):S117–S314. https://doi.org/10.1016/j.kint.2023.10.018.

25. Cheung AK, Chang TI, Cushman WC, et al. Executive summary of the KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Kidney Int. 2021;99(3):559–69. https://doi.org/10.1016/j.kint.2020.10.026.

26. National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management. 2023. https://www.nice.org.uk/guidance/ng136/chapter/Recommendations. Accessed

27. Accord Study Group, Cushman WC, Evans GW, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. New Engl J Med 2010;362(17):1575–85. https://doi.org/10.1056/NEJMoa1001286.

28. Rossing P, Caramori ML, Chan JCN, et al. Executive summary of the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease: an update based on rapidly emerging new evidence. Kidney Int. 2022;102(5):990–9. https://doi.org/10.1016/j.kint.2022.06.013.

29. Kidney Disease: Improving Global Outcomes Diabetes Work Group. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int 2022;102(5S):S1–S127. https://doi.org/10.1016/j.kint.2022.06.008.

30. de Boer IH, Khunti K, Sadusky T, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care. 2022;45(12):3075–90. https://doi.org/10.2337/dci22-0027.

31. Liabeuf S, Lambert O, Metzger M, et al. Adverse outcomes of proton pump inhibitors in patients with chronic kidney disease: the CKD-REIN cohort study. Br J Clin Pharmacol. 2021;87(7):2967–76. https://doi.org/10.1111/bcp.14713.

32. Fletcher BR, Damery S, Aiyegbusi OL, et al. Symptom burden and health-related quality of life in chronic kidney disease: a global systematic review and meta-analysis. PLoS Med. 2022;19(4):e1003954. https://doi.org/10.1371/journal.pmed.1003954.

33. Jenkinson C, Coulter A, Wright L. Short form 36 (SF36) health survey questionnaire: normative data for adults of working age. BMJ. 1993;306(6890):1437–40. https://doi.org/10.1136/bmj.306.6890.1437.

34. Elshahat S, Cockwell P, Maxwell AP, et al. The impact of chronic kidney disease on developed countries from a health economics perspective: a systematic scoping review. PLoS One. 2020;15(3):e0230512. https://doi.org/10.1371/journal.pone.0230512.

35. Paik JM, Patorno E, Zhuo M, et al. Accuracy of identifying diagnosis of moderate to severe chronic kidney disease in administrative claims data. Pharmacoepidemiol Drug Saf. 2022;31(4):467–75. https://doi.org/10.1002/pds.5398.

36. Carrero JJ, Fu EL, Vestergaard SV, et al. Defining measures of kidney function in observational studies using routine health care data: methodological and reporting considerations. Kidney Int. 2023;2023:53–69. https://doi.org/10.1016/j.kint.2022.09.020

37. Booker QS, Austin JD, Balasubramanian BA. Survey strategies to increase participant response rates in primary care research studies. Fam Pract. 2021;38(5):699–702. https://doi.org/10.1093/fampra/cmab070