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ORIGINAL ARTICLE

Healthcare resource utilisation and related costs of patients with CKD from the UK: a report from the DISCOVER CKD retrospective cohort

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ABSTRACT

Background. Chronic kidney disease (CKD) is widely reported to decrease quality of life, increase morbidity and mortality and cause increased healthcare resource utilisation (HCRU) as the disease progresses. However, there is a relative paucity of accurate and recent estimates of HCRU in this patient population. Our aim was to address this evidence gap by reporting HCRU and related costs in patients with CKD from the UK primary and secondary care settings.

Methods. HCRU and cost estimates of CKD were derived for UK patients included in the DISCOVER CKD cohort study using clinical records from the Clinical Practice Research Datalink linked to external databases. Patients with a history of transplant or undergoing dialysis were not included. HCRU and costs were stratified by CKD severity using the urinary albumin:creatinine ratio (UACR) and estimated glomerular filtration rate.

Results. Hospitalisation rates more than tripled between low (A1) and high (A3) UACR categories and the mean annual per-patient costs ranged from £4966 (A1) to £9196 (A3) and from £4997 (G2) to £7595 (G5), demonstrating that a large healthcare burden can be attributed to a relatively small number of patients with later stage CKD, including those with kidney failure and/or albuminuria.

Conclusions. HCRU and costs associated with CKD impose a substantial burden on the healthcare system, particularly in the more advanced stages of CKD. New interventions that can delay the progression of CKD to kidney failure may not only prolong the patient's life, but would also provide significant resource and cost savings to healthcare providers.

GRAPHICAL ABSTRACT
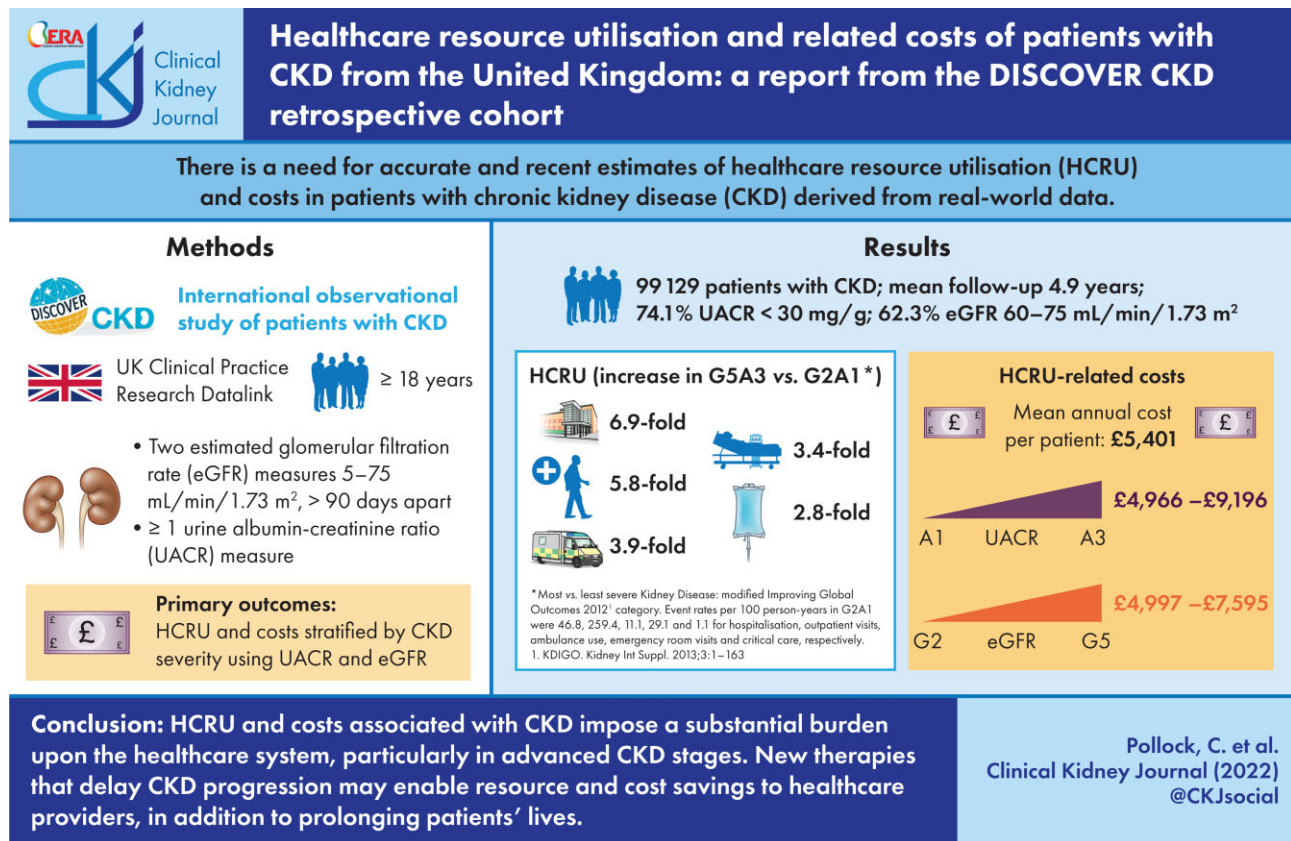
Keywords: chronic kidney disease, Clinical Practice Research Datalink, cost analysis, healthcare resource use, hospitalisations

INTRODUCTION

In the UK, like elsewhere, the prevalence of chronic kidney disease (CKD) is increasing [1, 2], driven by an ageing population and an increasing incidence of type 2 diabetes mellitus (T2D) [3–5]. Contemporary modelling projections from the UK predict that by 2025, CKD prevalence will increase a further 1%, to a staggering 14% of the adult population. In addition, projections also predict a changing profile of the prevalent CKD population, with an increase in the more advanced stages (3b–5) of ∼7% relative to the total CKD population by 2025 [6].

This increasing prevalence and changing patient profile are of concern to healthcare providers as patient outcomes worsen and costs increase as the disease progresses toward kidney failure. This increase in costs is driven by more frequent and expensive interactions with healthcare services, where costly and invasive procedures, such as dialysis, ultimately become a requirement for survival [7–9]. This is further exacerbated by the costs associated with the management of comorbidities and complications that are relatively frequent in this patient population, such as diabetes, anaemia and cardiovascular complications including heart failure (HF) [4, 10–14].

Despite a high unmet need in this patient population, the treatment landscape for CKD has not changed substantially until quite recently [8]. Sodium–glucose co-transporter-2 inhibitors (SGLT2is) and selective mineralocorticoid receptor antagonists (MRAs) have emerged as new classes of interventions in the management of CKD [15, 16]. While these are well-established in the management of T2D, recent phase 3 trials have also shown them to provide significant and sustained improvements in kidney- and cardiovascular-related outcomes for patients both with and without T2D [17–23]. In addition to the importance of efficacious therapies, categorisation of patients by estimated glomerular filtration rate (eGFR) and urinary albumin:creatinine ratio (UACR) is crucial for accurate prognosis and to guide patient management.

Economic tools underpinned by robust data sources are required to support the formal evaluation of such new and effective interventions and their subsequent integration into routine clinical practice. It is here that an accurate and thorough understanding of healthcare resource utilisation (HCRU) can be of great value, as economic evaluations in the CKD population are often generated using older HCRU estimates or data not derived from real-world evidence [8, 24–28]. Therefore this study sought to describe the HCRU of patients with CKD in the UK, stratified by both eGFR and UACR, to provide a valuable source of contemporary HCRU data to support accurate, evidence-driven health economic evaluations of next-generation therapies for CKD and to better inform the healthcare sector with resourcing requirements for more efficient service delivery.

MATERIALS AND METHODS

Study population

DISCOVER CKD is a hybrid, multinational, observational cohort study in patients with CKD. The patients included in the analysis reported here are a subset derived from DISCOVER CKD based on the UK retrospective patient cohort, which corresponds to patients recorded in the Clinical Practice Research Datalink (CPRD GOLD) electronic health records (EHR) database. The full DISCOVER CKD study was comprised of a retrospective patient cohort capturing secondary data from established anonymised datasets and a prospective cohort collecting primary and secondary data in patients individually recruited from participating centres in Italy, Japan, Sweden, Spain, the UK and the USA (ClinicalTrials.gov identifier: NCT04034992; ISAC protocol number: 19_226A4).

The DISCOVER CKD eligibility criteria have been previously described [29], but in brief the eligible patient cohort included adult patients with CKD after 1 January 2008 and ≥ 1 year of medical history available prior to the index date. Diagnosis was defined as documented diagnostic code (e.g. International Classification of Diseases, Tenth Revision) for CKD stages 3A through to kidney failure or two consecutive eGFR measures of <75 mL/min/1.73 m^2 recorded >90 days apart (maximum 730 days).

The following additional inclusion criteria were applied for this analysis: two consecutive eGFR measures of 5–75 ml/min/1.73 m^2 recorded >90 days apart (maximum 730 days) and one or more UACR measurement within 1 year before or any time up to 5 years after the index date. The UACR measure closest to the index was used to categorise patients.

The following additional exclusion criteria were applied: patients without two measures of eGFR <75 mL/min/1.73 m^2 recorded at least 90 days apart on or after 1 January 2008, death within 30 days of the index date (where available in the data source), a history of type 1 diabetes mellitus or a history of renal transplant or dialysis at the study index.

Baseline patient demographics and laboratory parameters were defined as the most recent variable prior to the index within a 1-year lookback period (1 year prior to the index). Medication usage at baseline was defined as any treatment received at the index or within the 1-year lookback period. Comorbidity history at baseline was defined as any history prior to the index spanning the patient's entire available medical history. For any repeated measures, the non-missing data closest to the index date were used.

The modified Kidney Disease: Improving Global Outcomes (KDIGO) 2012 classification system was used to assess CKD severity. The KDIGO classification system is an internationally recognized framework for appraising the severity and prognosis of CKD incorporating both eGFR and UACR measurements (Fig S1), which has been previously used to estimate disease-related risk and provide clinical guidance for the management of CKD in the UK [2, 8].

Study period

The study period covered in this analysis spanned January 2008–January 2020. Patients were followed up until the end of data collection, database end, loss to follow-up or death, whichever occurred first. The index date corresponded with the patient's baseline and was defined as the date of the second eGFR measurement recorded >90 days after the first measurement (maximum 730 days).

Data sources

This study used EHR data from CPRD GOLD, representing the primary care population with records coming directly from general practitioners (GPs), and linked Hospital Episode Statistics (HES) databases, representing the collection of secondary care data across the patient cohort: Admitted Patient Care (APC), Outpatient (OP), Accident and Emergency (A&E) and Office of National Statistics (ONS) death data.

This study is based in part on data from the CPRD obtained under licence from the UK Medicines and Healthcare products Regulatory agency. The data are provided by patients and collected by the National Health Service (NHS) as part of their routine care and support. The interpretation and conclusions contained in this study are those of the authors alone. Hospital Episode Statistics (HES)/Office of National Statistics (ONS) data are reused with the permission of the Health and Social Care Information Centre. All rights reserved.

Study endpoints

Study endpoints included in this analysis were patient follow-up (exposure time, patient-years), total length of hospital admission across all episodes, HCRU and associated costs. Number and incidence rates of HCRU included outpatient visits, hospitalisations, emergency room (ER) visits, intensive care unit stays (critical care), required use of an ambulance and GP visits. Total and annualised costs over the observation period were calculated from each HCRU category. HCRU and associated costs correspond to the overall resource utilisation of patients with CKD included in this study, not limited to those relating specifically to nephrological treatment.

Statistical analysis

Descriptive analysis for annualised HCRU/costs were undertaken for the aforementioned categories. The cost perspective was that of the NHS. Costs associated with HCRU were generated by applying the relevant Personal Social Services Research Unit (GP visits) and 2017/2018 NHS reference costs (outpatient visits, hospitalisations, ER visits, critical care and ambulance use); costs were inflated to 2019 values [30, 31]. Healthcare Resource Group (HRG) codes were mapped to costs on a per event basis and grouped into the corresponding HCRU categories. Patients were not censored for transplant or dialysis initiation during the study period, but the specific costs for such procedures were not included in this analysis. The costs predominantly reflect HCRU incurred by patients aside from the costs of treatment in specialist dialysis centres. Costs incurred during the follow-up period were summed per patient. From these, total and annual costs were calculated across the cohort. Mean costs were omitted from this analysis for subgroups where data were available for <11 patients; this included critical care costs for patients in the eGFR G5 category. Annualised event rates were expressed as the incidence of the outcome per 100 person-years. eGFR measures <5 mL/min/1.73 m^2 were excluded from the analyses.

RESULTS

Baseline characteristics

DISCOVER CKD captured a large patient cohort representative of the broad spectrum of CKD in UK clinical practice, [32] including 99 129 patients with CKD (Table 1). At baseline, the most common comorbidities were hypertension (58.7%) and T2D (37.3%),

Table 1. Baseline characteristics

Variable	Overall CKD cohort (n = 99 129)	Comorbid CKD and T2D (n = 36 960)	Comorbid CKD and HF (n = 5033)
Follow-up (years), mean (SD)	4.9 (2.9)	4.5 (2.9)	4.2 (2.7)
Demographics			
Female, n (%)	50 309 (50.8)	15 875 (43.0)	1934 (38.4)
Age (years), mean (SD)	68.5 (11.3)	68.0 (10.0)	72.5 (10.3)
KDIGO eGFR category (mL/min/1.73 m^2), n (%)			
G2[a] (60–75)	61 797 (62.3)	28 487 (77.1)	2473 (49.1)
G3a (45–<60)	28 248 (28.5)	6664 (18.0)	1650 (32.8)
G3b (30–<45)	7514 (7.6)	1473 (4.0)	720 (14.3)
G4 (15–<30)	1408 (1.4)	298 (0.8)	170 (3.4)
G5 (<15)	162 (0.2)	38 (0.1)	20 (0.4)
KDIGO UACR category (mg/g), n (%)			
A1 (<30)	73 440 (74.1)	27 605 (37.6)	3332 (66.2)
A2 (30–<300)	21 958 (22.2)	7728 (35.2)	1429 (28.4)
A3 (≥300)	3731 (3.8)	1627 (43.6)	272 (5.4)
Laboratory values, median (IQR)			
eGFR (mL/min/1.73 m^2)	64.0 (55.1–70.2)	67.8 (60.9–71.8)	59.8 (48.6–68.1)
UACR (mg/g)	10.4 (4.5–30.1)	10.6 (5.1–28.3)	17.7 (6.2–54.0)
Hb (g/dl)	13.7 (12.7–14.7)	13.6 (12.6–14.7)	13.3 (12.1–14.4)
Medical history/comorbidities at baseline, n (%)			
History of HF	5033 (5.1)	2193 (5.9)	5033 (100.0)
History of coronary heart disease	17 294 (17.4)	7549 (20.4)	2923 (58.1)
History of myocardial infarction	7380 (7.4)	3187 (8.6)	1690 (33.6)
History of hypertension	58 217 (58.7)	23 605 (63.9)	3214 (63.9)
History of T2D	36 960 (37.3)	36 960 (100.0)	2193 (43.6)
History of stroke	5046 (5.1)	2083 (5.6)	505 (10.0)
History of hyperkalaemia	449 (0.5)	230 (0.6)	81 (1.6)
Baseline medication use, n (%)			
RAAS inhibitors (ACE inhibitors and ARBs)	50 769 (51.2)	23 929 (64.7)	4308 (85.6)
Diuretics (MRAs, loop diuretics and thiazide diuretics)	17 426 (17.6)	13 896 (37.6)	3952 (78.5)
Anticoagulants	6149 (6.2)	2842 (7.7)	1726 (34.3)
Antiplatelets (aspirin, clopidogrel and other agents)	33 086 (33.4)	14 518 (39.3)	3113 (61.9)
Anti-hypertensive therapies [calcium channel blockers (DHP and non-DHP), beta blockers and alpha blockers]	42 823 (43.2)	20 325 (55.0)	4117 (81.8)

[a]Restricted G2 KDIGO category based on eGFR cut-off from study inclusion criteria.
CKD: chronic kidney disease; CPRD: clinical practice research datalink; eGFR: estimated glomerular filtration rate; HF: heart failure; KDIGO: Kidney Disease Improving Global Outcomes; T2D: type 2 diabetes; UACR: urine albumin-creatinine ratio.

with a history of HF reported less frequently (5.1%). The majority of patients (90.8%) had an eGFR of 45–75 mL/min/1.73 m^2 and had a UACR <30 mg/g (74.1%). A relatively high proportion of patients had an elevated UACR (A2–A3) but near-normal eGFR (G2; 13.8%), this was particularly prominent in patients with comorbid CKD and HF (15.2%) (Supplementary data, Table S1).

HCRU

Patients in the most severe KDIGO category (G5A3) had elevated HCRU compared with those in the least severe category (G2A1), driven by the rates of hospitalisation and outpatient visits, which were associated with a 6.9- and 5.8-fold increase, respectively. Similarly, patients in the G5A3 category displayed a 3.9- and 3.4-fold increase in ambulance use and ER visits, respectively, compared with the least severe category (Supplementary data, Table S2). For GP visits, there was a ≤1.4-fold increase across any KDIGO category. The mean length of hospital stay was also greater at worsened severities, increasing from 14.7 (G2A1) to 54.3 (G5A3) days.

Healthcare costs

Overall mean healthcare costs regardless of CKD stage were £5401 per patient per year (PPPY) and ranged from £4654 (G2A1) to £11 419 (G4A3; Fig. 1). Critical care costs for patients with G5A3 CKD were excluded due to the small number of events in this small subgroup of patients; nevertheless, costs were high in this most severe population. Hospitalisation and critical care accounted for the majority of healthcare costs across the cohort (Table 2, Table 3 and Fig. 2). Costs for each healthcare resource generally rose with increasing CKD severity, including hospitalisations, outpatient visits, critical care, GP visits, ER visits and ambulance use (Table 3).

HCRU in people with CKD and T2D

Rates of HCRU were higher in those with comorbid CKD and T2D compared with those with CKD without T2D: 62.1 versus 54.7 hospitalisations and 308.5 versus 274.5 outpatient visits per 100 patient-years, respectively. This general trend was observed across KDIGO categories and was particularly prominent in G4A3 patients, who had a 2.1-fold increase in hospitalisation
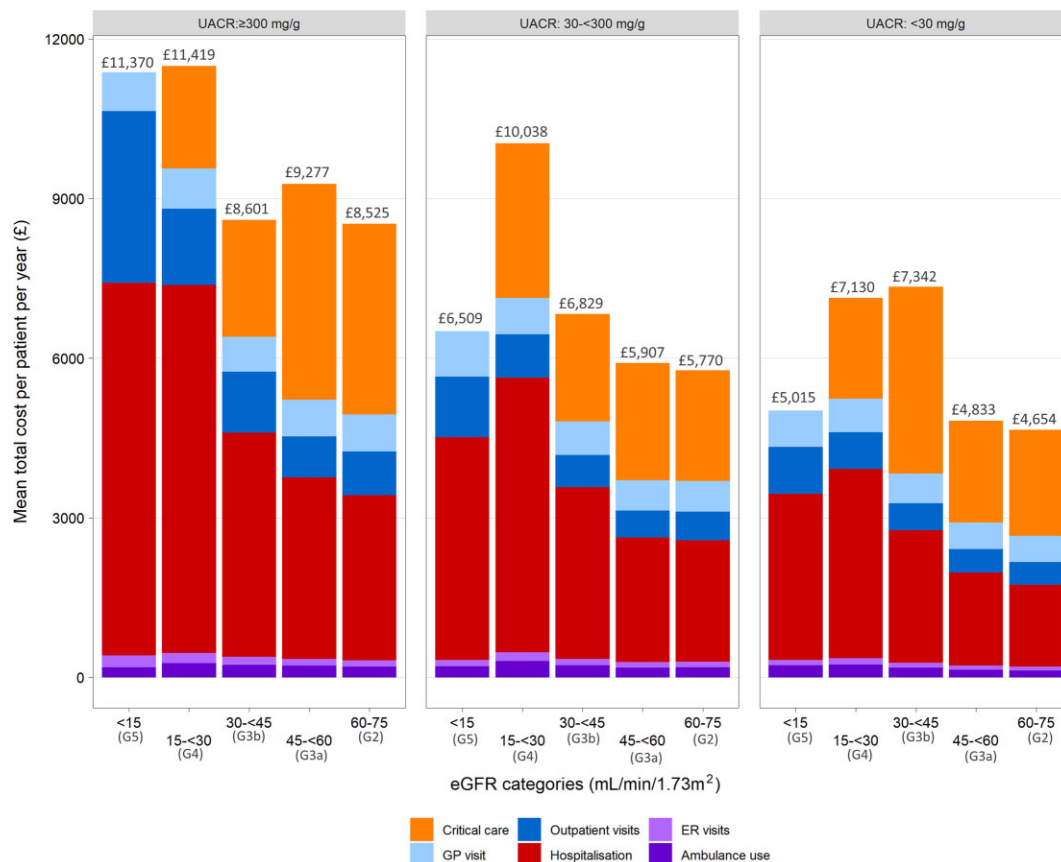
FIGURE 1: Mean annual per patient healthcare costs for the overall CKD cohort, stratified by KDIGO classification groups. eGFR <15 critical care costs excluded because of the small number of events (<11 patients with event).

rates and a 3.8-fold increase in the number of critical care visits between G4A3 patients with comorbid CKD and T2D compared with those with CKD without T2D (Supplementary data, Table S3 and S4).

Overall mean healthcare costs regardless of CKD stage were £6149 and £5076 PPPY for those with comorbid CKD and T2D compared with CKD without T2D, respectively. For the overall T2D cohort, cost burden was consistently elevated across all resource categories when compared with patients without T2D (Supplementary data, Table S5 and S6). Hospitalisation and critical care incurred the most significant costs for those with CKD and T2D (mean annual cost £2385 and £2357, respectively). Healthcare costs for patients with and without T2D stratified by eGFR and UACR categories are presented in Fig. 3.

HCRU in people with CKD and HF

For patients with comorbid CKD and HF, HCRU rates were greater across each category compared with those with CKD without HF. Rates of ambulance use, critical care and hospitalisation were particularly elevated in patients with HF compared with those without (2.6-, 2.2- and 1.7-fold increase, respectively). The increase in HCRU event rates as CKD worsened was generally greater for patients without HF compared with those with HF; particularly prominent was the difference in rates of hospitalisation and outpatient visits between lower and higher CKD

severities (G2A1–G4A3): hospitalisation (2.0- versus 11.6-fold difference) and outpatient visits (1.5- versus 2.9-fold difference) for patients with and without HF, respectively. This indicates that HCRU was already elevated at lower CKD severities for patients with HF (Supplementary data, Table S7 and S8).

Overall mean healthcare costs regardless of CKD stage were £7825 and £5223 PPPY for CKD patients with and without HF, respectively. For the overall HF cohort, the cost burden was consistently elevated across all resource categories (Supplementary data, Table S9 and S10). When stratified by eGFR, HCRU and associated costs were similar in the lower eGFR categories for patients with HF [mean total cost PPPY: £8586 (G3a)–£8793 (G4)] and were considerably less in patients with G2 CKD (£6744), driven by lower hospitalisation costs. When stratified by UACR, total healthcare costs were considerably higher in the most severe patients [mean total cost PPPY: £7127 (A1)–£15 562 (A3)], driven primarily by critical care and hospitalisation costs (Fig. 3).

DISCUSSION

This study shows that CKD represents a significant system-wide healthcare burden beyond the impact of dialysis, transplant and other treatment and management costs usually provided through specialist nephrology care, with a particularly high burden in the advanced stages of CKD. For example, mean rates

Table 2. Overall HCRU and costs

Variable	Mean (SD)	Median (IQR)	Range
Follow-up (years)	4.9 (2.9)	4.7 (2.6–6.9)	0.0–11.7
Outpatient visits			
Patients with outpatient visits, n (%)			37 790 (38.1)
Visit days per patient from index to end of follow-up	16.1 (20.6)	9.0 (4.0–20.0)	1.0–706.0
Visit days PPPY	3.6 (4.6)	2.3 (1.0–4.6)	0.1–121.8
Total cost per patient from index to end of follow-up	£2121 (2992)	£1190 (474–2633)	£0–107 429
Total cost PPPY	£481 (695)	£285 (125–596)	£0–37 005
Hospitalisations			
Patients with hospitalizations, n (%)			28 391 (28.6)
Admissions per patient from index to end of follow-up	4.3 (9.6)	2.0 (1.0–5.0)	1.0–557.0
Admissions PPPY	1.1 (2.3)	0.6 (0.3–1.1)	0.1–107.8
Total cost per patient from index to end of follow-up	£7217 (9085)	£4096 (1433–9609)	£0–168 852
Total cost PPPY	£1958 (3811)	£876 (304–2224)	£0.0–187 406
Length of stay across all hospital admissions (days)	19.0 (36.4)	6.0 (2.0–20.0)	0.0–1532.0
Emergency room visits			
Patients with emergency room visits, n (%)			24 930 (25.1)
Visit days per patient from index to end of follow-up	2.9 (3.4)	2.0 (1.0–3.0)	1.0–108.0
Visit days PPPY	0.7 (1.1)	0.4 (0.2–0.8)	0.1–48.5
Total cost per patient from index to end of follow-up	£342 (438)	£216 (133–422)	£0–13 498
Total cost PPPY	£84 (139)	£47 (22–96)	£0.0–5675
GP visits			
Patients with GP visits, n (%)			98 312 (99.2%)
Visit days per patient from index to end of follow-up	56.4 (51.8)	42.0 (21.0–75.0)	1.0–997.0
Visit days PPPY	12.1 (9.3)	9.8 (6.3–15.2)	0.1–182.6
Total cost per patient from index to end of follow-up	£2420 (2328)	£1785 (888–3198)	£30–42 705
Total cost PPPY	£524 (444)	£410 (259–648)	£4–11 266
Ambulance usage			
Patients with ambulance usage, n (%)			14 260 (14.4)
Use per patient from index to end of follow-up	2.3 (2.8)	1.0 (1.0–3.0)	1.0–92.0
Use PPPY	0.6 (1.0)	0.3 (0.2–0.7)	0.1–27.6
Total cost from index to end of follow-up	£588 (707)	£252 (252–756)	£252–24 185
Total cost per year	£162 (250)	£88 (49–179)	£22–7282
Critical care			
Patients with critical care visits, n (%)			2167 (2.2)
Visit days per patient from index to end of follow-up	1.3 (0.8)	1.0 (1.0–1.0)	1.0–10.0
Visit days PPPY	0.4 (0.6)	0.2 (0.2–0.4)	0.1–8.5
Total cost per patient from index to end of follow-up	£8097 (8392)	£6339 (3222–9763)	£0–130 865
Total cost PPPY	£2193 (4120)	£1280 (601–2386)	£0–88 032

PPPY: per patient per year.

of hospitalisation were particularly elevated in this CKD cohort and increased in line with CKD severity, with 3.2 hospitalisations PPPY and an average length of stay of 54 days for patients with G5A3 CKD. Paired with critical care, hospitalisation imposed the greatest cost and resource burden. In addition, while individuals with relatively normal kidney function (G2A1) used ambulances at a rate comparable to that of the general population in England, this increased to a 2-fold greater usage at a CKD severity of G3aA2 and to a 4-fold greater usage in G5A3 patients [33], and all KDIGO groups visited GPs at a >2-fold higher rate than the average individual [34]. While higher than the general population, rates of GP visits were generally lower in the more severe KDIGO categories and were independent of comorbid T2D or HF, which may indicate a shift in treatment setting from primary to secondary care, as treatment and follow-up likely transitioned to the secondary setting as CKD worsened. Additionally, when compared with the suggested frequency of eGFR/UACR monitoring visits in contemporary UK guidance, we observed a greater number of outpatient visits across all KDIGO categories in this CKD cohort [35].

As may be expected from previous studies, our data does demonstrate that hospitalisations are the biggest driver behind the cost burden of CKD, adding validity to the findings [25]. However, one of the strengths of this study is its reporting of several aspects of HCRU that are often overlooked because they are considered acute, short-term or lower impact, such as emergency admissions, critical care and ambulance use. These are services that are consistently overstretched and represent areas in which a reduction in CKD-related admissions could be of great benefit to local healthcare providers [36–39]. For example, shortages of beds, staff and ambulances can result in prolonged waiting times for emergency care [39], an issue driven by an ageing and ever-growing population [40]. It is through the detailed reporting of HCRU that this study may help local healthcare systems understand the true burden imposed by CKD.

With increasing prevalence, CKD is expected to comprise a significant and growing impact on both service delivery and costs to the NHS in the future [3–6]. Therefore, any interventions found to significantly delay CKD progression are expected to represent a significant offset to costs and resource use to the

Table 3. Healthcare costs per resource category, stratified by UACR and eGFR

Category	Total cost PPPY, mean (SD)			
	UACR 0–<30 mg/g	UACR 30–<300 mg/g	UACR ≥300 mg/g	Overall (per eGFR category)
Hospitalisation				
eGFR 60–75	£1534 (2657)	£2284 (4461)	£3101 (4797)	£1712 (3154)
eGFR 45–<60	£1750 (2910)	£2340 (4035)	£3413 (5989)	£1937 (3357)
eGFR 30–<45	£2493 (4600)	£3229 (4789)	£4212 (8074)	£2826 (4994)
eGFR 15–<30	£3559 (5445)	£5161 (10 946)	£6918 (20 265)	£4801 (11 520)
eGFR <15	£3119 (3347)	£4188 (4700)	£7000 (10 560)	£4748 (6770)
Overall (per UACR category)	£1702 (2998)	£2553 (4833)	£3804 (8401)	–
Outpatient visit				
eGFR 60–75	£431 (564)	£537 (724)	£826 (1138)	£458 (617)
eGFR 45–<60	£445 (602)	£508 (637)	£772 (875)	£469 (624)
eGFR 30–<45	£507 (738)	£601 (849)	£1148 (2800)	£579 (1066)
eGFR 15–<30	£688 (866)	£813 (1146)	£1432 (1488)	£873 (1145)
eGFR <15	£881 (604)	£1134 (1093)	£3226 (4319)	£1716 (2680)
Overall (per UACR category)	£443 (593)	£547 (737)	£959 (1671)	–
Ambulance usage				
eGFR 60–75	£133 (196)	£191 (318)	£201 (251)	£147 (230)
eGFR 45–<60	£146 (232)	£187 (289)	£226 (310)	£160 (252)
eGFR 30–<45	£184 (247)	£232 (300)	£237 (308)	£202 (269)
eGFR 15–<30	£243 (367)	£305 (484)	£271 (270)	£274 (411)
eGFR <15	£229 (214)	£211 (190)	£191 (224)	£209 (201)
Overall (per UACR category)	£145 (219)	£201 (316)	£222 (282)	–
ER visit				
eGFR 60–75	£73 (114)	£103 (187)	£119 (182)	£80 (133)
eGFR 45–<60	£74 (110)	£99 (167)	£119 (164)	£81 (127)
eGFR 30–<45	£90 (139)	£118 (199)	£152 (260)	£102 (170)
eGFR 15–<30	£116 (198)	£168 (290)	£188 (306)	£150 (260)
eGFR <15	£102 (93)	£117 (107)	£225 (236)	£147 (163)
Overall (per UACR category)	£75 (116)	£106 (187)	£133 (207)	–
GP visit				
eGFR 60–75	£490 (405)	£581 (472)	£696 (623)	£514 (429)
eGFR 45–<60	£494 (420)	£576 (482)	£687 (629)	£522 (449)
eGFR 30–<45	£558 (458)	£630 (514)	£655 (521)	£589 (483)
eGFR 15–<30	£633 (547)	£683 (573)	£757 (794)	£676 (611)
eGFR <15	£686 (637)	£859 (927)	£728 (595)	£774 (767)
Overall (per UACR category)	£497 (415)	£588 (486)	£691 (623)	–
Critical care				
eGFR 60–75	£1993 (3001)	£2075 (2984)	£3582 (11 980)	£2085 (3895)
eGFR 45–<60	£1913 (2434)	£2196 (4214)	£4059 (11 161)	£2105 (3948)
eGFR 30–<45	£3510 (6953)	£2019 (2154)	£2198 (2671)	£2862 (5427)
eGFR 15–<30	£1890 (1550)	£2908 (3920)	£1925 (2089)	£2279 (2797)
eGFR <15[a]	–	–	–	–
Overall (per UACR category)	£2104 (3427)	£2132 (3352)	£3388 (9790)	–

eGFR: estimated glomerular filtration rate; ER: emergency room; GP: general practitioner; PPPY: per patient per year; UACR: urine albumin creatinine ratio.
[a]eGFR <15 critical care costs are excluded from the individual subgroups because of the small number of events (<11).

NHS. Dialysis imposes a substantial cost burden on the NHS above and beyond the healthcare costs highlighted in our study, with recent estimates of £32 259 PPPY for dialysis [41] and £27 033 for the initial cost of a kidney transplant [42]. The costs of dialysis and transplant alone are more than six times greater than the overall healthcare costs reported here for patients with earlier stage CKD (G2–3a). These high costs emphasise the benefits to the healthcare system of early CKD detection and proactive management to delay patients' progression to the later stages of CKD, and further signifies the critical need for novel treatment options and effective implementation of new therapies with proven efficacy.

The smaller group of patients with the most advanced disease are responsible for a particularly large cost and resource utilisation burden when compared with the rest of the CKD cohort. This is evident when stratifying patients based on CKD severity, with mean annual per-patient costs increasing substantially to £11 419 at a severity of G4A3, an increase that was also observed when assessing UACR and eGFR separately. Thus increasing HCRU and costs align with all measured parameters of CKD severity. Patients with comorbid HF or T2D were also associated with greater costs than those with CKD without T2D/HF. Given the prevalence of T2D and cardiovascular disease is projected to increase, it can be expected that comorbid CKD will also increase. Patients with comorbidities associated with greater cost, such as T2D/HF and CKD, will place an increasing burden upon the healthcare system.

Some of the major strengths of this study include the extensive follow-up period and the granularity of HCRU and cost reporting. However, this study does not come without limita-
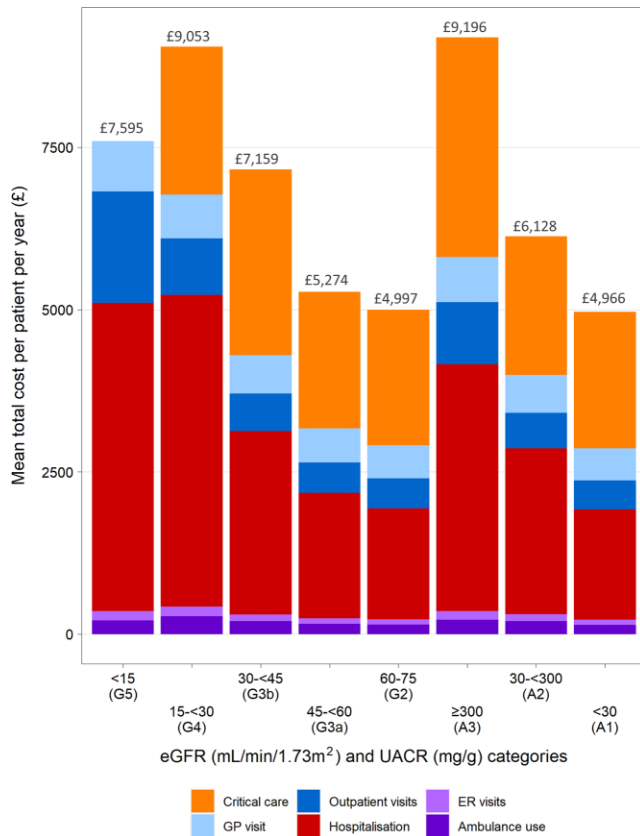
FIGURE 2: Mean annual per patient healthcare costs for overall CKD cohort, stratified by eGFR and UACR. eGFR <15 critical care costs excluded because of the small number of events (<11 patients with event).

tions. The lack of specific medication, dialysis and transplant costs resulted in an underestimate of the overall costs associated with CKD for patients with kidney failure. In addition, the exclusion of patients undergoing dialysis or transplant at the index resulted in a slight underrepresentation of patients with kidney failure compared with the overall real-world CKD population.

While the data captured from the CPRD were considered robust, the data reflect routine care and were not collected for research purposes. Consequently, data are prone to missingness, which was compounded by the limitations of the linked datasets used to categorise HCRU. For example, the HES was limited by a lack of prescription history and laboratory values, and details of specific outpatient departments utilised by patients during visits were not available, thus limiting the conclusions that can be drawn based on the exact morbidity responsible for healthcare utilisation. In addition, the CPRD does not collect data relating to the socio-economic status of individuals, which may not precisely match a modelled population and can influence HCRU [43]. Reflecting the inclusion criteria of the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease trial population, an eGFR range of 60–75 mL/min/1.73 m^2 was applied to define G2. Therefore HCRU and costs may be an overestimate if modelled using an eGFR range of 60–89 mL/min/1.73 m^2, which typically defines the G2 group [44, 45]. The long-term implications of preventing or delaying CKD progression are not directly addressed in this analysis, only postulated based on HCRU trends. Any conclusions based on the causal mechanisms of CKD in relation to HCRU outcomes should be treated with cau-

tion. In a cohort greatly affected by comorbidities and other underlying conditions, it cannot be concluded with certainty that all captured HCRU relates to CKD. However, due to the interrelated nature of CKD and its various sequalae, it was deemed important to capture all HCRU/costs of the cohort. There was no matching made between severity groups, therefore the differences in HCRU and costs as UACR and eGFR worsen may be influenced by confounding factors such as age. Finally, results from this analysis are only reflective of the UK and may have limited generalisability to other settings; in addition, regional/hospital-level practice differences are not accounted for across such a large cohort.

One additional consideration is that the UACR requirements applied to this study were beyond those of the broader DISCOVER CKD inclusion criteria. This greatly limited the number of eligible patients and resulted in ∼75% of the otherwise eligible DISCOVER CKD cohort being excluded from this study. The lack of available UACR data further highlights the need for more thorough recording and capture of UACR across EHRs to aid in the prognosis and management of CKD. This is particularly relevant for patients with comorbid CKD and HF, for which a high proportion (15.2%) had elevated UACR (A2–A3) but near-normal eGFR (G2). Thus a diagnosis of CKD may be missed when screening for eGFR only.

CONCLUSIONS

This study provides contemporary evidence of HCRU in patients with CKD where costs and HCRU were found to be substantial and increased, in line with worsened CKD severity. When factoring in the additional costs of dialysis, CKD can be expected to cost upwards of six times more between the early stages (G2–3a) and kidney failure. The evidence provided by this study will be highly valuable in supporting the evaluation of novel therapies for patients with CKD and to better inform the health sector with resourcing requirements to support more efficient healthcare delivery. The adoption of new and effective therapies that have been associated with delaying or halting disease progression into routine care for patients with CKD, paired with improved early screening and monitoring, particularly of UACR, could potentially play a major role in reducing the HCRU burden while also improving patient outcomes.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study were derived for UK patients included in the DISCOVER CKD study using clinical records from the Clinical Practice Research Datalink (CPRD GOLD) linked to external databases. Data underlying
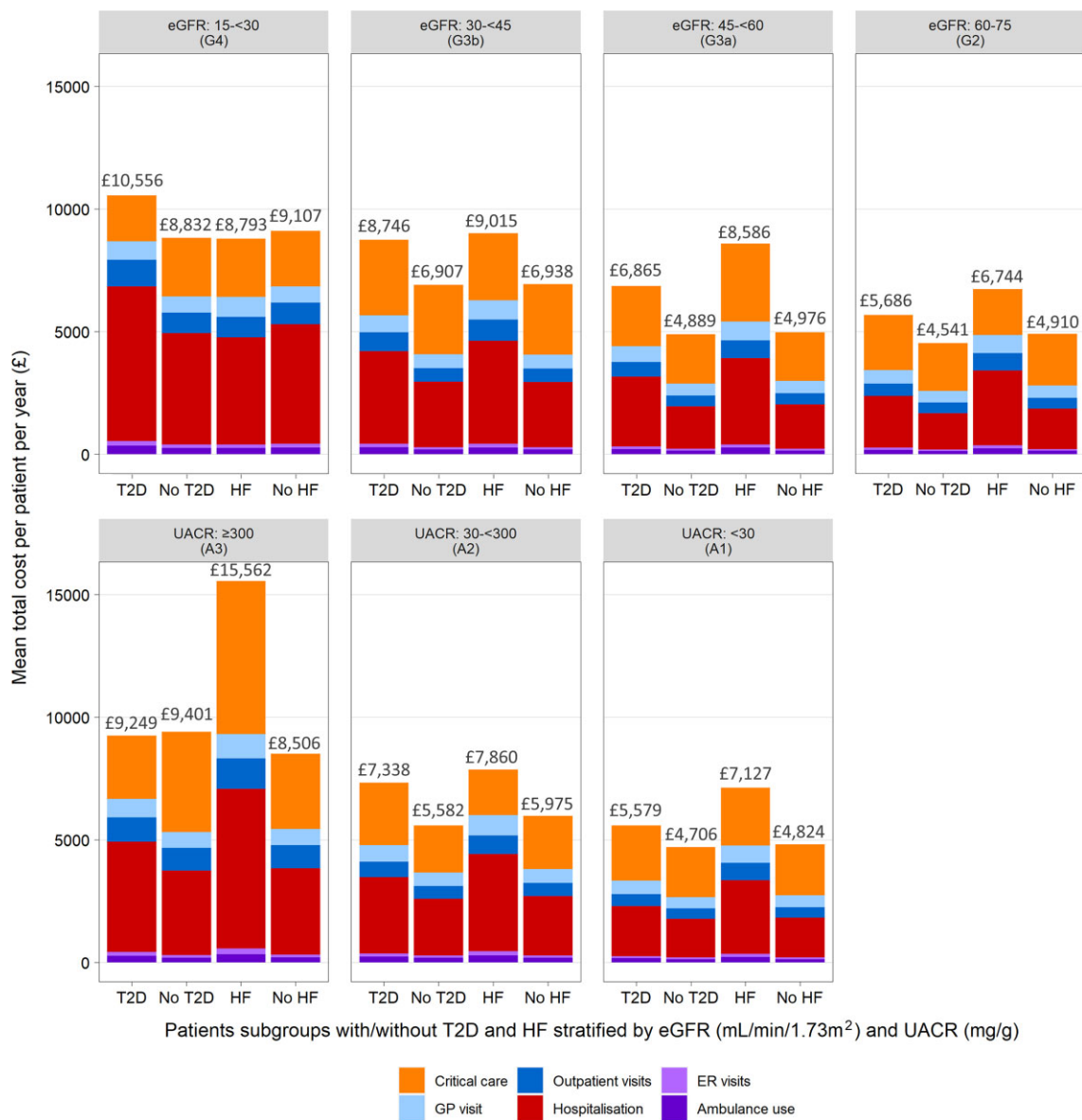
FIGURE 3: Mean annual per patient healthcare costs for patient subgroups with/without T2D and HF, stratified by eGFR and UACR. eGFR <15 subgroup excluded because of the small number of events across resource categories and subgroups (<11 patients with event)

the findings described in this article may be requested in accordance with AstraZeneca's data sharing policy described at https://astrazenecagroup-dt.pharmacm.com/DT/Home through www.vivli.org.

AUTHORS' CONTRIBUTIONS

All authors contributed to the study design, interpretation of results and review/approval of this manuscript.

CONFLICT OF INTEREST STATEMENT

J.J.G.S., M.A., T.C. and S.N. are employees and stockholders of AstraZeneca. C.P. has received consulting fees from AstraZeneca, Eli Lilly/Boehringer Ingelheim, Merck Sharp and Dohme, Novartis, Vifor, Amgen, Otsuka, Sanofi and Janssen and has received speaker fees from Novartis, Janssen Cilag, Otsuka and Vifor. J.J.C. has received institutional grants from AstraZeneca, Vifor and Astellas, speaker fees from AstraZeneca, Abbott and Nutricia and consultancy fees from AstraZeneca, Baxter Healthcare and Bayer. R.P.F. is an employee of Arbor Research Collaborative for Health, which receives global support for the ongoing DOPPS Programs (provided without restriction on publications by a variety of funders; for details see https://www.dopps.org/AboutUs/Support.aspx) and has received research grants from Fresenius Medical Care; consulting fees from

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