Clinical Outcomes in Patients with CKD and Rapid or Non-rapid eGFR Decline: A Report from the DISCOVER CKD Retrospective Cohort

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ABSTRACT

Introduction: This analysis examined the baseline characteristics and clinical outcomes of patients with chronic kidney disease (CKD) and rapid or non-rapid estimated glomerular filtration rate (eGFR) decline, using retrospective data from DISCOVER CKD (ClinicalTrials.gov, NCT04034992).

Methods: Data (2008–2020) were extracted from UK Clinical Practice Research Datalink, US TriNetX, US Limited Claims and Electronic Health Record Dataset, and Japan Medical Data Vision. Patients with CKD (two consecutive eGFR measures < 75 mL/min/1.73 m^2 recorded 90–730 days apart) were included. Rapid eGFR decline was defined as an annual decline of > 4 mL/min/1.73 m^2 at 2 years post-index;

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non-rapid eGFR decline was defined as an annual decline of ≤ 4 mL/min/1.73 m^2. Clinical outcomes assessed included all-cause mortality, kidney outcomes (composite risk of kidney failure [progression to CKD stage 5] or >50% eGFR decline, and kidney failure alone), cardiovascular events—including major adverse cardiovascular events (MACE; non-fatal myocardial infarction/stroke and cardiovascular death)—and all-cause hospitalization.

Results: Across databases, rapid eGFR decline occurred in 13.7% of 804,237 eligible patients. Mean annual eGFR decline ranged between −6.21 and −6.86 mL/min/1.73 m^2 in patients with rapid eGFR decline versus between −0.11 and −0.77 mL/min/1.73 m^2 in patients with non-rapid eGFR decline. Rapid eGFR decline was associated with increased comorbidity burden and medication prescriptions. Across databases, the composite risk of kidney failure or >50% decline in eGFR was significantly greater in patients with rapid versus non-rapid eGFR decline ($P<0.01$); all-cause mortality, kidney failure alone, MACE, and all-cause hospitalization each significantly increased in two databases ($P<0.01$–0.05).

Conclusion: Understanding patient factors associated with rapid eGFR decline in patients with CKD may help identify individuals who would benefit from proactive management to minimize the risk of adverse outcomes.

Trial Registration: ClinicalTrials.gov identifier, NCT04034992.

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Key Summary Points

Why carry out this study?

Identifying the risk factors for rapid estimated glomerular filtration rate (eGFR) decline in chronic kidney disease (CKD) may help patients at highest risk receive earlier diagnosis and initiation of treatment and more frequent monitoring to slow disease progression and reduce the risk of adverse clinical outcomes.

What did the study ask?

This analysis investigated the baseline characteristics and clinical outcomes of patients with rapid and non-rapid eGFR decline using retrospective data from the DISCOVER CKD observational cohort study.

Data were extracted from four databases: UK Clinical Practice Research Datalink (2008–2019); US TriNetX (2008–2020); US Limited Claims and Electronic Health Record Dataset (2012–2019); and Japan Medical Data Vision (2008–2017).

What was learned from the study?

Urine albumin-to-creatinine ratios and C-reactive protein levels were both higher, and anemia, atrial fibrillation, and acute kidney injury were all more prevalent, among patients with rapid versus non-rapid eGFR decline, suggesting that preventing or treating these conditions could prevent rapid declines in kidney function.

The risk of kidney failure or >50% decline in eGFR was significantly elevated among patients with rapid versus non-rapid eGFR decline in all four databases; all-cause mortality, kidney failure alone, major adverse cardiovascular events, and all-cause hospitalization were significantly elevated in two databases each.

INTRODUCTION

Rapid estimated glomerular filtration rate (eGFR) decline in patients with chronic kidney disease (CKD) is associated with worse clinical outcomes compared with non-rapid eGFR decline, independent of baseline eGFR [1–4]. Identifying comorbidities and patient characteristics associated with rapid eGFR decline remains challenging in clinical practice. eGFR decline has been associated with increased age, comorbidities including diabetes mellitus and hypertension, genetic mutations, previous eGFR decline, and current eGFR [1, 4–6].

Although risk calculators predicting clinical outcomes such as kidney failure and mortality have been developed from epidemiological data [7, 8], they do not include the rate of eGFR change over time, which may help to contextualize individual risk profiles [9].

Determining the relationships between patient baseline characteristics, rate of eGFR decline, and adverse clinical outcomes is a first step in isolating risk factors for rapid eGFR decline. This could direct prioritization of resources towards those patients at highest risk, ensuring they receive earlier and more intense diagnosis and treatment initiation and more frequent monitoring to reduce the risk of adverse clinical outcomes, and delay or even avoid the need for renal replacement therapy (RRT). Although several publications have reported on this topic, studies comparing patients with rapid or non-rapid eGFR decline using multiple international datasets are lacking. DISCOVER CKD (ClinicalTrials.gov, NCT04034992) is an ongoing international observational cohort study of patients with CKD, aiming to improve our understanding of the epidemiology, and clinical and economic burden of CKD, as well as the determinants of clinical and patient-reported outcomes in real-world CKD settings [10–14]. In this analysis, the baseline characteristics and clinical outcomes of patients with CKD and rapid or non-rapid eGFR decline were evaluated using retrospective data from DISCOVER CKD.

METHODS

Patient Population and Study Databases

The data used in this analysis are from a subset of patients from the DISCOVER CKD retrospective cohort [10], extracted from the following databases: UK Clinical Practice Research Datalink (CPRD) [15–17] linked to hospital episode statistics data (2008–2019); US TriNetX, a global federated health research analytics network dataset (2008–2020); US Limited Claims and Electronic Health Record Dataset (LCED; 2012–2019); and Japan Medical Data Vision (MDV; 2008–2017).

This analysis included adults aged ≥ 18 years (≥ 20 years for Japan MDV) at the index date, defined as the second of two consecutive eGFR measurements < 75 mL/min/1.73 m^2 recorded 90–730 days apart, on or after January 1, 2008. Patients were required to have continuous enrollment in the database of ≥ 12 months before the index date. Patients with < 30 days follow-up from index, a history of kidney transplant or chronic RRT, or a history of type 1 diabetes, polycystic kidney disease, lupus nephritis, or anti-neutrophil cytoplasmic antibody nephritis were excluded from this analysis.

Definition of Rapid and Non-rapid eGFR Decline

The CKD Epidemiology Collaboration equation [18] was used to calculate eGFR from records of serum creatinine measurements. Linear mixed models (separated by database) were used to estimate eGFR trajectories by extracting eGFR measurements recorded in the first 2 years post-index; eGFR values < 5 mL/min/1.73 m^2 were excluded from eGFR trajectory calculations as they were assumed to have been misrecorded. On the basis of calculated eGFR trajectories, patients were classified as having rapid or non-rapid eGFR decline. Rapid eGFR decline was defined as annual decline > 4 mL/min/1.73 m^2. Non-rapid eGFR decline was defined as annual decline ≤ 4 mL/min/1.73 m^2. Groupings were based on published literature [1, 2]. Only patients with ≥ 2 years follow-up were included

in the analyses. The baseline (time zero) for these patients was "reset" at 2 years post-index, at which point patient characteristics and outcomes were assessed.

Study Variables and Outcomes

Patient characteristics analyzed included age; sex; laboratory findings, including baseline eGFR and urine albumin-to-creatinine ratio (UACR), although UACR data were not available for the Japan MDV; comorbidities, including type 2 diabetes (T2D), stroke, coronary heart disease (CHD), heart failure (HF), hypertension, hyperkalemia, atrial fibrillation, and anemia; and prescribed medications, including renin-angiotensin-aldosterone system inhibitors (RAASi; comprising angiotensin-converting enzyme inhibitors [ACEi], angiotensin receptor blockers [ARB], and mineralocorticoid receptor antagonists), diuretics, sodium-glucose co-transporter-2 inhibitors (SGLT2i), insulin, potassium binders, and statins. Laboratory data and procedural history were captured at or within 12 months of baseline (index). Prescribed medications were assessed at or within 90 days of baseline. Comorbidity history used data captured at any point in a patient's medical history.

Risks of clinical outcomes with rapid versus non-rapid eGFR decline were assessed at 2 years post-index, after the initial 2-year window was used to calculate eGFR trajectories. Clinical outcomes included all-cause mortality; kidney outcomes, comprising the composite of kidney failure (progression to CKD stage 5 [sustained eGFR ≤ 15 mL/min/1.73 m^2 in patients with eGFR > 15 mL/min/1.73 m^2 at baseline or initiation of chronic RRT for > 30 days]) or > 50% decline in eGFR, and kidney failure alone; a composite of CV events (including major adverse CV events [MACE], defined as non-fatal myocardial infarction, non-fatal stroke, and CV death); hospitalization for HF (hHF); and all-cause hospitalization. For analyses of kidney outcomes, patients with baseline eGFR ≤ 15 mL/min/1.73 m^2 were excluded. Data on all-cause mortality were not captured in the US LCED, and data on hHF were not captured in the Japan MDV, because these databases

are generated from medical records data that did not include this information. The analysis observation period was from index date until death (censored at 3 years of follow-up), loss to follow-up, dialysis initiation, kidney transplant, or database end, whichever occurred first.

Statistical Analyses

Baseline (2 years post-index) characteristics, including prescribed medications, were summarized descriptively.

To compare risks of adverse clinical outcomes, Cox proportional hazards modelling was applied to calculate the adjusted hazard ratios and 95% confidence intervals. Models were adjusted for baseline age, sex, race (UK CPRD and US TriNetX), diastolic and systolic blood pressure (BP), body mass index, cholesterol, eGFR, natural logarithm of number of eGFR tests recorded before 2 years post-index, UACR, hemoglobin, serum potassium, medications, and history of hypertension, T2D, HF, stroke, or myocardial infarction. Risk of all-cause mortality stratified according to eGFR category at baseline was assessed for individual databases, and pooled for the UK CPRD, US TriNetX, and Japan MDV databases (patient confidentiality agreements relating to the US LCED forbade pooling with other databases). To account for missing data, a binary numerical indicator was used (data were coded as missing [0] or not missing [1]) for continuous variables; for categorical variables derived from continuous variables, a new category was added for missing data (if an underlying continuous variable was missing). For prior comorbidities and medications, no prior record (i.e., missing) was defined as lack of evidence of prior comorbidity or medication prescription. Sensitivity analyses included a competing risks analysis of adverse clinical outcomes to determine the potential impact of the competing risk of mortality on results.

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. This study used de-identified data and did not require data collection beyond that of routine clinical care. No identifiable information was collected or examined as part of the study. Ethical and scientific approval for use of CPRD data in the current study was obtained from the Independent Scientific Advisory Committee of CPRD (protocol number 19_172). Informed consent was waived by the East Midlands – Derby Research Ethics Committee because CPRD data are anonymized for research purposes (for further information, see https://cprd.com/safeguarding-patient-data). Ethics approval was not required for use of data from the US TriNetX and Japan Medical Data Vision for this study, in accordance with local or national guidelines.

RESULTS

Patient Attrition

The DISCOVER CKD cohort included data from >1.8 million patients. Overall, 804,237 patients across the four databases were eligible for this analysis (Supplementary Material Fig. S1).

Baseline Characteristics

The baseline characteristics of each cohort are summarized in Supplementary Material Table S1. Rapid eGFR decline occurred in 13.7% ($n = 110{,}494$) of patients overall, varying from 4.9% in the UK CPRD to 18.1% in the US TriNetX. The mean number of eGFR measurements per patient used to calculate eGFR slopes was 6.9–12.7 and 3.0–7.7 for patients with rapid and non-rapid eGFR decline, respectively. Mean annual eGFR decline ranged between -6.21 and -6.86 mL/min/1.73 m^2 for patients with rapid eGFR decline, and between -0.11 and -0.77 mL/min/1.73 m^2 for patients with non-rapid eGFR decline (Fig. 1). The median follow-up time per patient was 3.3–4.5 and 3.6–5.0 years for patients with rapid and non-rapid eGFR decline, respectively. In patients without (i.e., no eGFR measurement in the first 2 years) versus with eGFR slope data, mean age was numerically lower, and a higher proportion were female (Supplementary Material Table S2).
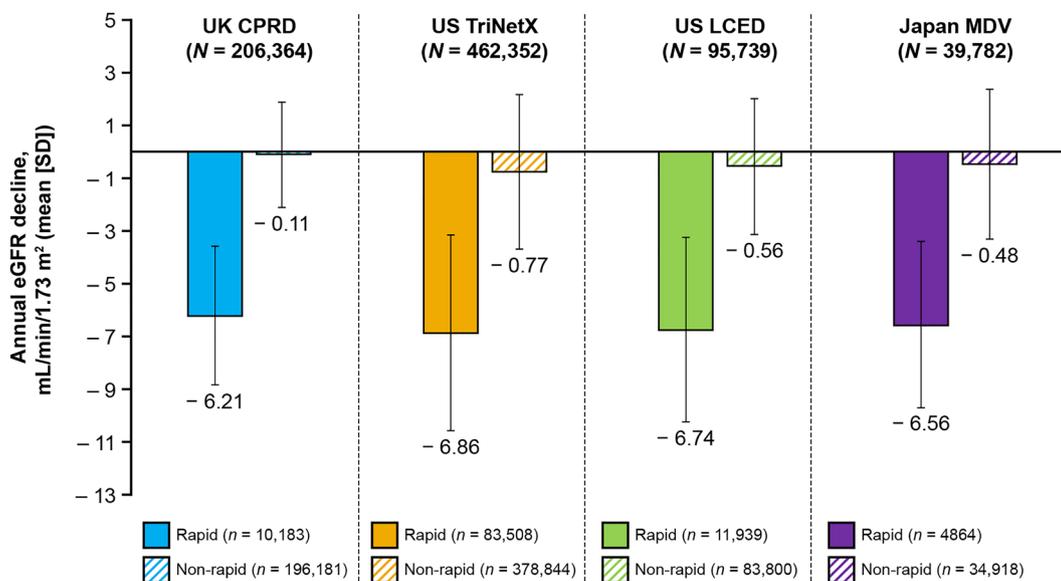
Fig. 1 Annual eGFR decline in patients with rapid versus non-rapid eGFR decline. *CPRD* Clinical Practice Research Datalink, *eGFR* estimated glomerular filtration rate, *LCED* Limited Claims and Electronic Health Record Dataset, *MDV* Medical Data Vision, *SD* standard deviation
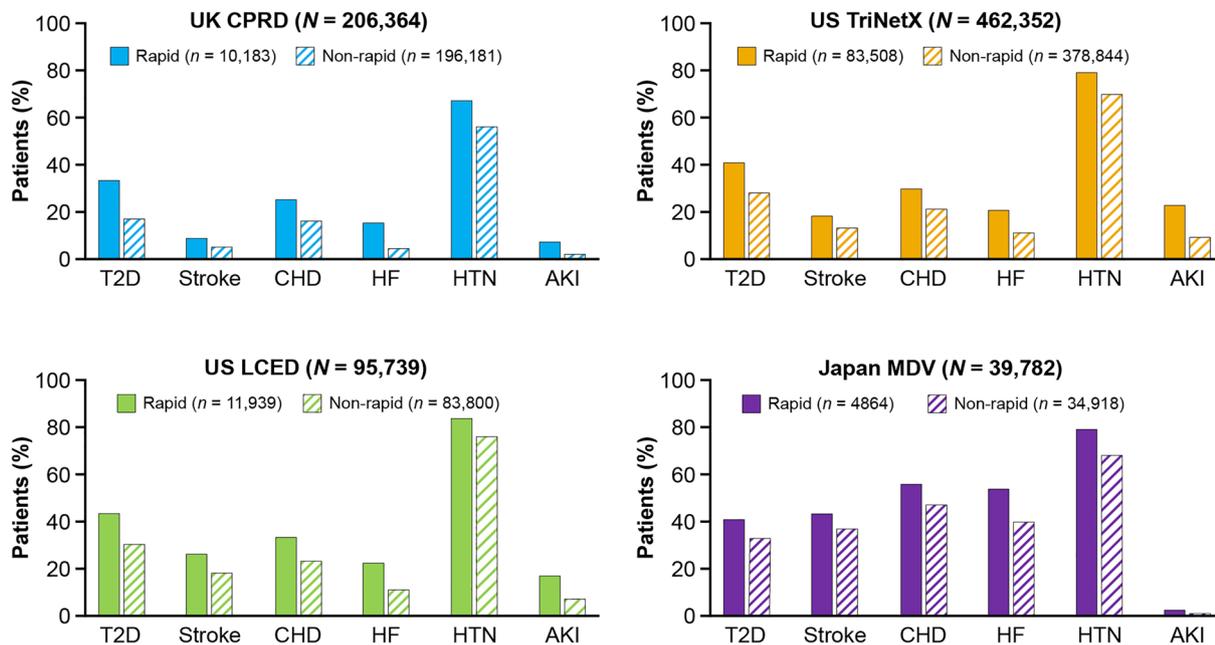
Fig. 2 Comorbidity burden in patients with rapid versus non-rapid eGFR decline (2 years post-index). CHD was ascertained via diagnostic codes for unstable angina and myocardial infarction. *AKI* acute kidney injury, *CHD* coronary heart disease, *CKD* chronic kidney disease, *CPRD* Clinical Practice Research Datalink, *eGFR* estimated glomerular filtration rate, *HF* heart failure, *HTN* hypertension, *LCED* Limited Claims and Electronic Health Record Dataset, *MDV* Medical Data Vision, *T2D* type 2 diabetes

In patients with rapid versus non-rapid eGFR decline, mean age and median UACR were numerically higher at baseline. Proportions of male and female patients, mean systolic and diastolic BP, mean high- and low-density lipoprotein (HDL and LDL) values, and median glycated hemoglobin (HbA1c) were comparable between groups (Supplementary Material Tables S1 and S3). Mean total cholesterol levels were numerically higher in patients with non-rapid versus rapid eGFR decline (Supplementary Material Table S3).

Prevalence of comorbidities was higher in patients with rapid versus non-rapid eGFR decline (Fig. 2; Supplementary Material Table S4). Hypertension was the most prevalent comorbidity in all patients. Patients in Japan had a greater overall comorbidity burden compared with patients in the USA and UK (Fig. 2).

The proportion of patients with prescribed medications at baseline was higher in patients with rapid versus non-rapid eGFR decline. The proportion of patients prescribed RAASi was

14.5–58.5% in patients with rapid eGFR decline and 10.8–42.2% in patients with non-rapid eGFR decline (Supplementary Material Table S5).

Clinical Outcomes

Across databases, the composite risk of kidney failure or > 50% decline in eGFR was significantly greater in patients with rapid versus non-rapid eGFR decline ($P < 0.01$), while all-cause mortality, kidney failure alone, MACE, and all-cause hospitalizations were each significantly increased in two databases ($P < 0.01$–0.05; Fig. 3). The risk of all-cause mortality among patients with eGFR ≥ 45 mL/min/1.73 m^2 at baseline was significantly higher in those with rapid versus non-rapid eGFR decline (Fig. 4). A competing risks analysis accounting for mortality demonstrated an overall greater risk of adverse clinical outcomes in patients with rapid versus non-rapid eGFR decline (Supplementary Material Fig. S2).

		Events (rapid), n	Events (non-rapid), n	HR (95% CI)
UK CPRD-HES	All-cause mortality	425	4621	1.17 (1.04–1.30)
(N = 107,159)	Kidney failure or > 50% decline in eGFR	608	1273	2.86 (2.54–3.21)
	Kidney failure	103	206	1.07 (0.81–1.42)
	MACE	375	5286	1.21 (1.08–1.36)
	hHF	82	683	1.18 (0.91–1.53)
	All-cause hospitalization	1899	42,191	1.14 (1.08–1.20)
US TriNetX	All-cause mortality	1274	7341	1.06 (0.99–1.13)
(N = 462,352)	Kidney failure or > 50% decline in eGFR	8808	20,652	1.84 (1.79–1.90)
	Kidney failure	3205	6478	1.12 (1.07–1.17)
	MACE	7145	54,413	1.00 (0.98–1.03)
	hHF	1107	6271	1.06 (0.98–1.13)
	All-cause hospitalization	8208	63,215	1.01 (0.99–1.04)
US LCED	All-cause mortality	–	–	NR
(N = 95,739)	Kidney failure or > 50% decline in eGFR	1086	2603	1.86 (1.71–2.01)
	Kidney failure	333	677	1.15 (0.99–1.34)
	MACE	774	7600	0.95 (0.88–1.03)
	hHF	38	230	0.89 (0.61–1.30)
	All-cause hospitalization	3363	37,494	0.97 (0.94–1.01)
Japan MDV	All-cause mortality	166	906	1.24 (1.04–1.48)
(N = 39,782)	Kidney failure or > 50% decline in eGFR	519	1196	2.52 (2.25–2.81)
	Kidney failure	179	377	1.43 (1.19–1.73)
	MACE	517	5617	1.11 (1.01–1.22)
	hHF	–	–	NR
	All-cause hospitalization	962	8188	1.19 (1.11–1.28)

Increased with non-rapid eGFR decline ← → Increased with rapid eGFR decline

Fig. 3 Clinical outcomes in patients with rapid versus non-rapid eGFR decline (2 years post-index). *$P < 0.01$ for rapid versus non-rapid progressors; **$P < 0.05$ for rapid versus non-rapid progressors. †Data not available. HRs were computed using Cox proportional hazards models adjusted for baseline age, sex, race (where available), diastolic blood pressure, systolic blood pressure, body mass index, high- and low-density lipoprotein, eGFR, urine albumin-to-creatinine ratio, medications, log (natural logarithm) of the number of eGFR tests recorded prior to 2 years post-index, hemoglobin, serum potassium, and history of hypertension, type 2 diabetes, HF, stroke, and MI. MACE includes non-fatal MI, non-fatal stroke, and cardiovascular death, defined by diagnostic codes. *CI* confidence interval, *CPRD* Clinical Practice Research Datalink, *eGFR* estimated glomerular filtration rate, *HES* hospital episode statistics, *hHF* hospitalization for heart failure, *HR* hazard ratio, *LCED* Limited Claims and Electronic Health Record Dataset, *MACE* major adverse cardiovascular event, *MDV* Medical Data Vision, *MI* myocardial infarction, *NR* not reported

DISCUSSION

In this analysis, mean annual eGFR decline ranged between −6.21 and −6.86 mL/min/1.73 m² in patients with rapid eGFR decline; in patients with non-rapid eGFR decline, mean annual eGFR decline ranged between −0.11 and −0.77 mL/min/1.73 m², which contrasts slightly with the mean creatinine clearance reported by the Baltimore Longitudinal Study of Aging for individuals without renal disease (−0.75 mL/min/1.73 m²) [19]. The relationship between age, sex, and eGFR decline is unclear. Previous studies have associated rapid eGFR decline with both older and younger age [1, 2, 20] and both male and female sex [2, 21]. In this analysis, mean age was higher in patients with rapid eGFR decline, but proportions of male and female patients were comparable.

		Events (rapid), n	Events (non-rapid), n	HR (95% CI)
UK CPRD-HES (*N* = 107,159)	60–75	242	2368	1.27 (1.07–1.50)
	45–< 60	136	1478	1.32 (1.06–1.63)
	30–< 45	43	612	1.41 (1.01–1.98)
	15–< 30	3	150	NR
US TriNetX (*N* = 462,352)	60–75	645	3673	1.14 (1.03–1.25)
	45–< 60	391	2032	1.34 (1.18–1.52)
	30–< 45	186	1117	1.22 (1.03–1.44)
	15–< 30	43	432	0.81 (0.59–1.12)
Japan MDV (*N* = 39,782)	60–75	80	398	1.49 (1.13–1.96)
	45–< 60	58	280	1.57 (1.14–2.16)
	30–< 45	21	159	1.34 (0.82–2.19)
	15–< 30	7	66	NR
Overall‡ (*N* = 708,498)	60–75	1415	10,054	1.30 (1.22–1.39)
	45–< 60	804	5744	1.44 (1.32–1.57)
	30–< 45	319	2664	1.37 (1.21–1.55)
	15–< 30	65	855	0.98 (0.75–1.27)

Increased with non-rapid eGFR decline ← | → Increased with rapid eGFR decline

Fig. 4 All-cause mortality in patients with rapid versus non-rapid eGFR decline (2 years post-index), stratified by eGFR category. *$P < 0.01$ for rapid versus non-rapid progressors; **$P < 0.05$ for rapid versus non-rapid progressors. †Data not available because of low event numbers. ‡Excluding data from LCED, where data on all-cause mortality were not available. Patients with eGFR ≤ 15 mL/min/1.73 m² were excluded from analyses, owing to confounding by dialysis. HRs were computed using Cox proportional hazards models adjusted for baseline age, sex, race (where available), diastolic blood pressure, systolic blood pressure, body mass index, high- and low-density lipoprotein, eGFR, urine albumin-to-creatinine ratio, medications, log (natural logarithm) of the number of eGFR tests recorded prior to 2 years post-index, hemoglobin, serum potassium, and history of hypertension, type 2 diabetes, heart failure, stroke, and myocardial infarction. *CI* confidence interval, *CPRD* Clinical Practice Research Datalink, *eGFR* estimated glomerular filtration rate, *HES* hospital episode statistics, *HR* hazard ratio, *LCED* Limited Claims and Electronic Health Record Dataset, *MDV* Medical Data Vision, *NR* not reported

Median UACR was higher in patients with rapid eGFR decline, consistent with previous findings [2, 22, 23]. Acute kidney injury, a risk factor for accelerated CKD progression [24], anemia, atrial fibrillation, and elevated mean C-reactive protein were also more common in patients with rapid eGFR decline, which may therefore be avoided by preventing or treating these conditions.

Elevated HbA1c is associated with rapid eGFR decline in patients with T2D [25]. In this analysis, T2D was more common in patients with rapid eGFR decline, but mean HbA1c was similar between patients with rapid and non-rapid eGFR decline. HbA1c recordings in patients without T2D may have impacted the calculated means.

Elevated BP, total cholesterol, HDL, LDL and proteinuria are risk factors for rapid eGFR decline [1, 2, 26–31]. BP is especially sensitive to eGFR, although strategies for managing BP in CKD vary widely in the real world [32]. In this analysis, mean systolic and diastolic BP, and HDL and LDL were comparable between patients with rapid and non-rapid eGFR decline despite

hypertension and other comorbidities being more common in patients with rapid decline. Mean total cholesterol was higher in patients with non-rapid eGFR decline. Our contradictory findings may be because more patients with rapid eGFR decline were receiving BP-lowering medications and/or statins. Alternatively, alongside the greater burden of CV comorbidities in patients with rapid eGFR decline, it is possible that higher statin use in these patients is accelerating eGFR decline.

Higher medication prescriptions in patients with rapid eGFR decline likely reflect their greater comorbidity burden, with diuretics used to manage many comorbidities including hypertension, CHD, and HF. Despite guidelines recommending that RAASi are prescribed at optimal doses [33], RAASi use was low overall (10.8–58.5%) and less than that reported elsewhere for patients with rapid or non-rapid eGFR decline (66–71%) [2]. Although low use of RAASi in our study could be due to suboptimal medication capture in the databases, it is more likely due to hyperkalemia-related RAASi discontinuation [34–37], even though this is associated with increased healthcare resource utilization and a higher risk of cardiorenal events [38–41]. Guidelines now recommend taking measures to reduce serum potassium, including the use of novel potassium binders, to restore and maintain normokalemia when necessary and enable the prescription of RAASi at optimal doses [33]. Elsewhere, it has been suggested that discontinuing RAASi in patients with advanced CKD may slow eGFR decline [42, 43]. This matter remains under debate: findings from the STOP-ACEi trial suggest that RAASi discontinuation has no clinically relevant impact on eGFR decline [44], while current KDIGO guidelines recommend continuing RAASi in patients with CKD even when eGFR falls [45].

In patients with rapid eGFR decline, the risk of kidney failure or > 50% eGFR decline was significantly increased across all databases (as anticipated); the risks of all-cause mortality, kidney failure alone, MACE, and all-cause hospitalization were each significantly increased in two databases, consistent with previous findings [2, 46, 47]. Although several factors may elevate the risk of adverse outcomes in patients

with rapid eGFR decline, Cox proportional hazards models adjusted for key comorbidities in our analysis suggest that eGFR decline rate is a key determinant.

The clinical outcomes assessed showed between-country differences. In patients with rapid eGFR decline, the risk of kidney failure alone was significantly increased in the US TriNetX and Japan MDV databases but not in the UK CPRD or US LCED databases. Similarly, the risk of MACE and all-cause hospitalization was increased in the UK CPRD and the Japan MDV databases but not in the US TriNetX or US LCED databases. This could be due to low baseline risk (most patients had stage 2–3a CKD and median UACR was relatively low), relatively short follow-up, differences in patient characteristics (primary care data in the UK versus secondary data in the USA and Japan), differences in local treatment guidelines, or variations in clinical practice and adherence to treatment guidelines.

Notably, the risk of all-cause mortality was lowest in patients with stage 4 CKD. This may be related to a ceiling effect of rapidly worsening renal function in patients who already had poor kidney function, or potentially due to a greater proportion of patients with stage 4 CKD being under specialist care and improved management. In two databases, risk of all-cause mortality stratified by baseline eGFR category (not reported in US LCED) was significantly increased in patients with rapid eGFR decline and eGFR ≥ 45 mL/min/1.73 m^2. Patients with mild-to-moderate CKD may therefore benefit from additional monitoring and proactive management to minimize the risk of adverse clinical outcomes. Previous studies have demonstrated that augmenting RAASi with SGLT2i can improve clinical outcomes and reduce the risk of mortality in patients with CKD [48–51]. SGLT2i use was very low overall, although prescriptions were more common in patients with rapid eGFR decline. This is likely due to the higher prevalence of T2D in these patients, with SGLT2i having shown that they can improve clinical outcomes in patients with CKD and T2D [48–51].

Strengths of this analysis include the very large cohort size (> 800,000 patients), regional scale (patients from the UK, USA, and Japan),

and inclusion of patients with a wide range of baseline eGFR values. Additional strengths include the granularity of data, the large number of covariates and outcomes captured, and the use of data from primary and secondary healthcare databases.

Limitations of this analysis include those that are inherent to retrospective studies, in that conclusions about causal relationships between baseline characteristics and rapid eGFR decline cannot be made. Additionally, approximately one-third of patients from the overall DIS-COVER CKD cohort were excluded from this analysis on the basis of the eligibility criteria. A high proportion of laboratory data were missing (including UACR and HbA1c measurements), and the proportion of missing data tended to be higher in patients with non-rapid eGFR decline. Furthermore, our findings are only applicable to patients meeting the analysis eligibility criteria within specified countries and healthcare systems. There is also the potential for coding errors, as data were not collected for research purposes. For example, data on race and ethnicity were only available in the UK CPRD and US TriNetX databases, medication prescription data were not fully captured, and there was no means of verifying adherence to medications. Differences between the data sources (primary versus secondary healthcare data) could also impact interpretation of our findings. Finally, although our data suggest associations between some patient baseline characteristics and rapid eGFR decline, there may be other unmeasured factors that are contributing, including genetic predisposition, environmental toxins, smoking status, race, occupational history, and BMI.

CONCLUSION

To the best of our knowledge, this is the most robust analysis of eGFR slopes performed to date in a global CKD population. Rapid eGFR decline was associated with increased comorbidity burden and medication prescriptions, and increased risk of adverse clinical outcomes. These findings emphasize the importance of routine monitoring of eGFR, as well as the often-overlooked UACR parameter, to identify patients at high risk of rapid eGFR decline who may benefit from proactive and more intense management, and early diagnosis and treatment, to minimize risks of adverse clinical outcomes.

Declarations

Conflict of Interest. Hiddo Heerspink reports grants and other fees from AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Pharma, Dimerix, Gilead, Janssen, Merck, Mitsubishi Tanabe, Mundipharma, Novo Nordisk, and Retrophin. Stephen Nolan, Matthew Arnold, Juan José García Sánchez, Eric Wittbrodt, Claudia Cabrera, and Hungta Chen are employees of, and may hold stock and/or stock options in, AstraZeneca. 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. 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, non-financial support from Akebia, AstraZeneca, Bayer, Boehringer, Novo Nordisk, and FibroGen; as well as personal fees from Travere Therapeutics and consulting fees from George Clinical outside the submitted work. Carolyn S.P. Lam is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from AstraZeneca, Bayer, Boston Scientific, Medtronic, Roche Diagnostics, and Vifor Pharma; has served as a consultant or on the advisory board/steering committee/ executive committee for Abbott Diagnostics, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Biofourmis, Boehringer Ingelheim, Boston Scientific, Corvia Medical, Cytokinetics, Darma Inc., Eko.ai Pte Ltd, Jana Care, Janssen Research & Development LLC, Medtronic, Menarini Group, Merck, MyoKardia, Novartis, Novo Nordisk, Radcliffe Group Ltd, Roche Diagnostics, Sanofi, Stealth BioTherapeutics, The Corpus, Vifor Pharma, and WebMD Global LLC; and serves as co-founder and non-executive director of Us2.ai Pte Ltd. Eiichiro Kanda is a consultant for AstraZeneca. Mitja Lainscak is supported by the Slovenian Research Agency; has received research support from Roche Diagnostics; has served as a consultant or on the advisory board/ steering committee for AstraZeneca, Boehringer Ingelheim, Novartis, and Vifor Pharma; has received personal fees from Abbott, Amgen, AstraZeneca, Boehringer Ingelheim, Novartis, Sanofi, Servier, and Vifor Pharma. Carol Pollock reports advisory board membership for AstraZeneca, Boehringer Ingelheim, Eli Lilly, and Vifor Pharma; as well as speaker fees for AstraZeneca, Janssen-Cilag, Novartis, Otsuka, and Vifor Pharma. David C. Wheeler reports personal fees and non-financial support from AstraZeneca, as well as 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 non-interventional studies and observational studies. This study used de-identified data and did not require data collection beyond that of routine clinical care. No identifiable information was collected or examined as part of the study. Ethical and scientific approval for use of CPRD data in the current study was obtained from the Independent Scientific Advisory Committee of CPRD (protocol number 19_172). Informed consent was waived by the East Midlands – Derby Research Ethics Committee because CPRD data are anonymized for research purposes (for further information, see https://cprd.com/safeguarding-patient-data). Ethics approval was not required for use of data from the US TriNetX and Japan Medical Data Vision for this study, in accordance with local or national guidelines.

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