RWD23

Association of eGFR decline and cardiovascular outcomes in chronic kidney disease patients

Feasibility of frequency matching replicating event-driven clinical trials with longer-term real-world data

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Objective

- The aim of this study was to evaluate the association of rapid eGFR decline (≥40%) mimicking the time horizon of a typical phase 3 CKD trial with long-term adverse kidney and CV outcomes in a real-world cohort of patients

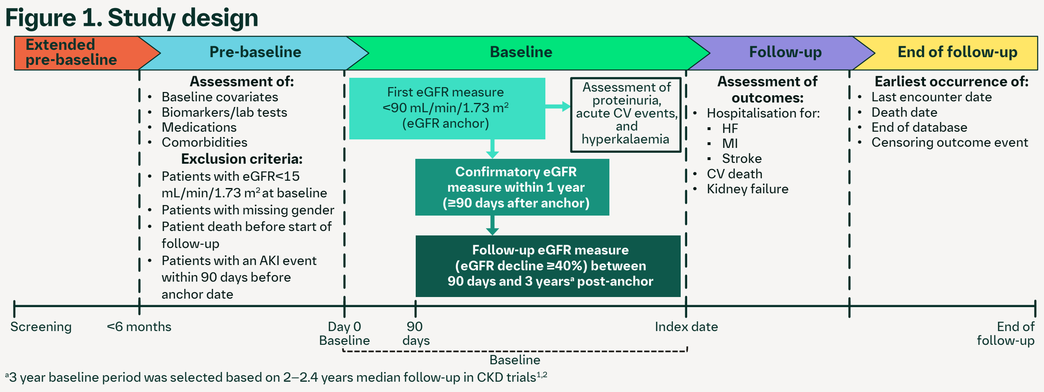
Introduction

- Sustained ≥40% decline in estimated glomerular filtration rate (eGFR), is widely accepted as a marker of disease progression alongside urine albumin-creatinine ratio (UACR) in chronic kidney disease (CKD)
- Evidence directly linking ≥40% eGFR decline to long-term health outcomes remains limited
  - Recent phase 3 CKD trials reported a median follow-up of 2–2.4 years[1,2]
  - Patients who experience an eGFR decline ≥40% during such trials do so over a relatively short time
- This study investigated the degree to which phase 3 clinical trial follow-up periods can be mimicked using real-world data to evaluate the association between eGFR decline (≥40%) and long-term adverse kidney and CV outcomes

Methods

- US Optum Market Clarity database linked claims and EHRs (January 2017–June 2024 were used to identify patients with CKD, defined as ≥2 eGFR measures <90 mL/min/1.73 m^2 within 1 year and ≥90 days apart (**Figure 1**)
  - eGFR measures were converted from serum creatinine results using the 2021 CKD-EPI formula[3,4]
  - The first valid eGFR date was the anchor date for the exposure group. The index date was the first eGFR measure of ≥40% decline between 90 days and 3 years from the anchor date. The baseline period spanned from the anchor eGFR date to the index date
  - Controls were selected from patients with CKD who did not experience eGFR decline ≥40%, assigning index dates to the randomly selected eGFR date between 90 days and 3 years from the anchor date
- Matching was conducted without replacement and exact matching (1:n, where n=[1,4])
  - Cases and controls were matched on age at anchor date, sex, eGFR stage, and duration of baseline period by 3 months intervals ranging from 3–36 months
  - The matched set was assigned a weight of 1 for each case and a weight of (1/n) for each control
  - Standardized mean difference (SMD) was used to compare the balance of matched covariates between the exposure and control groups before and after matching
  - Cox regression was used to calculate the crude and adjusted HR (95% CIs) of health outcomes during the follow-up period using matched and weighted cohorts. Pre-baseline comorbidities, medication usage, relevant laboratory tests, and demographics were adjusted in the model

Figure 1. Study design

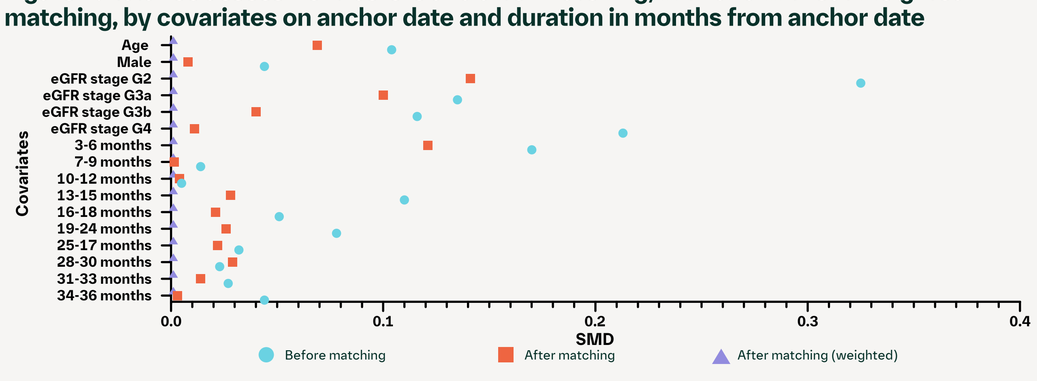


[a]3 year baseline period was selected based on 2–2.4 years median follow-up in CKD trials[1,2]

Results

- Almost all covariates achieved a SMD <0.1 after matching, indicating that the matching procedure resulted in an acceptable covariate balance between cases and controls (**Figure 2**)
  - After matching, the SMD for age reduced from 0.104 before to 0.069 after matching, and eGFR stage showed substantial improvement at each categorical level
  - When cases and controls were weighted further after matching, SMD=0 for all matched variables, indicating that cases and controls were equally distributed with no difference in the mean of each covariate

Figure 2. Balance assessment before and after matching, with and without weighted matching, by covariates on anchor date and duration in months from anchor date



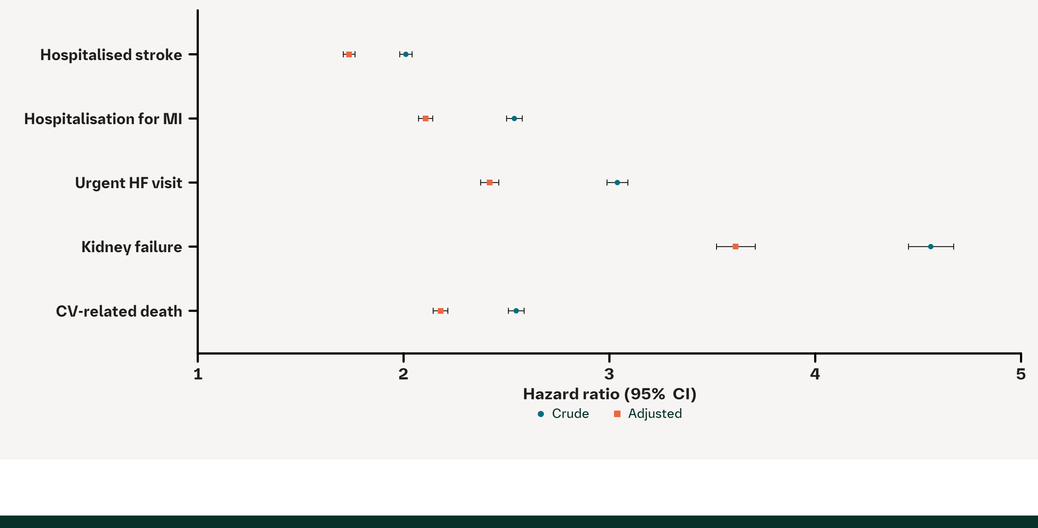
Results (continued)

- The final CKD population consisted of 116,828 cases matched to 414,084 controls
  - Patient demographics and pre-baseline covariates for cases and matched controls are presented in **Table 1**
- The mean (median) baseline duration was 572 (575) vs 585 (590) days for cases vs controls
- The risk of all follow-up health outcomes was consistently lower when adjusted for the study covariates compared with the crude model, revealing the impact of eGFR decline ≥40% as an important factor on long-term health outcomes (**Figure 3**)

Table 1. Demographics and pre-baseline covariates of exposure cases and matched controls, with and without weighted matching

	Matched dataset		Matched dataset (weighted)	
Cohort, N	CKD (N=116,828)	Control (N=414,084)	CKD (N=116,828)	Control (N=116,828)
Age, mean (SD)	71.86 (10.63)	72.61 (10.03)	71.86 (10.63)	71.86 (10.63)
Male, n (%)	48,046 (41.1)	168,756 (40.8)	48,046.0 (41.1)	48,046.0 (41.1)
Race/ethnicity, n (%)				
Caucasian	89,463 (76.6)	320,046 (77.3)	89,463.0 (76.6)	89,897.8 (76.9)
Black	17,770 (15.2)	53,443 (12.9)	17,770.0 (15.2)	15,211.2 (13.0)
Asian	1731 (1.5)	6681 (1.6)	1731.0 (1.5)	1963.4 (1.7)
Hispanic	1911 (1.6)	5775 (1.4)	1911.0 (1.6)	1717.0 (1.5)
Unknown	5953 (5.1)	28,139 (6.8)	5953.0 (5.1)	8038.6 (6.9)
Pre-baseline covariates, n (%)				
CVD	74,910 (64.1)	226,649 (54.7)	74,910.0 (64.1)	63,797.1 (54.6)
Type 2 diabetes	48,105 (41.2)	124,763 (30.1)	48,105.0 (41.2)	36,089.7 (30.9)
PAD	14,251 (12.2)	33,296 (8.0)	14,251.0 (12.2)	9309.4 (8.0)
Sleep disorder	11,057 (9.5)	29,878 (7.2)	11,057.0 (9.5)	8663.2 (7.4)
Hospitalisation for MI	1914 (1.6)	2915 (0.7)	1914.0 (1.6)	825.0 (0.7)
Hospitalised stroke	1654 (1.4)	2942 (0.7)	1654.0 (1.4)	832.8 (0.7)
Urgent HF visit	1830 (1.6)	2308 (0.6)	1830.0 (1.6)	659.2 (0.6)
Kidney failure	486 (0.4)	1247 (0.3)	486.0 (0.4)	396.9 (0.3)
Medications, n (%)				
Potassium	46,820 (40.1)	140,479 (33.9)	46,820.0 (40.1)	39,061.3 (33.4)
Beta-blocker	45,981 (39.4)	135,107 (32.6)	45,981.0 (39.4)	37,728.4 (32.3)
RAS inhibitor	32,394 (27.7)	103,139 (24.9)	32,394.0 (27.7)	29,158.4 (25.0)
Opioid	30,946 (26.5)	76,027 (18.4)	30,946.0 (26.5)	21,680.4 (18.6)

Figure 3. Hazard ratios (95% CI) of crude and adjusted follow-up outcomes analysed by Cox regression in the matched weighted dataset



Conclusions

- Using real-world administrative claims and EHR data, this study demonstrated that patients with CKD can be effectively matched based on the presence or absence of eGFR decline. This real-world data setting enables the evaluation of longer-term outcomes between these patient groups, which are often not feasible to assess within the constraints of clinical trials
- In this study, matched groups were well-balanced with comparable pre-baseline demographics and characteristics similar to that of a randomised controlled trial
- Longitudinal health outcomes will be assessed when data over a longer follow-up duration are available
- The association between sustained ≥40% eGFR decline with patient-relevant outcomes over time may support addressing crucial gaps for national reimbursement decisions

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Abbreviations
AKI, acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; EHR, electronic health record; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; PAD, pulmonary artery disease; RAS, renin-angiotensin system; Scr, serum creatinine; SMD, standardised mean difference.

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Disclosures
LZ, **CD**, and **VWJ** report employment by Boehringer Ingelheim. **BM** has received consulting honoraria from Boehringer Ingelheim.

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