Major cardiovascular events and subsequent risk of kidney failure with replacement therapy- a CKD Prognosis Consortium study

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Abstract

Background and Aims: Chronic kidney disease (CKD) increases risk of cardiovascular disease (CVD). Less is known about how CVD associates with future risk of kidney failure with replacement therapy (KFRT).

Methods: The study included 25,903,761 individuals from the CKD Prognosis Consortium with known baseline eGFR and evaluated the impact of prevalent and incident coronary heart disease (CHD), stroke, heart failure (HF), and atrial fibrillation (AF) events as time-varying exposures on KFRT outcomes.

Results: Mean age was 53 years (SD 17) and mean estimated glomerular filtration rate (eGFR) was 89 ml/min/1.73m^2, 15% had diabetes and 8.4% had urinary albumin-to-creatinine ratio (ACR) available (median 13 mg/g); 9.5% had prevalent CHD, 3.2% prior stroke, 3.3% HF and 4.4% prior AF. During follow-up there were 269,142 CHD, 311,021 stroke, 712,556 HF, and 605,596 AF incident events and 101,044 (0.4%) patients experienced KFRT. Both prevalent and incident CVD were associated with subsequent KFRT with adjusted hazard ratios (HR) of 3.1 (95% CI 2.9-3.3), 2.0 (1.8-2.1), 4.5 (4.2-4.8), 2.8 (2.6-3.1) after incident CHD, stroke, HF and AF, respectively. HRs were highest in first three months post CVD incidence declining to baseline after three years. Incident HF hospitalisations showed the strongest association with KFRT (HR 46 (95% CI 43-49) within 3 months) after adjustment for other CVD subtype incidence.

Conclusions: Incident CVD events strongly and independently associate with future KFRT risk, most notably after HF, then CHD, stroke, and AF. Optimal strategies for addressing the dramatic risk of KFRT following CVD events are needed.

Background

It is well established that chronic kidney disease (CKD) is a risk factor for developing cardiovascular disease (CVD)[1,2]. However, whether CVD is a risk factor for CKD progression and subsequent kidney failure with replacement therapy (KFRT, i.e. dialysis or kidney transplant) is less clear. Such bidirectional association is plausible and consistent with the hypotheses postulated in the cardiorenal syndrome[3,4]. Many consequences of CVD, including inflammation[5,6], oxidative stress[7], haemodynamic changes (e.g. renal congestion, neurohormonal activation)[8], and medical interventions (e.g. use of loop diuretics, radiocontrast agents)[9] may negatively impact kidney function.

Epidemiological data exploring CVD as a cause of CKD is scarce, and potentially limited by small sample sizes, single-center studies, the timing of the CVD event and varying definitions of CKD outcomes mostly focused on relative declines of estimated glomerular filtration rate (eGFR). Early reports disclosed that patients with *prevalent* CVD were at higher risk of receiving a diagnosis of CKD or having a more rapid eGFR decline[10-12]. More recently, *incident* major CVD events, particularly heart failure (HF) have been associated with a faster eGFR decline[13] and KFRT [14,15].

A comprehensive analysis evaluating the robustness and consistency of this association is lacking, perhaps because the outcome of KFRT is rare and requires large sample sizes with long follow-up. Using data from the multinational CKD-Prognosis Consortium, we sought to quantify the association of CVD incidence, prevalence and subtypes on subsequent risk of KFRT. We hypothesized that incident CVD events would be associated with increased risk of KFRT.

Methods

This study was approved for use of de-identified data by the institutional review board at the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA (#IRB00003324). The need for informed consent was waived by the institutional review board.

Populations

We included cohorts in the CKD-PC with available data for the present study. The details of CKD-PC are described elsewhere[16], but in brief, this consortium included both research cohorts and health system datasets, with participants from 41 countries from North America, Europe, the Middle East, Asia, and Australia. These cohorts included general population (screening cohorts and health systems), high-risk (specifically selected for clinical conditions, such as diabetes), and CKD (exclusively enrolling individuals with CKD) cohorts. For the present study, cohorts were required to have data on at least one CVD subtype and subsequent follow-up for KFRT as the outcome. Cohorts also needed to have baseline information on eGFR and some albuminuria data. In total, 81 cohorts had adequate data and agreed to participate. Further information on cohorts is available in Appendix 1. Individual patient data (IPD) level analysis was performed in two stages. First the analysis was conducted within each cohort and then the results were meta-analyzed. This permits IPD analysis of cohorts where the data must reside on a separate server (e.g., VA and OLDW).

Exposures: CVD types of interest

We explored the risk associated with prevalent and incident non-fatal coronary heart disease (CHD), stroke, HF, and atrial fibrillation (AF) events on the outcome of KFRT. Prevalent CHD was defined as positive history of myocardial infarction (MI), bypass grafting, or percutaneous coronary intervention. Incidence of CHD was defined as the occurrence of a *de novo* MI. Most cohorts did not have information on HF type, so we analyzed overall HF (see Appendix 1.4 for details and ICD codes).

Outcomes

The main outcome of interest was KFRT defined as initiation of chronic dialysis or transplant. Information on outcome ascertainment is provided in Appendix 1. The secondary outcome was the combined end point of kidney failure defined as KFRT or having a follow-up eGFR <15 ml/min/1.73m^2. We also considered mortality as a competing outcome.

Covariables

Demographic variables included age, sex, and race. Body mass index was modelled as linear spline with knot at 30 kg/m^2. Smoking status was recoded as current smoking, former smoking versus never smoking. eGFR was estimated by the CKD-EPI equation using age, sex, race, and serum creatinine[17]. eGFR was modelled as linear spline with knot at 60. Albuminuria was recorded as the urinary albumin-to-creatinine ratio (ACR) or protein-to-creatinine ratio and converted to ACR as done previously[18]. If these measurements were not available, we used dipstick proteinuria information and converted to ACR[18]. When albuminuria was missing more than 25% in a single study, a missing indicator was used (a value of 10 mg/g was used to anchor the missing ACR category); this occurred in health systems where the missing ACR indicator reflects existing clinical practice. Hyperlipidaemia status was controlled for with information on total cholesterol, HDL cholesterol and use of lipid lowering medication. Diabetes mellitus was defined as the use of glucose lowering drugs, a fasting glucose ≥7.0 mmol/L or non-fasting glucose ≥ 11.1 mmol/L, hemoglobin A1c ≥6.5%, or self-reported diabetes. Hypertension was modelled as continuous systolic blood pressure and antihypertensive medication use. These variables were imputed to the sample mean if less than 50% missing in a single study, otherwise the variables were excluded from the model.

Statistical Analyses

Descriptive data are presented as mean and standard deviation (SD) or median and inter quartile interval (IQI). Time to event analysis was analyzed for each CVD event separately with follow-up from baseline as the time scale. Baseline was selected on the first serum creatinine measurement 12 months after start date in health system cohorts to allow adequate information for determining prevalent CVD. Incident CVD was modelled as a time dependent exposure. Hazard ratios and 95% confidence intervals were obtained from Cox regression models in each cohort, adjusted for all available covariables. Estimates were meta-analyzed using a random effects meta-analysis to conservatively incorporate any between cohort variance. Following analysis of each CVD event type separately, we analyzed all four CVD subtypes in a single model adjusting for each other. The latter analysis was limited to cohorts that had data on all CVD subtypes. Timing of excess risk and absolute risk after CVD were estimated in the Optum Labs Data Warehouse (OLDW) cohorts only due to their large sample size and representativeness of health system data. The OLDW is a longitudinal, real-world data asset with de-identified administrative claims and electronic health record (EHR) data.[19] Time after incidence of CVD was modelled in three month categories to quantify a priori hypothesized higher risk proximal to the CVD event. Baseline absolute risk was estimated from a Fine and Gray model with mortality as a competing outcome for each CVD type[20]. Risks were expressed across categories of eGFR and ACR and adjusted to age 70 and 50% male to facilitate comparisons across CVD events. Absolute risk was not included for times without CVD since the focus of this risk analysis was time after an event and a comparison of absolute risk across CVD subtypes. In models adjusting for all subtypes of CVD, each was modelled as a time-varying covariate in a single model with all the CVD subtypes, censoring only for KFRT, death, and administrative censoring. As a result, risk is attributed to each of the CVD subtypes when each of multiple events occur. We only model the first CVD event of each subtype to avoid intractable model complexity in the setting of multiple hospitalisations.

Missingness in covariates was modelled with a missing indicator variable (see eAppendix 1). The variable most often missing was albuminuria, which reflects clinical practice. Sensitivity analyses adjusted for the last eGFR before the CVD event to conservatively remove the part of the risk associated with eGFR decline prior to the event. Analyses were done in Stata version 16 (StataCorp). Statistical significance was determined using a 2-sided test.

Results

Baseline characteristics

Across 25,903,761 patients from 81 cohorts, the mean age was 53 (SD 17), 52% were female, the mean baseline eGFR was 89 ml/min/1.73m^2 (SD 23), 8.8% were black, 15% had diabetes and 8.4% had ACR available (median 13 mg/g, IQI 6-36); 2,450,902 (9.5%) had prevalent CHD, 824,717 (3.2%) prior stroke, 848,609 (3.3%) HF and 1,071,615 (4.4%) a history of AF (**Table 1** and **Tables S1-S3**).

Incidence of CVD and KFRT

During a mean follow up of 4.2 years 269,142 (1.0%) participants experienced CHD, 311,021 (1.2%) stroke, 712,556 (2.8%) HF and 605,596 (2.5%) AF incident events. Respective mean (SD) age for these incident events were 69 (13), 71 (13), 72 (12) and 73 (11) years, with details in **Table S3**. In this follow-up period, 101,044 participants developed KFRT in the overall population, whilst 221,659 participants developed the combined end point of KFRT or eGFR <15 ml/min/1.73m^2 in the subpopulation with repeated eGFR available after the index eGFR (**Table S4**). Among participants who developed KFRT, 53% experienced CVD events (including both prevalent and incident cases) prior to KFRT, compared to only 17% experiencing CVD events among participants who did not develop KFRT. **Figure 1** shows the distribution of CVD events by occurrence of KFRT during follow-up.

Prevalent and incident CVD and subsequent risk of KFRT

Patients with prevalent CHD, stroke, HF, and AF at cohort entry were at higher risk of future KFRT with adjusted hazard ratios of 1.21 (95% CI 1.17, 1.26), 1.14 (1.10, 1.18), 1.41 (1.34, 1.49), and 1.12 (1.07, 1.18) respectively (**Table 2; Table S5** shows further details of progressive adjustment and sex stratified analyses). Incident CVD during follow-up was strongly associated with subsequent risk of KFRT with hazard ratios ranging from 1.98 for stroke to 4.50 for HF; Forest plots show the meta-analysis results were supported by the majority of the cohorts (Figure S1). Analysis of each CVD event adjusted for all the other CVD events in 55 cohorts showed that the largest hazard ratio for KFRT was associated with HF. Among prevalent events, the hazard ratios were 1.12 (1.08, 1.15), 1.07 (1.03, 1.11), 1.37 (1.31, 1.44), and 0.98 (0.94, 1.02) for CHD, stroke, HF, and AF adjusted for each other. For incident events, the hazard ratios were 1.49 (1.38, 1.61), 1.33 (1.22, 1.45), 3.69 (3.36, 4.04), and 1.39 (1.28, 1.52) for CHD, stroke, HF, and AF adjusted for each other.

The excess risk was highest in the months following the CVD events, persisted for two years and returned to baseline three years after CVD among those who survived (**Figure 2, Table S6**). This analysis was limited to the OLDW cohorts since their large sample size (greater than 19 million) allowed for a detailed examination of the change in hazard ratio of KFRT for each quarter year. This revealed adjusted relative hazards of KFRT ranging from 45 (95% CI 41, 49) for stroke to 106 (102, 110) for HF in the first 3 months following the CVD event. The risks declined progressively until three years after each event. An analysis adjusting each incident CVD event for the other events showed very high risk persisting for HF with an adjusted hazard ratio of 46 (95%CI 43, 50) in the first months after HF incidence. In contrast, adjusted for HF and the other CVD events, the adjusted hazard ratio for CHD, stroke and AF

declined markedly with remaining short term risks ranging from 2.1 to 3.6 which declined to less than two-fold after 3 months but stayed statistically significant for over a year.

Sensitivity analyses showed that the excess risk associated with CVD remained, even after adjustment for the most recent eGFR recorded prior to the CVD event (**Table S7**). Results were consistent if shorter follow-up time after the CVD event was considered (**Table S8**) as well as for the secondary broader outcome including eGFR <15 ml/min/1.73m^2 during follow-up (**Table S9**). Interaction models showed that the hazard ratios of KFRT after CVD incidence were somewhat smaller at lower eGFR and higher albuminuria (**Table S7 and S8**).

Absolute risk of KFRT

The 2-year risk of KFRT following CVD events was higher at lower eGFR and elevated ACR with highest absolute risk in HF compared to other CVD subtypes. The 2-year risk of KFRT in eGFR 15-29 and ACR 300+ was 21.1%, 17.9%, 25.6%, and 19.1% for CHD, stroke, HF, and AF adjusted to age 70 and half male population after taking death into account as a competing outcome (**Table 3**). The risk of death after CVD events was substantial and higher with lower eGFR and higher ACR (**Table S10**). Among those with eGFR above 60 ml/min/1.73m^2, the risk of KFRT was higher among younger individuals with diabetes (**Table S11**).

Discussion

In this large multinational individual participant meta-analysis, we observed strong associations between major CVD events and subsequent risk of KFRT. The risk of KFRT was strikingly elevated after incident HF, but also after CHD, stroke and AF. Excess risk was present for prevalent CVD events but much higher for incident CVD events, particularly HF with consistent results across subgroups and a wide range of sensitivity analyses. Given the poor clinical and patient-reported outcomes as well as the excessive healthcare costs of KFRT[21-23], our results have implications on need of detection and monitoring of kidney disease measures, including eGFR and albuminuria, as well as on need of therapeutic strategies to delay KFRT after CVD events.

Previous smaller studies have shown prevalent or 'baseline' CVD to be associated with subsequent accelerated decline in eGFR[10-12]. However, studies of prevalent CVD and future eGFR decline are biased by their inability to take into account the decline in eGFR that occurs between the CVD event and subsequent entry into the cohort studied. Hence these analyses give limited insight into the degree of risk directly attributable to the CVD event. Our results are in agreement with analyses of the Atherosclerosis Risk in Communities (ARIC) study, which examined the impact of incident CVD and future KFRT, in both degree of risk and effect of each of the CVD subtypes[14]. However, the number of KFRT events in ARIC was small (n=210), and was limited to US participants. In the Stockholm CREAtinine Measurements (SCREAM) project, incident CVD was associated with an acceleration in decline in eGFR over the subsequent two years post CVD event[13]. This was most marked for HF events, with lesser magnitude of acceleration in eGFR decline observed following CHD events. However, quantification of pre-post eGFR slopes depended on testing and on surviving two years post CVD event.

The complex mechanisms underlying the increased risk of KFRT in patients with CVD in general and with HF in particular are outlined in Figure S2. On one hand, both conditions share common risks factors, such as hypertension, diabetes, smoking, obesity and physical inactivity[1,24], so these could be thought of as confounders. Conversely, both conditions share mediating pathophysiological mechanisms, often inducing a 'vicious cycle' of dysregulated homeostasis including neurohormonal activation, anaemia, endothelial dysfunction, arterial calcification and fibrotic responses leading to kidney disease[25]. We are unable to attribute causality, or clearly distinguish confounding from mediation, in these associations. However, the observed greater than 50-fold relative hazard within months of HF incidence, which diminishes nearly all the way to baseline three years later, demonstrating an extremely strong temporal association.

The bidirectional, inter-dependent interaction between HF and kidney dysfunction is well acknowledged, with worsening HF being a risk factor for decline in kidney function, whilst lower eGFR predicts adverse outcomes, including mortality, in patients with HF[26]. The relationship between evidence-based medicines for treatment of HF (e.g. renin angiotensin-aldosterone system inhibition) and decline in kidney function is controversial with much evidence coming from observational data which is susceptible to indication bias[27] as they may be prone to indication bias. We did not have access to prescribing information for the duration of follow up in all cohorts to evaluate this. For other CVD subtypes, acute kidney injury is common in the setting of atherothrombotic CVD events such as stroke or CHD. Subsequent KFRT risk may reflect loss of eGFR after an episode of AKI or *de novo* accelerated eGFR decline as suggested previously[28,29].

Our findings have clinical implications on risk stratification and informing decisions around therapeutic interventions, intensity of monitoring kidney disease measures, and planning for long term KFRT. eGFR monitoring is already emphasized by cardiology guidelines[30], and creatinine is included in some risk calculators for predicting survival of patients with HF[31]. Albuminuria testing is an additional, inexpensive early sign of kidney damage to add to routine secondary CVD prevention workup, hence informing KFRT risk and CVD prognostication simultaneously[32-34]. Our results evidence the need for preventing KFRT through established therapies including renin angiotensin system inhibition[35-37], sodium glucose transport 2 (SGLT2) inhibition[38] and finerenone[39,40]. These agents have demonstrated efficacy in both reducing albuminuria and delaying eGFR decline with additional cardiovascular benefits. Prudent use of diuretics to ensure 'decongestion' has a role in both treatment of HF and maintenance of kidney function[27]. Routine care data and clinical trials shows suboptimal use of guideline based cardio- and nephroprotection with opportunities for improvement[41,42].

Collaboration between nephrology and cardiology is crucial in personalizing preparation for KFRT. For example: creation of an arteriovenous fistula for haemodialysis risks exacerbating pre-existing HF[43]; Management of CKD- related complications such as anaemia, acidosis and mineral bone disorders; Long-term planning to consider dialysis modality and/or consider whether kidney transplantation is feasible. Indeed, workup of kidney transplant candidates with cardiovascular disease is controversial and requires advance planning[44]. Patients at highest risk of CKD progression are likely to benefit from additional management efforts, including avoidance of nephrotoxins like non-steroidal anti-inflammatory drugs, proton-pump inhibitors, warfarin or certain antibiotics.

Strengths of this study include the large sample sizes of the study populations; the clinical and geographic diversity of the participants in both general population and high cardiovascular risk cohorts; and the rigorous analytical approach. However, limitations also exist. Misclassification is amplified by any heterogeneity in how CVD subtypes were determined or defined across cohorts as well as baseline eGFR and albuminuria measurement at a single visit. Consistency of our findings despite this inevitable heterogeneity favors, however, true and generalizable associations. We lack data on a number of important variables such as inflammation, socioeconomic status, complete medication history and exposure to radiocontrast, and some covariates were not present in all cohorts. Whilst CHD, HF and stroke are likely to represent cardiovascular events with a definitive date of occurrence, the incidence and timing of atrial fibrillation diagnosis may be prone to acquisition bias[45]. Some cohorts rely on health record coding for outcomes, and lack detailed phenotyping of CVD subtypes, such as ejection fraction by echocardiography in HF or distinction between ischaemic/haemorrhagic strokes. Inherent to observational studies, residual confounding may exist, and we are unable to separate the effect that incident CVD has *per se* on KFRT risk from that of CVD-management, nor did we evaluate acute kidney injury risks and mediation of KFRT risk. Understanding best management strategies within secondary CVD prevention that may alter CKD progression warrants further study and may serve to individualize treatment pathways. Finally, absolute risk estimates and the time dependent analysis of risk after CVD had to be limited to the OLDW cohorts, due to their large sample size, availability of all four CVD subtypes, and representativeness of health care systems.

In summary, we show evidence that incident CVD events are strongly and independently associated with risk for KFRT, with greatest risk in the first year following HF, then CHD, stroke, and AF. Patients, clinicians and healthcare systems engaged with the management of

major CVD should be aware of this risk to optimize long-term care and ensure that those at highest risk receive appropriate evaluation, counselling, therapy, and referral for management of progressive CKD.

Acknowledgements:

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Funding

The CKD Prognosis Consortium (CKD-PC) Data Coordinating Center is funded in part by a program grant from the US National Kidney Foundation and the National Institute of Diabetes and Digestive and Kidney Diseases (R01DK100446). A variety of sources have

supported enrollment and data collection including laboratory measurements, and follow-up in the collaborating cohorts of the CKD-PC. These funding sources include government agencies such as national institutes of health and medical research councils as well as foundations and industry sponsors listed in **Appendix 3**.

Data Availability Statement: Under agreement with the participating cohorts, CKD-PC cannot share individual data with third parties. Inquiries regarding specific analyses should be made to ckdpc@jhmi.edu. Investigators may approach the original cohorts regarding their own policies for data sharing (e.g., https://sites.cscc.unc.edu/aric/distribution-agreements for the Atherosclerosis Risk in Communities Study).

Disclosure: Dr. Mark reports grants and personal fees from Boehringer Ingelheim, personal fees and non-financial support from Napp, personal fees and non-financial support from Astrazeneca, personal fees from GSK, personal fees from Pharmacosmos, and personal fees from Astellas outside the submitted work. Dr. Carrero is a Statistical Editor for the European Heart Journal. Dr. Matsushita reports grants from NIDDK, during the conduct of the study; grants and personal fees from Kyowa Kirin, personal fees from Akebia, personal fees from Kowa, and personal fees from Fukuda Denshi outside the submitted work. Dr. Grams reports grants from National Kidney Foundation and from Kidney Disease Improving Global Outcomes outside the submitted work. Dr. Coresh reports grants from National Institute of Health and National Kidney Foundation during the conduct of the study; consulting at Healthy.io and scientific advisor to SomaLogic outside the submitted work. Dr. Chalmers reports grants from National Health and Medical Research Council of Australia and grants and personal fees from Servier International outside the submitted work. Dr. Chan reports consulting from CSL Vifor, honorarium for giving a talk from Fresenius Medical Care, and

grants from NIH-NIDDK outside the submitted work. Dr. Chang reports personal fees from Novartis, personal fees from Amgen, personal fees from Reata, grants from Novo Nordisk, and grants from Bayer outside the submitted work. Dr. de Zeeuw reports personal fees from Merck during the conduct of the study; personal fees from Bayer, Boehringer Ingelheim, and Travere outside the submitted work. Dr. Evans reports institutional grants from Astellas pharma, AstraZeneca, and Vifor Pharma, honoraria form Astellas pharma, AstraZeneca, Baxter healthcare, and Fresenius Medical Care, support for attending meetings from Baxter healthcare, participation on a DSMB or Advisory Board for Astellas pharma, AstraZeneca, and Vifor pharma, and a leadership or fiduciary role on the Steering Committee of the Swedish Renal Registry, outside the submitted work. Dr. Gutierrez reports personal fees from Akebia, personal fees from Amgen, personal fees from AstraZeneca, personal fees from Reata, personal fees from Ardelyx, and personal fees from QED outside the submitted work. Dr. Heerspink reports grants and honoraria for steering committee to his institution from Abbvie, grants and honoraria for steering committee and payments for advisory boards to his institution from AstraZeneca, honoraria for steering committee and payments for advisory boards from Bayer, grants and honoraria for steering committee and payments for advisory boards to his institution from Boehringer Ingelheim, honoraria for steering committee to his institution from CSL Behring, Chinook, Dimerix, Gilead, grants and honoraria for steering committee to his institution from Janssen, honoraria for steering committee to his institution from Eli-Lilly, Merck, Mitsubishi Tanabe, grants and honoraria for steering committee to his institution from Novo Nordisk, and honoraria for steering committee to his institution from Travere Pharmaceuticals outside the submitted work. Dr. Herrington reports SHARP was funded by Merck & Co., Inc., Whitehouse Station, NJ USA, during the conduct of the study; he received grants from Boehringer Ingelheim, grants from Eli Lilly, grants and fellowship from MRC UK, and fellowship from Kidney Research UK outside the submitted work. Dr.

Major reports grants from NIHR and grants from Kidney Research UK during the conduct of the study. Dr. Nadkarni reports personal fees, non-financial support and other support (Scientific Cofounder, have equity/stock options, royalties and consulting) from Renalytix, personal fees and non-financial support from Pensieve Health, non-financial support and other support (Scientific Cofounder, have equity/stock options) from Nexus I Connect, Sole proprietor of Data2Wisdom LLC, personal fees from Variant Bio, personal fees from Qiming Capital, personal fees from Cambridge Consulting, personal fees from Daiichi Sankyo, and personal fees from Menarini Health outside the submitted work. Dr. Rahman reports grants from NIH during the conduct of the study. Dr. Stempniewicz reports being a current employee of GSK and employed at AMGA at the time of this study. Dr. Wheeler reports personal fees from AstraZeneca during the conduct of the study; personal fees from Amgen, Astellas, Bayer, Boehringer Ingelheim, Gilead, GlaxoSmithKline, Janssen, Mundipharma, Merck Sharp and Dohme, Tricida, Vifor and Zydus, and personal fees from AstraZeneca outside the submitted work. Dr. van den Brand reports being an employee and stakeholder of Binnovate Digital Health BV outside the submitted work. All other coauthors have nothing to disclose.

Some of the data reported here have been supplied by the United States Renal Data System. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US Government.

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FIGURE TITLES AND LEGENDS

Figure 1. CVD events distribution by occurrence of KFRT during follow-up. Both prevalent and incident CVD events are included. Among individuals who developed KFRT events are limited to CVD prior to KFRT while among individuals without KFRT all events during follow-up are included

Figure 2. Adjusted hazard ratios and 95% confidence intervals of kidney failure replacement therapy (KFRT) associated with different cardiovascular (CVD) events modelled (A) separately or (B) simultaneously adjusted for each other by timing after the incident CVD event in OLDW

Dots show the hazard ratio and whiskers are the 95% confidence intervals. The dots are plotted in the center of 3 month windows (e.g., for 0-3 months, the dot is at 1.5 months or 0.125 years).

Structured Graphical abstract. Hazard ratios (and 95% confidence intervals) for the risk of kidney failure with replacement therapy (KFRT) associated to developing heart failure (HF), myocardial infarction (MI), atrial fibrillation (AF) or stroke, across 81 global cohorts and graphically depicted using the OLDW database.