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

Patrick B Mark, MB, ChB, PhD*, Juan J Carrero, PharmD, PhD*, Kunihiro Matsushita, MD, PhD, Yingying Sang, MSc, Shoshana H Ballew, PhD, Morgan E Grams, MD, PhD, Josef Coresh, MD, PhD, Aditya Surapaneni, PhD, Nigel J Brunskill, MD, PhD, John Chalmers, MD, PhD, Lili Chan, MD, MS, Alex R Chang, MD, MS, Rajkumar Chinnadurai, MD, Gabriel Chodick, PhD, Massimo Cirillo, MD, Dick de Zeeuw, MD, PhD, Marie Evans, MD, PhD, Amit X Garg, MD, PhD, Orlando Gutierrez, MD, Hiddo JL Heerspink, PhD, Gunnar H Heine, MD, William G Herrington MD, Junichi Ishigami, MD, PhD, Florian Kronenberg, MD, Jun Young Lee, MD, PhD, Adeera Levin, MD, Rupert W Major, MD, PhD, Angharad Marks, MD, MSc, PhD, Girish N Nadkarni, MD, MPH, David MJ Naimark, MD, MSc, Christoph Nowak, MD, PhD, Mahboob Rahman, MD, MS, Charumathi Sabanayagam, PhD, Mark Sarnak, MD, MS, Simon Sawhney, MD, PhD, Markus P Schneider, MD, Varda Shalev, MD, Jung-Im Shin, MD, PhD, MPH, Moneeza Siddiqui, PhD, MPH, Nikita Stempniewicz, MSc, Keiichi Sumida, MD, MPH, José M Valdivielso, PhD, Jan van den Brand, PhD, Angela Yee-Moon Wang, MD, PhD, David Wheeler, MD, Lihua Zhang, MD, Frank LJ Visseren, MD, PhD†, Benedicte Stenge, MD, PhDl†

*co-first authors; †co-last authors

Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, Scotland, UK (PB Mark)

Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Huddinge, Sweden (JJ Carrero)

Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (K Matsushita, Y Sang, SH Ballew, M Grams, J Coresh, A Surapaneni, J Ishigami, JI Shin)

John Walls Renal Unit, Leicester General Hospital, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom, Department of Cardiovascular Sciences, University of Leicester, Leicester, United Kingdom (N Brunskill, RW Major)

The George Institute for Global Health, University of New South Wales, Sydney, NSW, Australia (J Chalmers)

Department of Medicine, Division of Nephrology, Icahn School of Medicine at Mount Sinai, New York, New York (L Chan, GN Nadkarni)

Department of Nephrology and Kidney Health Research Institute, Geisinger Medical Center, Danville, Pennsylvania (AR Chang)

Department of Renal Medicine, Salford Care Organisation, Northern Care Alliance NHS Foundation Trust, Salford, UK (R Chinnadurai)

Medical Division, Maccabi Healthcare Services, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel (G Chodick)

Department of Public Health, University of Naples “Federico II”, Italy (M Cirillo)

Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center, Groningen, Netherlands (D de Zeeuw, HJL Heerspink)

Department of Clinical Intervention, and Technology (CLINTEC), Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden (M Evans)

ICES, London, Ontario, Canada; Division of Nephrology, Western University, London, Ontario, Canada (AX Garg)

Departments of Epidemiology and Medicine, University of Alabama at Birmingham, Birmingham, AL (O Gutierrez)

Saarland University Medical Center, Internal Medicine IV, Nephrology and Hypertension, Homburg, Germany (GH Heine)

Medical Research Council Population Health Research Unit at the University of Oxford, Nuffield Department of Population Health (NDPH), and Clinical Trial Service Unit and Epidemiological Studies Unit, NDPH, University of Oxford, Oxford, UK (WG Herrington)

Division of Genetic Epidemiology, Department of Medical Genetics, Molecular and Clinical Pharmacology, Medical University of Innsbruck, Innsbruck, Austria (F Kronenberg)

Transplantation Center, Wonju Severance Christian Hospital, and Department of Nephrology, Yonsei University Wonju College of Medicine, Wonju 26426, Korea (JY Lee)

Division of Nephrology, University of British Columbia, Vancouver, Canada (A Levin)

Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, Scotland, UK (A Marks)

Sunnybrook Hospital, University of Toronto, Toronto, ON, Canada (DMJ Naimark)

Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden (C Nowak)

Division of Nephrology, Department of Medicine, Case Western Reserve University, Cleveland, OH (M Rahman)

Singapore National Eye Centre, Singapore Eye Research Institute, Singapore, Singapore; Yong Loo Lin School of Medicine, National University of Singapore, Singapore; Duke-NUS Medical School, Singapore, Singapore (C Sabanayagam)

Division of Nephrology at Tufts Medical Center, Boston, Massachusetts (M Sarnak)

University of Aberdeen, Aberdeen, Scotland, UK (S Sawhney)

Department of Nephrology and Hypertension, Friedrich-Alexander Universität Erlangen-Nürnberg, Erlangen, Germany (MP Schneider)

Institute for Health and Research and Innovation, Maccabi Healthcare Services and Tel Aviv University, Tel Aviv, Israel (V Shalev)

Division of Population Health and Genomics, School of Medicine, University of Dundee, Dundee, UK (MK Siddiqui)

AMGA (American Medical Group Association), Alexandria, Virginia and OptumLabs Visiting Fellow (N Stempniewicz)

Division of Nephrology, Department of Medicine, University of Tennessee Health Science Center, Memphis, TN (K Sumida)

Vascular & Renal Translational Research Group, IRBLleida, Spain and Spanish Research Network for Renal Diseases (RedInRen. ISCIII) , Lleida , Spain (JM Valdivielso)

Department of Nephrology, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands (J van den Brand)

Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong (AYM Wang)

Centre for Nephrology, University College London, London, UK (D Wheeler)

National Clinical Research Center of Kidney Disease, Jinling Hospital, Nanjing University School of Medicine, Nanjing, Jiangsu, P.R. China (L Zhang)

Department of Vascular Medicine, University Medical Center Utrecht, Utrecht, The Netherlands (FLJ Visseren)

University Paris-Saclay, UVSQ, University Paris-Sud, Inserm, Clinical Epidemiology team, CESP, Villejuif, France (B Stengel)

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 requiring replacement therapy (KFRT).

Methods: We analyzed data on 25,903,761 individuals from the CKD Prognosis Consortium with baseline eGFR and follow-up for CVD and KFRT. We assessed 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 required 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. HF showed the strongest association with KFRT (HR 46 (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 need for kidney failure 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 aspects 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 need for 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 need for 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 urine albuminuria data. In total, 81 cohorts had adequate data and agreed to participate. Further information on cohorts is available in Appendix 1.

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 occurence 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 dialysis or transplant. 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 and the missing ACR indicator stands reflect clinical practice. Hyperlipidemia 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. Estimates were meta-analyzed using a random effects meta-analysis. Following analysis of each CVD event type separately, we analyzed all 4 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 competing risk of mortality model 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. 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 with a threshold P value of <0.05.

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 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 distribution 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**). 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. Analysis of each CVD event adjusted for the other CVD events in 55 cohorts

showed 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 S5**). 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 (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 risks persisting for HF with an adjusted hazard ratio of 46 (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 S6**). Results were consistent if shorter follow-up time after the CVD event was considered (**Table S7**) as well as for the secondary broader outcome including eGFR <15 ml/min/1.73m^2 during follow-

up (**Table S8**). Interaction models showed that the hazard ratios of KFRT after CVD incidence were somewhat smaller at lower eGFR and higher albuminuria (**Table S6 and S7**).

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 S9**). Among those with eGFR above 60 ml/min/1.73m^2, the risk of KFRT was higher among younger individuals with diabetes (**Table S10**).

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 were 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, particulary 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 function 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 kidney function[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 generally 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 results in ARIC was relatively small (n=210), and the study only included participants from US. 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 a 1.09 ml/min/1.73m^2/year faster decline post-event compared to pre-event, and a similar but lesser magnitude decline observed following CHD events. However, quantification of pre-post eGFR slopes depended on testing and on surviving two years post CVD event.

The mechanisms underlying the increased risk of KFRT in patients with CVD in general and with HF in particular, are complex. On one hand, both conditions share common risks factors, such as hypertension, diabetes, smoking, obesity and physical inactivity[1,24]. On the other hand, accumulated evidence suggests that both conditions have shared deleterious pathophysiological mechanisms often inducing a 'vicious cycle' of dysregulated homeostatic mechanisms including neurohormonal activation, anaemia, endothelial dysfunction, arterial calcification and fibrotic responses leading to the injury in the kidney[25].

The large increase in need for KFRT in the immediate 90 days following a HF event requires detailed consideration. The risk was highest early after the CVD event, remained elevated for up to three years after the CVD event for HF, but waned for other CVD subtypes. Some KFRT events following HF may be described as 'type 1 cardiorenal syndrome' whereby acute kidney injury occurs in the setting of renal haemodynamic compromise accompanying decompensated HF[26-28]. Patients with HF are particularly susceptible to kidney insults. A previous report has highlighted the cumulative impact of multiple HF hospitalisations on subsequent increased risk of KFRT in patients attending nephrology clinics in Canada[15]. The presence of HF has been shown to be a consistent risk factor for acute kidney injury in studies of community prescribing, reiterating the notion that kidney function is precarious in people with HF and susceptible to acute deterioration[29,30]. Some HF events may represent diagnostic coding of the clinical syndrome of 'fluid overload' representing the inability of the kidneys to handle salt and water in advanced CKD. For other CVD subtypes, acute kidney injury is common in the setting of major atherothrombotic CVD event such stroke or CHD and

subsequent KFRT risk may reflect subsequent loss of kidney function after an episode of AKI or *de novo* accelerated eGFR decline as suggested previously[31,32].

Our findings have clinical implications on risk stratification and informing decisions around therapeutic interventions, intensity of kidney function monitoring, and planning for long term KFRT. Although eGFR monitoring is already emphasized by cardiology guidelines[33], and creatinine is included in some risk calculators for predicting survival of patients with HF[34], albuminuria testing is an additional and inexpensive early sign of kidney damage[35,36] that can be added to the routine workout for secondary CVD prevention and hence inform KFRT risk simultaneously[37]. Measures of albuminuria add prognostication to current risk calculators for secondary CVD management[38,39]. Our results also evidence the need of preventing KFRT through established therapies. Indeed, there are several pharmacological strategies that have demonstrated efficacy in improving albuminuria and delaying eGFR decline and/or KFRT onset in persons with established CVD, with or without HF, including renin angiotensin system inhibition[40-42], sodium glucose transport 2 (SGLT2) inhibition[43-45] and finerenone[46,47]. Judicious use of diuretics and optimal fluid management has a role in both treatment of HF and maintenance of kidney function[48]. Whilst these therapies are nowadays mainstay of both cardio- and nephroprotection in clinical guidelines, routine care data shows suboptimal use and evidence opportunities for improvement[49,50].

Future studies should identify CVD patients at highest risk of CKD progression. Such patients may benefit from additional management efforts to avoid damage or overload to the kidneys, including the avoidance of nephrotoxins like non-steroidal anti-inflammatory drugs, proton-pump inhibitors, warfarin or certain antibiotics, whilst proactive use of SGLT2 inhibition may both reduce risk of HF hospitalisation and KFRT risk in appropriate patients[43,51]. Those at highest risk of progressive CKD may also require management of CKD specific complications

such as anaemia, acidosis, mineral bone disorders and long-term planning to consider dialysis modality and/or consider whether kidney transplantation is feasible. Collaborative efforts between nephrology and cardiology are crucial in personalising preparation for KFRT. For example, creation of an arteriovenous fistula as access for haemodialysis may promote left ventricular hypertrophy and elevation in natriuretic peptides, risking exacerbating pre-existing HF[52]. The workup of kidney transplant candidates with existing cardiovascular disease is controversial and requires more advance planning than in those without CVD[53].

Strengths of this study include the large sample sizes of the study populations; the clinical and geographic diversity of the participants; and the rigorous analytical approach. However, some limitations should also be acknowledged. There are potential sources of misclassification: from heterogeneity on how CVD subtypes were determined or defined across cohort; and from defining baseline eGFR or albuminuria status by a single level. We would argue that the consistency of our findings despite this inevitable heterogeneity speaks, however, in favor of generalizability. We could neither examine whether the severity/subtype of HF or stroke modify our conclusions, nor the contribution of socioeconomic status. 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 across cohorts, depending on how actively clinicians 'screen' for AF (i.e., the prevalence of 'asymptomatic' AF varies widely depending on the age and risk profile)[54]. 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. Understanding best management strategies within secondary CVD prevention that may alter CKD progression warrants further study and may serve to individualize treatment pathways. The time dependent analysis of risk after CVD had to be limited to the largest datasets.

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 and stroke. Patients, clinicians and healthcare systems engaged with the management of major CVD should be aware of this risk to optimise long-term care ensuring that those at highest risk receive appropriate counselling, therapy and referral for management of progressive CKD.

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CKD-PC investigators/collaborators (cohort acronyms/abbreviations are listed in **Appendix 2** in the Supplement**:**

ADVANCE: John Chalmers, Mark Woodward; **ARIC:** Josef Coresh, Kunihiro Matsushita, Jung-Im Shin, Junichi Ishigami; **CanPREDDICT:** Adeera Levin, Ognjenka Djurdjev, Mark Canney, Mila Tang; **CARE FOR HOMe:** Gunnar Heine, Insa Emrich, Sarah Seiler, Kyrill Rogacev; **CRIB:** David Wheeler, Jonathan Emberson, John Townend, Martin Landray; **CRIC:** Jing Chen, Jordana Cohen, Michael Fischer; **GCKD:** Markus P Schneider, Anna Köttgen, Heike Meiselbach, Kai-Uwe Eckardt; **Geisinger:** Alex R. Chang, Kevin Ho, Jamie Green, H. Lester Kirchner; **GLOMMS:** Simon Sawhney, Corri Black, Angharad Marks; **Gubbio:** Massimo Cirillo; **Hong Kong CKD:** Angela Yee-Moon Wang, Sharon Wong, Sharon Cheung, Henry Wu; **ICES-KDT:** Amit Garg; **LCC:** Nigel Brunskill, Laura Gray, Rupert Major, James Medcalf; **Maccabi:** Varda Shalev, Gabriel Chodick; **MASTERPLAN:** Jack Wetzels, Peter Blankestijn, Arjan van Zuilen, Jan van de Brand; **MDRD:** Mark Sarnak, Lesley Inker, Andrew S Levey; **MMKD:** Florian Kronenberg, Barbara Kollerits, Eberhard Ritz; **Mt Sinai BioMe:** Girish N Nadkarni, Erwin P Bottinger, Ruth JF Loos, Stephen B Ellis; **Nanjing CKD:** Haitao Zhang, Lihua Zhang, Zhihong Liu; **Nefrona:** José M Valdivielso, Marcelino Bermúdez-López, Milica Bozic, Serafí Cambray; **NephroTest:** Benedicte Stengel, Marie Metzger, Martin Flamant, Pascal Houillier, Jean-Philippe Haymann; **OLDW:** Nikita Stempniewicz, John Cuddeback, Elizabeth Ciemins; **PSP-CKD:** Nigel Brunskill, Rupert Major, David Shepherd, James Medcalf; **RCAV:** Csaba P. Kovesdy, Keiichi Sumida; **REGARDS:** Orlando M Gutierrez, Paul Muntner, David Warnock; **RENAAL:** Hiddo JL Heerspink, Michelle Pena, Dick de Zeeuw; **SCREAM:** Juan J Carrero,

Edouard L Fu, Carl Gustaf Elinder, Peter Barany; **SEED:** Tien Yin Wong, Charumathi Sabanayagam, Ching-Yu Cheng, Miao Li Chee; **SHARP:** Colin Baigent, Martin Landray, William G Herrington, Natalie Staplin; **SKS:** Philip Kalra, Rajkumar Chinnadurai, James Tollitt, Darren Green; **SMART:** Frank Visseren, Joep van der Leeuw; **SRR-CKD:** Marie Evans, Helena Rydell, Maria Stendahl, Mårten Segelmark; **Sunnybrook:** David Naimark, Navdeep Tangri; **UK Biobank:** Christoph Nowak, Johan Ärnlöv; **West of Scotland:** Patrick B Mark, Jamie P Traynor, Peter C Thomson, Colin C Geddes; **YWSCC:** Jae Won Yang, Jae-Seok Kim, Jae Il Shin

CKD-PC Steering Committee: Josef Coresh (Chair), Shoshana H Ballew, Alex R. Chang, Ron T Gansevoort, Morgan E. Grams, Orlando Gutierrez, Tsuneo Konta, Anna Köttgen, Andrew S Levey, Kunihiro Matsushita, Kevan Polkinghorne, Elke Schäffner, Mark Woodward, Luxia Zhang

CKD-PC Data Coordinating Center: Shoshana H Ballew (Assistant Project Director), Jingsha Chen (Programmer), Josef Coresh (Co-Principal Investigator), Morgan E Grams (Co-Principal Investigator; Director of Nephrology Initiatives), Kunihiro Matsushita (Director), Yingying Sang (Lead Programmer), Aditya Surapeneni (Programmer), Mark Woodward (Senior Statistician)

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Table 1. Overall baseline characteristics of 81 participating cohorts

Baseline characteristics – Overall		
Number of cohorts		81
Sample size, total		25,903,761
Median (25^{th}-75^{th} percentile)		165,729 (9,512-366,016)
Age (SD), years		53 (17)
Female, %		52%
Black, %		8.8%
eGFR (SD), ml		89 (23)
ACR £	N	2,178,788 (8.4%)
	Median (IQI), mg/g	13 (6-36)
Dipstick	N	5,605,219
	Trace	8.9%
	+	6.8%
	++	2.9%
	>++	0.90%
Smoker	Current, %	7.8%
	Former, %	10%
Diabetes, %		15%
Hypertension, %		36%
SBP (SD), mmHg		126 (17)
HTN meds, %		18%
Total Cholesterol (SD), mM		4.7 (1.0)
HDLC (SD), mM		1.3 (0.4)
Lipid lowering meds, %		13%
BMI (SD), kg/m^2		30 (7)

Supplementary tables 1 and 2 show details of the characteristics in each cohort at baseline and the number of KFRT events during follow up.

£ PCR was converted to ACR when ACR was not available.

ACR: albumin-to-creatinine ratio ; BMI : body mass index; eGFR: estimated glomerular filtration rate; HDLC high density lipoprotein cholesterol; HTN meds: hypertension medications; SBP : systolic blood pressure.

Table 2. Adjusted hazard ratios of kidney failure replacement therapy (KFRT) after different cardiovascular events by prevalence, incidence, and timing after the incident event modelled separately and simultaneously adjusted for each other.

	Cardiovascular event types modeled separately			
	CHD	**Stroke**	**HF**	**Atrial fibrillation**
All participants, N	25,902,290	25,902,290	25,858,471	24,353,175
Prevalent CVD, N	2,450,902	824,717	848,609	1,071,615
Incident CVD, N	269,142	311,021	712,556	605,596
Incident KFRT, N	100,931	100,931	98,001	93,600
	HRs (95%CI) of KFRT after Baseline Prevalent CVD			
Prevalent CVD	1.21 (1.17, 1.26)	1.14 (1.10, 1.18)	1.41 (1.34, 1.49)	1.12 (1.07, 1.18)
	HRs (95%CI) of KFRT after Incident CVD During Follow-up			
Incident CVD	3.09 (2.87, 3.32)	1.98 (1.83, 2.14)	4.50 (4.17, 4.85)	2.84 (2.63, 3.06)

	Cardiovascular event types adjusted for each other			
	CHD	**Stroke**	**HF**	**Atrial fibrillation**
All participants	24,333,904			
Prevalent CVD, N	2,389,565	806,562	836,417	1,071,399
Incident CVD, N	255,291	293,547	693,115	604,601
Incident KFRT, N	92,348			
	HRs (95%CI) of KFRT after Baseline Prevalent CVD			
Prevalent CVD	1.12 (1.08, 1.15)	1.07 (1.03, 1.11)	1.37 (1.31, 1.44)	0.98 (0.94, 1.02)
	HRs (95%CI) of KFRT after Incident CVD During Follow-up			
Incident CVD	1.49 (1.38, 1.61)	1.33 (1.22, 1.45)	3.69 (3.36, 4.04)	1.39 (1.28, 1.52)

Footnote: When modelled separately, but limited to individuals free of all CVD at baseline, the adjusted hazard ratios (95% CIs) for incident CVD events are 3.35 (3.12-3.59) for MI, 2.20 (2.02-2.40) for stroke, 4.76 (4.48-5.06) for HF, and 3.43 (3.14-3.75) for atrial fibrillation.
CHD: coronary heart disease; CVD: cardiovascular disease; HF: heart failure; KFRT: kidney failure replacement therapy;
Model adjusted to age, sex, black race, eGFR, smoking status, diabetes mellitus, systolic blood pressure and antihypertensive medication use, total cholesterol, HDL cholesterol and use of lipid lowering medication use, body mass, missing indicator of ACR and logtransformed ACR. Details of modelling in method section.

Table 3. Absolute 2-year risk of KFRT after incident CVD in the Optum Labs Data Warehouse (OLDW) by eGFR and ACR category

	eGFR	All participants				ACR <30 or missing				ACR 30-299				ACR 300+			
		CHD	Stroke	HF	AF	CHD	Stroke	HF	AF	CHD	Stroke	HF	AF	CHD	Stroke	HF	AF
N	90+	45609	48397	88507	77038	42767	45313	82029	50390	2104	2297	4559	3402	738	787	1919	791
	60-89	82966	99212	215338	211302	77830	92808	200269	160355	3636	4655	10784	11327	1500	1749	4285	2442
	45-59	32789	41675	111743	96564	29735	37936	101483	79123	2059	2575	6863	6956	995	1164	3397	1879
	30-44	21201	24691	80702	62272	18286	21450	69905	50666	1824	2046	6737	5897	1091	1195	4060	1995
	15-29	10190	9570	39442	27253	7977	7614	31274	20076	1010	950	3834	2997	1203	1006	4334	1746
Age and sex adjusted risk of KFRT accounting for death as a competing risk	90+	0.2%	0.2%	0.3%	0.3%	0.2%	0.2%	0.3%	0.2%	0.5%	0.4%	0.4%	0.4%	1.1%	0.3%	1.3%	0.4%
	60-89	0.3%	0.2%	0.4%	0.3%	0.2%	0.2%	0.3%	0.2%	0.5%	0.3%	0.6%	0.5%	1.2%	0.9%	1.3%	0.8%
	45-59	0.9%	0.5%	1.0%	0.8%	0.8%	0.4%	0.9%	0.7%	0.7%	0.4%	1.5%	1.1%	3.9%	2.1%	3.0%	1.6%
	30-44	2.4%	1.8%	2.8%	2.3%	2.1%	1.4%	2.4%	2.0%	3.4%	2.3%	3.4%	3.2%	6.2%	5.6%	7.3%	5.3%
	15-29	11.9%	9.0%	14.0%	10.6%	10.1%	7.5%	12.1%	9.4%	14.4%	9.9%	14.6%	12.1%	21.1%	17.9%	25.6%	19.1%

Footnote: Risk of KFRT takes into account death as a competing risk and is age and sex adjusted to age 70 and half male to allow comparisons across the CVD subtypes.
ACR: albumin-to-creatinine ratio ; CHD: coronary heart disease; CVD : cardiovascular disease; eGFR: estimated glomerular filtration rate; HF: heart failure; KFRT: kidney failure replacement therapy

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

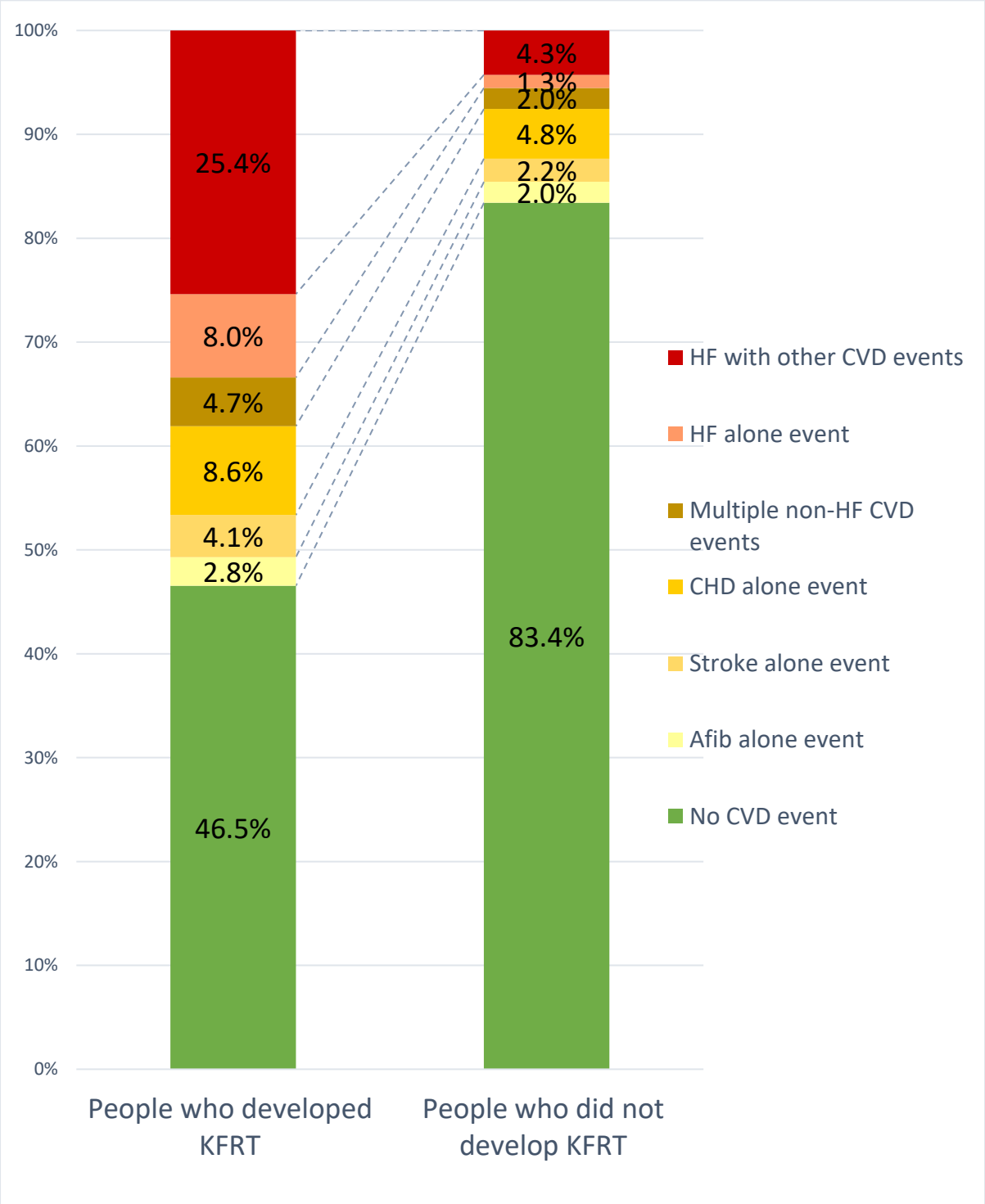
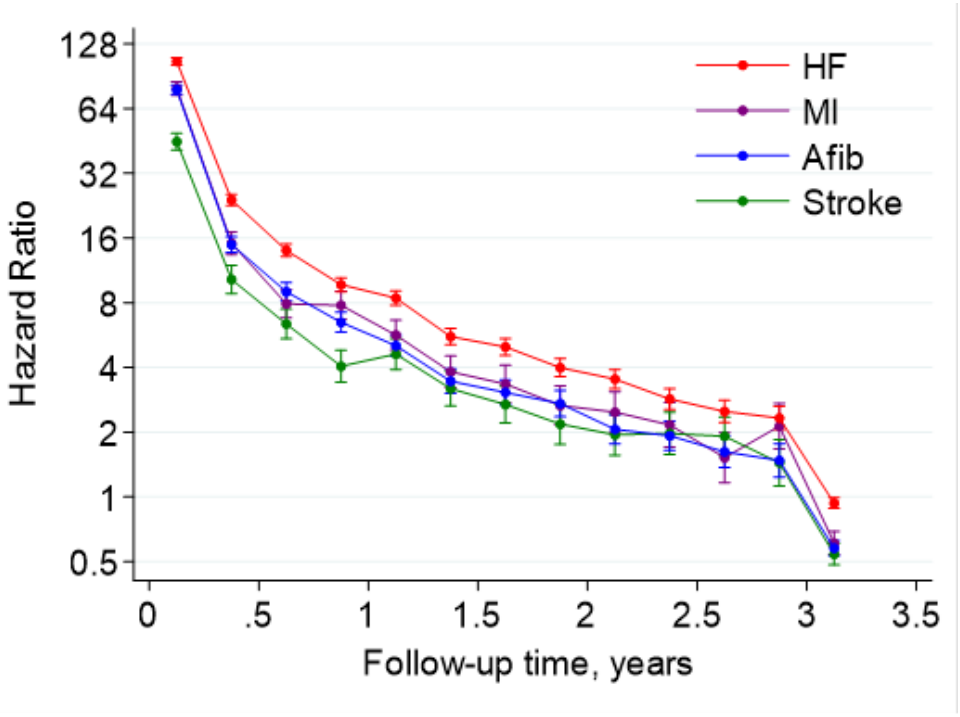


Figure 2. Adjusted hazard ratios of kidney failure replacement therapy (KFRT) associated with different cardiovascular (CVD) events modelled (A) separately or (B) simultaneously adjusted for each other by timing after the incident CVD event in OLDW

Panel A



Panel B