Chronic kidney disease

GFR slope as a surrogate marker for future kidney failure

Jennifer S. Lees[1,2†] and Patrick B. Mark[1,2]

1. School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK
2 Glasgow Renal and Transplant Unit, NHS Greater Glasgow and Clyde, Glasgow, UK

[†]E-mail: Jennifer.Lees@glasgow.ac.uk

Standfirst
Kidney failure is a serious but rare consequence of progressive chronic kidney disease. A meta-analysis of individual participant-level trial data, across heterogeneous treatments and disease groups, has shown glomerular filtration rate (GFR) slope to be a valid, fit-for-purpose, and robust surrogate marker of kidney failure.

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Chronic kidney disease (CKD) will soon be the fifth leading cause of death globally[1]. Kidney failure requiring replacement therapy (KRT) — that is, dialysis or a kidney transplant — is a serious but rare consequence of CKD. However, projected estimates expect the number of people requiring KRT to rise by more than 400% in the next 10 years, dramatically increasing treatment burden and placing extreme pressure on healthcare budgets. Additional preventative measures to reduce these pressures in an aging and increasingly multimorbid population are therefore urgently needed. Identifying interventions that can attenuate the risk of kidney failure are plagued by difficulties in capturing this uncommon outcome within the 2-to-5-year duration of many trials. Where benefit has been demonstrated, trials have often been conducted in the highest-risk groups and/or among patients with advanced CKD. However, it is in the earlier stages of CKD that preventative strategies are likely to yield the greatest benefit. New findings, indicating that glomerular filtration rate (GFR) slope can be reliably used as a surrogate endpoint for kidney failure in clinical trials[2], and may enable the more efficient evaluation of new therapies.

Progression to kidney failure necessarily warrants a deterioration in kidney function. GFR slope — a quantitative measure of GFR decline over time — has long been considered a biologically plausible surrogate marker that sits on the causal pathway towards kidney failure; however, the validity of GFR slope across the spectrum of underlying cause and severity of CKDremained uncertain. In an analysis of individual participant-level data (IPD) across 66 treatment comparisons in 186,132 participants, Inker et al[2] have demonstrated a very strong association between total GFR slope (computed from baseline to 3 years; R^2 =0.97, Bayesian credible interval 0.82-1.00) and a moderate association between chronic GFR slope (starting at 3 months after randomization; R^2 =0.55, Bayesian credible interval 0.25-0.77) and kidney failure (defined as kidney failure with KRT, sustained GFR <15 ml/min/1.73 m^2 and/or a doubling of serum creatinine). The strengths of this report are in the analysis of IPD from heterogeneous trials (across patients with diabetes, CKD of unspecified cause, glomerular and cardiovascular disease), a range of interventions with and without acute effects on GFR (including mineralocorticoid receptor antagonists and SGLT2 inhibitors) and individuals at an early stage of CKD (mean GFR 68 ml/min/1.73 m^2). The association of total GFR slope with the clinical end point is arguably stronger than for other widely used and accepted surrogate end points, such as HbA1c for trials of patients with diabetes[3], and meets FDA requirements as a valid, fit-for-purpose, and robust surrogate marker of kidney failure.

Compared to analyses of kidney failure outcomes, analyses of GFR slope are more likely to provide adequate statistical power for the detection of treatment-associated effects across subgroups and enable the detection of signals for interventions that might improve kidney failure risk at earlier stages of CKD (both inside and outside of ‘CKD trials’). GFR slope may also add to the outputs of clinical trials and contribute to the regulatory approval process for new drugs to prevent kidney failure, though GFR slope itself is unlikely to translate to being a therapeutic target in clinical practice. The reason for the different strengths of association between total and chronic slope with kidney failure is unclear and at odds with the results of a prior meta-analysis from the same group[4]. However, this observation may be due to the magnitude of observed acute effects (drug-associated change in GFR in the first ~3 months of treatment) on GFR slope. Large acute drug effects on GFR may ‘negate’ effects on chronic slope, falsely leading to the conclusion that there is no association between chronic slope and the clinical outcome. Consideration of acute effects and the validity of time frames for calculation of chronic GFR slope are statistically complex.

Further general concerns regarding the use of surrogate markers must also be considered. Between 2010 and 2012, nearly half of the new drugs that obtained FDA approval did so based on surrogate end points; in fact, 78% of drugs for chronic obstructive pulmonary disease

and 100% of drugs for Type 1 or Type 2 diabetes were approved based on surrogate end points [3]. However, surrogate endpoints tend to overestimate the benefit on patient-relevant final outcomes. In progressive CKD, the likelihood of reaching kidney failure is reduced by the competing (and more common) risk of death without kidney failure, particularly for patients at earlier stages of CKD[5]. Surrogate outcomes may also fail to identify serious adverse events. Rosiglitazone is perhaps the most memorable example of this, which was FDA-approved based on improvement in HBA1c, but subsequently found in a spotlight meta-analysis to be associated with an increased risk of myocardial infarction and cardiovascular death[6]. CKD progression is associated with a higher rate of cardiovascular (including atherosclerotic cardio- and cerebrovascular disease, arrhythmia, heart failure), cancer, infection-related and all-cause mortality — all of which are more common than kidney failure (Figure 1). Of note, these events are not directly detected by GFR slope.

As a safety outcome, GFR slope does have potential to add value. Although not validated for this purpose, GFR slope could be considered an indicator of the probability of experiencing other adverse events associated with progressive CKD. Furthermore, CKD progression has been detected as an unexpected consequence of other treatments, for example, immune checkpoint inhibitors, which have revolutionised the treatment of some cancers[7], and intravitreal VEGF inhibitors, which are used in the treatment of neovascular eye diseases. Although rarely explored in the original VEGF inhibitor trials[8], the development of proteinuria and progressive CKD is likely to be particularly important for high-risk groups, such as individuals with diabetic retinopathy. Linkage and meta-analysis of trial and healthcare data obtained from the routine measurement of kidney function in such high-risk groups will enhance our ability to identify both efficacy and safety issues using GFR slope.

There are some further considerations. Though described as GFR slope, the analysis used estimated GFR slope calculated from serum creatinine ($eGFR_{cr}$) in participants with mean age <65 years. In older individuals ($\geq$65 years), who constitute most of the population treated for CKD in clinical practice, measured GFR (using iohexol or radioisotope clearance methods) declines more rapidly even in healthy individuals[9] and more steeply in male versus female adults[9]. Moreover, increasing age is associated with a greater average loss of muscle mass (and thus serum creatinine) in male versus female adults. Together, these factors suggest that the performance of $eGFR_{cr}$ slope may vary by sex, particularly at extremes of age, and/or under conditions that are associated with changes in muscle mass (for example, neurological disease, chronic obstructive pulmonary disease and cancer).

Substantial evidence now supports the combined use of two markers (creatinine and cystatin C: $eGFR_{cr\text{-}cys}$) to improve accuracy in estimates of kidney function, even in cases in which $eGFR_{cr}$ and $eGFR_{cys}$ demonstrate substantial discrepancies from each other and from measured GFR[10]. Small observational cohorts show substantial intra-individual variation in GFR slopes according to the sampled biomarker. Consideration should be given to whether $eGFR_{cys}$ or $eGFR_{cr\text{-}cys}$ slopes might more accurately reflect GFR decline and the trajectory towards kidney failure, particularly in populations in which a change in serum creatinine over time is substantially influenced by non-GFR factors.

The anticipated economic impact of the growing population with progressive CKD is vast. Limitations aside, the report by Inker et al. should improve confidence in the validity of GFR slope as a robust, surrogate marker of the future risk of kidney failure. Although we would not advocate bypassing clinical outcome trials, the widespread availability and measurement of kidney function biomarkers should encourage the inclusion of GFR slope as an exploratory and/or safety end point across a wide variety of trials, with the potential to influence regulatory approvals. Ongoing validation of total and chronic GFR slopes across other disease areas, treatment interventions, participant subgroups and consideration of alternative GFR biomarkers would be welcome.

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Competing interests

Outside the submitted work, J.S.L. has received personal lectureship honoraria from Astra Zeneca, Pfizer and Bristol Myers Squibb. P.B.M. reports lecture fees and/or fees for participating advisory boards and trial end point committees from Vifor, GSK, Astra Zeneca, Pharmacomsos, Napp, Astellas, Boehringer Ingelheim, and grants from Boehringer Ingelheim outside the submitted work.

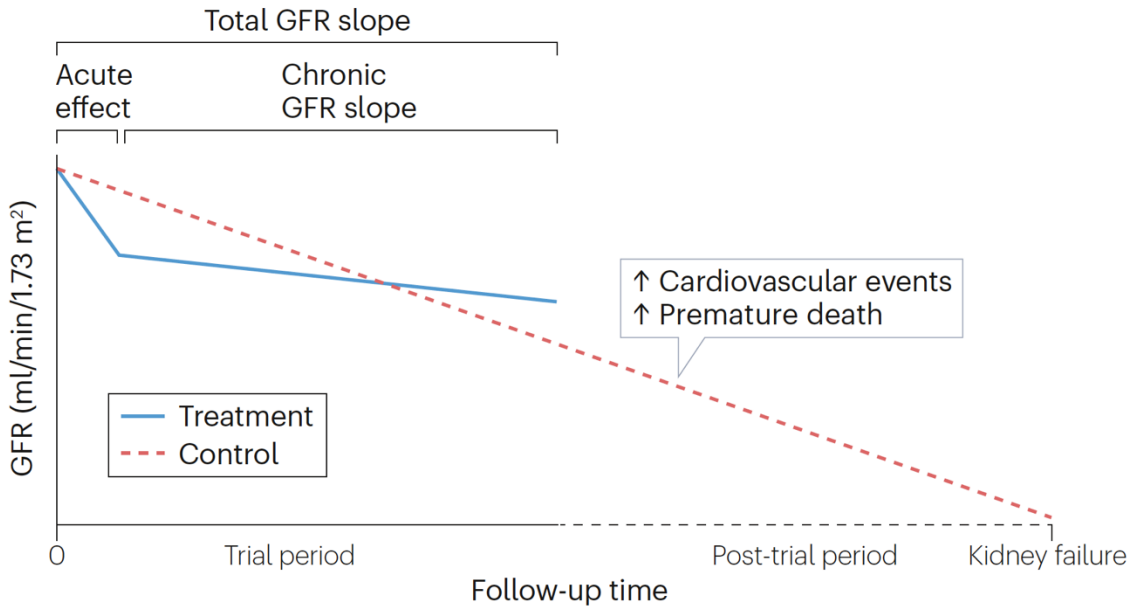

Figure 1 | The potential associations of glomerular filtration rate (GFR) decline with adverse outcomes. Acute drug effects, chronic GFR slope and total GFR slope are calculated during the trial follow-up period for treatment (blue line) and control (red dotted line) groups. Total or chronic GFR slope during the trial period are measures of chronic kidney disease (CKD) progression over time. Steeper, negative GFR slope indicates higher likelihood of future kidney failure. GFR slope may also indicate other risks associated with chronic kidney disease progression (such as cardiovascular events and premature death) but does not directly account for these risks.