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STATE OF THE ART REVIEW
Clinical trials

Decline in glomerular filtration rate as an endpoint in heart failure clinical trials: challenges and solutions

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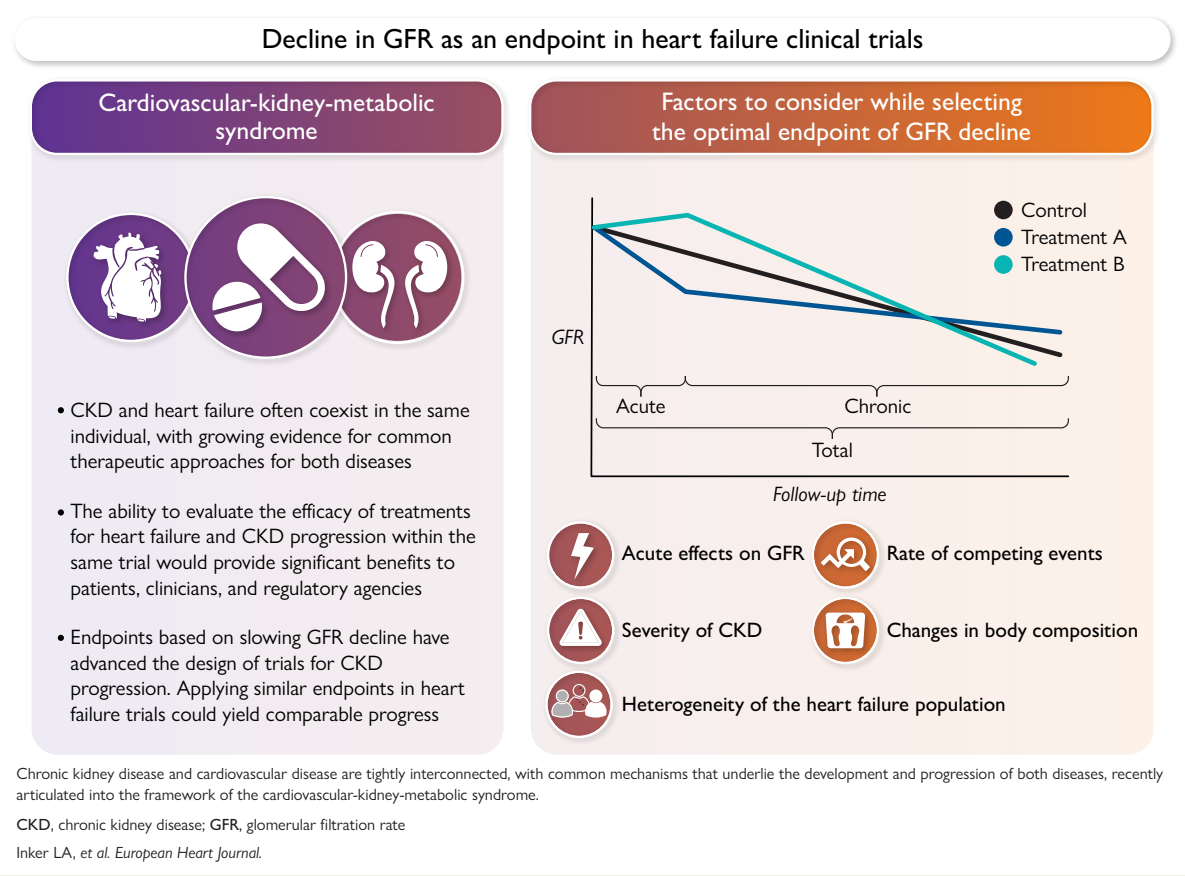
Graphical Abstract



Chronic kidney disease and cardiovascular disease are tightly interconnected, with common mechanisms that underlie the development and progression of both diseases, recently articulated into the framework of the cardiovascular-kidney-metabolic syndrome.

CKD, chronic kidney disease; **GFR**, glomerular filtration rate

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Abstract

Chronic kidney disease (CKD) and cardiovascular disease are tightly interconnected, with common mechanisms that underlie the development and progression of both diseases, recently articulated into the framework of the cardiovascular-kidney-metabolic syndrome. CKD and heart failure commonly coexist in the same individual, with increasing evidence for common therapies in both disease states. It is valuable for patients, clinicians, and regulatory agencies to understand how to best assess CKD progression in patients with heart failure for evaluation of individual patients and as part of an endpoint for outcome trials. Given the relatively short duration of most heart failure outcome trials, early measures of CKD progression prior to the occurrence of clinical events of kidney replacement therapy would be desirable. Such surrogate measures include slowing of the decline in glomerular filtration rate (GFR) decline either computed as annualized mean change in GFR (GFR slope) or time to substantial declines in GFR by specified threshold percentages (40% or 50% GFR decline). Regulatory agencies accept these endpoints for full drug approval which has enabled progress in design and conduct of trials for CKD progression. Application of these endpoints in heart failure outcome trials has the potential for similar progress. However, an immediate reduction in GFR is common following initiation of several of the guideline directed therapy for heart failure. Understanding how to best interpret an immediate GFR reduction vs long term kidney benefit is critical to optimal assessment of endpoint in an outcome trial and in the use of these medications for management of patients with heart failure. Here, the intersection of heart failure and CKD is described, how GFR and its change over time are assessed in both individual patients and in interventional trials, the evidence supporting use of GFR changes as endpoints in CKD progression trials, and the challenges and possible solutions for the use of GFR as endpoint in heart failure outcome trials and for care of individual patients, guided by case studies to inform the discussion.

Keywords Glomerular filtration rate • GFR slope • Chronic kidney disease • Heart failure • Randomized control trials

Introduction

Chronic kidney disease (CKD) and cardiovascular disease are tightly interconnected, now articulated into the American Heart Association's framework of the cardiovascular–kidney–metabolic (CKM) syndrome. CKD and heart failure often coexist in the same individual, with a complex interplay between each disease.[1] Given the shared mechanisms underlying the development and progression of both diseases, along with growing evidence for common therapeutic approaches, evaluating the efficacy of treatments for heart failure and CKD progression within the same trial would provide significant benefits to patients, clinicians, and regulatory agencies.

Progression of CKD is typically slow and asymptomatic. Endpoints based on slowing GFR decline that occurs prior to the onset of kidney failure have advanced the design and execution of trials of CKD progression.[2–11] Applying similar endpoints in heart failure trials could yield comparable progress. Currently, there is a great deal of heterogeneity in the assessment of GFR, as well as definitions for kidney endpoints, in clinical trials for heart failure.[12] A more consistent approach would improve comparison among the studies and interventions, facilitating better care for patients with heart and kidney disease. The goal of this paper is to briefly describe the intersection of heart failure and CKD, how GFR and its change over time are assessed in both individual patients and in interventional trials, the evidence supporting the use of GFR changes as endpoints in CKD progression trials, and the challenges and possible solutions for the use of GFR as an endpoint in heart failure outcome trials and for the care of individual patients, guided by case studies to inform our discussion (see Table *1* for CKD terminology).

Chronic kidney disease and assessment of glomerular filtration rate

Globally, kidney failure is estimated to affect over 840 million people, with poor outcomes and high healthcare costs.[16,20] In all countries reporting data, earlier stages of CKD, defined as GFR <60 ml/min per 1.73 m^2 or the presence of markers of kidney damage, most commonly albuminuria, present for >3 months, are reported to occur in 10%–15% of the population.[21,22] Patients at earlier CKD stages are at risk for progression to kidney failure, as well as for extensive morbidity across a wide range of acute and chronic conditions such as infections, anaemia, and muscle wasting, the most important of which is cardiovascular disease (*Figure 1*).[16]

GFR is only one of the functions of the kidney but is widely accepted as the best overall index of kidney function because it is generally reduced after widespread structural damage and most other functions of the kidney decline in parallel with GFR. GFR is measured using plasma or urinary clearance of exogenous filtration markers. These are complex procedures and therefore reserved for specialized settings. GFR is most commonly ascertained using estimated GFR from concentration of endogenous filtration markers measured in blood samples, particularly creatinine (eGFRcr). Cystatin C is increasingly used as another filtration marker to estimate GFR, either alone (eGFRcys) or in combination with creatinine (eGFRcr-cys).[16]

The level of any filtration marker is determined by both GFR and physiological processes other than GFR, referred to as non-GFR determinants. Non-GFR determinants include generation, tubular secretion or reabsorption, and extrarenal elimination of the marker (*Figure 2*).

Important non-GFR determinants for creatinine are muscle mass, physical activity, and diet. Cystatin C is less affected than creatinine by these factors but is associated with adiposity, smoking, thyroid abnormalities, and chronic inflammation.[24] Recognition of the presence of non-GFR determinants can improve assessment of GFR and therefore clinical decision-making. For example, patients with sarcopenia will have low serum creatinine levels and therefore have falsely high eGFRcr compared with the level of their true GFR. In contrast, obese patients will have high serum levels of cystatin C and falsely low levels of eGFRcys, compared with their true GFR (see Supplementary data online, *Table S1*).

In most studies, eGFR using creatinine (eGFRcr) and eGFR using cystatin (eGFRcys) have similar accuracy when compared with the gold standard of measured GFR, whereas eGFR using the combination of

Table 1 CKD terminology

Kidney terms	Definition/comment
Physiology	
Kidney function	The kidney has many functions, including excretory, endocrine, and metabolic functions. GFR is one component of excretory function but is widely accepted as the best overall index of kidney function because it is generally reduced after widespread structural damage and most other functions of the kidney decline in parallel with GFR in CKD
GFR	The rate at which plasma is filtered by the glomeruli. GFR is the product of the average filtration rate of the individual nephron and total number of nephrons. Generally accepted as the best overall index of kidney function in health and disease[13]
Single-nephron GFR	The GFR of the individual nephron. It is the product of filtration pressure and ultrafiltration coefficient[13]
Glomerular pressure	Hydrostatic and oncotic pressure within the glomerular capillary and Bowman space, which are affected by systemic and kidney haemodynamic factors. The filtration pressure is the difference between transcapillary hydrostatic and oncotic pressure gradients[13]
Measured GFR	GFR ascertained by urinary or plasma clearance of exogenous filtration markers (e.g. inulin, iothalamate, iohexol, and EDTA)[13]
Estimated GFR	GFR ascertained by serum concentration of endogenous filtration markers (e.g. creatinine and cystatin C)[13]
Non-GFR determinants	Factors that affect serum level of filtration markers other than GFR. These include generation (for endogenous filtration markers only), tubular handling, or extrarenal elimination of the filtration marker[13]
Clinical terms to define kidney disease	
Acute kidney injury	Increase in serum creatinine by 0.3 mg/dL or more within 48 h, increase in serum creatinine to 1.5 times or more than the baseline of the prior 7 days; urine volume <0.5 ml/kg/h for at least 6 h[14]
Acute kidney disease	AKI or GFR <60 ml/min/1.73 m^2 or decrease in GFR by 35% or markers of kidney damage for less than 3 months.[14] Note: AKD may be superimposed on CKD
Worsening kidney function	Increase in serum creatinine by 0.3 mg/dL and >25% or increase in cystatin C by 0.3 mg/L or decline in eGFR by 20% over 72 h[15]
Chronic kidney disease	GFR <60 ml/min/1.73 m^2 or markers of kidney damage for >3 months (e.g. albuminuria)[16]
Kidney failure	GFR <15 ml/min/1.73 m^2 or treatment with dialysis or transplant[17]
Kidney failure with replacement therapy (KFRT)	Kidney failure treated with dialysis or transplant
Changes in GFR or endpoints used for trials	
True clinical endpoint	Kidney failure[17]
Established clinical endpoint	Kidney failure or doubling of serum creatinine[18]
Time to a pre-determined decline in GFR	Interval change in GFR. Can be computed as an absolute or percentage changes. For use in classifying individual study participants
Continuous change in GFR	Changes in GFR from one time point to another. May be computed using linear or mixed models and expressed as annualized change (i.e. slope) or as change from baseline for use in describing mean changes in study groups
GFR slope	Annualized change in GFR computed using linear models[19]
Acute slope	Change in GFR in the acute phase following the beginning of treatment. Most commonly ascertained 2–6 months following initiation of treatment
Chronic slope	Change in GFR in the chronic phase following the acute phase to end of follow-up. It is hypothesized to reflect a change in the number of nephrons. It can be estimated from baseline to measurements off treatment at the end of the study
Total slope	Change in GFR from baseline to end of follow-up
GFR slope treatment effects	The difference between treatment arms in the GFR slope. Thus, acute or chronic effects are the mean difference between treatment arms in the acute or chronic phase, respectively

eGFRcr	Urine albumin to creatinine ratio, mg/g					eGFRcr	Urine albumin to creatinine ratio, mg/g				
	<10	10-20	30-299	300-999	≥1000		<10	10-20	30-299	300-999	≥1000
	All-cause mortality: 82 cohorts 26444384 participants; 2604028 events						Kidney failure with replacement therapy: 57 cohorts 25466956 participants; 158846 events				
≥105	1.6	2.2	2.9	4.3	5.8	≥105	0.5	1.2	2.9	7.7	25
90-104	Ref	1.3	1.8	2.6	3.1	90-104	Ref	1.8	4.3	12	43
60-89	1	1.3	1.7	2.2	2.8	60-89	2.3	4.9	10	27	85
45-59	1.3	1.6	2	2.4	3.1	45-59	13	19	37	89	236
30-44	1.8	2	2.5	3.2	3.9	30-44	50	58	115	240	463
15-29	2.8	2.8	3.3	4.1	5.6	15-29	283	301	443	796	1253
<15	4.6	5	5.3	6	7	<15	770	1040	1618	2297	2547
	Cardiovascular mortality: 76 cohorts 26022346 participants; 776441 events						Heart failure: 61 cohorts 24603016 participants; 1132443 events				
≥105	1.4	2	3	4.1	5.4	≥105	1.2	1.7	2.7	4.2	6.9
90-104	Ref	1.3	1.9	2.7	3.6	90-104	Ref	1.3	2	2.8	4.2
60-89	1	1.4	1.7	2.4	3.2	60-89	1.1	1.4	1.9	2.7	4.2
45-59	1.4	1.7	2.2	2.8	3.8	45-59	1.6	1.8	2.4	3.4	5
30-44	2	2.3	2.8	3.7	4.6	30-44	2.2	2.5	3.1	4.2	6.5
15-29	3.2	3.1	3.5	5	6.5	15-29	3.6	3.5	4.1	5.8	8.1
<15	6.1	6.4	6.4	7.3	8.2	<15	5.1	5.7	5.8	7.9	9.9

Figure 1 Categorical analysis of the associations of estimated glomerular filtration rate (eGFR) and albuminuria with adverse. Ref, reference cell. Numbers reflect the adjusted hazard ratio compared with the reference cell. Adjustment variables included age, sex, smoking status (current, former, never), systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, body mass index, use of antihypertensive medications, and a medical history of diabetes, coronary heart disease, stroke, heart failure, atrial fibrillation, peripheral artery disease, cancer, and chronic obstructive pulmonary disease, where relevant. For further details, see Grams *et al.* JAMA 2023.[23] The colours were determined for each outcome separately using the following rule: the percentile shaded the darkest green colour corresponds to the proportion of cells in the grid without CKD (e.g. 6 out of 35 cells with eGFR ≥60 ml/min/1.73 m^2 and ACR <30 mg/g), and the percentile shaded the darkest red colour corresponds to proportion expected to be at highest risk (e.g. 11 out of 35 cells with eGFR <15 ml/1.73 m^2 and ACR 1000+ mg/g). In this manner, the numbers of green and red cells are consistent across outcomes, but the patterns are allowed to differ. The unit of eGFR is ml/min/1.73 m^2. Modified with permission from the Writing Group for the CKD Prognosis Consortium, Grams ME, Coresh J, Matsushita K, Ballew SH, Sang Y, *et al.* Estimated glomerular filtration rate, albuminuria, and adverse outcomes: an individual-participant data meta-analysis. JAMA. 2023;330(13):1266–1277[23]

both markers (eGFRcr-cys) is more accurate than either eGFRcr or eGFRcys, most likely because the use of markers decreases the impact of the non-GFR determinants of either filtration marker.[13,16,25] In these studies, large errors, defined as eGFR >30% of measured GFR, are estimated to be ~10% for eGFRcr-cys compared with 15% for eGFRcr or eGFRcys.[25,26] In people with advanced heart failure, all estimates of GFR are likely to have greater error due to greater variation in the presence of non-GFR determinants.[27] For example, in an analysis of the subset of the PARADIGM-HF study, while overall both estimates of GFR were similar, large differences between eGFRcr and eGFRcys were noted in almost 20% of patients.[28,29] This study did not have measured GFR to evaluate which eGFR was more accurate. In three small studies in moderate to advanced heart failure where measured GFR using gold standard methods was performed, large errors of ~25%–50% were observed regardless of which eGFR was used.[24,27,30,31] In a large referral population in Sweden, eGFRcr-cys was more accurate than eGFRcr and eGFRcys in patients with a diagnostic code for heart failure, presumably because diagnostic codes are used for people with mild as well as advanced forms of the disease.[32]

The recently updated Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines provide guidance on how to incorporate cystatin C into the care of patients with heart failure.[16] For all populations, the guidelines recommend physicians measure cystatin C to estimate eGFRcr-cys for clinical decision such as the use of potentially toxic medications or those with a narrow therapeutic window or if there are concerns about low or high muscle mass or dietary protein intake that reduce the accuracy of eGFRcr (*Figure 2* and Supplementary data online, *Table S1*). In our view, the agreement or discordance between eGFRcr and eGFRcys provides further guidance.[24] In patients with CKD or in the general population cohorts, when eGFRcr and eGFRcys are discordant, eGFRcr-cys is the most accurate. While this has not been confirmed for patients with heart failure or sarcopenia or who are obese, it is reasonable to use this same approach. Furthermore, as demonstrated in *Figure 2*, when the clinical decision requires a high level of precision, the guidelines recommend measuring GFR using the gold standard methods of plasma or urinary clearance of exogenous filtration markers. If measured GFR is not available, it is reasonable to measure creatinine clearance in timed urine collections,

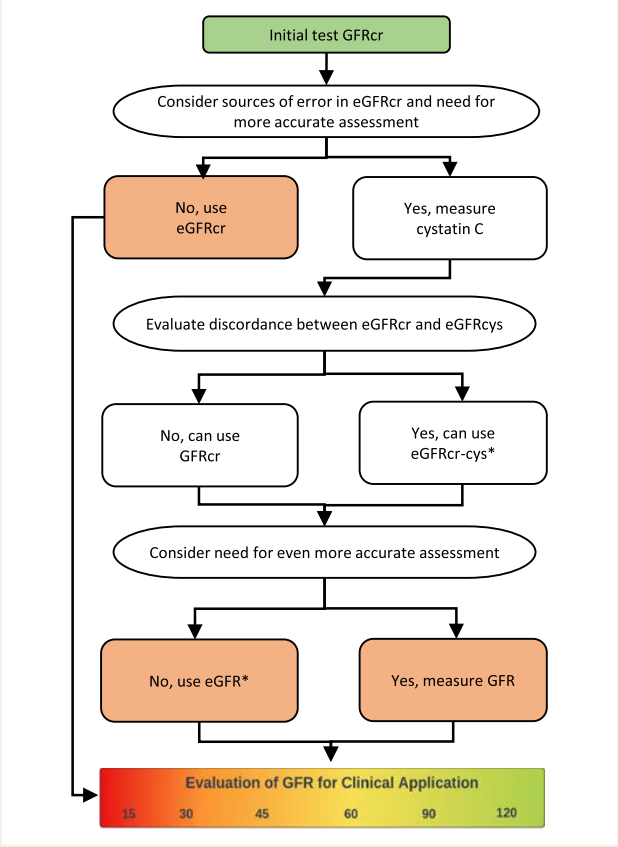


Figure 2 Algorithm for assessment of GFR in patients with symptomatic heart failure. The algorithm describes the approach to the evaluation of GFR. Our approach is to use initial and supportive testing to develop a final assessment of true glomerular filtration rate (GFR) and to apply it in individual decision-making at a single point in time. For the general population, the initial test for evaluation of GFR is often eGFRcr, because creatinine is measured routinely as part of the basic metabolic panel. For heart failure patients with Stage C or higher, measurement of cystatin C in all patients is recommended. It is then recommended that discordance between eGFRcr and eGFRcys should be assessed. If eGFRcr and eGFRcys are not discordant (not within 15 ml/min per 1.73 m^2 or 20%–30% of each other), then accuracy of eGFRcr, eGFRcys, and eGFRcr-cys is similar. If eGFRcr and eGFRcys are discordant, eGFRcr-cys is generally more accurate than either eGFRcr or eGFRcys, unless there is a greater number of factors that affect serum levels of creatinine or cystatin C. Non-GFR determinants of creatinine include extremes of muscle mass or dietary protein intake of medications that affect tubular secretion of creatinine. Non-GFR determinants of cystatin C include very high levels of inflammation, high catabolic states, and exogenous steroid use. If an even more accurate assessment of GFR is needed for a clinical decision, such as might be required in transplant evaluation, then GFR should be measured using plasma or urinary clearance of exogenous filtration markers, or if not available, then a 24 h urine collection for creatinine can be performed. For stable patients with heart failure, yearly measurements of cystatin C, with repeated measurements with change in clinical decision or critical decisions are being made, would be prudent. *Use eGFRcr or eGFRcr-cys depending on discordance between eGFRcr and eGFRcys. Modified with permission from Adingwupu OM, Barbosa ER, Palevsky PM, Vassalotti JA, Levey AS, Inker LA. Cystatin C as a GFR estimation marker in acute and chronic illness: a systematic review. Kidney Med 2023 Sep 19;5(12):100727[24]

especially in hospitalized patients with care teams that can ensure better adherence.[16]

Intersection of heart failure and chronic kidney disease

Pathophysiology

The presence of CKD is an independent risk factor for the development of heart failure. Among people with established heart failure, it is estimated that 42% of patients have CKD.[33] The presence of CKD increases risk for mortality and cardiovascular events, with risk increasing with more severe stages of CKD.[34,35] The pathophysiological mechanisms that contribute to the parallel development of these diseases are diverse and not well understood. In rare cases, a unifying disease, such as amyloid, may lead to both heart and kidney failure. Establishing the cause of CKD may therefore better inform treatment of heart failure. More commonly, however, in line with the CKM construct, excess or dysfunctional adiposity and other metabolic risk factors such as metabolic syndrome and diabetes underlie the development of CKD and CVD in many individuals.[36] Even among people without these shared risk factors, CKD is common in patients with heart failure. The mechanisms are not completely understood, but it is hypothesized that elevated levels of circulating cytokines and inflammatory biomarkers observed in heart failure likely contribute to endothelial dysfunction that is believed to be a key component in the development of irreversible kidney damage and fibrosis.[37,38]

Assessment of change in glomerular filtration rate in patients with heart failure

The level of GFR is the product of the number of functioning nephrons and the average level of GFR of individual nephrons (single-nephron GFR). Changes in single-nephron GFR can be caused by changes in glomerular pressure and may be reversible, whereas loss of nephrons from CKD causes permanent reduction in GFR. Within individuals, there may simultaneously be a reduction in the number of nephrons and in the work of individual nephrons.[39] In general, changes in single-nephron GFR occur over a short duration (days to months), whereas changes due to loss of nephrons occur over a longer duration. Both reversible and persistent decline in GFR is common in patients with worsening heart failure.[40–44] In two separate ambulatory clinical populations with heart failure, a large decline in GFR was noted.[45,46] In one of the cohorts, the rate of decline was similar to several CKD cohorts and greater than in patients with GFR <60 ml/min per 1.73 m^2 in large clinical populations (*Figure 3*).[45]

The mechanisms driving GFR change in patients with heart failure are complex, evolve over time, and are multifactorial. For a patient with heart failure, an observed change in GFR might be secondary to heart failure or its treatment; damage to the kidney that is unrelated to heart failure; or changes in non-GFR determinants of the filtration marker rather than a true change in GFR. In addition, mechanisms driving GFR change differ across the LVEF spectrum. In heart failure with reduced ejection fraction (HFrEF), in patients with stable chronic heart failure or during acute exacerbations, excess neurohormonal activity, sodium and water avidity, and fluctuations in cardiac haemodynamics may be present. All of this may contribute to decreased kidney perfusion and GFR decline.[51–55] In heart failure with mildly reduced ejection fraction (HFmrEF) or in heart failure with preserved ejection fraction (HFpEF), the mechanisms of eGFR decline may be even broader due to the more heterogenous patient population. Older individuals with HFmrEF and HFpEF more often

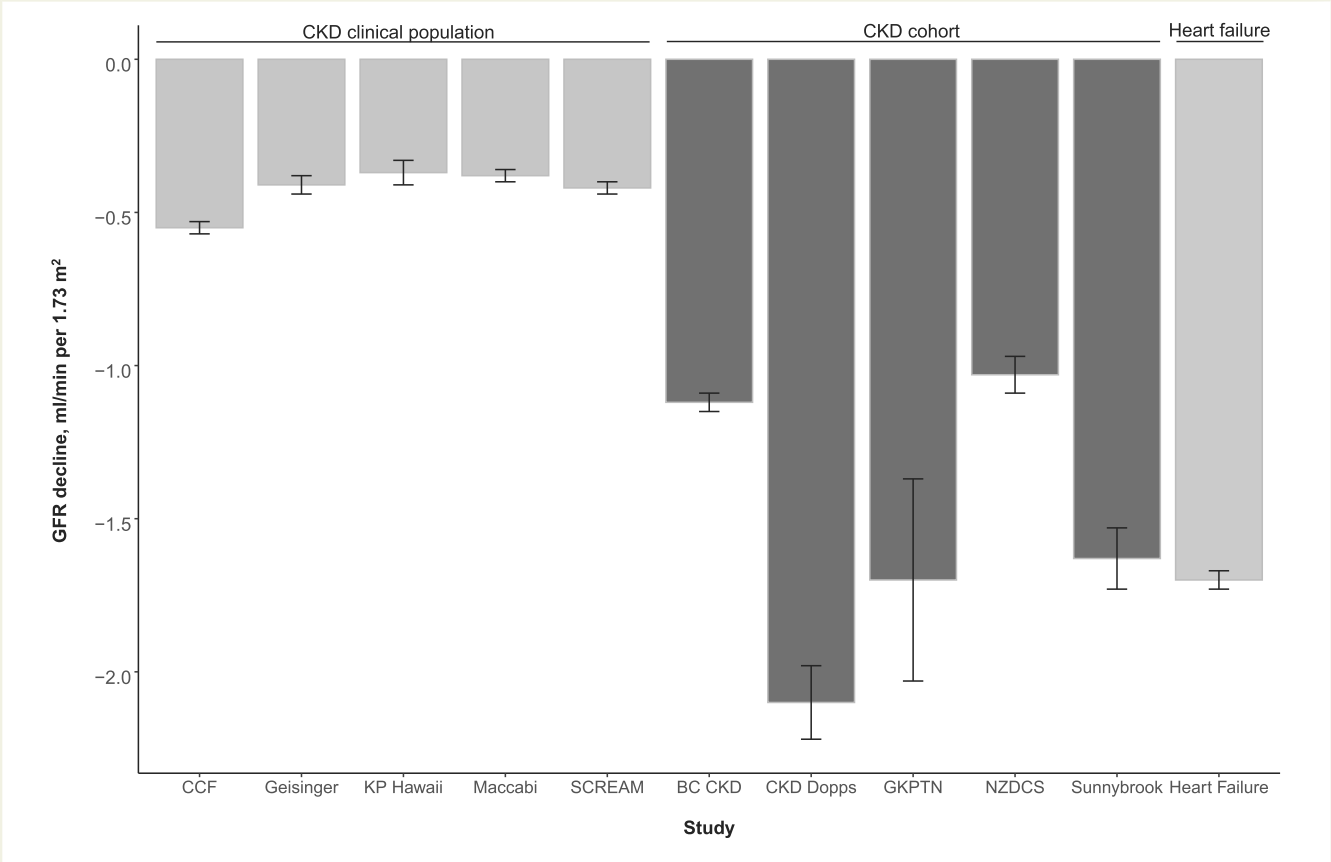


Figure 3 Annualized rates of eGFR decline in primary CKD cohorts compared with heart failure. Comparison of the rate of annualized eGFR decline in clinical populations with CKD (defined by eGFR <60 ml/min per 1.73 m^2, first set of bars),[47] CKD observational studies or registries (mean eGFR <60 ml/min per 1.73 m^2, second set of bars),[47–49] compared with a cohort with heart failure from ambulatory heart failure clinics (mean eGFR of 67 ml/min per 1.73 m^2, last bar).[50] eGFR: estimated glomerular filtration rate; CKD, chronic kidney disease; CCF, Cleveland Clinic Foundation; BC, Biomarkers Consortium; DOPPS, Dialysis Outcomes and Practice Patterns Study; GKPTN, Global Kidney Patients Trials Network; NZDCS, New Zealand Diabetes Cohort Study; SCREAM, Stockholm Creatinine Measurements Project

have common comorbidities such as hypertension, diabetes, or CKD that influence GFR trajectories, independent of the status of their heart failure.

During acute heart failure exacerbations, the excess neurohormonal activity, sodium and water avidity, and fluctuations in cardiac haemodynamics will be present and greater than in stable chronic heart failure. In addition, patients may be taken off their preadmission guideline-directed therapy which would lead to an increase in GFR, while the acute changes in cardiac haemodynamics and increase in central venous pressures that define the acute exacerbation may lead to further fluctuations in GFR. In addition, slow plasma refill during rapid diuresis for the treatment of acute decompensated heart failure could worsen the hypoperfusion to the kidney, stimulate further neurohormonal activation, and lead to declines in eGFR.[56] High doses of loop diuretics can exacerbate tubular dysfunction by leading to distal tubular hypertrophy.

Considerations in the management of acute and chronic heart failure in patients with CKD

Current best practice for management of symptomatic chronic Stage C heart failure is guideline-directed therapy that consists of β-blockers, angiotensin receptor–neprilysin inhibitors (ARNi), angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), sodium–glucose transport protein 2 inhibitors (SGLT2i), and mineralocorticoid receptor antagonists (MRA),[57] with specific recommendations based on heart failure classification by left ventricular ejection fraction (LVEF).[57] Of those, ACEi or ARB, SGLT2i, and MRA have been demonstrated to also slow the rate of CKD progression.

Management of symptomatic chronic heart failure in patients with CKD can be challenging. First, there are contraindications to heart failure therapies for patients depending on the severity of CKD. For example, patients with advanced CKD may be ineligible for advanced heart failure therapies, such as durable mechanical circulatory support devices, including left ventricular assist devices or heart transplantation, or participation in clinical trials. Initiation of SGLT2i is contraindicated for patients with GFR <20 ml/min per 1.73 m^2 due to lack of proven efficacy, even though the KDIGO guidelines assert that once initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 20 ml/min per 1.73 m^2, unless it is not tolerated, or kidney failure replacement therapies are initiated.[16] Second, ACEi or ARB, SGLT2i, and MRA can induce an immediate decline in GFR following therapy initiation. Such declines are not thought to indicate a lack of benefit on longer-term outcomes for CKD progression or heart failure.[58–60]

Real-world evidence suggests that GFR declines following initiation of therapies, leading to reduced dose or medication discontinuation

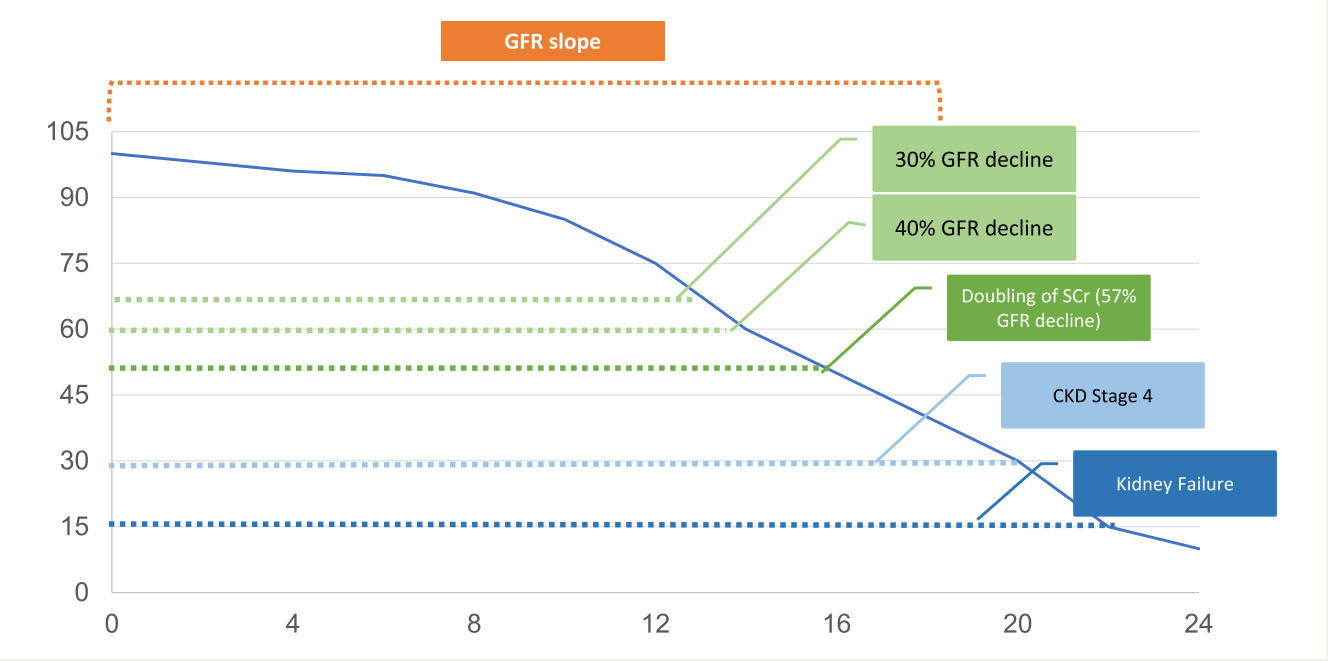


Figure 4 Use of changes in GFR to indicate progression of CKD. Endpoints on change in GFR can be captured using GFR slope or time to a designated GFR decline. The traditional clinical event is treated kidney failure with replacement therapy (KFRT) or GFR <15 ml/min per 1.73 m^2, the GFR threshold defined as kidney failure (applied only in patients with GFR >25 ml/min per 1.73 m^2 at baseline). Endpoints of time to 30% and 40% GFR decline and continuous changes in GFR are now validated as surrogate endpoints. For use in trials, it is recommended to confirm events based on change in GFR at the next visit before designating the change as an event.[69] Also depicted here is the CKD Stage 4 or GFR threshold of 30 ml/min per 1.73 m^2. While not commonly used as an endpoint, CKD Stage 4 is associated with a very high rate of adverse events and an increase in care and is a relevant clinical event

as well as to greater hesitation by cardiologists to initiate medications in other patients with CKD.[61] Collaboration between cardiologists and nephrologists, and other members of the care team, will optimize guideline-directed therapy. Current recommendations from both kidney and heart failure guidelines groups are to perform careful assessment for other causes of GFR decline, assess for renal artery stenosis, and repeat blood tests for eGFR in patients with acute decline in GFR of ~20% or greater.[16,62] In our experience for most patients, contraindication to continuing medication is not found.[63,64]

For management of acute heart failure, there are additional challenges. In these settings, decongestion is an important priority, but there is a decreased response to diuretics due to a diminished capability in CKD to excrete sodium and water. Upward to one-third of patients are likely to experience an acute GFR decline in the setting of acute decompensated heart failure. With concomitant decongestion, there is no evidence for association of acute eGFR decline with adverse outcomes, whereas with persistent congestion, acute decline may signify a worse prognosis.[65] Thus, acute GFR decline can be tolerated in the setting of decongestion but leads to uncertainty in care decisions in many specific cases.[66,67]

Endpoints for chronic kidney disease progression

Over the past two decades, a large body of research has developed and validated endpoints for trials of CKD progression. Discussed below are the key considerations for the use of change in GFR as an outcome with special focus on heart failure, where its use raises specific challenges. These issues and our recommendations for selection of an endpoint considering these factors are outlined in *Table 2*.

Traditional endpoints for chronic kidney disease progression are not adequate to evaluate treatment benefit across the range of chronic kidney disease

The clinical event of kidney failure with replacement therapy occurs only after a prolonged disease course that may extend 10–20 years,[68] a timeframe that is not feasible for trials of early or even moderate stage of CKD (*Figure 4*).

Even using a wider definition of the clinical endpoint of the composite of kidney failure with replacement therapy, untreated kidney failure defined as GFR <15 ml/min per 1.73 m^2 and doubling of serum creatinine (equivalent to a 57% decline in GFR) restricts the study population to those with advanced or rapidly progressive disease (*Table 1* and *Table 3*).[70] Importantly, earlier stages of CKD are associated with high rates of morbidity, mortality, and cost; therefore, it is worth preventing further progression of CKD, even at stages prior to kidney failure. In addition, treatments initiated earlier have a greater impact on the prevention of kidney failure (*Figure 5*).

Even small reductions in the annual rate of GFR decline can translate into substantially longer time before reaching kidney failure. For example, a reduction in GFR decline from 5 to 3 ml/min/1.73 m^2 per year, if applied from a GFR of 60 ml/min/1.73 m^2 rather than 20, can delay dialysis initiation by many more years. Finally, earlier treatments also allow for therapies that can target fibrosis, the final common pathway for progression of kidney damage, regardless of the initiating cause of CKD.

Table 2 Summary of recommendations for the use of GFR decline as endpoints in trials of heart failure populations

Factor	Considerations in the use of GFR slope	Considerations in the use of time to event
Acute effect of an intervention	Total GFR slope over long periods is robust to the presence of an acute effect. Past studies suggest that computation of total slope over 3 years is robust to the presence of acute effect[a62,65] Chronic slope does not incorporate acute effect. May consider assessment of treatment effects post withdrawal of treatment	Very large GFR decline (i.e. 40% or greater) or the clinical endpoint (kidney replacement therapy or GFR <15) is robust to the presence of acute effect
Rate of CKD progression in the heart failure population	Appropriate for use across a range of CKD severity[64] but requires some progression over the course of the study	All time-to-event endpoints are less informative at less severe or slowly progressive CKD. Time-to-event endpoints may be used if populations are enriched for individuals at greater risk of progression, such as those with higher levels of albuminuria
Mortality rate of the heart failure population	Use of mean change in GFR can capture CKD progression as patients are unlikely to reach kidney failure. Incorporate CVD and mortality events into the GFR slope model can overcome bias from informative censoring	All time-to-event endpoints are less informative in populations with a high censoring event rate. Survival models that accommodate competing risks may be considered
Heterogeneity of the heart failure population	Consider methods to analyse changes in GFR that do not require the assumption of linearity. Restricting GFR measurements in study visits	
Changes in body composition	Consider methods to assess GFR that are not impacted by body composition[b]	Consider methods to assess GFR that are not impacted by body composition

[a]This does not indicate that every participant must be followed for 3 years, rather enough participants have follow-up to compute the total slope over this duration.
[b]As described in *Figure 3*, use eGFRcr when eGFRcr and eGFRcys are concordant, and use eGFRcr-cys when eGFRcr and eGFRcys are discordant. Measure GFR or creatinine clearance using 24 h urine collection when a precise level of GFR is needed for clinical decision-making. See *Figure 3*.

Glomerular filtration rate decline as a surrogate endpoint in trials of chronic kidney disease progression

Across many diseases, the use of surrogate endpoints allows for more efficient trials as well as evaluation of treatments earlier in the disease course.[71] For progression of CKD, the key surrogate endpoints are changes in albuminuria and GFR (*Table 3*). Support for the use of surrogate endpoints may come from biological, epidemiological, and trial-level evidence, with the latter providing the most rigorous evaluation of surrogacy. The biological rationale for GFR decline as an endpoint of CKD progression is very strong. Change in GFR over time is the definition for the progression and remission of kidney disease; patients cannot reach kidney failure in the absence of a decline in GFR. Many studies demonstrate very strong epidemiological associations between both baseline GFR and changes in GFR and subsequent development of kidney failure. These studies, together with the extensive collaborative analyses of observational cohorts and randomized trials from our research group, have provided the epidemiological and trial-level evidence to support endpoints based on changes in GFR, defined as 30% and 40% reduction in eGFR and annualized rate of GFR decline (i.e. GFR slope) (*Figures 4* and *Figure 6*).[7–11,19,47,69,72–77]

Many interventions in GFR cause a rapid change in GFR, commonly referred to as acute effects, that differ from the longer-term treatment effect during the subsequent 'chronic phase' (*Figure 7*).[78]

Thus, changes in GFR over the course of a study can be evaluated as the total change from baseline (i.e. total GFR slope or time to GFR decline) or as changes during the chronic phase. Our trial-level analyses demonstrate that across the collection of 66 previously conducted trials, treatment effects on the total GFR slope over 3 years (3-year total slope) predict with high accuracy the treatment effects on the traditional clinical endpoint.[19] The strength of this trial-level association is arguably stronger than widely used surrogate endpoints in other fields.[83–86] The results were consistent across levels of severity of CKD, as defined by GFR, albuminuria, and rate of progression in the control arm, and across causes of CKD.[87]

Challenges in the use of glomerular filtration rate decline in heart failure

Acute effects of an intervention on glomerular filtration rate

Acute effects can be negative (i.e. lower GFR following treatment initiation) or positive (i.e. increase in GFR following treatment initiation). Negative acute effects are most commonly secondary to a decrease in haemodynamic pressures in the glomeruli from the medication. This results in a decrease in the single-nephron GFR only in the treatment arm. Positive acute effects may result from an increase in haemodynamic pressures on the glomerulus, reduction in glomerular inflammation, or a decrease in muscle mass or other non-GFR determinants of creatinine. In contrast, chronic effects are thought to primarily reflect the impact of the treatment on the number of functioning nephrons and therefore may be more reflective of the impact of the treatment on the true progression of CKD.

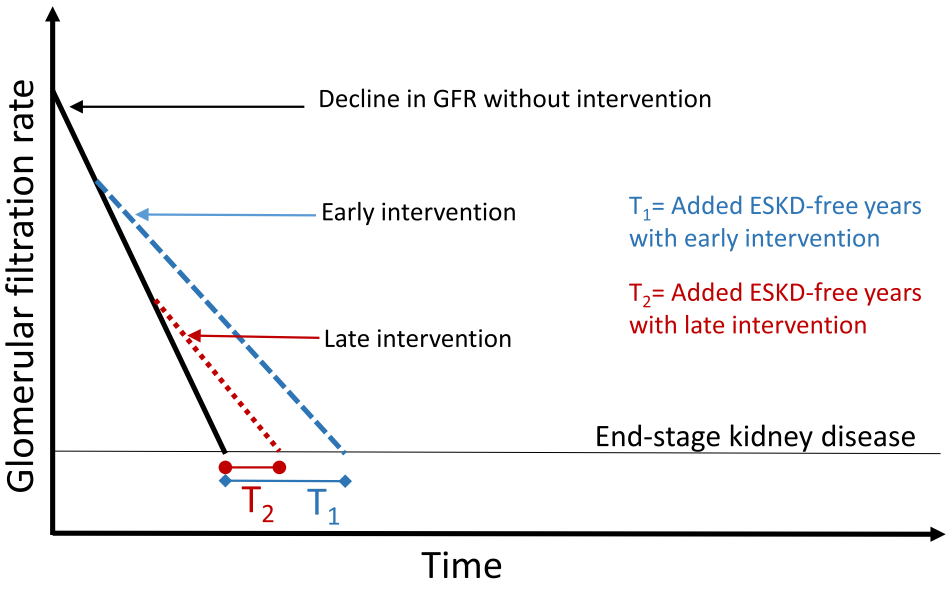


Figure 5 Importance of early treatment to slow progression to kidney failure. Most CKD patients progress to kidney failure over many years, so to obtain sufficient clinical events, most randomized control trials (RCTs) are restricted to patients with rapidly progressive or late-stage disease. However, therapies that are effective in early-stage disease may not be effective in late-stage disease when irreversible damage to the kidney and other organs may have occurred. Reused with permission from Inker LA, Chaudhari J. GFR slope as a surrogate endpoint for CKD progression in clinical trials. Curr Opin Nephrol Hypertens; 2020 Nov;29(6):581–590[18]

For analysis of the mean change in GFR, an acute effect will have a larger impact when the GFR decline is assessed over a short period of time. Evaluation of GFR change over a short duration for an intervention with a large negative acute effect may falsely indicate that an intervention is not beneficial (time point A on *Figure 7A*), whereas if followed for longer durations, the benefit becomes apparent (time point B on *Figure 7A*). Conversely, if the intervention leads to a positive acute effect, assessment of total GFR change over a short duration may overstate the long-term benefit of the treatment. Consistent with this, treatment effects on the total slope computed over 2 years were less strongly associated with treatment effects on the established clinical endpoint than were treatment effects on the 3-year total slope (*Figure 6*).[19]

The chronic effect is thought to capture better the longer-term impact of the therapy on kidney structure and function. Our trial-level analyses showed weaker associations for the chronic slope compared with the 3-year total slope (*Figure 6*). This also likely reflects the impact of the acute effect. As the duration of follow-up increases, the relative contribution of the chronic effect will increase. In practice, patients are often treated for a longer period of time than is the usual duration of a clinical trial; therefore, treatment effects on the chronic change in GFR may be of greater relevance for clinical decision-making by patients and their physicians.

Considerations in heart failure

For most heart failure therapies, acute effects are most likely going to be negative and secondary to neurohormonal activation or changes in pressure that occur in heart failure or its treatment, as described above. The EMPEROR trials demonstrate the impact of negative acute effects and the importance of careful selection of a GFR-based endpoint. As shown in *Figure 7C and D*, and Supplementary data online, *Table S2*, there was a large negative acute effect in both the EMPEROR-Reduced and EMPEROR-Preserved trials.[80,81] Thus, the magnitude of the estimated treatment effect on the total slope was less than for the chronic slope in both studies. In EMPEROR-Reduced, there was a strong treatment benefit on the chronic slope, so even with the short duration of a median follow-up of 16 months, a significant treatment benefit was seen on the total change from baseline and on both time to 40% and 50% decline.[80,88,89] In contrast, the significant effect on the chronic slope in EMPEROR-Preserved was attenuated compared with that of the effect in EMPEROR-Reduced.[81,90] As such, there was a weaker treatment effect on the total slope and a non-significant treatment effect on the time to 40% and 50% decline.[81] A subsequent analysis computed the change in GFR from baseline to post-treatment measurements (i.e. 4 weeks after treatment discontinuation, see *Figure 7E*). This approach better approximated treatment effects on the chronic slope, supporting this strategy for removing the impact of the acute negative effects on the evaluation of long-term benefit of the treatment.[91]

Rate of chronic kidney disease progression in the heart failure population

For populations with high levels of GFR or who have slowly progressive disease, all GFR-based time-to-events will occur rarely during the typical duration of a clinical trial, leading to insufficient power to evaluate the benefit of an intervention over a reasonable time frame (*Figure 4*). As shown in *Figure 8*, left panel, only the participants indicated in the red lines with rapid progression would be counted as events. If a

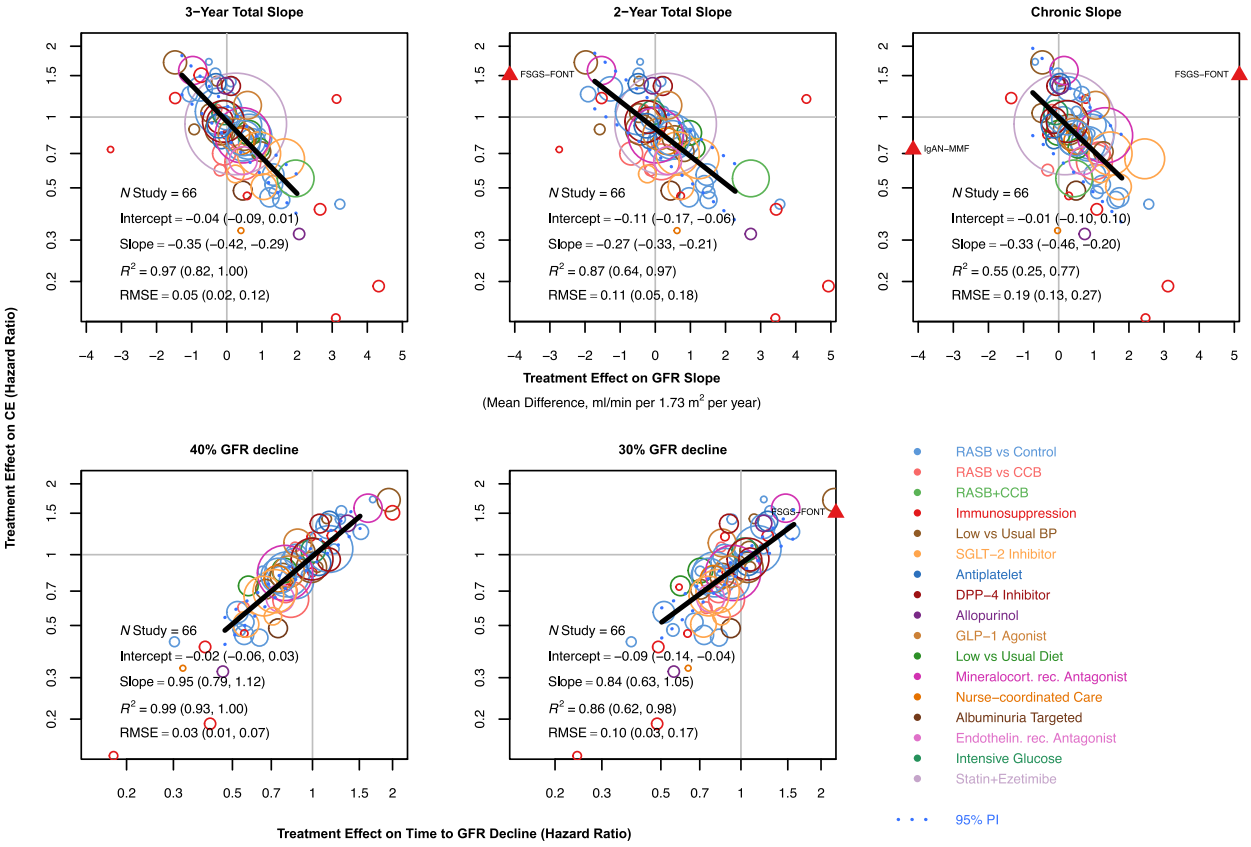
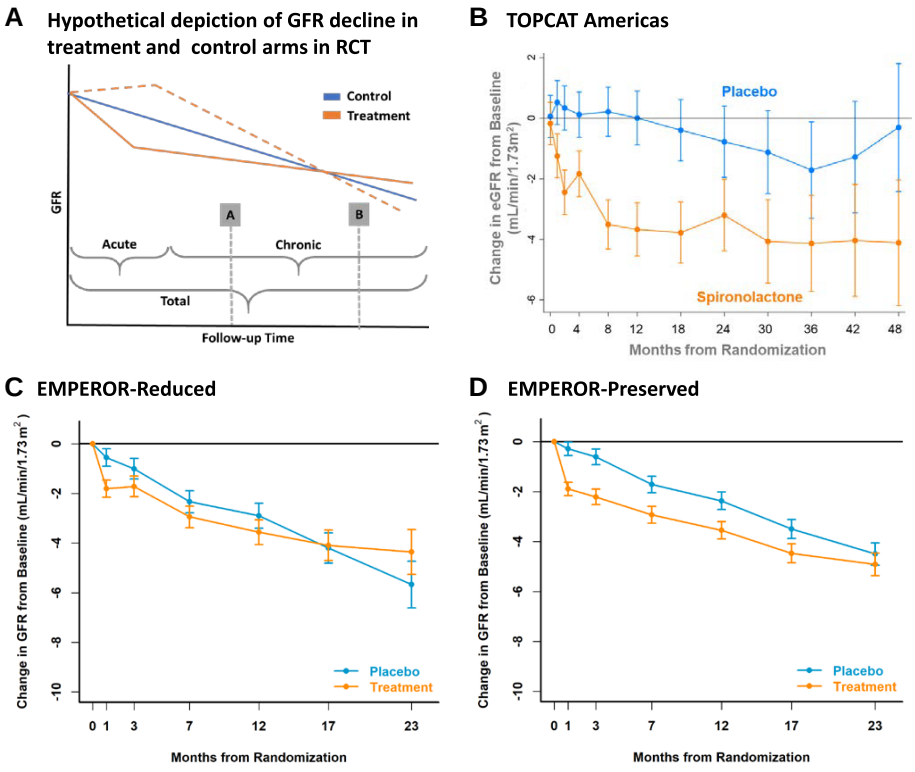


Figure 6 Trial-level analyses for the association between treatment effects on GFR slope or time to thresholds of GFR decline and treatment effects on the clinical endpoint. Shown in each plot is the relationship between estimated treatment effects on the clinical endpoint, defined as kidney failure with replacement therapy (KFRT), GFR <15 ml/min per 1.73 m^2, or doubling of serum creatinine, equivalent to 57% decline in GFR, and on surrogate endpoints of GFR slope or time to GFR decline. Endpoints that include time to GFR decline also include KFRT, GFR <15 ml/min per 1.73 m^2, and the GFR decline was confirmed at two consecutive visits. The three panels in the top row have been published previously.[19] Treatment effects on GFR slope are expressed as mean differences for the treatment minus control groups and are expressed in ml/min per 1.73 m^2/year. Positive values reflect treatment benefit. Treatment effects on the clinical endpoint and on time to 30% or 40% GFR decline are expressed as hazard ratios. Hazard ratios <1 indicate treatment benefit. Circles represent separate studies with the size of the circle proportional to the number of events (kidney failure with replacement therapy, GFR <15 ml/min per 1.73 m^2, or doubling of serum creatinine). The colours of circles indicate intervention types. The black line is the line of regression through the studies. The blue dashed lines are the 95% pointwise Bayesian confidence band. The triangles indicate studies where the estimated treatment effects are beyond the margins. The meta-regression supports validity of GFR slope as a surrogate endpoint if (i) the slope of the meta-regression line has a large magnitude with Bayesian credible intervals that do not cross 0; (ii) the intercept is close to 0 and with a Bayesian credible interval that does not cross 0, implying absence of a substantial average effect on the clinical endpoint when the treatment does not affect GFR slope; (iii) the R^2 of the meta-regression is large, indicating strong associations ($R^2 > 0.72$) or modest association ($R^2 = 0.49$–0.72), so that treatment effects on GFR slope account for most of the variation in treatment effects on the clinical endpoint. The surrogate endpoints shown in the panels in the left and middle columns include change from baseline and thus include both effects on the acute and chronic slope. The bottom two panels were initially published using a smaller set of studies and less rigorous methods but were updated using the studies and methods used in the top panels.[75] RASB, renin–angiotensin system blockers; CCB, calcium channel blocker; BP, blood pressure; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1, RMSE, root mean square error; SGLT2, sodium–glucose cotransporter

study only included participants with moderate to slow progression as indicated in the orange or green lines, a time-to-event analysis would not have captured benefit. Assessment of mean changes in GFR evaluates the average treatment effect across all participants in a trial.

Considerations in heart failure

In prior heart failure trials, the mean initial GFR was generally 60–70 ml/min per 1.73 m^2. Thus, clinical endpoints will not occur in a large enough number of patients to provide adequate statistical power with a feasible sample size. For example, in the TOPCAT trial, the mean rate of GFR change in the control arm was negligible (*Figure 7* and Supplementary data online, *Table S2*).[79] In this study, all of the observed change in GFR was related to the acute effect of the medication and cannot inform as to the impact of the drug on CKD progression over the longer term. Future studies may decide to enrich for individuals at risk for progression as has been done in a recent trial of patients with heart failure.[92]



E Summary

	TOPCAT-Americas N=1,767	EMPEROR-Reduced N=3,730	EMPEROR-Preserved N=5,988
Median follow-up, months	40	16	26
Baseline eGFR (SD) (exclusion criteria)	64±22 (<30 excluded)	62.0±22 (<20 excluded)	60.6±20 (<20 excluded)
UACR >30mg/g, n (%)	20.0 (7.0, 88.4)	4,121 / 9,673 (42.6)	
Chronic GFR slope in the control arm	-0.6 (-1.7 to 0.5)	-2.28 (-2.73 to -1.83)	-2.65 (-2.87 to -2.43)
Treatment effect on chronic slope, mL/min/1.73m²/year	0.1 (-1.4 to 1.7)	1.73 (1.10-2.37)	1.36 (1.06-1.66)
Treatment effect on total slope, mL/min/1.73m²/year	-2.5 (-3.4 to -1.6)	0.87 (0.25-1.50)	0.43 (0.13-0.73)
Annualized change in eGFR from baseline to the off-treatment period		1.77 (0 .80 to 2.74)	0.94 (0.60 to 1.27)
Number of deaths	387	515	849
Treatment effect on clinical kidney endpoint, *N events*	1.26 (0.84, 1.90), *93*	0.52 (0.29-0.92), *51*	0.78 (0.54-1.13), *112*
Treatment effect on time to 40% GFR decline , *N events*	1.95 (1.43, 2.65), *177*	0.51 (0.33– 0.79), *88*	0.95 (0.73-1.24), 220

Figure 7 Acute changes in GFR following treatment initiation. Some therapeutic interventions can have an acute, or immediate, treatment effect on GFR that is unrelated to potential long-term kidney protective effects. The four panels show hypothetical changes (*A*) and examples from trials in heart failure (*B*–*D*). (*A*) Hypothetical depiction of GFR decline in treatment and control arms in a randomized control trial. Time points A and B indicate two possible stopping times for a clinical trial. Given the large acute effect in this hypothetical trial, the use of total slope from baseline to A would result in false negative for benefit. Computation of GFR slope to time B would result in correct assessment of treatment benefit. (*B*) eGFR decline in TOPCAT-Americas ($N = 1767$) evaluating steroidal MRA in patients with reduced ejection fraction.[79] (*C*) eGFR decline in EMPEROR-Reduced in patients with reduced ejection fraction, a trial evaluating SGLT2i ($N = 3730$).[80] (*D*) EMPEROR-Preserved a trial evaluating SGLT2i in patients with preserved ejection fraction ($N = 5988$).[81] The mean change in eGFR shown in *C* and *D* was drawn using least square regression during the on-treatment phase. (*E*) Summary of treatment baseline kidney parameters and treatment effects on CKD progression among TOPCAT, EMPEROR-Reduced, and EMPEROR-Preserved. For both EMPEROR-Reduced and EMPEROR-Preserved, assessment of treatment effect on the change in eGFR from baseline to eGFR ascertained 4 weeks after treatment discontinuation better approximated treatment effects on the chronic slope. Kidney clinical event defined as >50% decline in eGFR, kidney failure (dialysis, transplant or sustained eGFR <15 ml/min/1.73 m^2 for patients with baseline eGFR >30 ml/min/1.73 m^2 or sustained eGFR <10 ml/min/1.73 m^2 for patients with baseline eGFR <30 ml/min/1.73 m^2) or death due to kidney failure. Treatment on 40% decline includes sustained decrease in eGFR by 40% or greater, sustained decrease in GFR to <10–15 ml/min/1.73m^2, and dialysis or renal transplantation. Treatment effect on eGFR slope computed as the mean difference between treatment arms. For other details related to computation of the GFR change, see Supplementary data online, *Table S2*. Panel *B* reused with permission from Vaduganathan M, Ferreira JP, Rossignol P, Neuen BL, Claggett BL, Pfeffer MA. Effects of steroidal mineralocorticoid receptor antagonists on acute and chronic estimated glomerular filtration rate slopes in patients with chronic heart failure. Eur J Heart Fail; 2022 Sep;24(9):1586–1590[82]

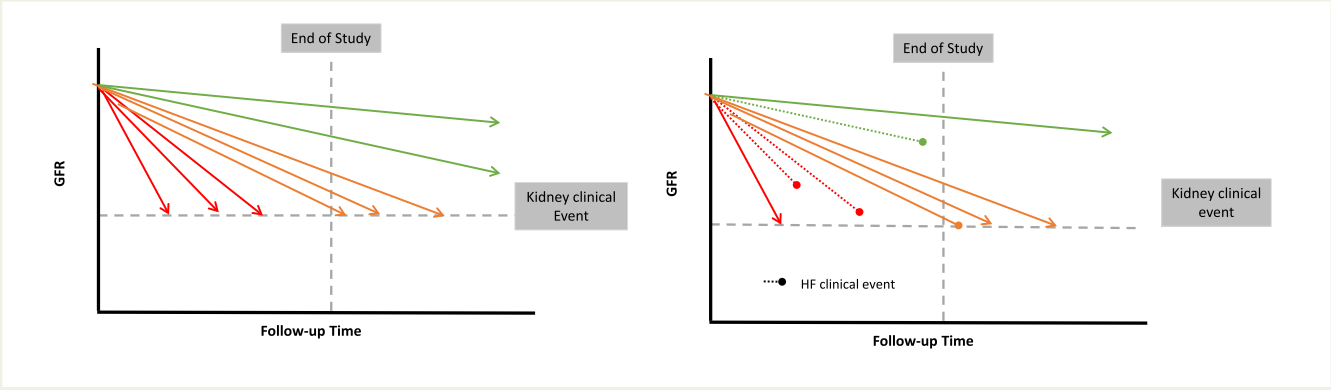


Figure 8 Influence of rapid progressors on time to event analyses for CKD progression. Left panel: rapid progressors reach events and influence results of time-to-event analyses. However, the broader population may include people who still have progressive CKD and require treatment. Treatment effects on GFR slope allow estimation of clinical benefit in the overall population. Right panel: in heart failure, there is an additional concern of a high rate of censoring events for heart failure or mortality. GFR models for GFR decline that accommodate these informative censoring events can overcome this challenge

Mortality rate in heart failure populations

A key challenge in the use of change in GFR as an endpoint are events that preclude assessment of GFR subsequent to these events. In CKD populations, these events are typically kidney failure or mortality. If rates of these events are high, the missing GFR values might not be missing at random, potentially biasing estimates of mean GFR change. Any method to analyse change in GFR should consider methods to address such informative censoring. Failure to do so can lead to overestimation of the treatment effects on GFR slope.[93,94]

Considerations in heart failure

In heart failure populations, the estimated 5-year mortality rates range from 40% to 75%,[95–97] with death often occurring prior to reaching kidney failure. Thus, evaluation of treatments for heart failure only on the kidney failure outcome could miss the impact of these treatments on benefit on earlier CKD stages (*Figure 8*, right panel). The use of endpoints based on time to lesser GFR decline or mean change in GFR will allow assessment of CKD progression prior to death. Models that include informative censoring in analyses of mean change in GFR will diminish the bias from missing GFR measurements.

Heterogeneity of the heart failure population

In many populations, despite individual variability in GFR, when assessed as the average over the group, GFR trajectories have been approximately linear over the typical duration of the chronic phase of past clinical trials. Thus, the primary method to analyse the mean GFR change has used a two-slope model that assumes the mean GFR change is linear following the acute effect.[93,98] This approach increases statistical power by incorporating all available GFR measurements and considers informative censoring events in populations with high rates of dialysis or death. An alternative method that does not require linearity to be assumed is a mixed model with repeated measures (MMRM) but requires a set planned follow-up time for all patients.

Considerations in heart failure

Acute heart failure exacerbations, hospitalizations, and changes in concomitant therapies that influence GFR are more common even for stable patients with heart failure enrolled in trials. These factors increase the possibility for non-linearity of the chronic change in GFR.[43,99–101] Thus, using models that do not require the assumption of linearity may be required. Restricting GFR measurements in study visits (i.e. not including GFR ascertained in the acute settings) will also help to minimize the impact of these intercurrent events.

Changes in body composition

Despite limitations of serum creatinine at the patient level as described above,[24,102,103] surrogate endpoints based on eGFRcr decline have performed well in past trials of CKD progression (*Figure 6*). Theoretically, the performance will not be as strong in interventions that affect creatinine, such as dietary interventions or interventions causing profound weight loss. However, while treatments of dietary protein reduction may lead to immediate (acute) increases in GFR, the longer-term (chronic) GFR slope provides similar information as other interventions. Several novel medication classes, such as nutrient-stimulated hormone-based therapeutics including GLP-1RA, modify body composition which could in turn impact serum creatinine and eGFR based on creatinine. Comparison of treatment effects on eGFRcr and eGFRcys in a study of GLP-1RA did not show any difference.[104]

Considerations in heart failure

In those with progressive heart failure, increase in frailty and sarcopenia are common. If a therapy for heart failure that is being evaluated is hypothesized to affect body composition, it would be reasonable to consider alternative methods to evaluate GFR (*Figure 3*).[16]

Integrating glomerular filtration rate decline into the trial design of studies of heart failure

Endpoints based on GFR decline provide opportunities to concurrently evaluate treatment benefit on CKD progression and heart failure. These endpoints have been accepted by regulatory agencies including qualification of GFR slope as a surrogate endpoint by the European Medicines Agency and are being used in numerous trials, including as an endpoint to support full approval.[7,9] Nevertheless, changes in

Table 3 CKD endpoints and considerations for their use

Endpoint	Definition	Kidney domain	
		Marker	Considerations for applications in RCT design
Clinical endpoint	Characteristic or variable that reflects how a patient feels or functions, or how long a patient survives	Kidney failure (GFR <15 ml/min per 1.73 m^2 or the initiation of dialysis or transplantation. Doubling of serum creatinine (equivalent to a 57% decline in eGFR) is commonly incorporated and considered part of the established endpoint[a59]	Limited to advanced disease or rapidly progressive populations
Surrogate endpoint	Biomarkers are intended to substitute for a clinical endpoint benefit, harm, or lack thereof. Surrogates can be validated, reasonably likely[b]	Change in urine albumin[c]	Treatment effect in the range of ~30% is required to have high confidence for a treatment effect in the clinical endpoint in a future trial
Intermediate endpoint	Characteristic intermediate on the causal pathway between an intervention and the clinical endpoint. Stronger biological connections than a surrogate	Time to 30% or 40% threshold of GFR decline[d48,49]	For 30%, any acute effect may lead to false conclusions[e] For 40%, large acute effect may lead to false conclusions and reduced utility at high GFR
		Total GFR slope[f]	A 2–3-year follow-up period may be required to estimate slopes in the presence of acute effects For chronic and total slope, estimated treatment effects would be 0.5–1.0 ml/min/1.73 m^2 per year[50]
		Chronic GFR slope	Treatment effect defined from an initial on-treatment measurement to end-of-treatment

[a]Kidney failure is often defined as a composite endpoint. See International Society of Nephrology consensus paper for details.[59]
[b]Surrogate endpoint can be classified by the level of clinical validation as either a validated, reasonably likely, or candidate based on the level of scientific evidence.
[c]Urine albumin or total protein.
[d]Requires confirmatory measurement. In analyses evaluating these endpoints, sustained decline was defined as change in GFR observed at the next visit if not the last visit.[66].
[e]Acute effect is the immediate effect of an intervention which differs from the longer-term slope. This can be related to changes in the true GFR or in the endogenous filtration marker used to estimate the GFR.
[f]Treatment effect on total slope defined as total slope from randomization to end-of-treatment.

GFR, whether measured as time to event or as mean change, are not suitable for all studies. In the design of any trial, the goal in selection of an endpoint is to maximize power, minimize the risk of false-positive conclusions, and provide meaningful information as to the impact of therapy on disease progression. The relative value of one endpoint over another will depend upon the specific population to be enrolled in the trial, the intervention to be evaluated, and other study design parameters.

For selection of the optimal endpoint for evaluation of CKD progression, the essential first question is whether the study population is expected to experience sufficient CKD progression over the study duration to detect an improvement in the rate of progression. If sufficient progression is expected, the second question is how to best capture the difference in progression between treatment arms. The key parameters to consider in addressing this question are the presence and magnitude of the expected acute effect, expected mortality rate, frequency and nature of expected intercurrent events, and the presence of non-GFR determinants of serum creatinine, both at study initiation and any changes secondary to the intervention (*Table 2*).

For studies aiming to enhance power through GFR slope, the 3-year total slope remains robust despite acute effects. Notably, this does not require that all participants be followed for the entire 3-year period, but rather that enough participants are monitored to calculate the total slope over this duration.

Conclusions and next steps

Improved understanding of optimal ways to interpret GFR will improve the care of heart failure patients.

In trials, incorporating the assessment of benefit on both heart failure and CKD will increase the efficiency of understanding the broad impact of new therapies. Changes in GFR are now validated surrogate endpoints and can be observed earlier in the course of disease compared with traditional clinical endpoints, necessary for study populations with heart failure. The use of the endpoints based on GFR change could be highly informative, but wise use is required to avoid false conclusions. Collaboration with statisticians and

investigators who are experienced in evaluating GFR changes in trials is essential for success.

For the care of individual patients, wise use focuses on the recognition that there are multiple causes of GFR decline, some of which are expected due to medication. Collaboration with nephrologists is crucial to differentiate between acute reductions in GFR that are expected due to medications and those that are more concerning, ultimately leading to more effective use of guideline-directed therapy. Broad knowledge is vital to facilitate therapeutic acceptance; thus, ideally general and heart failure cardiologists, endocrinologists, primary care doctors, and patients are also educated as to the acceptable limits of GFR decline. Pharmacists play a key role and can serve as valuable resources for educating patients about these medications.[16] Finally, collaboration with nephrologists and widespread education on how to incorporate confirmatory tests for GFR, including cystatin-based GFR estimates or measured GFR for selected patients, will also enable optimal care.[16,24]

Future investigations are underway to address several of the questions and challenges raised here. Novel methods to integrate information across types of endpoints such as hierarchical composite endpoints or other methods have been proposed for CKD and might be a strategy to incorporate both heart failure events and CKD progression in future studies.[105] Ultimately, the incorporation of markers of acute or chronic kidney damage, such as albuminuria, may also help to better elucidate the impact of the intervention on kidney structure and function.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

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Data Availability

No data were generated or analysed for this manuscript.

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