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Citation for published version (APA):
Patel, R. B., Ter Maaten, J. M., Ferreira, J. P., McCausland, F. R., Shah, S. J., Rossignol, P., Solomon, S. D., Vaduganathan, M., Packer, M., Thompson, A., Stockbridge, N., & Zannad, F. (2021). Challenges of Cardio-Kidney Composite Outcomes in Large-Scale Clinical Trials. *Circulation*, *143*(9), 949-958. https://doi.org/10.1161/CIRCULATIONAHA.120.049514

Circulation

Challenges of Cardio-Kidney Composite Outcomes in Large-Scale Clinical Trials

ABSTRACT: Patients with chronic cardiovascular or metabolic diseases, including diabetes, hypertension, obesity, and heart failure, often have comorbid kidney disease. Long-term outcomes are worse in the setting of both cardiac and kidney disease compared with either disease in isolation. In addition, the clinical presentations of certain acute cardiovascular events (such as heart failure) and worsening kidney function overlap and may be challenging to distinguish. Recently, certain novel treatments have demonstrated beneficial effects on both cardiac and kidney outcomes. Sodium-glucose cotransporter-2 inhibitors have exhibited concordant risk reduction and clinically important benefits in chronic kidney disease with and without diabetes, diabetes and established cardiovascular disease or multiple atherosclerotic vascular disease risk factors, and heart failure with reduced ejection fraction with and without diabetes. Primary trial results have revealed that sacubitril-valsartan therapy improves cardiovascular outcomes in patients with chronic heart failure with reduced ejection fraction and post hoc analyses suggest favorable kidney effects. A concordant pattern of kidney benefit with sacubitril-valsartan has also been observed in chronic heart failure with preserved ejection fraction. Given the complex interplay between cardiac and kidney disease and the possibility that treatments may show concordant cardio-kidney benefits, there has been recent interest in formally acknowledging, defining, and using composite cardio-kidney outcomes in future cardiovascular trials. This review describes potential challenges in use of such outcomes that should be considered and addressed before their incorporation into such trials.

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Over the past 3 decades, composite outcomes have been frequently incorporated into the study designs of cardiovascular clinical trials. In the current era, composite end points are commonly used to bolster the number of captured events and provide a broader assessment of efficacy or safety of a therapy. Years ago, composite outcomes were used to evaluate therapies in the setting of acute myocardial infarction (MI).[1,2] To accelerate the study of potential therapies for acute MI and also to account for multiple types of events across a similar mechanistic pathway (eg, nonfatal MI and stroke), a combination of outcomes was proposed and ultimately incorporated into cardiovascular clinical trials. Since then, the global landscape of cardiovascular disease has shifted from predominantly atherosclerotic disease toward several growing cardiovascular and metabolic epidemics, including heart failure (HF), obesity, and diabetes. It has become recognized that a few select cardiovascular therapies possess kidney as well as cardiovascular benefits. However, traditional cardiovascular composite outcomes do not capture this full scope of clinical benefit. To date, kidney outcomes have infrequently been considered as components of primary composite outcomes in cardiovascular clinical trials for several reasons, most importantly because of the analytic challenges that arise with their use in composite outcomes. Despite this, there has been interest in the use of a composite of cardiovascular and kidney events in future large-scale clinical trials.[3] This review aims to describe potential challenges with the use of cardio-kidney composite outcomes that should be considered and addressed before their incorporation into such trials.

TRADITIONAL COMPOSITE OUTCOMES IN CARDIOVASCULAR CLINICAL TRIALS

Traditionally, composite outcomes in cardiovascular clinical trials have been focused narrowly on cardiovascular events, regardless of the trial population. The composite outcome should capture clinically meaningful outcome events while increasing the power of the study to assess the effect of a treatment. Thus, the composite outcome should be sensible and tailored to the treatment being studied. For example, the most commonly used combined cardiovascular outcome in trials of drugs that affect atherosclerosis or thrombosis is termed major adverse cardiac events and usually includes nonfatal stroke, nonfatal MI, and cardiovascular death. Depending on the study population, the composite outcome of major adverse cardiac events is typically tailored to enrich for mechanistically related events. For example, stent thrombosis, hospitalization for unstable angina, and revascularization have occasionally been added to the major adverse cardiac events outcome in trial populations of ischemic heart disease.[4] In trials where the treatment is thought to alter physiologic pathways related to mechanical or electric failure of the heart (eg, HF trials), the most commonly used end point is a composite outcome of the first HF hospitalization or cardiovascular death. To capture the treatment effect on the total burden of HF hospitalizations, recurrent HF events have been recently incorporated in HF with preserved ejection fraction trials.[5] Whereas traditional composite outcomes may aim to be mechanistically related, they may be more heterogeneous if the expected effect of therapy may influence a broad variety of cardiovascular outcomes.

RISE OF CARDIO-KIDNEY COMPOSITE OUTCOMES

Several intersecting lines of evidence have increased the scientific interest in cardio-kidney composite outcomes (Figure 1). First, the coexistence of both disease states is relatively common. Patients with chronic kidney disease (CKD) often have other cardiovascular conditions, such as HF, hypertension, and diabetes.[6–10] Furthermore, >50% of deaths in CKD are cardiovascular in nature and the coexistence of cardiovascular disease and CKD is associated with worse prognosis. For instance, in chronic HF, kidney disease is a frequent
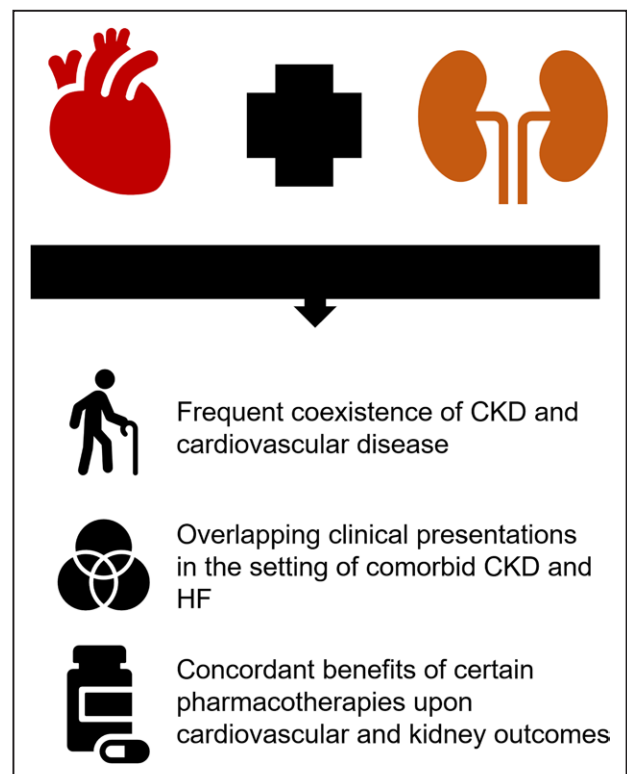
Figure 1. Rationale for recent scientific interest in composite cardio-kidney outcomes.
CKD indicates chronic kidney disease; and HF, heart failure.

comorbidity, and the occurrence of worsening kidney function may be associated with an increase in risk of adverse long-term clinical outcomes.[11] Furthermore, certain cardiovascular and kidney events have overlapping clinical presentations, which creates challenges in discriminating events in the adjudication process. For example, in a patient with stage 4 CKD who presents with progressive dyspnea, evidence of pulmonary edema, and rise in serum creatinine, it may be difficult to differentiate a hospitalization for volume overload in the setting of kidney disease from a traditional HF hospitalization event.[12]

Recently, certain pharmacotherapies have shown concordant benefit within both organ systems. For example, in the CREDENCE trial (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy), treatment with the sodium-glucose cotransporter-2 inhibitor canagliflozin reduced both major adverse cardiac and kidney events compared with placebo among patients with type 2 diabetes and albuminuric CKD.[13] In EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), empagliflozin reduced cardiac events in patients with diabetes and established cardiovascular disease, and post hoc analyses suggested benefits in reducing kidney events.[14,15] In the primary results of the PARADIGM-HF trial (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure), sacubitril-valsartan demonstrated beneficial effects on cardiovascular outcomes in patients with HF with reduced ejection fraction, and, in post hoc analyses, sacubitril-valsartan led to a slower rate of decline in estimated glomerular filtration rate (eGFR) as compared with enalapril.[16,17] Similarly, in PARAGON-HF (Prospective Comparison of ARNI With ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction), the incidence of a kidney composite outcome was lower in the sacubitril-valsartan as compared with the valsartan arm.[5,18] In aggregate, because of the frequent coexistence between these cardiac and kidney disease states, the overlapping clinical presentations of cardiac and kidney events, and the recently demonstrated effect of certain select medical therapies on disease progression within both organ systems, some have proposed primary cardio-kidney composite outcomes in future trials of cardiovascular therapies.

Features of a Reasonable Composite Outcome

A composite outcome comprises 2 or more distinct component end points (Table 1).[19] The individual component outcomes should be clinically relevant and, ideally, of clinical importance to patients. This is specifically important in the case of kidney component outcomes,

Table 1. Properties of a Reasonable Composite Outcome

Feature*
Comprising 2 or more distinct, component outcomes
Used in cases when an individual outcome lacks statistical power
Individual component outcomes are relatively similar in their clinical importance to patients
Components of a composite should be biologically and mechanistically related
There are consistent relative risk reductions across individual outcomes

*Characteristics do not need to be universally true for all composite outcomes, and several examples of cardiovascular composite outcomes in clinical trials do not meet any of the listed characteristics.

as both clinical and laboratory-based kidney outcomes are frequently used. In the case of cardio-kidney outcomes, the onset of end-stage kidney disease (itself a composite, often defined as receipt of chronic dialysis, transplantation, or a sustained eGFR <15 mL/min/1.73 m^2) serves as a watershed event, and thus could be considered as a component of a cardio-kidney composite outcome. Analyses of observational studies, randomized controlled trials, and simulation-based data have supported the use of a marked and sustained decline in eGFR (such as a confirmed ≥40% decline in eGFR) as a surrogate end point in trials of CKD.[20,21] Hence, such events have often been included as a component of a kidney composite end point. There are several other biomarker-based kidney outcomes that have been used in previous clinical trials, which have been summarized in a recent report from the National Kidney Foundation, Food and Drug Administration, and European Medicines Agency.[22] A proposed hierarchy of such kidney outcomes has also been outlined,[22–24] which may be particularly useful to determine specific biomarker-based outcomes that have been accepted and validated as surrogate end points for use in future trials using cardio-kidney composite outcomes.

HISTORY OF CARDIO-KIDNEY COMPOSITE OUTCOMES: A MIXED EXPERIENCE

Cardio-kidney composite outcomes have been used previously in a small number of outcome trials in various populations with mixed results. The trials that have previously used such composites serve as important lessons for the future use of cardio-kidney composite outcomes across specific trial populations.

Diabetic and Nondiabetic CKD

Given the prevalence of cardiovascular disease in patients with CKD, trials in patients with CKD have traditionally been most likely to use composite cardio-kidney outcomes (Table 2). ALTITUDE (Aliskiren Trial in Type 2

Table 2. Cardiovascular Trials Incorporating Primary Cardio-Kidney Composite Outcomes or Coprimary Cardio-Kidney Outcomes

Trial	Study population	Intervention	N	Type of composite outcome	Primary composite outcome	Primary results
Chronic kidney disease						
ALTITUDE[25]	Type 2 diabetes and evidence of albuminuria or cardiovascular disease	Aliskiren 300 mg daily versus placebo	8561	Efficacy	Death from cardiovascular causes or cardiac arrest, nonfatal myocardial infarction, nonfatal stroke, heart failure hospitalization, ESKD, death secondary to kidney failure, need for RRT, or sustained doubling of serum creatinine above normal	Aliskiren did not reduce the primary composite compared with placebo (HR, 1.08 [95% CI, 0.98–1.20]; P=0.12)
CREDENCE[13]	Type 2 diabetes and CKD (eGFR 30 to 90 mL/min/1.73 m² and UACR >300 mg/g)	Canagliflozin 100 mg daily versus placebo	4401	Efficacy	ESKD (dialysis, kidney transplant, eGFR <15 mL/min/1.73 m²), sustained doubling of serum creatinine, or death from renal or cardiovascular disease	Canagliflozin reduced primary composite compared with placebo (HR, 0.70 [95% CI, 0.59–0.82]; P=0.00001)
EMPA-KIDNEY	CKD (eGFR 20 to <45 mL/min/1.73 m² or ≥45 to <90 mL/min/1.73 m² with UACR ≥200 mg/g)	Empagliflozin versus placebo	6000	Efficacy	Kidney disease progression (ESKD, sustained eGFR <10 mL/min/1.73 m², renal death, or sustained decline of eGFR ≥40% from baseline) or cardiovascular death	Ongoing
DAPA-CKD[26]	eGFR 25 to 75 mL/min/1.73 m², UACR 200 to 5000 mg/g, and maximally tolerated ACEi or ARB	Dapagliflozin versus placebo	4304	Efficacy	Kidney disease progression (≥50% sustained decline in eGFR or reaching ESKD), cardiovascular death or renal death	Dapagliflozin reduced primary composite compared with placebo (HR, 0.61 [95% CI, 0.51–0.72]; P<0.001)
Acute heart failure						
CARRESS-HF[27]	Acute heart failure with worsened kidney function and evidence of persistent congestion	Ultrafiltration versus stepped pharmacologic therapy	188	Efficacy + safety	Change in serum creatinine and change in weight (bivariate response)	Ultrafiltration was inferior to pharmacologic therapy in bivariate outcome because of increase in creatinine in ultrafiltration group (P=0.003)
DOSE-AHF[28]	Acute symptomatic heart failure	Low-dose versus high-dose intravenous diuretic and intravenous bolus or continuous intravenous infusion diuretic	308	Efficacy + safety	Coprimary outcomes of global assessment of symptoms and change in serum creatinine from baseline	Low-dose versus high-dose diuretic: no difference in coprimary outcomes; bolus versus continuous: no difference in coprimary outcomes
ROSE-AHF[29]	Acute heart failure with kidney dysfunction (eGFR 15 to 60 mL/min/1.73 m²)	Nesiritide or low-dose dopamine versus placebo	360	Efficacy + safety	Coprimary outcomes: 72-hour cumulative urine volume and change in cystatin C at 72 hours	Low-dose dopamine or nesiritide did not have an effect on coprimary outcomes compared with placebo
PROTECT[30]	Acute heart failure with dyspnea, CrCl 20 to 80 mL/min, BNP >500 pg/mL or NT-proBNP >2000 pg/mL, IV loop diuretic	Intravenous rolofylline	2033	Efficacy + safety	Evidence of improvement in dyspnea, death, or heart failure admission at 7 days, worsening symptoms or signs of heart failure by day 7, or worsening kidney function (increase of serum creatinine of >0.3 mg/dL or initiation of hemodialysis at day 7)	Rolofylline did not improve primary outcome compared with placebo (OR, 0.92 [95% CI, 0.78–1.09]; P=0.35)

ACEi indicates angiotensin-converting enzyme inhibitor; ALTITUDE, Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints (Core and Extension Phases); ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CARRESS, Effectiveness of Ultrafiltration in Treating People With Acute Decompensated Heart Failure and Cardiorenal Syndrome; CKD, chronic kidney disease; CrCl, creatinine clearance; CREDENCE, Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy; DAPA-CKD, A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease; DOSE-AHF, Determining Optimal Dose and Duration of Diuretic Treatment in People With Acute Heart Failure; eGFR, estimated glomerular filtration rate; EMPA-KIDNEY, The Study of Heart and Kidney Protection With Empagliflozin; ESKD, end-stage kidney disease; NT-proBNP, N-terminal pro–B-type natriuretic peptide; OR, odds ratio; PROTECT, Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function; ROSE, Renal Optimization Strategies Evaluation in Acute Heart Failure and Reliable Evaluation of Dyspnea in the Heart Failure Network; RRT, renal replacement therapy; and UACR, urine albumin–to–creatinine ratio.

Diabetes Using Cardiovascular and Renal Disease Endpoints [Core and Extension Phases]) assessed the effect of aliskiren, a direct renin inhibitor, in patients with type 2 diabetes and CKD, cardiovascular disease, or both.[25] This trial used a combined cardio-kidney composite, defined as a composite of the time to cardiovascular death or a first occurrence of cardiac arrest with resuscitation, nonfatal MI, nonfatal stroke, unplanned hospitalization for HF, end-stage kidney disease, death attributable to kidney failure, the need for renal replacement therapy with no dialysis or transplantation available or initiated, or a doubling of the serum creatinine level. There was no significant difference in the occurrence of the primary outcome in the aliskiren group compared with the placebo group (hazard ratio, 1.08 [95% CI, 0.98–1.20]; P=0.12).[25] When analyzed as distinct outcomes, there was a trend toward a higher occurrence of cardiovascular events in the aliskiren group (13.8% versus 12.8%; P=0.09), whereas no difference was observed for kidney events (6.0% versus 5.9% for aliskiren versus placebo; P=0.74).

More recently, the CREDENCE trial[13] revealed favorable effects of canagliflozin on a primary combined cardio-kidney outcome, consisting of a composite of dialysis, transplantation, or a sustained eGFR of <15 mL/min/1.73 m^2, a doubling of the serum creatinine level, or death from kidney or cardiovascular causes. Treatment with canagliflozin was associated with a significantly decreased risk of the primary outcome (hazard ratio, 0.70 [95% CI, 0.59–0.82]; P<0.001).[13] When assessing the different components of the outcome, the beneficial effect of canagliflozin was consistent across the kidney-specific composite (hazard ratio, 0.66 [95% CI, 0.53–0.81]; P<0.001), as well as the cardiovascular secondary outcome of cardiovascular death or hospitalization for HF (hazard ratio, 0.69 [95% CI, 0.59–0.83]; P<0.001). CREDENCE builds on the growing body of evidence on the beneficial effect of sodium-glucose cotransporter-2 inhibition on both cardiovascular and kidney events.[31,32]

DAPA-CKD (A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease) and EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin) were designed to assess the effect of other sodium-glucose cotransporter-2 inhibitors on kidney and cardiovascular events in patients with CKD with and without diabetes. DAPA-CKD evaluated the effect of dapagliflozin in albuminuric patients with CKD with and without diabetes; its primary outcome was a cardio-kidney composite outcome of time to first occurrence of a ≥50% sustained decline in eGFR or reaching end-stage kidney disease (defined as sustained eGFR <15 mL/min/1.73 m^2, chronic dialysis treatment, or receiving a renal transplant), cardiovascular death, or renal death and a secondary outcome was all-cause death. DAPA-CKD was halted owing to overwhelming efficacy, because dapagliflozin demonstrated a significant reduction in risk of the primary cardio-kidney composite outcome and all secondary outcomes, including death from any cause.[26] The primary outcome in EMPA-KIDNEY is a cardio-kidney composite outcome of time to first occurrence of "kidney disease progression" (end-stage kidney disease, defined as initiation of maintenance dialysis or receipt of a kidney transplant, sustained eGFR decline <10 mL/min/1.73 m^2, renal death, or sustained decline in eGFR ≥40% from baseline) or cardiovascular death. EMPA-KIDNEY may elucidate whether the cardio-kidney benefits demonstrated in CREDENCE and DAPA-CKD are consistent across the therapeutic class and whether such benefits extend to higher eGFR categories of CKD (up to eGFR of 90 mL/min/1.73 m^2 [in the presence of albuminuria] and to a cohort without albuminuria).

In the primary composite outcomes of CREDENCE, EMPA-KIDNEY, and DAPA-CKD, the only cardiovascular event included in the composite is cardiovascular death, the most common mode of death in patients with CKD. There has been recent interest in including nonfatal cardiovascular events (eg, HF hospitalization, MI, and stroke) in addition to kidney events to cardio-kidney composite outcomes as was done in ALTITUDE.[3]

Acute HF

Several trials in acute HF have incorporated kidney outcome measures as part of combined primary efficacy and safety outcomes (Table 2). Such composite outcomes were initially incorporated because of clinical concern that decongestive therapies may come at a cost of acute worsening of kidney function. Although combining safety (ie, the harms of a therapy) and efficacy end points into an aggregate outcome has been common in acute HF trials, it important to note the difference between small, transient changes in creatinine and marked or irreversible changes in kidney function. The latter may reflect clinically significant acute injury to the kidney or the onset or progression of CKD, but the clinical significance of the former is less clear. Transient increases in creatinine during decongestion for acute HF may not be associated with adverse long-term prognosis and may indeed signify adequate decongestion,[33] limiting the usefulness of this type of outcome as a safety or efficacy metric. One example of an acute HF trial that incorporated transient changes in creatinine in its composite was PROTECT (Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function).[30] In this trial, the cardio-kidney outcome included a composite of treatment success (improvement in

dyspnea) and treatment failure (death or HF admission at 7 days, worsening symptoms or signs of HF by day 7, or worsening kidney function, defined as an increase from randomization to day 7, confirmed at day 14, of serum creatinine of >0.3 mg/dL or initiation of hemodialysis at day 7). Such individual components may be considered of markedly different clinical significance to patients. Although rolofylline improved dyspnea compared with placebo in PROTECT, it was not beneficial with respect to the primary composite outcome (odds ratio, 0.92 [95% CI, 0.78–1.09]) because of worsening kidney function (12.7% versus 11.1%).[30] Whereas the effect of the drug under investigation may have been superior with respect to a cardiovascular efficacy outcome, the neutral results of the study may have been largely driven by inclusion of the change in creatinine, a component of unclear clinical significance.[34]

Chronic HF

The most common composite outcome in chronic HF clinical trials comprises cardiovascular death and HF hospitalization. There have been no trials of chronic HF that have used primary cardio-kidney composite outcomes. Many evidence-based therapies for HF have pharmacodynamic effects on eGFR and can reduce eGFR in patients with HF. However, such changes in kidney function do not necessarily indicate true injury to the kidney and may not be deleterious in the short or long term. In CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) and SOLVD (Studies of Left Ventricular Dysfunction), patients with HF who received enalapril had statistically significant increases in creatinine levels compared with placebo and an increase in kidney adverse events.[35,36] In chronic HF, cardio-kidney composite outcomes should ideally capture longer-term events of clinical importance, rather than transient changes in kidney function of uncertain clinical significance. How best to define such outcomes remains unclear, making it challenging to use cardio-kidney composite outcome in trials of chronic HF. Analyses of data from recently completed and future HF trials should be conducted to better understand this issue.

SPECIFIC CHALLENGES OF CARDIO-KIDNEY COMPOSITE OUTCOMES

The use of composite clinical outcomes has become increasingly common across cardiovascular clinical trials. From 2011 to 2016, there were 140 published cardiovascular clinical trials in prominent medical journals that used primary composite clinical outcomes.[37] On a recent search query of ClinicalTrials.gov, >200 unpublished, registered phase 3 cardiovascular clinical trials had primary outcomes that were composite in nature.[37]

The growth of composite clinical outcomes has been accompanied by unique challenges for trialists, statistical analysts, and clinicians. Whereas the challenges of using cardio-kidney composite outcomes mirror those of any composite outcome, there remain several specific considerations (Figure 2).

Composite Outcomes to Assess "Net Clinical Benefit"

Kidney events have traditionally been incorporated in cardiovascular trials as part of safety outcomes given the hemodynamic effects of many previously investigated therapies on kidney function. As such, common safety outcomes have included hyperkalemia or rise in serum creatinine. Some have proposed a composite cardio-kidney outcome comprising both efficacy and safety components to evaluate net clinical benefit of cardiovascular efficacy and kidney safety; however, such composites are often difficult to interpret because the kidney and cardiovascular components are not of similar clinical importance.

Composite Outcomes to Assess Kidney and Cardiovascular Benefits

Whereas some therapies may possess both kidney and cardiovascular benefits, it can be challenging to assess such effects in a composite outcome. One key issue is that the kidney events of greatest clinical importance are often infrequent and late events in cardiovascular trials specifically, whereas cardiovascular events manifest earlier. Hence, in many cardiovascular trials, kidney events would not be expected to contribute in a meaningful way to the composite outcome results unless a trial is of sufficient power and follow-up to evaluate both short- and long-term clinical events (eg, CARMELINA [Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus]).[38] To address this issue, the win ratio is a statistical approach that attempts to analyze composite outcomes when the individual components are of varying clinical importance. Such analyses allow for investigators to choose the order of components on the basis of clinical importance, which are then given a higher priority in the analysis.[39,40] However, the order of events based on clinical importance may be especially challenging when combining both cardiovascular and kidney outcomes as opposed to ranking either sets of outcomes in isolation. For example, in a trial of chronic HF, it is unclear whether a HF hospitalization or sustained decline in eGFR is more clinically important, as both events are associated with high subsequent 1-year mortality, and although one event is defined by a change in a laboratory measure,
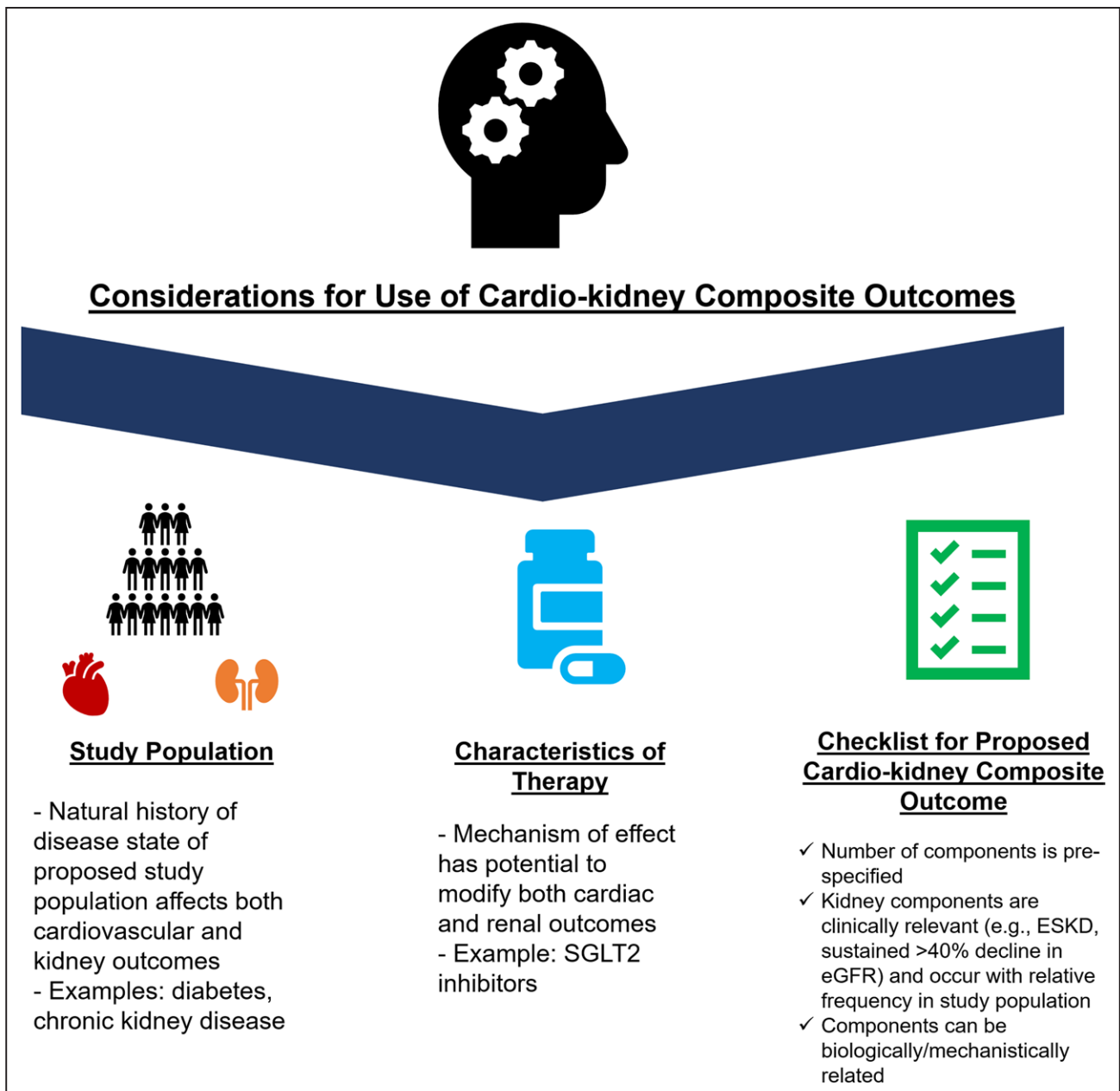
Figure 2. Challenges of cardio-kidney composite outcomes in trial design.
eGFR indicates estimated glomerular filtration rate; ESKD, end-stage kidney disease; and SGLT2, sodium-glucose cotransporter-2.

it is capturing irreversible loss of function of a vital organ.[6,41] Furthermore, the win ratio cannot address another major concern in cardio-kidney composite outcomes, which is the potential for heterogeneity of treatment effects across the kidney and cardiovascular components of the composite. Outcome weighting has been proposed to assist in the interpretation of composites. However, weighting is a subjective process, and weighting does not address the rarity of hard kidney events. A competing risk analysis to account for the potential of noncardiovascular or nonrenal death would not fully address these concerns related to cardio-kidney composite outcomes.

Given these issues, alternative strategies for evaluating the cardiac and kidney events benefits of therapies may be more sensible in many settings. Such strategies include specifying a cardiovascular composite as the primary outcome and kidney outcomes as distinct, prespecified secondary outcomes in cardiovascular trials. To date, this has been perhaps the most commonly used approach. HF trials such as PARADIGM-HF,[17] PARAGON-HF,[5] DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure),[42] and the EMPEROR trial program (EMPEROR-Reduced [Empagliflozin Outcome Trial in Patients With

Chronic Heart Failure With Reduced Ejection Fraction] and EMPEROR-Preserved [Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction])[43,44] and diabetes trials such as EMPA-REG OUTCOME,[14] CANVAS (Canagliflozin Cardiovascular Assessment Study),[31] and DECLARE-TIMI 58 (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events)[45] provide examples of this approach. Another strategy that has been used is to conduct parallel trials, one using a kidney composite in a trial population enriched for such events and the other using a cardiovascular composite in a trial population enriched for cardiovascular events. Finerenone is a third-generation mineralocorticoid receptor antagonist with potentially less hyperkalemia than spironolactone that is being studied compared with placebo in patients with type 2 diabetes and diabetic kidney disease in 2 parallel trials (FIGARO-DKD [Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease] and FIDELIO-DKD [Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease]). In the FIGARO-DKD trial, the outcome is a composite of cardiovascular death, nonfatal MI, nonfatal stroke, or HF hospitalization. In the FIDELIO-DKD trial, the outcome is decrease in eGFR >40%, end-stage kidney disease, or renal death. A recent press release has announced that finerenone reduced the primary composite end point in the FIDELIO-DKD trial[46]; full trial results are expected shortly. It is notable that parallel trial designs like FIGARO-DKD and FIDELIO-DKD require a larger aggregate study population to enroll and increased costs.

CONCLUSIONS

Chronic kidney disease commonly coexists with several cardiovascular and metabolic disease states, including HF and diabetes. In parallel, most deaths among patients with CKD are attributable to cardiovascular causes. Recently, novel cardiometabolic therapies in diabetes have demonstrated mechanistically plausible concordant risk reduction in both clinically important kidney and cardiovascular outcomes. The potential for additional novel therapies to improve both cardiac and kidney risk profiles raises the possibility of cardio-kidney composite outcomes in future cardiovascular clinical trials. However, efficacy composite outcomes are interpretable only if the kidney and cardiovascular outcomes are clinically meaningful and plausibly mechanistically influenced by an investigational therapy in a concordant fashion. Further challenges in the analysis and interpretation of cardio-kidney composite outcomes need to be well understood before considering cardio-kidney composite outcomes in cardiovascular trials.

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