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CURRENT OPINION
Pulmonary circulation

Cardiovascular outcome trials in patients with chronic kidney disease: challenges associated with selection of patients and endpoints

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Although cardiovascular disease is a major health burden for patients with chronic kidney disease, most cardiovascular outcome trials have excluded patients with advanced chronic kidney disease. Moreover, the major cardiovascular outcome trials that have been conducted in patients with end-stage renal disease have not demonstrated a treatment benefit. Thus, clinicians have limited evidence to guide the management of cardiovascular disease in patients with chronic kidney disease, particularly those on dialysis. Several factors contribute to both the paucity of trials and the apparent lack of observed treatment effect in completed studies. Challenges associated with conducting trials in this population include patient heterogeneity, complexity of renal pathophysiology and its interaction with cardiovascular disease, and competing risks for death. The Investigator Network Initiative Cardiovascular and

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Renal Clinical Trialists (INI-CRCT), an international organization of academic cardiovascular and renal clinical trialists, held a meeting of regulators and experts in nephrology, cardiology, and clinical trial methodology. The group identified several research priorities, summarized in this paper, that should be pursued to advance the field towards achieving improved cardiovascular outcomes for these patients. Cardiovascular and renal clinical trialists must partner to address the uncertainties in the field through collaborative research and design clinical trials that reflect the specific needs of the chronic and end-stage kidney disease populations, with the shared goal of generating robust evidence to guide the management of cardiovascular disease in patients with kidney disease.

Keywords Cardiovascular diseases • Chronic renal insufficiency • Chronic kidney failure • Clinical trials as topic

Introduction

Cardiovascular disease is a major health burden for patients with chronic kidney disease (CKD), and therapies are needed to improve cardiovascular outcomes in this population.[1] Although some cardiovascular trials have been designed to recruit appropriately sized subgroups of patients with CKD,[2] most cardiovascular clinical trials exclude patients with advanced CKD or underreport characteristics relevant to CKD [e.g. baseline serum creatinine, creatinine clearance, estimated glomerular filtration rate (eGFR), the extent of albuminuria].[3,4] Consequently, the efficacy and safety of cardiovascular therapies in these patients is uncertain.[5–7]

Cardiovascular outcome trials are challenging to conduct in CKD populations, but well-designed randomized controlled trials are needed to inform optimal management of these patients.[8,9] Promoting meaningful progress in this area requires identifying and addressing the specific impediments to conducting cardiovascular outcome trials in patients with CKD.

The Investigator Network Initiative Cardiovascular and Renal Clinical Trialists (INI-CRCT) is an international organization of academic cardiovascular and renal clinical trialists dedicated to improving outcomes among patients who have both chronic kidney and cardiovascular disease. To advance cardiovascular outcomes research in patients with CKD, INI-CRCT convened a meeting of regulators and experts in nephrology, cardiology, and clinical trial methodology, within the framework of a Cardiovascular Clinical Trialists (CVCT) workshop to discuss challenges associated with designing cardiovascular outcome trials in CKD. This paper summarizes the insights from the INI-CRCT meeting and identifies a research agenda to advance the field.

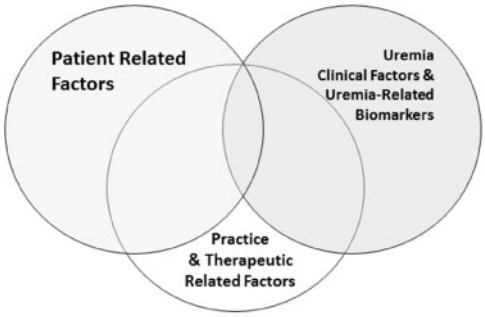
Patient selection

Few large cardiovascular outcome trials have been conducted specifically in the CKD or end-stage kidney disease (ESKD) populations on dialysis[10] (Supplementary material online, *Table S1*). Some trials have reported beneficial treatment effects on cardiovascular outcomes,[11,12] but others were inconclusive because of study design limitations (e.g. open-label, small sample size, suboptimal target population).

The pathophysiologic mechanisms of CKD that predispose patients to cardiovascular disease and subsequent cardiovascular events are complex and overlapping (*Figure 1*).[1,5] As CKD progresses, more pathophysiologic pathways are potentially involved in downstream cardiovascular events. Whether a single pathophysiologic pathway predominates, or if the processes collectively contribute to cardiovascular events, is unclear. If the latter, a single therapy is unlikely to have a sizable benefit. Additionally, as CKD progresses to irreversible ESKD, the potential for any treatment to exert a beneficial effect on morbidity and mortality may diminish.

Some authors have argued that targeting early CKD stages is important for cardiovascular primary prevention trials.[5] Although this population has lower event rates than does an advanced ESKD population, the increased sample size consequent on this lower event rate may be offset by the greater likelihood of modifiable risk in earlier CKD stages and the potential for a larger treatment effect. In contrast, although ESKD patients are more likely to have high event rates, non-cardiovascular causes may account for a substantial portion of events, and these events may be less likely to respond to a cardiovascular therapy.[10] Enrolling patients at high risk for cardiovascular events (i.e. late or end-stage CKD) in clinical trials can reduce the sample size, but only if the patients are at risk of an outcome that the treatment can influence. Otherwise, many of the events constitute 'noise', thus reducing the power of a trial.[13,14] Critical steps to advance the field include conducting studies to better characterize the CKD pathophysiology that contributes to cardiovascular outcomes, developing therapies that interrupt these pathophysiologic processes, identifying patients with the target pathophysiology, and enrolling these patients in randomized controlled trials to test the intervention (*Figure 2*). Cardiovascular clinical trials should report the distribution of patients across CKD stages, and where feasible, examine trial results according to pre-specified CKD stage subgroups. Such analyses, while not definitive, can provide insight into the consistency of treatment effects across subgroups of CKD severity and inform the design of future studies.

An important aspect of designing a clinical trial is identifying a patient population with the disease of interest in whom the outcome of interest is likely to occur over the course of the trial. Imaging and biomarkers are widely used in cardiovascular clinical trials to establish the presence of relevant phenotypic disease characteristics and for enrichment, but criteria and cut-points used to establish the presence of diseases such as heart failure in patients with advanced CKD or those on dialysis may need to be modified.[15] For example, the Acute Dialysis Quality Initiative (ADQI) has proposed that at least 1 of 8 echocardiographic criteria[16] should be abnormal (based on the thresholds of the American Association of Echocardiography consensus guideline[17]) to establish echocardiographic evidence of structural heart disease in patients with ESKD on dialysis.



Patient Related Factors	Practice & Therapeutic Related Factors	Uremia Clinical Factors and Uremia-Related Biomarkers
• Volume overload • Anemia • High sympathetic activity • Insulin resistance • Hemodynamic instability during hemodialysis • Infections • Dyskalemia • Hypertension • Blood pressure variability	• Exposure to bioincompatible dialysis conditions	• Metabolic bone disorder & related mediators • Low grade inflammation • Oxidative stress • Uremic toxins • Post-translational protein modifications • Accumulation of atherogenic remnant lipoproteins • Endogenous nitric oxide synthase (NOS) inhibitors

Figure 1 Intersection of risk factors for cardiovascular disease in chronic kidney disease patients.

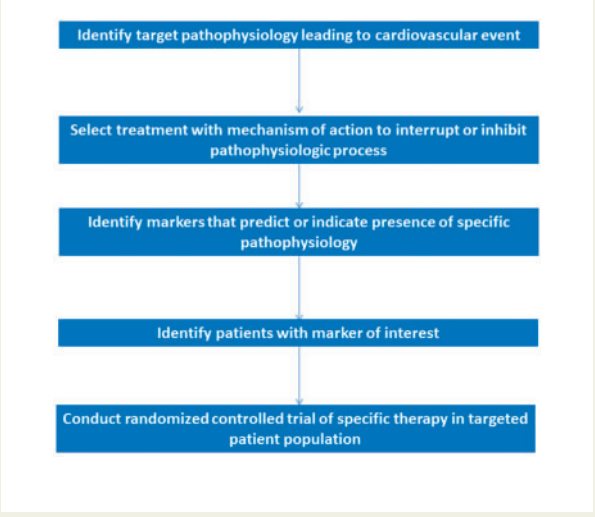


Figure 2 Approach to precision medicine for cardiovascular outcome trials in patients with chronic kidney disease. Adopting a precision medicine approach may increase the likelihood of successfully identifying effective therapies for cardiovascular disease in patients with chronic kidney disease since many pathophysiologic processes may be at play in these patients. First, the pathophysiologic target of interest that is suspected to lead to cardiovascular events should be identified. Next, a treatment should be selected with a mechanism of action known to modulate the pathophysiologic target of interest. Biologic markers that predict or indicate that the pathophysiology is present need to be identified and validated so that patients with the underlying pathophysiology can be reliably identified. Randomized, controlled trials of the specific therapy in the patients with the pathophysiology should be conducted.

Biomarkers (e.g. cardiac troponin [cTn], B-type natriuretic peptide, urinary albumin or urinary protein excretion rate, calcification propensity assay) may also guide optimal patient selection if used to select for a population with a form of disease that is likely to be affected by the intervention. For example, cTn levels above a reference value are prognostic for all-cause mortality in stable haemodialysis patients.[18] Although a cTn concentration above some value may select a study population that is at greater risk of death, this approach would be helpful only if the probability is reasonably high that the treatment under study would impact the specific type of mortality predicted by elevations in cTn concentrations.

Endpoint selection and definitions in chronic kidney disease cardiovascular outcome trials

Endpoint definitions

A task force has developed a standard set of definitions for cardiovascular endpoint events for cardiovascular clinical trials.[19] Although this effort represents an important advance for cardiovascular outcome trials, outstanding questions remain regarding whether these definitions are optimal for trials conducted in patients with advanced CKD, including those on dialysis (*Table 1*).[20] For example, the standard definition of a heart failure endpoint event requires the presence of at least one new or worsening symptom, objective evidence of heart failure, and initiation or intensification of treatment for heart failure.[19] However, many physical manifestations of CKD overlap with those of heart failure. Indeed, signs of volume overload and symptoms of

Table 1 Limitations of standard endpoint definitions in patients with chronic kidney disease

- Difficult to determine whether some signs and symptoms commonly used to identify an endpoint event (e.g. heart failure) are attributable to cardiovascular disease or to the underlying kidney disease
- Heterogeneity in clinical practice (e.g. decision to hospitalize, decision to dialyze)
- Some biomarkers (e.g. natriuretic peptides) may be altered in chronic kidney disease and interpretation can be challenging, whereas kidney specific criteria do not appear to be needed for other biomarkers (e.g. cardiac troponin to diagnose acute myocardial infarction)

dyspnea in patients on dialysis could be due to a missed haemodialysis session, overestimation of dry weight, or non-adherence to dietary sodium and fluid restrictions. Biomarker findings, such as elevated natriuretic peptide levels, which can provide laboratory evidence of new or worsening heart failure, may result from decreased renal clearance of these markers in patients with CKD. Imaging findings may also be difficult to interpret. For example, in patients with ESKD, right heart pressures increase before haemodialysis.[16,21,22] For these reasons, it may be difficult to determine whether symptoms and signs suggestive of heart failure result from impaired kidney function, true heart failure, or both. Moreover, clinical patient management (i.e. the decision to hospitalize for heart failure symptoms or not, what constitutes an urgent heart failure visit in the dialysis setting) is substantially heterogeneous across and within countries, which makes application of standard definitions of heart failure events difficult, even in studies that use endpoint adjudication committees. Although this problem is not unique to clinical trials in patients with kidney disease, it may be exacerbated in this population. All these factors may lead to inaccurate identification of heart failure events and create challenges for conducting and interpreting study results. Clinical trials of haemodialysis patients could use the staging system the AQDI proposed (*Figure 3*) to define heart failure endpoint events if the prognostic value of the system is validated in robust, prospective trials.[16]

Diagnosing acute MI in patients with CKD and elevated cTn levels presents a clinical dilemma and often requires extended evaluation for an accurate diagnosis. However, studies suggest that cTn level is equally effective in diagnosing MI in patients with CKD and those with normal renal function.[23] If the level of elevated cTn values is unchanging, and the timing of the event makes a rising and/or falling pattern unlikely, the elevated cTn level, even if substantial, likely reflects chronic myocardial injury. However, if a rising and/or falling pattern of the cTn values is present then the aetiology of the abnormal cTn values could be, for example, acute heart failure or acute MI. A diagnosis of acute MI is more likely when a rising and falling pattern is accompanied by ischaemic symptoms, new ischaemic electrocardiogram changes, or loss of myocardial function by imaging. No data suggest CKD patients require different criteria for the cTn decision levels.[24]

Composite endpoints

Many cardiovascular outcome trials use composite endpoints to increase the event rate, and therefore increase the power (if the treatment exerts an effect on all components of the composite), or to reduce the sample size or decrease the duration of a clinical trial.[25] Composite endpoints may also be chosen to characterize the clinical picture more comprehensively, since outcomes other than mortality are important to patients.[25–27] As others have noted, the limitations of composite endpoints can overshadow their strengths if the individual components differ greatly in their importance or diverge in their response to treatment, thus clouding interpretation and reducing statistical power.[14,27]

The most suitable choice of components of the composite endpoint for a cardiovascular outcome trial conducted specifically in the CKD population depends on the specific therapy being tested. In general, a cause-specific (i.e. cardiovascular) composite primary efficacy endpoint, in contrast to one that includes all-cause mortality, may be more appropriate for cardiovascular outcome trials in CKD patients since non-cardiovascular causes of death are not uncommon in the CKD population and the intervention is unlikely to reduce the rate of such deaths. A treatment's effect on all-cause mortality would still need to be examined from a safety perspective. Renal endpoints are relevant in a CKD population even if the primary intervention target is cardiovascular disease, and a composite endpoint reflecting both cardiovascular and renal outcomes may be desirable, especially if the intervention is expected to affect both systems. A challenging problem is which endpoints to combine and how to interpret the results of the composite endpoint. The Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy (CREDENCE) (NCT02065791) trial is an ongoing study designed to enroll 4200 patients with CKD and compare the effect of canagliflozin to placebo on the primary endpoint of time-to-first end-stage kidney disease, doubling of serum creatinine, renal death, or cardiovascular death.[28] Inspection of the treatment effect on each component individually will be critical to the interpretation of this study to assess whether a single component drove the overall effect, or whether all components showed consistent effects.

The typical approach to analysis of composite outcomes in clinical trials has been to compare treatment groups with respect to the time to the first event in the composite. A variety of statistical methods are available that consider not only the first event but also events that occur after the first event.[29] Novel methods that analyse components in order of clinical severity or that account for differential effect among the components of the composite have generated interest among clinical trialists.[25,30] Application of these methods may be particularly beneficial for cardiovascular outcomes trials in CKD, since composite endpoints are likely to be constructed with components of differing clinical significance (i.e. for CKD early stages: cardiovascular death combined with a change in renal function; for advanced

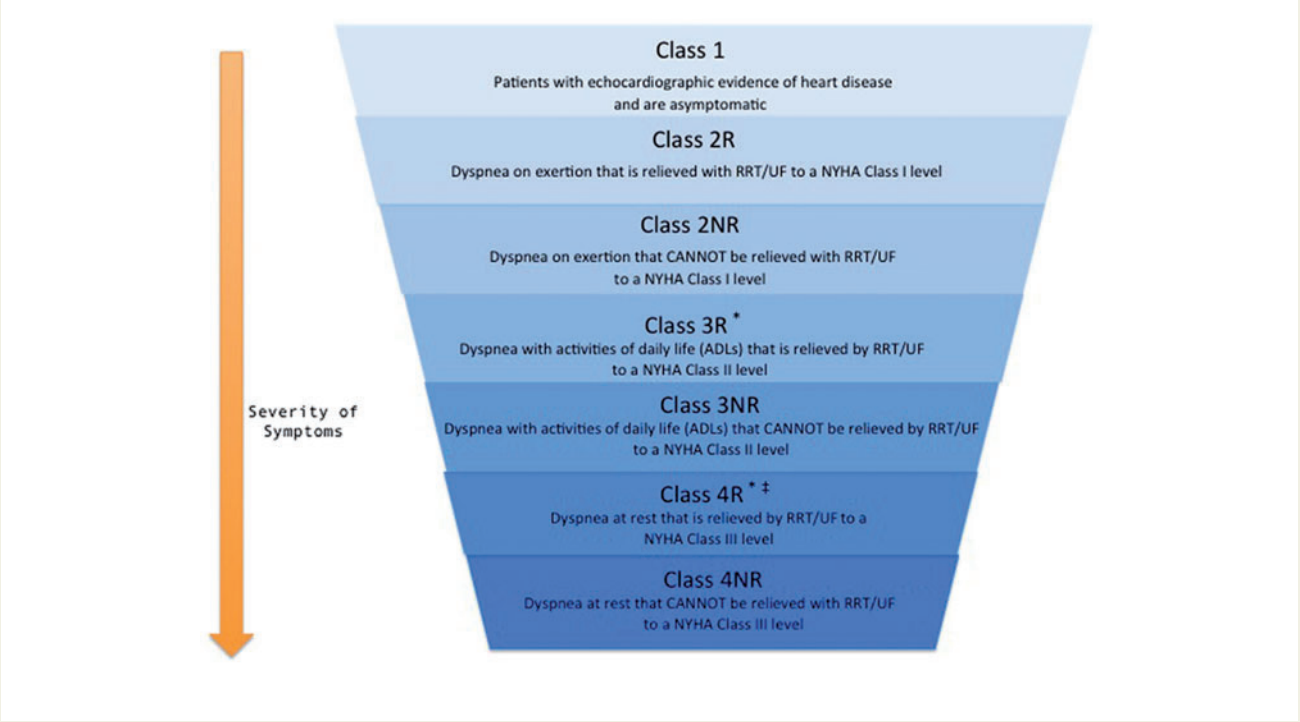


Figure 3 Acute dialysis quality initiative heart failure in end stage kidney disease classification system. Classification is determined by an assessment of dyspnea before and after renal replacement therapy (RRT)/ultrafiltration (UF). Patients who have the same class assessment before and after RRT/UF are scored by their post-treatment assessment. The classification scheme assumes that the class assignment represents the patient's achievement of optimized UF and is representative of the patient's usual level of dyspnea before and after RRT/UF. *If dyspnea symptoms improve to class I levels, the patient would be classified as class 2R. ‡If dyspnea symptoms improve to class II levels, the patient would be classified as class 3R. ADQI, Acute Dialysis Quality Initiative; ESKD, end-stage renal disease; NYHA, New York Heart Association. Reprinted with permission from Chawla *et al.* J Am Coll Cardiol 2014;63:1246–1252.

CKD: CV death, chronic renal replacement therapy or a GFR <15 mL/min/1.73 m^2 or a change in renal function). When a treatment is anticipated to have different effects on the various outcomes within the composite the analysis must recognize the correlation of the multiple events within a person and must be designed in a way that captures these effects.

Competing risks

Most cardiovascular outcome trials use composite primary endpoints to evaluate both survival and clinically relevant endpoints that measure the patients' morbidity. Competing risks can be challenging when using composite endpoints. Patients with CKD, and especially ESKD on dialysis, are at high risk of non-cardiovascular causes of death (e.g. sepsis, malignancy). Obviously, patients who die from non-cardiovascular causes are no longer at risk for cardiovascular death. The extent to which competing risks might bias the study result depends on the number, type, and distribution of deaths in a study. The complications of competing risks can be avoided if all-cause mortality is the endpoint, but, as previously noted, this approach may not be prudent or even feasible because of the necessary sample size. More research is needed to determine the clinical importance and relevance of competing risks analysis in cardiovascular outcomes trials studying patients with CKD and to ensure statistical analysis plans account for competing risks where appropriate to ensure unbiased presentation of results.

Cardiovascular clinical trialists recognize the importance of patient-reported outcomes, particularly in disease states with high morbidity (e.g. heart failure).[26] While it would be hard to demonstrate an acceptable benefit:risk ratio for a small treatment effect on symptoms in a population where the background rate of important events (e.g. death) is high, understanding whether a treatment affects the key symptoms of a disease is important. From a regulatory perspective, a meaningful effect on patient symptoms could result in additional labelling claims. Patient-reported endpoints are also necessary for health technology assessments and can provide clinicians and patients with useful information to support patient education and decision-making.[31]

Research agenda to advance clinical trial science and improve patient outcomes in chronic kidney disease

The INI-CRCT recommends the following research priorities to advance the field towards achieving improved cardiovascular outcomes for patients with CKD:

(1) Conduct analyses to evaluate composite endpoints, testing various combinations of endpoints that reflect cardiovascular and renal outcomes across the spectrum of CKD, including ESKD on dialysis. Registry cohorts, electronic medical records, and databases from completed clinical trials may be appropriate data sources for such studies.
(2) Conduct analyses to (i) determine the impact of competing risks in analysis of cardiovascular outcome trials of patients across the CKD spectrum using various composite endpoints constructed with both cardiovascular and renal components; and (ii) provide guidance for selecting appropriate analytic methods to handle competing risks for specific CKD/ESKD populations based on the components of the endpoints.
(3) Develop patient-reported outcomes as supportive endpoints (i.e. secondary endpoints or endpoints to support health technology assessment), raise awareness about sources of bias when using these endpoints, and provide guidance to researchers about methods to minimize bias (e.g. avoiding missing data, using statistically valid methods for handling missing data).
(4) Develop a core set of cardiovascular outcomes that are critical to decision making by patients/caregivers, clinicians and regulators, and that are defined and reported in a standard way that allows robust conclusions of relative effectiveness.
(5) Harmonize evaluation metrics and clinical data definitions (e.g. for an heart failure event) for cardiovascular trials in patients on dialysis to facilitate research and improve management of dialysis patients.[32]

Conclusions

Because of the linkage of cardiovascular and renal disease and prevalence of cardiovascular disease in patients with CKD, therapies are needed to improve cardiovascular outcomes in patients with CKD. This common objective among cardiovascular and renal clinical trialists creates an opportunity to collaborate in the design of rigorous clinical trials that address the specific needs of the CKD population. The INI-CRCT has identified priority areas for research, primarily involving selection of patients and endpoints, and aims to pursue collaborative initiatives among cardiovascular and renal clinical trialists to encourage relevant research efforts. This research should inform the design of future clinical trials and ultimately generate robust evidence to guide the management of CKD patients with cardiovascular disease (*Figure 4*).

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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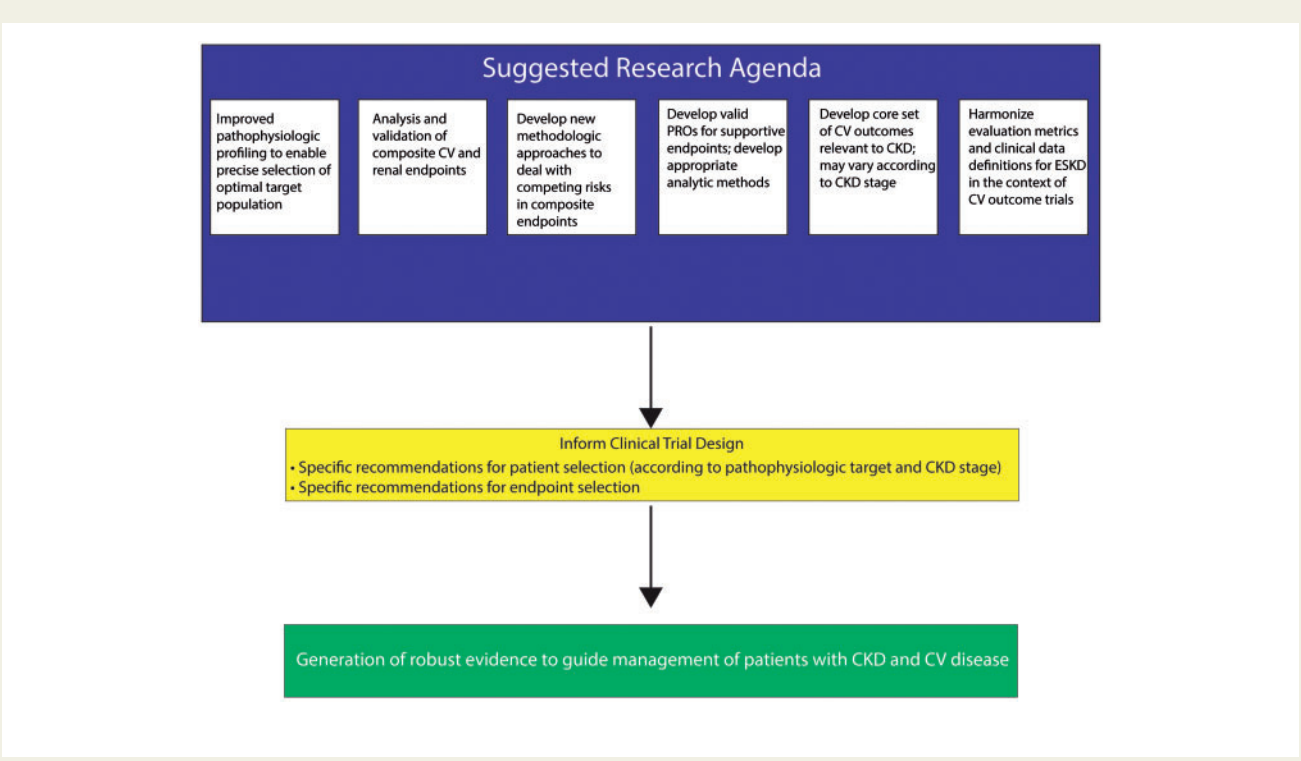

Figure 4 Research agenda. Completing the priorities outlined in the CRCT research agenda will inform clinical trial design for future clinical trials and will enable specific recommendations to be made regarding patient selection and endpoint selection, which will in turn enable robust evidence to be generated that will guide the management of patients with CKD and cardiovascular disease. CKD, chronic kidney disease; CRCT, Cardiovascular and Renal Clinical Trialists; CV, cardiovascular; ESKD, end-stage kidney disease; PRO, patient reported outcome.

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