Circulation

WHITE PAPER

Cardiorenal Syndrome Revisited

ABSTRACT: Cardiorenal syndromes have been categorized into 5 clinical subtypes based on which organ is perceived to be the primary precipitant of the vicious and interrelated cycle of declining function in both organs. This clinical classi cation has broadened interest in cardiorenal interactions, but it is merely descriptive, does not rely on or inform predominant pathophysiology, and has produced little change in either practice or the research agenda. In contrast, recent scienti c work identi es common pathophysiological pathways for several categories of cardiorenal syndromes, suggesting a unifying pathogenesis. Fibrosis is a common consequence of in ammation- and oxidative stress–related endothelial dysfunction in aging, hypertension, diabetes mellitus, obesity, ischemia, and organ injury. It is a common feature in heart failure and chronic kidney disease. Therefore, we suggest that brosis may be not only a marker but also the primary driver of pathophysiology in several cardiorenal syndromes. Interstitial brosis in the heart, large arteries, and kidneys may play a key role in the pathophysiology of the cardiorenal syndrome continuum. Focusing on brosis as a disease mediator might enable the identi cation of brosis-related biotargets that could potentially be modulated with renin-angiotensin-aldosterone system inhibitors, mineralocorticoid receptor antagonists, or other novel anti brotic agents in development. This conceptual approach may be an effective new strategy for the prevention and treatment of brosis within the cardiorenal syndrome continuum.

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Key Words: cardio-renal syndrome brosis heart failure renal insuf ciency

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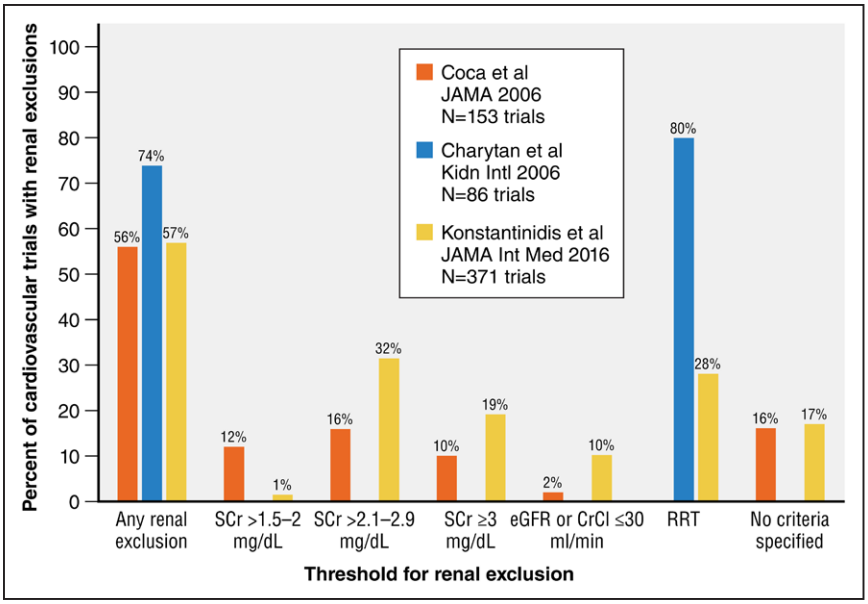

Figure 3. Summary of data from published systematic reviews reporting the percent of cardiovascular trials that excluded patients with kidney impairment and the thresholds applied for the exclusion.
CrCl indicates creatinine clearance; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy; and SCr, serum creatinine. Reprinted from Zannad and Rossignol[84] with permission of the publisher. Copyright ©2017, American Heart Association.

kidney disease, identification of patients with pathophysiology likely to respond to treatment under study) or the choice of study end points and how to define them (ie, differentiating worsening heart failure from worsening renal function, interpreting biomarkers affected by impaired kidney function [natriuretic peptides, high-sensitivity cardiac troponin], statistical handling of competing risks) are critical decisions that, if incorrect, can prevent a trial from answering its intended question. A limited body of evidence is available to researchers on which to base assumptions used in clinical trial design, but we have previously suggested research priorities to help address these knowledge gaps (Figure 4) and harmonize the approach to clinical investigation across disciplines.[86] It is encouraging that specific cardiorenal trials evaluating cardiovascular and renal outcomes are now underway.[87]

Specific training in cardiorenal medicine and the emergence of a new generation of cardiorenal specialists may be justified given the complexity of interactions between the renal and cardiovascular systems. This may apply to both the basic research level and the usual care setting. Closer collaboration between nephrologists and cardiologists has been encouraged as a mechanism to advance clinical research efforts in cardiorenal syndrome.[84,86,88] Such a collaboration may, for instance, lead to better persistence in the long-term use of lifesaving drugs (ie, RAAS inhibitors), with improved management of recurrent worsening renal function or hyperkalemia

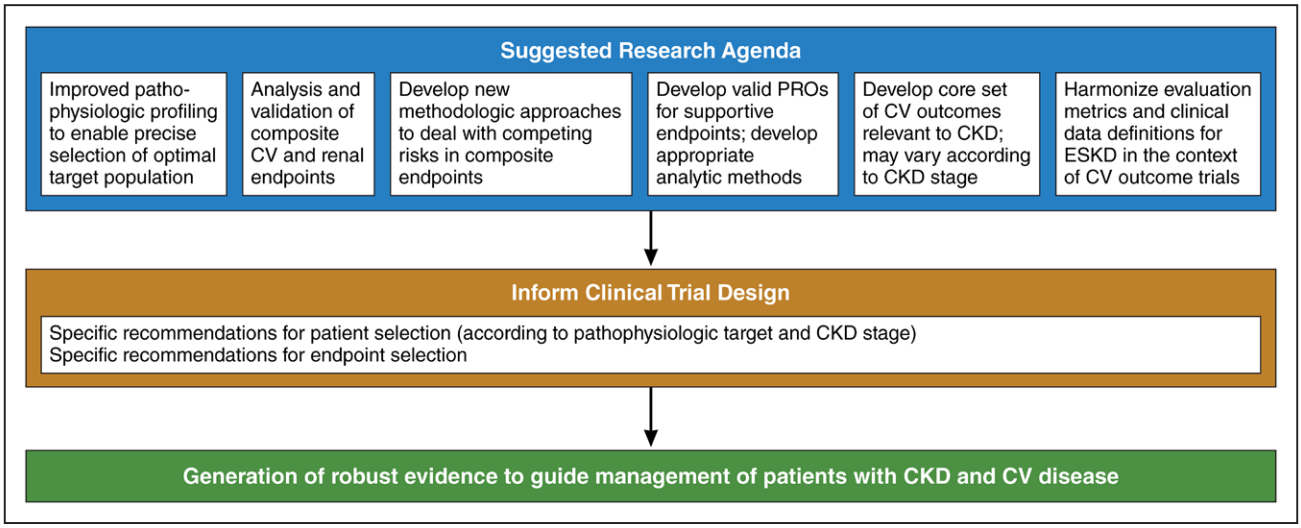

Figure 4. Research agenda.
Completing the priorities outlined in the Cardiovascular and Renal Clinical Trialists (CRCT) research agenda will inform clinical trial design for future clinical trials and will enable specific recommendations to be made on patient selection and end point selection, which will in turn enable robust evidence to be generated that will guide the management of patients with chronic kidney disease (CKD) and cardiovascular (CV) disease. ESKD indicates end-stage kidney disease; and PRO, patient-reported outcome. Reprinted from Rossignol et al[86] with permission of the publisher. Copyright ©2017, Oxford University Press.

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