How Should We Modify Recommended Renin–Angiotensin–Aldosterone System Inhibition When Facing the Cardiorenal Syndrome?

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In the advent of the characterization of the cardiorenal syndrome, nephrologists and cardiologists alike frequently toil with the conceptualization of the balance between cardiac and kidney function. This is particularly pertinent in the setting of newly diagnosed left ventricular failure (LVF) in patients with pre-existing chronic kidney disease (CKD), for example, post-myocardial infarction or nonischemic cardiomyopathy. Another common dilemma is the patient with progressive deterioration of both heart and kidney function leading to refractory congestive symptoms despite recurrent heart failure hospitalizations.

Renin–angiotensin–aldosterone system (RAAS) blockade with angiotensin-converting enzyme inhibitors or mineralocorticoid receptor antagonists is associated with reduced mortality in LVF. Despite supportive observational data, there is a paucity of corroborating randomized evidence for a mortality benefit in patients with CKD and systolic LVF because these patients were excluded from the trials. Whether these mortality benefits actually apply to those with pre-existing CKD is unclear.

Although angiotensin-converting enzyme inhibitor therapy in LVF is often associated with a reduction in glomerular filtration rate, the threshold level of acceptable reduction in glomerular filtration rate seems entirely arbitrary in contemporary practice. It is difficult to decide whether the associated reduction in mortality of RAAS blockade in LVF justifies the potential for adverse effects such as hyperkalemia in those with significant CKD.

Therefore, to apply these theoretical benefits, clinicians are willing to accept a greater degree of kidney dysfunction despite a paucity of evidence. The threshold at which the risks of the long-term adverse effects of RAAS blockade are considered unjustifiable in these patients has not been characterized to date.

In addition, hesitance regarding the risk of hyperkalemia in CKD often results in clinicians choosing one class of RAAS blockade over the other, rather than using them in combination. Whether the risk:benefit ratio is greater for angiotensin-converting enzyme inhibitor or mineralocorticoid receptor antagonist therapy in this context is unclear.

It may be more achievable to maintain lower doses of RAAS blockade in CKD and LVF, but there is uncertainty as to whether the potential mortality benefits are transferable at lower doses because the randomized trials in non-CKD patients targeted the higher end of the dosing range. Although we lack adequate bases of evidence for many situations, daily clinical practice nonetheless requires decisions to be made for individual patients. In summary, some of the challenging questions relating to renin–angiotensin–aldosterone inhibition in chronic heart and kidney disease include the following: (1) Is there benefit to improve outcomes when RAAS antagonists are used in patients with moderate-severe renal dysfunction and heart failure with low ejection fraction? (2) If only one antagonist is tolerated without unacceptable hyperkalemia, hypotension, or further worsening of renal dysfunction, should it be an angiotensin-converting enzyme inhibitor, angiotensin receptor blocking agent, or mineralocorticoid antagonist? (3) Lower doses of the RAAS antagonist may be better tolerated in CKD, but are the potential benefits maintained at doses lower than those proven in the trials? (4) At what level of chronic kidney impairment, if any, should RAAS antagonists be discontinued in the setting of combined heart failure and kidney disease?

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References


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