Response to Sexton: Inhibiting the Renin–Angiotensin–Aldosterone System in Patients With Heart Failure and Renal Dysfunction

Common Sense or Nonsense?

Javed Butler, MD, MPH; Michael M. Givertz, MD

Common sense is genius dressed in its working clothes. Ralph Waldo Emerson, American essayist (1803–1882)

Modulation of the renin–angiotensin–aldosterone system (RAAS) has revolutionized the management of patients with heart failure and reduced ejection fraction (HFrEF) (Figure). Before clinical trials with angiotensin-converting enzyme (ACE) inhibitors, there were no therapies proven to improve survival in patients with HFrEF, barring cardiac transplantation in a small, select group of patients with advanced HF. Subsequent studies with both ACE inhibitors and angiotensin receptor blockers (ARB), as well as β-blockers and mineralocorticoid receptor antagonists (MRA), have shown significant reduction in morbidity and mortality in patients with HFrEF across the spectrum of pathogenesis (ischemic and nonischemic) and functional class. Despite impressive benefits across multiple trials, the use of RAAS antagonists in clinical practice poses multiple challenges, as eloquently stated in this issue’s Challenges for the Basis of Practice by Sexton. In particular, most pivotal studies did not include patients with moderate or severe chronic kidney disease (CKD), who now may comprise ≤50% of patients with ambulatory HF and two thirds of patients hospitalized with acute HF. Similarly, although evidence supports the use of ACE inhibitors or ARBs to slow progression of renal dysfunction in patients with diabetes mellitus and CKD, these studies excluded patients with HF in general. The interactive effect of RAAS antagonists on populations of patients with HF and CKD may be elucidated, in part, from post hoc analyses of pivotal studies (Table), but ultimately individual patient decisions must be made by clinicians. Furthermore, these decisions are often made against a demographic backdrop of older age and greater comorbidities than observed in patients who participated in clinical trials, as well as uncertain patient adherence to pharmacological and nonpharmacological strategies. The challenge, as proposed by Stevenson, is “to make a good decision with flawed data, which includes unbiased trials with limited relevance and relevant experience with unlimited bias.” Sexton raises 4 specific questions to be addressed in patients with HFrEF with renal dysfunction.

Is There Benefit to Improve Outcomes When RAAS Antagonists Are Used in Patients With Moderate to Severe Renal Dysfunction and Heart Failure With Low Ejection Fraction?

There are only sparse data in general and no randomized controlled trial data to guide clinicians in this scenario. Furthermore, there is not a uniform definition of moderate to severe renal dysfunction in the setting of HF. Indeed, the term cardiorenal syndrome has been defined in both clinical and pathophysiological terms, and formal staging systems have been proposed. There are credible data, however, that show substantial benefit with RAAS antagonists in patients with HFrEF and with CKD, separately. Because the combination of these diseases puts patients at particularly high risk, especially after a HF admission, it is reasonable to assume that the use of RAAS antagonists will be beneficial in this cohort. Observational data and subgroup analyses (Table) support this assertion, but many questions remain, including:

1. Because moderate to severe renal dysfunction still encompasses a relatively large population, is there a threshold that alters the balance between benefit and risk?
2. Does it matter if the renal dysfunction is primary or secondary, reversible or irreversible?
3. Are there subgroups within this population that are affected differently by the use of RAAS antagonists, such as those with diabetes mellitus or uncontrolled hypertension?
4. When there is limited blood pressure to work with, should treatment with RAAS antagonists or β-blockers take precedence?

In general, patients with HFrEF with moderate to severe renal dysfunction should be given a trial of ACE inhibitor or ARB therapy. Currently, MRAs are contraindicated in patients with an estimated glomerular filtration rate (GFR) <30 mL/min and should be used cautiously in those with GFRs between

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30 and 45 mL/min. Patients should be closely monitored for complications, including hyperkalemia and worsening renal function, and hypotension, dehydration, and excess potassium supplementation should be avoided. Unless there are known intolerances or contraindications, a trial with these agents is warranted until further data are available.

If Only 1 Antagonist Is Tolerated Without Unacceptable Hyperkalemia, Hypotension, or Further Worsening of Renal Dysfunction, Should It Be an ACE Inhibitor, ARB, or Mineralocorticoid Antagonist?

Given the emphasis on comprehensive neurohormonal blockade to attenuate disease progression in HF, the need to choose one agent over another deserves careful consideration. Our first recommendation would be to try and use a combination of ACE inhibitor (or ARB) and MRA at lower doses if at all possible. Moderate hyperkalemia, for example, may be avoided by stopping potassium supplements in addition to salt substitutes or other high potassium-containing foods that may have been recommended in the face of diuresis. Ongoing use of oral potassium binders to facilitate chronic ACE inhibitor (or ARB) and MRA therapy is limited by the side effect of the commonly available agents. If complications or intolerance mandates use of only 1 agent, then it is prudent to use an ACE inhibitor or ARB rather than an MRA. This recommendation is based not on clinical trials data per se, but the fact that all MRA studies assessed efficacy and safety of aldosterone antagonism on top of baseline ACE inhibitor or ARB therapy. The use of MRAs in patients with HFrEF not taking an ACE inhibitor (or ARB) is unknown, whereas there are substantial data with the use of ACE inhibitor or ARB therapy in the absence of an MRA.

If the patient can take either an ACE inhibitor or ARB, then ACE inhibitor is the preferred first-line therapy as endorsed by practice guidelines. If an ACE inhibitor is not tolerated for a noncardiorenal limitation (eg, cough), ARB therapy alone is recommended. Although arguably a different population, it should be noted that MRA therapy in the Treatment of Preserved Cardiac Function with an Aldosterone Antagonist (TOPCAT) trial was not able to show an improvement in its primary end point among patients with HF and preserved ejection fraction—a trial that did not require ACE inhibitor or ARB therapy and included some patients with moderate renal dysfunction and mild left ventricular dysfunction (ejection fraction ≥45%).

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?

Both the Assessment of Treatment with Lisinopril and Survival (ATLAS) and the Heart Failure End point Evaluation of

### Table. Interactive Effects of Neurohormonal Antagonists on Heart Failure and Renal Dysfunction

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Effect on Heart Failure</th>
<th>Effect on Renal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBIS³</td>
<td>Bisoprolol</td>
<td>Positive</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>CKD&gt;non-CKD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MERIT-HF⁴</td>
<td>Metoprolol succinate</td>
<td>Positive</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>CKD&gt;non-CKD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAVE⁵</td>
<td>Captopril</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>CKD&gt;non-CKD</td>
<td></td>
<td>mean eGFR ↓ 3.8</td>
</tr>
<tr>
<td>SOLVD⁴</td>
<td>Enalapril</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>CKD&gt;non-CKD</td>
<td></td>
<td>RR of WRF 1.33*</td>
</tr>
<tr>
<td>Val-HeFT⁷</td>
<td>Valsartan</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>CKD&gt;non-CKD</td>
<td></td>
<td>mean eGFR ↓ 3.8</td>
</tr>
<tr>
<td>RALES⁸</td>
<td>Spironolactone</td>
<td>Positive</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>CKD&gt;non-CKD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPHECUS⁹</td>
<td>Eplerenone</td>
<td>Positive</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Non-CKD&gt;CKD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CIBS indicates Cardiac Insufficiency Bisoprolol Study; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EPHECUS, Eplerenone Post-AMI Heart Failure Efficacy and Survival; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Chronic HF; RALES, Randomized Aldactone Evaluation Study; RR, relative risk; SAVE, Survival And Ventricular Enlargement; Val-HeFT, Valsartan Heart Failure Trial; and WRF, worsening renal function.
Angiotensin II Antagonist Losartan (HEAAL) trials suggest that high doses of RAAS antagonists are superior to lower doses in improving outcomes in patients with HFrEF. However, the benefits were modest and low doses were better tolerated with less hypotension, hyperkalemia, and renal dysfunction. Notably, these trials did not have a placebo arm, and hence the incremental value of low-dose ACE inhibitor or ARB over placebo is not known. However, subsequent registry data demonstrate better event-free survival in older patients discharged on relatively low doses of RAAS antagonists. Furthermore, in a dose-ranging study of carvedilol in patients with HFrEF, low-dose β-blocker therapy was superior to placebo, whereas higher doses were associated with better outcomes. Continuing with the logic that patients with HF and renal dysfunction are at higher risk for worse outcomes and that both groups individually benefit from ACE inhibitor or ARB therapy, low doses are presumably better than no doses. The deleterious effects of angiotensin II on various target tissues are likely to be mitigated at least partially with low doses. The same argument can be made for using low doses of MRAs in patients with HFrEF at higher risk for hyperkalemia or worsening renal function, although more safety data in real-world populations are needed.

At What Level of Chronic Kidney Impairment, If Any, Should RAAS Antagonists be Discontinued in the Setting of Combined Heart Failure and Kidney Disease?

Although seemingly straightforward, this question requires further clarification. First, the clinician must assess the rapidity with which kidney function has declined, that is, in the inpatient setting with chronic, slow progression versus more rapid worsening during a hospital admission. Second, the risks of hyperkalemia or further decline in GFR must be considered. Because a certain reduction in GFR with the use of RAAS antagonists is expected based on changes in intraglomerular hemodynamics and filtration fraction, a higher threshold should be maintained for stopping these agents if the overall clinical picture is stable. Temporary discontinuation in the face of transient lower blood pressure or intercurrent illness may be reasonable. The serum creatinine level above which RAAS antagonists should be avoided must be individualized, although we would advise against starting these agents in nondialysis patients with a serum creatinine >3.0 mg/dL (or GFR <15–20 mL/min). However, once patients progress to renal replacement therapy, an ACE inhibitor or ARB can be used safely for blood pressure control and other presumed organ-specific benefits. For black patients with HFrEF and renal dysfunction, hydralazine and nitrates should be used per guideline recommendations. Although subgroup data from the Vasodilator in Heart Failure Trial (V-HeFT) II showed no difference in annual mortality rates between enalapril and placebo, these data from an era when standard therapy for HF was considerably different than contemporary care, including β-blockers and device based therapy, do not help to guide alternative therapy in the current era.

An even more difficult problem arises in patients hospitalized with acute HF who have more rapidly worsening renal function, usually in the face of intravenous diuretic therapy. In this increasingly common scenario, stopping ACE inhibitor, ARB, or MRA therapy (or lowering their dose) in the short-term is prudent, especially among patients with hypertension. The thresholds for holding RAAS antagonists must be individualized and depends on knowledge of the patient’s baseline blood pressure and renal function and current perfusion status. In practice, serum creatinine levels that have risen to >2.5 to 3.0 mg/dL, especially among patients with systolic blood pressures <90 to 100 mm Hg, should trigger orders to hold these medications. Whether lower thresholds (eg, serum creatinine >2.0 mg/dL and systolic blood pressure <110 mm Hg) warrant withdrawal of ACE inhibitor or ARB therapy deserves further study. Unless an MRA is needed for potassium retaining effects in patients undergoing aggressive intravenous diuresis, we recommend holding these agents as well along with the ACE inhibitor or ARB.

As is evident, these recommendations are largely based on common sense, logic, and current medical practice. In Complications: A Surgeon’s Notes on an Imperfect Science, Atul Gawande writes, “There is science in what we do, yes, but also habit, intuition, and sometimes plain old guessing.” These tendencies are understandable, but fraught with miscalculations and highlight the gap between science and practice. There are numerous examples in clinical medicine where common sense was proven to be wrong, underscoring the importance of asking scientific questions and critically analyzing the data. Collecting data on how to best treat patients with HFrEF and renal dysfunction and what benefits (versus risks) to expect is imperative because this patient population continues to grow and is a major burden on the healthcare economy. Moreover, the advent of novel RAAS antagonists (eg, selective nonsteroidal aldosterone blockers), better tolerated potassium binding polymers, and improved understanding of cardiorenal physiology may all affect successful treatment of this challenging patient population.

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