Aldosterone Antagonism and Myocardial Infarction

From Animals to Man and Back*
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Inhibiting the renin-angiotensin system has proven to be one of the most fruitful therapeutic strategies in cardiovascular medicine. Believed to have evolved to maintain blood volume and perfusion pressure in conditions of hemorrhage or hypovolemia, the renin-angiotensin-aldosterone system (RAAS) is upregulated in the setting of left ventricular (LV) dysfunction or heart failure (1). Pharmacologic inhibitors of this system—including renin inhibitors, angiotensin-converting enzyme (ACE) inhibitors, aldosterone antagonists, and angiotensin receptor blockers—were all initially designed for the treatment of hypertension, and, with the exception of renin inhibitors, are currently clinically used for this indication. Nevertheless, the benefits of inhibiting the RAAS have extended well beyond this initial therapeutic target.

Animal models of ventricular dysfunction and heart failure provided the initial impetus for early clinical work demonstrating the unique hemodynamic benefits of ACE inhibitors (2–5). These animal and early clinical experiments were followed by placebo-controlled trials in late 1980s and early 1990s, which demonstrated that treatment with ACE inhibitors reduced morbidity and mortality in both heart failure and post-myocardial infarction patients (6–11). In these studies, ACE inhibitors were used in addition to conventional therapy, which was at the discretion of the treating physician. Because few agents had demonstrated benefit in these clinical settings, ACE inhibition became almost required therapy when tolerated for patients with heart failure or myocardial infarction (MI) complicated by heart failure or LV dysfunction (12,13).

By the late 1990s, there was increasing interest in alternative and complementary methods for inhibiting the RAAS in patients with cardiovascular disease. New clinical trials were initiated in patients with heart failure or following infarction to test two separate classes of RAAS inhibitors—the newly developed angiotensin receptor blockers (14–16) and the previously available aldosterone antagonist spironolactone. The ELITE II trial directly compared an angiotensin receptor blocker to an ACE inhibitor in heart failure patients, yet it failed to show a mortality benefit to receptor blockade over ACE inhibition. The ValHEFT trial, in contrast, was designed to assess the benefit of adding an angiotensin receptor blocker to conventional therapy in heart failure, which included ACE inhibition in the majority of patients (16). Although concerns about the safety of combination therapy remained, mechanistic evidence suggested a potential benefit of adding an angiotensin receptor blocker to an ACE inhibitor in heart failure (17). Furthermore, the phenomenon of angiotensin and aldosterone “escape,” in which both angiotensin and aldosterone levels, initially lowered by ACE inhibition, would eventually increase to pretreatment levels, was well known (18,19). Despite these potential benefits of combined therapy, the ValHEFT trial did not demonstrate a survival benefit with valsartan added to conventional therapy, although the addition of valsartan resulted in a clear reduction in the incidence of heart failure. The recently reported Candesartan in Heart Failure (CHARM) trial, further demonstrates the clinical benefit of adding an angiotensin receptor blocker to standard therapy in heart failure patients (20).

Despite the fact that spironolactone had been successfully used in the treatment of hypertension for some time (21), it had not been tested in a broader range of cardiovascular disorders. The first major trial to assess the use of an aldosterone antagonist in patients with LV dysfunction, the Randomized Aldactone Evaluation Study (RALES), assessed the effect of spironolactone compared with placebo among optimally managed heart failure patients (22). Mortality was reduced by 30% in patients treated with spironolactone. This finding, however, was met with some reservation in the general cardiology community. Inhibiting the aldosterone receptor was believed to confer only partial inhibition of the RAAS. Angiotensin II (ang II), rather than aldosterone, was thought to mediate most of the deleterious effects of RAAS activation. In addition to its vasoconstrictor effect, ang II is recognized to promote vascular smooth muscle cell growth and proliferation and myocyte hypertrophy (23). Traditionally, the effects of aldosterone inhibition were thought to be primarily in the kidney, where aldosterone stimulates retention of sodium and water and secretion of potassium in the distal tubule. Yet a growing body of evidence suggests that aldosterone, like angiotensin, mediates a variety of actions throughout the cardiovascular system and may play a role in cardiac and vascular fibrosis and ventricular remodeling (24–27). Aldosterone, like ang II, stimulates fibroblast growth and syn-

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the Cardiovascular Division, Brigham and Women’s Hospital, Boston, Massachusetts. Dr. Solomon receives research support and has served as a consultant for Novartis and AstraZeneca. Dr. Pfeffer has received honoraria and/or educational or research grants, or has served as a consultant for AstraZeneca, Aventis, Bristol-Myers Squibb, Mitsubishi, Novartis, and Pfizer. The Brigham and Women’s Hospital has been awarded patents regarding the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in selected survivors of myocardial infarction. Dr. Pfeffer is among the co-inventors. Licensing agreements with Novartis and Merck are not linked to sales.
thesis of fibrillar collagen (28). Additionally, aldosterone induces both oxidative stress and a proinflammatory response, an effect that can be attenuated with spironolactone (29).

Many therapies that have proven beneficial in heart failure patients have also shown benefit in patients following MI. This is in part due to the fact that a large percentage of heart failure patients are survivors of MI and that many of the neurohormonal systems—including the RAAS—that are activated in heart failure are also activated following infarction. Additionally, the RAAS has been implicated in healing and remodeling following MI: angiotensin is directly involved in collagen synthesis and breakdown pathways (30) and may mediate post-MI tissue repair (31).

In this issue of the Journal, a report by Fracarollo et al. (32) furthers our understanding of the role of aldosterone receptor blockade following MI. Epleronone, a selective aldosterone receptor antagonist with fewer side effects than spironolactone (33,34), was compared in a rat MI model with placebo, the ACE inhibitor trandolapril, or a combination of eplerenone and trandolapril. There were significant hemodynamic benefits to treatment with eplerenone and even greater benefits with the combination of agents. These hemodynamic improvements included a decrease in $\tau$ (tau), the time constant of relaxation, a reduction in end-diastolic volume and pressure, and, most importantly, a substantially leftward shift of the pressure-volume loops with an overall reduction in LV remodeling. In addition, these mechanistic data provide important insight into the cellular and biochemical mechanisms of the incremental benefit of aldosterone receptor blockade. Both collagen type I gene expression and collagen content in the noninfarcted myocardium were decreased by ACE inhibition, but the normally observed increases in collagen content following infarction were essentially abolished by eplerenone or the combination of eplerenone and trandolapril. Combination therapy additionally prevented SERCA2 and ATPase downregulation, and decreased both beta-myosin heavy chain and atrial natriuretic factor gene expression.

The results of this study (32) are of particular importance in light of the recently published EPHESUS trial (35). In this double-blind, placebo-controlled study, eplerenone was compared to placebo in patients with LV dysfunction following infarction who were already receiving standard therapy. Treatment with eplerenone led to a 15% reduction in overall mortality and a 17% reduction in cardiovascular deaths in patients treated with eplerenone. Heart failure was reduced by 23%, and sudden death by 21%, in the eplerenone group. Of note, 87% of patients enrolled were already being treated with ACE inhibitors and 75% received beta-blockers, indicating that the aldosterone inhibitor indeed provided incremental benefit to optimal therapy.

The RALES and EPHESUS studies firmly establish the incremental value of aldosterone receptor blockade in patients with heart failure and high-risk MI. The results of the Fracarollo study (32) along with those of EPHESUS, demonstrate the bidirectionality of the bench-to-bedside model. Just as clinicians are being challenged to evaluate new therapies on background use of other proven agents, this animal study has adopted a similar experimental design to assess the incremental value of an aldosterone antagonist in the setting of ACE inhibition. In this case, the rat infarct model, which provided much of the rationale for clinical use of ACE inhibitors used in heart failure and following infarction, has offered important basic insights into the results of a clinical trial. Taken together, the clinical trial and experimental results provide a compelling rationale for combined approaches to inhibiting the renin-angiotensin aldosterone system after infarction.

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