COMMENTARY

Renin Angiotensin Aldosterone System Blockade in Practice: A Clinical Perspective

Virendra K Misra, Wael Al-Mahmeed

Institute of Cardiac Sciences, Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates.

Corresponding author: Dr. Wael Al-Mahmeed Email: walmahmeed@skmc.ae
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Introduction

Although it has been over a century since RAAS was discovered by Robert Tigerstedt in 1897 (1), it took up to 1981 for the first ACE inhibitor (ACEI), Captopril, to be approved by the Food and Drug Administration (FDA) for human use in the United States. Since then numerous ACEI's have come into the market (2). The group of physicians from Dubai Hospital have recently reviewed in this Journal the role of renin-angiotensin-aldosterone system (RAAS) inhibition in the renal continuum (3) and in the current issue, they elaborated further on RAAS in the cardiovascular continuum by examining the trial evidence and clinical practice (4). The authors have comprehensively described the benefit of different angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and direct renin inhibitors in cardiovascular as well as renal protection (3,4)

Mechanistic Aspects

The mechanism by which ACEIs act in heart failure (HF) is not completely understood (3,4). The CONSENSUS trial two decades ago firmly established that ACEI's favourably influence the course of HF, and paved the way for a series of large scale trials that evaluated ACEIs through cardiovascular disease continuum (5). Early similar trials in post-MI myocardial dysfunction and HF such as SOLVD, SAVE, AIRE, TRACE and SMILE (6-10) have all shown ACEIs favourably mediated outcome post-MI and HF as discussed in the reviews The ATLAS study compared the efficacy and safety of low and high doses of ACE inhibitor on the risk of death and hospitalization in HF, and provided first evidence of the importance of up-titrating ACE inhibitor in HF to the highest tolerated dose (11). The landmark HOPE trial in patients with CV risk factors but no HF showed that Ramipiril-treated patients had a 22% lower relative risk compared to placebo of the primary composite of CV death, MI, or stroke. The benefit of the ACEI Perindopril was also observed in the EUROPA trial in low-

risk cohort with coronary artery disease (CAD) but no LV dysfunction or HF. After 4.2 years, Perindopril reduced the relative risk for the composite of CV death, cardiac arrest or MI by 20% (12). The ANBP2 trial comparing ACEI's with diuretics as antihypertensives showed that ACEIs reduced CV events or all-cause mortality particularly in men despite similar reductions of BP in the two groups (13). A number of observations suggest that ACEI's and ARBs prevent the development of new or recurrent atrial fibrillation in a variety of clinical settings. Evidence that these agents reduce the incidence of AF in patients who have had an MI comes from the TRACE and SOLVD, Val-HeFT trials (14,15). ARBs such as Losartan, Valsartan, Irbesartan, Candesartan, Telmisartan etc. block the binding of angiotensin II to the AT1 receptor. One important consequence of this difference is that ARBs do not affect kinin metabolism and consequently do not appear to induce cough in contrast to ACEIs.

ACEI's, ARBs or Both: The evidence base!

Mounting evidence suggests that ARBs share the same clinical spectrum as ACE inhibitors in a variety of settings such as hypertension, HF, and chronic renal failure. However, there are differences between these two classes of drugs. In addition to the differential effect of kinins, inhibition of angiotensin II formation with an ACEI will diminish the activity of both the AT1 and AT2 receptors, whereas the ARBs only diminish AT1 activity (16). The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study provided first evidence of cardio-protection afforded by an ARB. In LIFE, 9,193 patients received either losartan or atenolol over a period of at least 4 years who had hypertension and evidence of LVH (17,18). At similar and marked reduction in BP for both arms, Losartan significantly reduced the composite of CV death, stroke or myocardial infarction. This benefit was almost exclusively due to the reduced risk for fatal or non-fatal stroke, while the incidence of CV death or MI was not different between the treatment arms. ARBs also reduce the sympathetic activation seen in heart failure as illustrated by the Val-HeFT trial. A meta-analysis reporting effects of ACEIs and ARBs in patients without heart failure, suggest that ARBs significantly reduced the risk of the composite outcome by 7.0%, significantly reduced the risk of new-onset diabetes by 10.6%. Significant heterogeneity among trials was found only for CV death. The effects on major clinical events of ARBs in patients without HF have been evaluated in several trials reporting conflicting results (19). In the RENAAL study, diabetic patients with nephropathy, Losartan compared with placebo reduced the incidence of a doubling of the serum creatinine concentration (risk reduction, 25 percent; P=0.006) and end-stage renal disease (risk reduction, 28 percent; P=0.002) but had no effect on the rate of death. There was no reduction of mortality from cardiovascular causes. Although the rate of first hospitalization for heart failure was significantly lower with losartan (risk reduction, 32 percent; P=0.005). The level of proteinuria declined by 35 percent with losartan (P<0.001) (20).

In the SCOPE, Candesartan in hypertensive elderly patients failed to reduce the primary composite outcome of CV death, MI, whereas it resulted in a significant 42% RR reduction in stroke in comparison with other antihypertensive treatment and new-onset DM (21). In contrast, in a small study enrolling high-risk patients, Candesartan, compared with placebo, significantly reduced the risk of a composite outcome including CV death, MI, and coronary revascularization. In the TRANSCEND trial in which ACEI-intolerant patients were assigned to either Telmisartan or placebo, there was a 13% reduction in the secondary combined endpoint, including CV death, MI, and stroke (p = 0.05) However the primary outcome of hospitalization for HF was not significantly reduced (22). In the NAVIGATOR trial, a double-blind with 9306 stable patients, were enrolled with impaired glucose tolerance with or at high risk of developing CV disease, Valsartan reduced the occurrence of DM by 14% but failed to reduce CV morbidity or mortality (23). In a meta-analysis, ARBs significantly reduce the composite outcome of CV death, MI, and stroke by 7.0%, as well as stroke by 9.1% and new-onset DM by 10.6% in high-risk, mostly diabetic or glucose-intolerant patients without HF enrolled in randomized clinical trials (24). A meta-analysis of 147020 patients, clearly suggested that ARB were not associated with an increased risk of MI, angina, or death. Risk of stroke, HF, and new onset of DM was reduced (25). Combining ACEIs and ARBs did not give additional benefit. VALIANT trial did not find a benefit of combined therapy with valsartan and captopril compared to monotherapy with either drug alone in patients with HF occurring within 10 days after an acute MI (26). Similar results also suggested by combination of Telmisartan with Ramipril with no further clinical benefit and seems to be associated with higher rates of adverse effects than either treatment alone (27). Other clinical trials also did not support combination therapy either, thus, combining ACEIs and ARBs is not recommended and should only be considered in special circumstances(28).

Addition of spironolactone to RAAS blockade

The usefulness of spironolactone in heart failure was studied in RALES (29). Eplerenone, the first selective aldosterone receptor antagonist, does not have the undesirable side effects of spironolactone related to its affinity for estrogen and androgen receptors and is in use since 2004 worldwide. The EPHESUS study also demonstrated beneficial effects of Eplerenone in patients with ventricular dysfunction associated with acute myocardial infarction (30). The additional benefit of aldosterone receptor blockade to ACEI or ARB therapy was attributed to antagonizing the "aldosterone breakthrough phenomenon" in which aldosterone is synthesized via non-renin-angiotensin pathways (31,32). Thus, these clinical trials offered a precious lesson that specific blockade of aldosterone is associated with significant additional benefits in patients with cardiovascular diseases receiving other RAAS inhibitors (33). Chymase which is stored in mast cells get activated upon its release and converts angiotensin I into angiotensin II. Chymase also releases latent transforming growth factor (TGF)-β from latent TGF-β binding protein of the extracellular matrix. Inhibition of chymase activity is a type of RAAS blockade and interestingly angiotensin II primarily comes by chymase activity in the human cardiomyocyte and vasculature. Oral non-peptide chymase inhibitors have been developed and their cardiovascular protective effect, especially their antifibrotic effect, was demonstrated in animal models. However, to date none of the chymase inhibitors have progressed to clinical trials. Also, we should keep in mind that the effects of chymase inhibition are attributed not only to the inhibition of chymase-dependent angiotensin II production but also to the inhibition of chymase-dependent TGF-β activation (34).

Role of direct renin inhibition

Renin controls the first, rate-limiting step of the RAAS. The first oral direct renin inhibitor (PRA), Aliskiren, was approved for the treatment of hypertension in 2007. This new class of RAAS blockers offers new therapeutic options for various kinds of cardiovascular diseases (35). It is known that ACEIs and ARBs both cause a compensatory increase in PRA, and direct renin inhibition decreases the PRA and, in turn, the production of angiotensin II and aldosterone. We also know that elevated plasma renin activity is associated with increased risk of major cardiovascular events such as acute myocardial infarction, chronic heart failure, and hypertension (36). The ATMOSPHERE trial is currently examining the efficacy of Aliskiren monotherapy and its combination with Enalapril as compared to Enalapril monotherapy on morbidity and mortality in patients with chronic heart failure (37). Combining direct renin inhibitor with ACE inhibitor or ARB to define cardio protection and cardio-renal outcome in different clinical trials are underway. Initial studies combining Aliskiren with an ARB have shown beneficial effects on hypertension and reno-protection. The results of ongoing clinical studies of Aliskiren combinations with an ACE inhibitor or ARB are eagerly awaited (38).

Disclosures

The authors report no conflicts of interest in this work. All the Trials' acronyms are spelled out in the cited references list and in the accompanying review.

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