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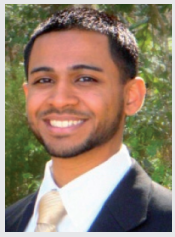

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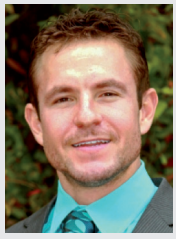

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"…there is evidence, both direct and circumstantial, to indicate that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may only partially extinguish the effects of the renin–angiotensin–aldosterone system."

The renin–angiotensin–aldosterone system (RAAS) plays a critical role in the homeostatic control of vascular tone and extracellular volume. Although its activation is typically a compensatory mechanism to alleviate a reduction in blood pressure (BP), chronic activation of the RAAS contributes to endothelial dysfunction, tissue fibrosis, cellular remodeling and, ultimately, cardiorenal complications [1]. For decades, pharmacotherapy has been available to intercept the debilitating effects of the system's major effector peptide, angiotensin II, along the cardiorenal continuum. Preventing the binding of angiotensin II to its receptor, AT_1, either by reducing production of angiotensin II or by occupying the receptor, has been the method for dimming RAAS-mediated cardiorenal disease. ACE inhibitors (ACEIs) and ARBs have proven to be successful in reducing cardiovascular and renal events; however, there is evidence, both direct and circumstantial, to indicate that ACEIs and ARBs may only partially extinguish the effects of the RAAS [2,3].

Plasma renin activity (PRA) is used to quantify the level of RAAS activity, and it has been shown to independently predict major vascular events and mortality in patients with stable chronic vascular disease [4]. While ACEIs and ARBs initially mitigate the activity of angiotensin II, they promote a compensatory increase in PRA owing to interruption of negative feedback – juxtaglomerular cells in the kidney sense a loss of AT_1 receptor stimulation [5]. During ACEI therapy, angiotensin II levels initially fall but later rebound due to ACE-independent mechanisms (i.e., ACE-escape or angiotensin II reactivation). For example, serine proteases, such as chymase, are released secondary to the elevated bradykinin levels and convert angiotensin I to angiotensin II independent of ACE [6]. These alternate pathways may account for up to 40% of angiotensin II activation [7]. ARB therapy results in unopposed AT_2 activation and also blocks the deleterious effects of angiotensin II, regardless of its origin. Unfortunately, ARBs are unable to block all AT_1 receptors and may permit aldosterone escape (i.e., aldosterone breakthrough). Collectively, these alternate pathways could result in the full potential of ACEI or ARB therapy never being fully realized.

It has been hypothesized that simultaneously employing ACEIs and ARBs might extinguish the RAAS more completely and may provide clinical utility in patients with essential hypertension as positive results emerged in both heart failure and chronic kidney disease patients. The use of an ACEI would reduce the levels of angiotensin II, while the concurrent use of an ARB would protect the AT_1 receptor from breakthrough angiotensin II and increase

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divert angiotensin II to the AT_2 receptor which might protect cells from ischemic injury and apoptosis [8]. However, recent data from the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) has all but shattered the idea that less RAAS is more. ONTARGET suggested that combining these agents does not provide any incremental benefit but increases the rate of hypotension, hyperkalemia, renal dysfunction, and syncope in high-risk patients with cardiovascular disease and diabetes [9]. Unfortunately, the tantalizing hypothesis of dual RAAS blockade as a panacea for hypertension, which was based on studies in heart failure and proteinuria, did not come to fruition.

The direct renin inhibitor (DRI), aliskiren, represents a newer class of RAAS blocking agents that offer more proximal and more comprehensive interruption of the RAAS. By directly blocking the enzymatic activity of renin, aliskiren interferes with the rate-limiting step in the activation of the RAAS. When used as monotherapy or in combination with other RAAS blocking agents, DRIs have been shown to effectively interrupt the RAAS and decrease PRA levels [10]. Coupling a DRI with an ACEI, ARB or aldosterone antagonist is an alternative to combining an ACEI and ARB. There are three reasons that may make the former a more sensible option. First, the reactive rise in PRA, which is independently associated with an increased risk for cardiovascular events, is neutralized with DRIs. Second, when given in combination with an ACE or ARB, there are theoretical advantages. With DRI and ACEI therapy the RAAS is inhibited at two sequential steps and bradykinin is able to mediate a menu of favorable effects, including vasodilation. Teaming a DRI and ARB blocks the system at the receptor level (ARB) while minimizing a rise in PRA (DRI), which can reignite the RAAS and overcome the receptor blockade. Indeed, the combination has been shown to result in a 50% reduction in aldosterone levels over ARB monotherapy [11]. Any angiotensin I escaping DRI will be freely converted to angiotensin II and bind the AT_2 receptor. Third, studies have shown an incremental drop in BP with a DRI/ACEI or DRI/ARB combination, as well as signals for organ protection [12,13].

> **"While the reductions in blood pressure and surrogates seen in these studies combining direct renin inhibitors/angiotensin-converting enzyme inhibitors or direct renin inhibitors/angiotensin receptor blockers are promising, the clinical utility of this strategy and its position on the hypertension treatment ladder remains unclear pending the results of large cardiorenal outcome trials."**

To date, trials assessing the effectiveness of DRI/ACEI or DRI/ARB combination have provided positive results in reducing BP. When compared with their individual monotherapies over a period of 8 weeks, the combination of aliskiren and valsartan provided significant additional reductions in systolic and diastolic BP ($p < 0.0001$) and 24-h systolic and diastolic BP ($p < 0.0001$) in patients with stage 1 and 2 hypertension [8]. As add-on therapy in patients unresponsive to hydrochlorothiazide (HCTZ) monotherapy, the combination of aliskiren and valsartan provided greater reductions in systolic and diastolic BP than aliskiren plus HCTZ, valsartan plus HCTZ or HCTZ alone [14]. Similar to an ACEI and ARB combination strategy, DRIs have been shown to reduce surrogate end points in heart failure patients (i.e., B-type natriuretic peptide [BNP], N-terminal pro-BNP and left ventricular hypertrophy) and in diabetic kidney disease (i.e., proteinuria) when combined with either an ACEI or ARB [12,15]. Conversely, results from the Aliskiren Study in Post-MI Patients to Reduce Remodeling (ASPIRE) program demonstrated aliskiren's inability to positively affect left ventricular remodeling in a population of post-MI patients. The tolerability of combining a DRI with an ARB was found to be similar to the individual components, with the exception of a higher rate of hyperkalemia (>5.5 mmol/l) [8].

> **"...the tantalizing hypothesis of dual renin–angiotensin–aldosterone system blockade as a panacea for hypertension ... did not come to fruition."**

While the reductions in BP and surrogates seen in these studies combining DRIs/ACEIs or DRIs/ARBs are promising, the clinical utility of this strategy and its position on the hypertension treatment ladder remains unclear pending the results of large cardiorenal outcome trials. In the meantime, we must interpret the DRI/ACEI or DRI/ARB combination data with cautious enthusiasm given the results of ONTARGET, which contrast with those of studies in heart failure and proteinuria. The highly anticipated Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Disease Endpoints (ALTITUDE) program is well underway and will reveal much needed cardiorenal outcome data with the use of a DRI/ACEI or DRI/ARB in diabetic patients. Additionally, novel agents are approaching the market that will enhance our understanding of the RAAS (i.e., Ang-[1–7] agonist, chymase inhibitors, AT_2 activators and Pro[renin] receptor blockers) [16–19]. Although premature in their development process, the fate of these agents is greatly awaited. ACEIs, ARBs and DRI have been invaluable tools for reducing the risk of cardiovascular disease, but by no means have they conquered the malady. Future studies will hopefully reveal whether less RAAS is more, or not.

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