Curr Diab Rep (2010) 10:32–36
DOI 10.1007/s11892-009-0081-y

Pleiotropic Effects of Inhibitors of the RAAS in the Diabetic Population: Above and Beyond Blood Pressure Lowering

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Published online: 19 January 2010

Abstract Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are indispensable therapeutic agents for treating hypertension and proteinuria in patients with diabetes mellitus. Studies have shown that the renin-angiotensin-aldosterone system (RAAS) has effects on various organ systems, including the central nervous system, heart, and kidneys. Angiotensin II has major deleterious effects on vascular compliance, vascular relaxation, and plasma markers of inflammation, which are surrogate markers of cardiovascular disease. Evidence is established from major trials that ACE inhibitors and ARB therapy improve these surrogate markers and reduce cardiovascular disease, renal disease, and stroke. Accumulating evidence also supports the newer class of medication, the direct renin inhibitor aliskiren, as beneficial in hypertensive persons with diabetes mellitus. In this article, we review the mechanisms through which inhibitors of the RAAS benefit persons with hypertension and decrease the development of cardiovascular and renal disease above and beyond blood pressure lowering.

Keywords Angiotensin-converting enzyme inhibitors · Angiotensin receptor blockers · Renin-angiotensin-aldosterone system · Diabetes

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Clinical Trial Acronyms

ALLAY	Aliskiren Left Ventricular Assessment of Hypertrophy
ALOFT	Aliskiren Observation of Heart Failure Treatment
ALTITUDE	Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints
AVOID	Aliskiren in the Evaluation of Proteinuria in Diabetes
CAPPP	Captopril Prevention Project
HOPE	Heart Outcomes Prevention Evaluation
MICRO-HOPE	Microalbuminuria, Cardiovascular and Renal Outcomes
ONTARGET	Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial

Introduction

There is paramount evidence that inhibitors of the renin-angiotensin-aldosterone system (RAAS) offer special benefits beyond blood pressure control to the diabetic population. It has been shown that angiotensin II affects surrogate markers of cardiovascular disease, renal disease, and stroke [1–4]. Furthermore, persons with an altered RAAS appear to have impaired insulin sensitivity and glucose metabolism placing them at a higher risk for diabetes [5–12]. Studies show that angiotensin-converting enzyme (ACE) inhibitor therapy appears to improve insulin sensitivity and glucose metabolism [5, 6, 9–11]. The effectiveness of angiotensin receptor blocker (ARB) therapy appears to be equivalent to ACE

inhibitor therapy, possibly even with a refined side-effect profile [13•]. Furthermore, there is evidence that a relationship exists between hypertension, type 2 diabetes mellitus, and the cardiometabolic syndrome [5, 6]. Therefore, therapy with ACE inhibitors and ARBs offers us an opportunity to positively impact on the multiple comorbidities associated with hypertension and type 2 diabetes mellitus. The RAAS appears to affect multiple organ systems. In this article, we outline inhibitors of the RAAS that can offer success in reducing the development of cardiovascular disease, renal disease, and stroke.

Pleiotropic Effects of RAAS Inhibitors

RAAS inhibitors have been proven to be excellent medications for blood pressure control. They are generally used by most physicians as the first-line medication for hypertensive patients with diabetes mellitus. RAAS inhibitors control hypertension; however, another major reason they are used is that they have been proven by numerous trials to decrease cardiovascular and renal morbidity and mortality. They inhibit the production of angiotensin II, which has been shown to contribute to vasculopathy and hypercoagulability. In addition, diabetes mellitus and hypertension also have been shown to promote coagulopathy and vasculopathy through activation of the RAAS. Therefore, RAAS inhibitors can interrupt the perpetual detrimental effects of these diseases. They can limit the multiple effects of diabetes mellitus and hypertension on the cardiovascular, renal, and central nervous system. Furthermore, trials have compared RAAS inhibitors to other antihypertensive medications, and RAAS inhibitors, for example, have been proven to be superior in decreasing albuminuria in diabetic nephropathy. This further proves the pleiotropic effects of RAAS inhibitors, which are above and beyond blood pressure control [1–4].

Etiology of Hypertension and Insulin Resistance

Hypertension is a worldwide epidemic that affects about 65 million people in the United States. It is a significant modifiable risk factor for coronary heart disease (CHD) and chronic kidney disease. It has been reported that an increase of 20 mm Hg in systolic blood pressure or 10 mm Hg in diastolic blood pressure doubles the risk of CHD across the blood pressure range of 115/75 to 185/115 mm Hg in persons 40 to 70 years of age [14]. Therefore, control of blood pressure is critical; it has been shown to reduce stroke by 35% to 40%, myocardial infarction by 20% to 25%, and heart failure by 50% [15•].

Hypertension has been demonstrated to be related to insulin resistance and resultant hyperinsulinemia [13•]. Insulin resistance causes abnormalities in insulin signaling, which includes resistance to effects of insulin on peripheral tissues and the vasculature [14]. Insulin leads to activation of the RAAS and, therefore, contributes to the etiology of hypertension. Many other mechanisms contribute to the etiology of hypertension in the insulin-resistant state, which includes endothelial cell dysfunction, left ventricular hypertrophy, dyslipidemia, hyperglycemia, microalbuminuria, and progressive chronic kidney disease [13•]. Microalbuminuria, a marker of nephropathy, is also a significant component of the cardiometabolic syndrome. It also impairs vascular compliance with loss of normal nocturnal lowering of systolic and diastolic blood pressure. Therefore, microalbuminuria is an important marker of renal disease and, as a result, CHD morbidity and mortality.

Angiotensin II, Its Production, and Its Relationship to Vasculopathy

To adequately understand the effects of angiotensin II, we will briefly review the RAAS. Angiotensin II is produced in the rate-limiting step of the RAAS (Fig. 1). Prorenin is transformed to renin in the kidneys and subsequently secreted to cleave angiotensinogen to angiotensin I. ACE converts angiotensin I, which is biologically inactive to angiotensin II. Angiotensin II subsequently binds to AT1 receptors to stimulate various biological effects (eg, vasoconstriction, release of vasopressin, release of aldosterone from the adrenal cortex) and a number of other effects [16•].

ACE inhibitors block the conversion of angiotensin I to angiotensin II and ARBs inhibit the AT1 receptor, and both of these drug classes have been shown to have beneficial effects in hypertensive patients. Another class of medications, the direct renin inhibitor aliskiren, directly inhibits renin and, therefore, the rate-limiting step in the RAAS. This is another addition to the armamentarium of RAAS inhibition that offers a novel approach to preventing target organ damage and cardiovascular events [16•].

Angiotensin II exerts its many effects directly on endothelial cells and vascular smooth muscle cells [1, 6, 17]. One of the many effects is generation of reactive oxygen species, which contribute to opposing the beneficial vascular action of nitric oxide [18–20]. Angiotensin II stimulates production of proinflammatory molecules such as plasminogen activator inhibitor and processes that contribute to vascular inflammation and increased coagulopathy [1, 18–20].

It has been shown that diabetes mellitus, insulin resistance, and hypertension also promote hypercoagulability and impair fibrinolysis [21–24]. Another important observation of why

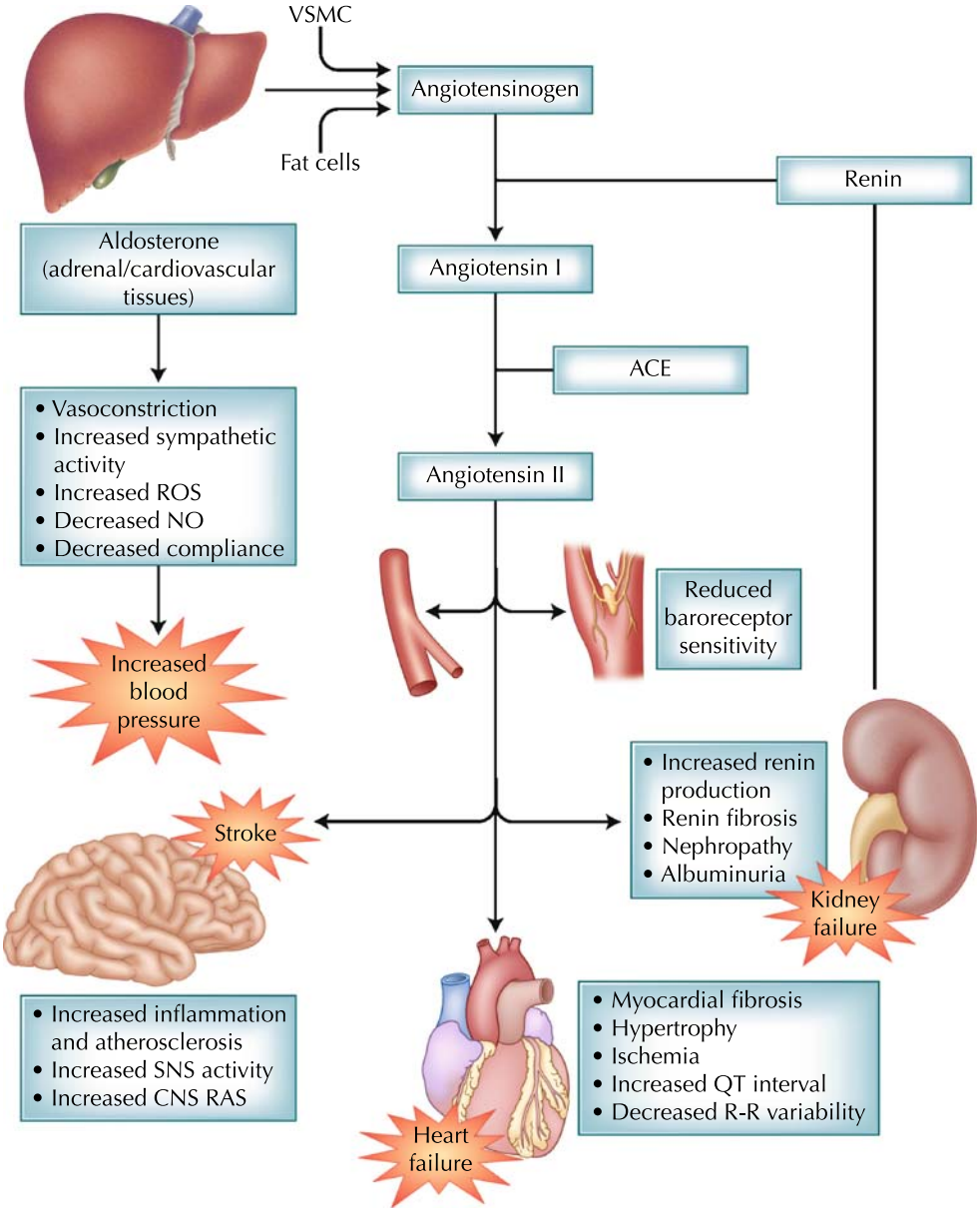

Fig. 1 The renin-angiotensin-aldosterone system (RAAS) portraying the effects of angiotensin II. *ACE* angiotensin-converting enzyme, *CNS* central nervous system, *NO* nitric oxide, *ROS* reactive oxygen species, *SNS* sympathetic nervous system, *VSMC* vascular smooth muscle cell. (*From* McFarlane [6]; with permission.)

inhibitors of the RAAS improve inflammatory markers is the tissue ACE appears to deactivate tissue plasminogen activator production, further perpetuating the inflammatory state of the vasculature [25]. This is another way ACE inhibitors improve fibrinolysis and further reduce the impact of diabetes mellitus, insulin resistance, and hypertension.

Angiotensin II additionally has been shown to increase arterial wall stiffness, thus impairing vascular compliance [1]. Vascular compliance is an important predictor of vasculopathy, and antihypertensive medications, especially RAAS inhibitors, have had a positive impact [26]. Studies have shown that ACE inhibitors and ARBs exert a beneficial effect on vascular compliance by increasing distensibility and decreasing media-lumen ratio of the microvasculature [27].

RAAS Inhibition and Its Impact on Diabetic Nephropathy

Type 2 diabetes mellitus is the leading cause of end-stage renal disease in the United States today. Chronic renal disease has a major economic impact on health care costs in the United States and is a significant public health problem. Furthermore, diabetic nephropathy, which is indicated by the presence of albuminuria, is associated with a definite increase in the rate of cardiovascular events [28•]. Inhibitors of the RAAS have been shown to be more effective in reducing albuminuria than other classes of antihypertensives, and thus help limit the progression of renal disease by angiotensin II [29–32]. This benefit can therefore reduce the rate of diabetic nephropathy and the associated cardiovascular risk.

Trials of RAAS Inhibitors Demonstrating Pleiotropic Effects

Various trials have studied the pleiotropic effects of RAAS inhibitors and have propelled RAAS inhibitors to the forefront of blood pressure control in diabetic patients. The ACE inhibitor ramipril was analyzed in the HOPE trial. This trial included 3577 patients with diabetes mellitus, and the use of ramipril was associated with a 25% risk reduction in myocardial infarction, stroke, and cardiovascular death [13•]. In addition, the substudy MICRO-HOPE also revealed that ramipril decreased the development of diabetic nephropathy [13•]. CAPPP also proved that ACE inhibitors lower the risk of fatal and nonfatal myocardial infarction, stroke, and cardiovascular deaths [9]. This further substantiates the fact that ACE inhibitors have a positive impact on the cardiovascular, renal, and cerebrovascular systems. An additional trial, the recent ONTARGET trial, demonstrated that telmisartan had a similar benefit to ramipril in high-risk vascular disease and diabetic patients. This important study showed that ARB therapy is just as efficacious as ACE inhibitor therapy in patients with vasculopathy.

More recent studies have shown that the direct renin inhibitor aliskiren is equivalent in efficacy to ACE inhibitors and ARBs when used as monotherapy in blood pressure reduction in diabetic patients [33]. Aliskiren is an adequate blood pressure medication for use in diabetic patients. In the ALLAY trial, aliskiren was shown to be just as superior in reducing left ventricular mass index as the ARB losartan [34•]. Moreover, in the ALOFT trial, findings revealed that aliskiren was just as safe and efficacious as other RAAS inhibitors in patients with heart failure [34•]. There also have been studies that showed that the combination of aliskiren with an ACE inhibitor or an ARB is also beneficial. In the AVOID study, adding aliskiren to ARB treatment reduced the mean urinary albumin-to-creatinine ratio by 20% [34•]. This revealed that aliskiren is advantageous when combined with ARB therapy in reducing renovascular disease in diabetic patients. Further studies, such as the ALTITUDE trial, aim to show whether adding aliskiren to conventional ACE and ARB therapy would further reduce cardiovascular and renal morbidity and mortality in high-risk hypertensive patients with diabetes [34•].

Conclusions

Pharmacologic inhibition of the RAAS, which includes ACE inhibitors and ARBs, has become an integral part of the treatment of hypertension in diabetic patients. Increased RAAS activity, particularly angiotensin II, has been shown to have detrimental effects on various organ systems such as the heart, kidneys, and the central nervous system. Therefore, interruptions in the RAAS can afford special benefits in persons with the cardiometabolic syndrome. Hypertension is a significant risk factor for cardiovascular and renal disease and its relationship with insulin resistance and resultant diabetes has been investigated. Studies continue to show that RAAS inhibitors are not only impressive in reducing blood pressure, but also in changing the inherent course of heart failure and proteinuric renal disease [33]. Studies even support the newest member of the RAAS inhibition armamentarium, the direct renin inhibitor aliskiren, as having favorable effects on vasculopathy, cardiovascular disease, and diabetic nephropathy. We will continue to observe how renin inhibition has a place in the novel pharmacologic approach of RAAS inhibition and prevention or possible reversal of target organ damage.

Disclosure No potential conflicts of interest relevant to this article were reported.

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