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Pharmacological interventions into the renin–angiotensin system with ACE inhibitors and angiotensin II receptor antagonists: effects beyond blood pressure lowering

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***Abstract*:** Hypertension is recognized as an important risk factor for cardiovascular morbidity and mortality. Lowering of blood pressure has been shown to minimize the risk of cardiovascular events, with the majority of antihypertensives demonstrating a similar ability to reduce coronary events and stroke for a given reduction in blood pressure. Agents that modify the activity of the renin–angiotensin system (RAS) have been proposed to exhibit additional effects that might go beyond simple blood pressure lowering. The RAS is a crucial system that regulates extracellular fluid volume and blood pressure. Proposed potential benefits of RAS blockade that go beyond blood pressure lowering include a reduction in platelet aggregation and thrombosis, blunting of cardiac and vascular remodeling, favorable metabolic effects and reno- and cerebro-protection. However, factors such as treatment adherence, duration of action of antihypertensive agents and differences in effects on central *versus* brachial blood pressure may also result in apparent differences in efficacy of different antihypertensives. The aim of this review article is to examine the available data from clinical studies of antihypertensive drugs for evidence of effects that might legitimately be claimed to go beyond simple blood pressure lowering.

Keywords: ACE inhibitors, angiotensin II, blood pressure, RAS, renin–angiotensin system

Introduction

Hypertension is recognized as an important risk factor for cardiovascular morbidity and mortality [Gu *et al.* 2012]. Numerous interventional studies, the earliest of which were published almost 50 years ago, convincingly show that lowering of blood pressure (BP) with drug treatment improves morbidity and mortality in such patients [Veterans Administration Cooperative Study Group on Antihypertensive Agents, 1967, 1970]. Since then, the main aim of antihypertensive treatments has been to ensure adequate BP control to minimize the risk of cardiovascular events [Gu *et al.* 2012]. This concept is supported by meta-analyses of hypertension intervention trials, which have demonstrated that all classes of BP-lowering drugs, with the exception of β-blockers, have a similar ability to reduce coronary events and stroke for a given reduction in BP [Carlberg *et al.* 2004; Bangalore *et al.* 2008; Law *et al.* 2009].

While the predominant role of BP lowering as the mediator of cardiovascular protection through the use of antihypertensive therapy has been widely accepted, experimental and clinical studies have claimed additional effects of certain BP-lowering strategies. In this context, agents modifying the activity of the renin–angiotensin system (RAS), such as angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs), may exhibit effects beyond BP lowering.

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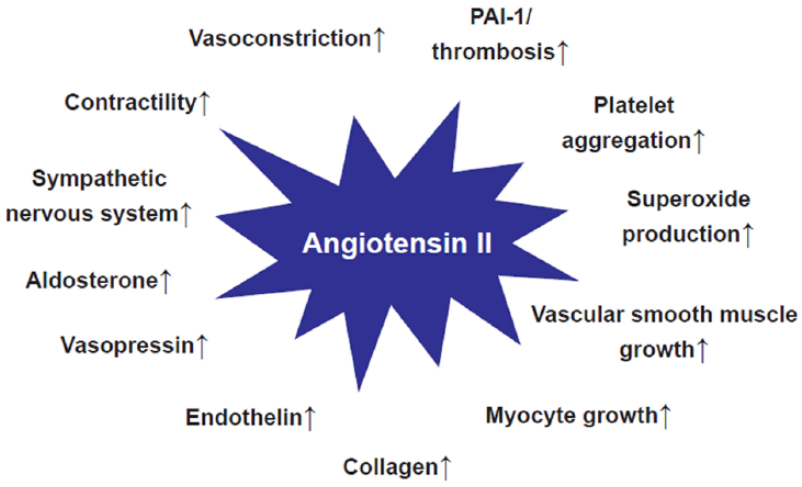

Figure 1. Proposed (patho)physiological effects of angiotensin II *via* angiotensin II type 1 (AT_1)-receptor stimulation (Adapted from [Burnier and Brunner, 2000]).

One aspect of this hypothesis relies on data from different sources suggesting that high plasma renin activity may itself be an independent predictor of risk for major vascular events and mortality in both hypertensive patients, and in patients with high cardiovascular risk [Verma *et al.* 2011]. However, it remains unclear how much of this observation may be related to confounding circumstances such as pre-existing therapies (e.g. diuretics), or other conditions such as volume depletion or undiagnosed heart failure in the patients investigated.

In addition to these clinical data, support for effects beyond BP by ACE-Is and ARBs has been derived from experimental studies in which effects of the RAS on various regulatory functions capable of modifying cardiovascular disease mechanisms have been described (Figure 1) [Burnier and Brunner, 2000].

Finally, it has been claimed that certain ARBs or their metabolites may exhibit a glitazone-like partial agonistic activity on the peroxisome proliferator-activated receptor-gamma (PPARγ) *in vitro*, with telmisartan being the only ARB to show an effect at physiologically achievable plasma concentrations [Kintscher and Unger, 2005]. Such a PPARγ modification may contribute to the low rate of new onset diabetes observed in most interventional trials of certain RAS blockers [Elliott and Meyer, 2007]. However, clinical evidence from large interventional studies did not demonstrate the superiority of telmisartan with respect to new onset diabetes when compared with ramipril in the Ongoing Telmisartan Alone or in Combination with Ramipril Global Endpoint Trial (ONTARGET), or compared to placebo in the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) trial [Yusuf *et al.* 2008]. Therefore, the clinical relevance of the proposed effect of certain ARBs on PPARγ, at least with respect to carbohydrate metabolism, remains questionable.

In view of the ongoing controversy about many of the effects beyond BP lowering that have been proposed for both ACE-Is and ARBs, this short review examines the clinical evidence for such effects in an attempt to identify those which have proven clinically relevant.

Clinical efficacy of ACE-I and ARB independent of BP lowering

Convincing support for cardiovascular protection by ACE-Is and ARBs independent of an effect on BP was provided by studies in patients with heart failure and post-myocardial infarction (MI), in which such treatment provided marked prognostic improvement in the presence of minor or no effects on BP [SOLVD Investigators, 1991; Pfeffer *et al.* 1991, 2003; Cohn and Tognoni, 2001; Granger *et al.* 2003; Shamshad *et al.* 2010]. In order to understand the effects of both ACE-Is and ARBs in these particular clinical indications, one has to appreciate the complex interplay of the RAS with the sympathetic nervous system. In contrast to other predominantly arterial

vasodilatory substances such as hydralazine, reflex tachycardia is not observed with such interventions [Royster *et al.* 1990]. Vasodilation resulting in afterload reduction without reflex sympathetic activation and volume retention may underlie, at least in part, the marked effects seen with both ACE-I and ARB both in patients with congestive heart failure and post-MI [De Leeuw and Kroon, 2008].

As an example, the first published clinical trial to examine the benefits of RAS intervention on morbidity and mortality was a relatively small study conducted in 253 patients with congestive heart failure (New York Heart Association [NYHA] functional class IV) and published in 1987 by the CONSENSUS Trial Study Group. This study examined the effects of the addition of the ACE-I enalapril, dosed at 2.5–40 mg/day, to conventional vasodilator therapy (including hydralazine, prazosin, and nitrates). At the end of 6 months, the crude mortality rate in the enalapril arm was 26%, compared with 44% in the placebo group, a relative reduction of 40% ($p = 0.002$) [CONSENSUS Trial Study Group, 1987]. In addition, mortality was reduced by 31% at 1 year ($p = 0.001$), with a 27% reduction in death rate at the end of the study ($p = 0.003$) [CONSENSUS Trial Study Group, 1987].

In addition, numerous studies in patients with renal disease, mostly those with diabetic nephropathy, have demonstrated renal protection by ACE-Is and ARBs that cannot be ascribed to an effect on arterial BP [Düsing, 2016]. Renal physiological studies have demonstrated that angiotensin II exerts a vasoconstrictor effect preferentially in the postglomerular (efferent) arterioles [Arima and Ito, 2000]. Consequently, by decreasing efferent arteriolar tone, RAS inhibition reduces filtration pressure and may thus act as a means of renoprotection [Van Der Meer *et al.* 2010].

The RAS: friend or foe?

The RAS is the crucial system that regulates extracellular fluid volume and BP through renal sodium chloride (NaCl) retention and vasoconstriction [MacGregor *et al.* 1981; Burnier and Brunner, 2000]. In the presence of volume depletion (e.g. low NaCl intake, acute or chronic hemorrhage, diarrhea, or excessive vomiting) activation of this system will serve to maintain, not to increase BP. However, in subjects on high-salt diets in whom BP is more often high than low, and vascular death more common than hemorrhage or dehydration, this system is likely to participate in the pathogenesis of hypertension and the resulting organ damage [Brown, 2007]. Under these circumstances, pharmacological interventions to reduce the activity of the RAS (e.g. with ACE-Is or ARBs) have proven beneficial in numerous interventional studies.

Multiple lines of evidence demonstrate that the increased peripheral resistance in hypertension is mediated not only by vasoconstriction, but that structural changes within the resistance vessels may play an important role [Mulvany, 2012; Renna *et al.* 2013]. Furthermore, experimental and clinical data suggest that the RAS may play a 'growth factor-like' role in this remodeling process within the small resistance vessels [Campbell-Boswell and Robertson, 1981; Geisterfer *et al.* 1988; Gibbons *et al.* 1992]. In agreement with this concept, clinical studies have shown a more effective 'reverse remodeling' of resistance arteries with ACE-Is and ARBs *versus* β-blockers [Mulvany, 1996; Schiffrin, 2002]. However, more recent data have suggested that vasoconstriction itself may represent an unspecific mechanism underlying this structural remodeling, and that this can be prevented by vasodilator therapy, which includes ACE-Is and ARBs [Mulvany, 2012]. This would also explain the poor performance of nonvasodilator β-blockers used in most of the comparator studies in terms of regression of vascular structural changes in hypertension.

Similarly, left ventricular hypertrophy (LVH) in the heart predominantly represents structural adaptation to increased pressure (like in aortic stenosis). Again, various lines of evidence suggest a role for the RAS in this adaptive process. This appears to be supported by the observation that the effectiveness of different classes of antihypertensive drugs in reducing LVH varies, with ACE-Is, ARBs and calcium channel blockers (CCBs) being more effective than β-blockers [Klingbeil *et al.* 2003]. In this context it should be considered that antihypertensives may affect BP in the central aorta differently from that measured over the brachial artery [Williams *et al.* 2006]. This was demonstrated in a subgroup analysis of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) [Dahlof *et al.* 2005], the Conduit Artery Function Evaluation (CAFE) study [Williams *et al.* 2006]. The CAFE study recruited 2199 patients from five ASCOT centers. Following treatment with either atenolol ± thiazide-based

therapy or amlodipine ± perindopril-based therapy, aortic pressure and brachial systolic BP were assessed. Despite similar brachial systolic BP between treatment groups during and at the end of the study, substantial reductions in central aortic pressure were observed in those patients who received the amlodipine-based therapy as compared to the atenolol-based regimen [Williams *et al.* 2006]. Other studies have also demonstrated that atenolol is less effective than other antihypertensive agents in reducing central aortic pressure [Mackenzie *et al.* 2009]. Such substantially dissimilar effects on aortic pressures compared with brachial BP may explain the variation in clinical outcomes seen for the different antihypertensive treatments, and may also underlie the poor efficacy of atenolol in regressing LVH [Hashimoto *et al.* 2007].

When considering effects beyond BP for the RAS and consecutively RAS blockers, it is also interesting to note that this system is stimulated during diuretic treatment. The RAS is also markedly activated in Bartter's/Gitelman's syndrome in which tubular reabsorption of NaCl is impaired, mimicking chronic diuretic treatment. In spite of marked RAS activation in these syndromes, patients do not develop hypertension and cardiovascular remodeling [Calo and Maiolino, 2015].

Yet another mechanism by which the RAS may confer effects beyond BP lowering is related to the presence of different angiotensin II receptors. Plasma renin converts angiotensinogen released by the liver into angiotensin I. Angiotensin I is subsequently converted to angiotensin II, predominantly by ACE. The principal effects of the RAS are then mediated *via* the binding of angiotensin II to type 1 (AT_1) receptors [Paul *et al.* 2006], which then induces a range of (patho)physiological effects. In this context, it is important to note that ACE-Is and ARBs act at different points in the RAS. Thus, ARBs specifically block the binding of angiotensin II to the AT_1 receptor [Esteras *et al.* 2015] Blockade of AT_1 receptors by an ARB results in increased angiotensin II levels and consequently increased stimulation of unblocked AT_2 receptors [Fournier *et al.* 2004]. In contrast, ACE-Is block the hydrolysis of angiotensin I to angiotensin II, resulting in lower angiotensin II levels and consequently reduced stimulation of both AT_1 and AT_2 receptors. Questions, however, remain as to whether any effects beyond BP lowering occur through differential actions of these drugs on AT_1 and AT_2 receptors.

Claiming effects beyond BP lowering: what factors should be considered?

Although it is possible that differences in clinical efficacy observed with RAS interventions indicate effects beyond BP lowering, the variation seen could also be due to other factors, which should seriously be considered before claiming such an effect.

Adherence to prescribed antihypertensive medication is one such factor that should be taken into account. In this context, it should be noted that adherence in clinical trials may be generally higher than in the routine clinical setting [Megometschnigg, 1999]. However, marked nonadherence is also regularly observed in clinical trial settings. An early study had suggested that persistence with antihypertensive therapy is lowest with diuretics and highest with ARBs slightly ahead of ACE-Is [Bloom, 1998]. This principal finding has recently been supported by a meta-analysis demonstrating similar differences in adherence for different classes of antihypertensives [Kronish *et al.* 2011]. Lowest adherence to antihypertensive therapy was observed with diuretics and β-blockers, while highest adherence was seen with ACE-Is and ARBs [Kronish *et al.* 2011]. Even between ACE-Is and ARBs, differences in adherence and persistence could be demonstrated with ARBs being slightly superior to ACE-Is (Figure 2). Therefore, long-term adherence to antihypertensive therapy, together with other factors, may depend on the class of antihypertensive agent prescribed. These differences may, in part, be due to the adverse events associated with some drugs [Kronish *et al.* 2011].

It is important to note that patient adherence has been shown to be high at the time of a doctor's visit, a phenomenon named white coat compliance [Urquhart, 1994; Düsing *et al.* 2001]. Thus, differences in adherence with prescribed treatment in the period between two doctor's visits may result in poor overall control of BP. This may be particularly prevalent in patients receiving drugs that are associated with low levels of patient adherence. This lack of control of BP may not be evident to the physician, however, as white coat compliance often ensures adequate BP control is achieved at the time of the doctor's visit. Within randomized clinical trials, it is possible that poor adherence with treatment administered in one arm of the study may result in a perceived greater benefit for the other treatment arm. Such bias may, in time, lead to suggestions of additional benefits beyond a simple antihypertensive action.

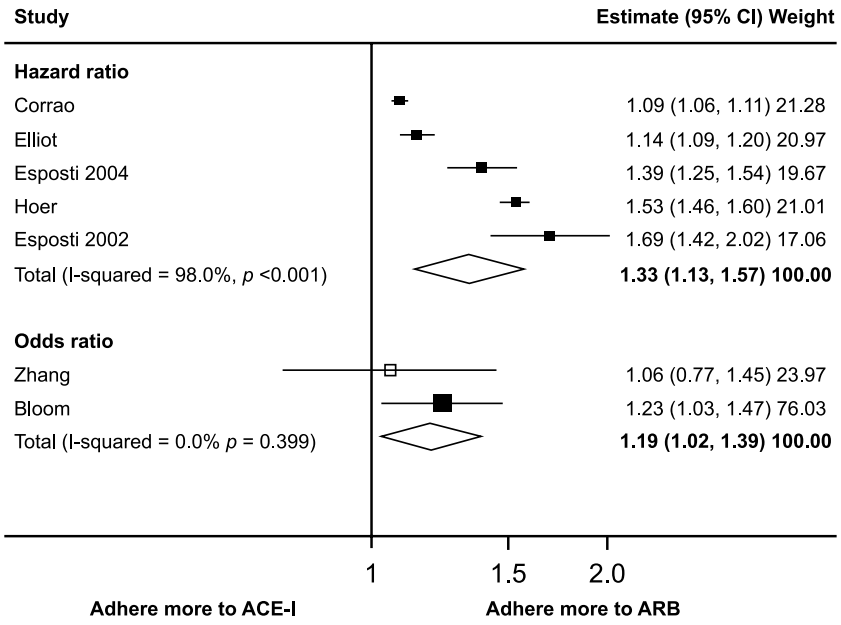

Figure 2. Adherence to ARBs compared with ACE-Is: meta-analysis results. Hazard ratios and odds ratios with 95% CI on a logarithmic scale for individual or pooled study data for relative risk of adherence. Black boxes indicate studies in which adherence was measured as persistence; white box, study in which adherence was measured as compliance. Various adjustments were performed (Adapted from [Kronish *et al.* 2011]).
ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CI, confidence interval.

Low treatment adherence may be particularly problematic in patients who are prescribed drugs with a relatively short duration of action. In such patients, a missed dose is more likely to result in a period without therapeutic coverage. For example, the β-blockers betaxolol and atenolol when taken consistently as a monotherapy are equally effective in controlling BP. However, owing to the relatively short-term duration of action of atenolol, the BP and heart rate response to betaxalol is significantly superior in the 24 hours following a missed dose, as demonstrated in a double-blind, 6-week study comparing once-daily oral betaxolol and atenolol in 114 patients with mild-to-moderate hypertension [Johnson and Whelton, 1994]. Similar BP and heart rate responses were seen in these patients. However, when patients randomly received placebo in either the fifth or sixth week of the study to simulate the effect of missing doses, the magnitude and duration of the BP lowering effect was significantly greater for betaxolol than for atenolol as calculated from ambulatory BP monitoring data [Johnson and Whelton, 1994].

These data should be considered against the background of recent studies using electronic medication event monitoring showing that on any given day, antihypertensive medication is not taken within the respective time frame by approximately 8% of patients [Burnier *et al.* 2013]. In such subjects, drugs with long (and more 'forgiving') duration of action may compensate for an irregular intake of medication when the dosing interval is prolonged beyond 24 hours. In contrast, drugs with a short duration of action will not offer this protection, with considerable variation in BP.

As an example, in the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial [Jamerson *et al.* 2008] combination therapy with benazepril-amlodipine was superior to benazepril-hydrochlorothiazide in reducing cardiovascular events in patients with hypertension, in spite of similar BP lowering in the two treatment arms. Effects beyond BP have been widely claimed to explain the clinical outcome of the trial. Alternatively, it should be noted that amlodipine is a long-acting and thus 'forgiving' drug with an elimination half-life of 40–60 hours [Abernethy, 1992]. In contrast, the comparator drug hydrochlorothiazide is short-acting with an elimination half-life of approximately 9–10 hours just permitting effective once daily dosing [Welling, 1986; Ernst and Moser,

2009]. Therefore, the clinical outcome in ACCOMPLISH could simply be due to differences in therapeutic coverage resulting from the comparison of a long-acting with a short-acting drug [Meredith, 1999].

Thus, before concluding effects beyond BP lowering for any antihypertensive, it is important to verify the apparent superior efficacy observed is not merely a consequence of other factors such as better adherence, differences in the duration of action, or in reducing central aortic pressure not mirrored by differences in brachial BP.

Is there evidence of effects beyond BP lowering?

In the presence of conflicting data from experimental and small clinical studies, a key challenge is to examine the outcomes of large clinical trials of RAS inhibitors for evidence of clear effects beyond BP lowering. As discussed earlier in this article, interventional trials in congestive heart failure, post-MI and in patients with chronic renal disease have provided clear evidence of improvements in surrogate as well as hard morbidity and mortality endpoints, largely independent of BP lowering.

In other trials often cited, the evidence for such an effect remains controversial. For example, in the Heart Outcomes Prevention Evaluation (HOPE) trial, over 9000 high-risk patients with vascular disease or diabetes (including 47% with hypertension) were randomized to receive the ACE-I ramipril or placebo over a 5-year period [Yusuf *et al.* 2000]. Death, MI and stroke were significantly reduced in ramipril-treated patients, but only minor changes in office BP were observed (-3/-2 mmHg). However, these results must be interpreted cautiously as further analysis from a small HOPE substudy, in which ambulatory BP was monitored over a 24-hour period, found significant differences in systolic and diastolic BP throughout the day [Svensson *et al.* 2001]. Thus, 24-hour ambulatory BP was significantly reduced in ramipril-treated patients (-10/-4 mmHg, $p = 0.03$), mainly because of a more pronounced BP-lowering effect at night (-17/-8 mmHg, $p < 0.001$). As the study drugs were taken at night in the HOPE trial, the effects on cardiovascular morbidity and mortality seen with ramipril in this patient group may, to a larger extent than initially ascribed, relate to effects on BP patterns over the 24 hour period [Yusuf *et al.* 2000; Svensson *et al.* 2001; Düsing, 2016].

The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study compared the benefits of the ARB losartan with those of the β-blocker atenolol [Dahlof *et al.* 2002]. LIFE claimed that losartan confers additional benefits beyond BP lowering, as despite a similar reduction in BP with both drugs, losartan was associated with a greater reduction in the combined primary endpoint of cardiovascular death, stroke and MI than atenolol [Dahlof *et al.* 2002]. However, a number of questions arise regarding the choice of the comparator in this study. As previously noted, β-blockers such as atenolol are associated with poorer treatment adherence compared with an ARB such as losartan [Kronish *et al.* 2011] and are less effective than other antihypertensive agents in reducing central aortic pressure [Mackenzie *et al.* 2009]. Consequently, some meta-analyses have shown β-blockers to be less effective in the prevention of cardiovascular complications, especially stroke, than other antihypertensive agents [Carlberg *et al.* 2004; Bangalore *et al.* 2008].

Several proposed effects of angiotensin II mediated by AT_1 receptors claimed on the basis of experimental or small clinical studies (Figure 1) have not been supported by data from larger clinical trials. This especially applies to the proposed effects on platelet aggregation and fibrinolysis.

Physiologically, angiotensin II induces platelet activation and promotes platelet aggregation [Brown and Vaughan, 2000; Larsson *et al.* 2000]. Therefore, RAS blockade with either ACE-Is or ARB should be associated with reduced platelet function. However, there are marked discrepancies between the clinical and laboratory effects of different ACE-Is and ARBs studied in this respect [Blann *et al.* 2003]. In addition, no relevant difference in platelet function compatible with a favorable effect due to RAS blockade compared with other agents has ever been observed in either ACE-I or ARB intervention trials [Düsing, 2016]. Also, in some studies, most classes of antihypertensive agents exhibit some degree of antiplatelet activity, but this is likely due to an improvement in endothelial dysfunction seen with BP lowering [Blann *et al.* 2003].

Whether blockade of the RAS results in clinically relevant changes in fibrinolytic activity has also been questioned. Fibrinolysis occurs physiologically through a complex regulation and interplay of fibrinolytic factors with a continual dissolution of microscopic clots in the circulation by

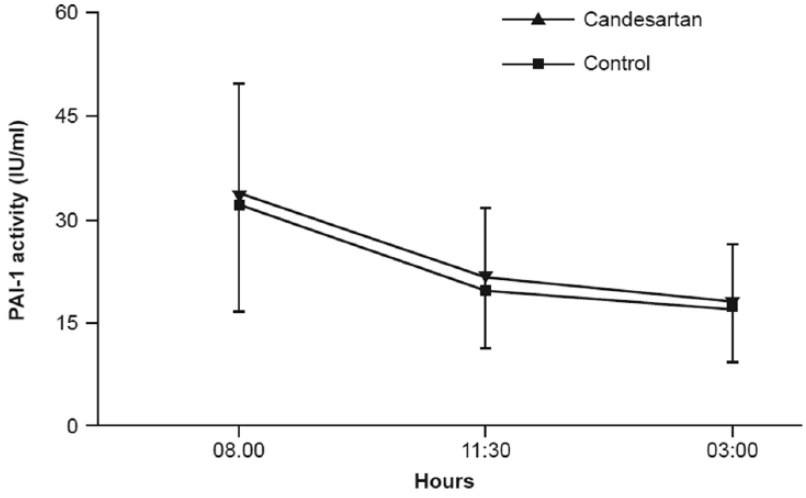

Figure 3. PAI-1 activity in 74 patients randomly assigned to a 7-day treatment period with either 16 mg candesartan or placebo (Control). (Adapted from [Skurk *et al.* 2004]).
PAI-1, plasminogen activator-inhibitor-1; IU, international units.

plasmin. Through effects on plasminogen activator-inhibitor-1 (PAI-1), angiotensin II has been proposed to prevent the conversion of plasminogen to plasmin, thus preventing the breakdown of fibrin. Accordingly, *in vitro* studies imply that angiotensin II induces PAI-1 expression in endothelial cell cultures [Vaughan *et al.* 1995]. A first study *in vivo*, in which four normotensive subjects and six hypertensive patients received an intravenous infusion of angiotensin II demonstrated a rapid increase in circulating levels of PAI-1 [Ridker *et al.* 1993]. However, other study groups were unable to confirm an increase in PAI-1 levels in response to angiotensin II infusion or following ARB treatment (Figure 3) [Lottermoser *et al.* 2000, 2004; Skurk *et al.* 2004].

ACE-Is and ARBs may be associated with a reduced rate of new-onset diabetes compared with other antihypertensives. A network meta-analysis of 22 clinical trials involving 143,153 patients showed that the lowest incidence of new-onset diabetes occurs in those who are treated with an ARB or ACE-I [Elliott and Meyer, 2007]. The mechanisms for this metabolic effect remain unclear. Peripheral vasodilation without reflex activation of the sympathetic nervous system by ACE-I and ARB may improve the microcirculation in the musculature and could thereby improve insulin sensitivity [Düsing, 2007]. In addition to this simple concept, various cellular mechanisms have been speculated to participate in this effect [Düsing, 2007; Hershon, 2011; Sauter *et al.* 2015]. This metabolic effect of RAS blockers could indeed represent a relevant clinical effect beyond BP lowering since the clinical consequences of their modest effect on glucose metabolism may take long time periods to translate into clinical benefits not covered, and therefore not detected, by clinical trials.

Interestingly, an opposite effect on glucose metabolism has recently been demonstrated for statins. Thus, a population-based study of 8749 nondiabetic patients indicated that statin treatment is associated with a 46% increase in new-onset diabetes [Cederberg *et al.* 2015]. It is interesting to speculate that the combination of a RAS inhibitor with a statin may reduce hypercholesterolemia and BP with less or no increased risk of new-onset diabetes.

It has been proposed that drugs that activate AT_2 receptors *via* increased angiotensin II levels, such as diuretics, calcium antagonists, and ARBs, are associated with trends for more beneficial stroke reduction than drugs devoid of such activation, such as β-blockers and ACE-Is despite an equal fall in arterial pressure [Fournier *et al.* 2004]. Inhibition of AT_1 receptor stimulation following ARB administration results in enhanced angiotensin II binding to and stimulation of AT_2 receptors [Siragy, 1999]. Activation of the AT_2 receptor has been shown to mediate several potentially beneficial effects in the cardiovascular system, including vasodilation, antiproliferation, and apoptosis. Also, cerebroprotective effects of ARBs have been demonstrated *in vivo* in experimental stroke models [Fernandez *et al.* 1986; Dalmay *et al.* 2001]. In

addition, while ARBs have been shown to be as effective as ACE-I in terms of reducing the risk of MI and cardiovascular mortality, head-to-head comparison of ACE-Is and ARBs in six trials with a total of 49,924 patients showed a slightly greater degree of stroke protection for ARB [Reboldi *et al.* 2008]. Further studies are required to show whether this cerebroprotective effect of ARB represents a true benefit that goes beyond simple BP lowering.

Conclusion

Before concluding that agents modulating the RAS might have actions that go beyond BP lowering, several factors should be taken into consideration. One crucial aspect in this regard is patient adherence with the prescribed treatment regimen. Among the many factors involved, the class of medication prescribed can have a significant impact on patient adherence. In addition, it is important to consider the duration of action of the drug and thus any potential period of noncoverage that might arise if doses are missed. Observed differences in central BP compared with brachial BP have also been observed and may impact the apparent efficacy of a treatment regimen. To date, experimental and clinical studies have failed to provide definitive evidence of specific effects of RAS blockade beyond BP lowering in terms of regression of vascular or myocardial remodeling, fibrinolysis and platelet function. In contrast, there is still inconclusive evidence suggesting that ARBs may exert cerebroprotective effects, perhaps *via* stimulation of AT_2 receptors. Furthermore, both ACE-Is and ARBs have positive effects on glucose metabolism. However, the mechanism and the clinical relevance of this effect remain unclear.

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Conflict of interest statement

The author declares that there is no conflict of interest.

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