Regulation of the renin–angiotensin system in coronary atherosclerosis: A review of the literature

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Abstract: Activation of the renin–angiotensin system (RAS) is significant in the pathogenesis of cardiovascular disease and specifically coronary atherosclerosis. There is strong evidence that the RAS has effects on the mechanisms of action of atherosclerosis, including fibrinolytic balance, endothelial function, and plaque stability. Pharmacological inhibition of the renin angiotensin system includes angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and renin inhibitors. These agents have clinical benefits in reducing morbidity and mortality in the management of hypertension. In addition, ACE inhibitors and ARBs have shown to be effective in the management of congestive heart failure and acute myocardial infarction. This review article discusses the biochemical and molecular mechanisms involving the RAS in coronary atherosclerosis as well as the effects of RAS inhibition in clinical studies involving coronary atherosclerosis.

Keywords: angiotensin II, atherosclerosis, endothelium, inflammation, vasculature

Introduction

Since the initial elucidation of angiotensin II (angII) over fifty years ago, it has become evident that the renin–angiotensin system (RAS) plays a pivotal role in normal hemodynamics and regulation of volume status. Furthermore, activation of the RAS is significant in the pathogenesis of cardiovascular processes. Initial studies have focused on the importance of RAS blockade in left ventricular dysfunction. However, there is an effect of the RAS on progression of coronary atherosclerosis through its influence on fibrinolytic balance, vascular endothelial function, inflammation and plaque instability (Tsikouris and Cox 2003; Kon and Jabs 2004).

ACE inhibitors and angiotensin receptor blockers (ARBs) and more recently direct renin inhibitors are agents used to block the effects of the RAS. While they have been used effectively in hypertension and renal disease (Kon and Jabs 2004), their effects on reducing the morbidity and mortality associated with heart failure and myocardial infarction have triggered extensive research into the benefits of these agents beyond blood pressure reduction (The SOLVD Investigators 1991, 1992; Pfeffer et al 1992). Three large trials have assessed the efficacy of ACE inhibitors in stable coronary disease with conflicting results (HOPE 2000; Fox et al 2003; PEACE 2004). There are ongoing trials of ARBs in this patient population. Furthermore, the recent release of direct renin inhibitors potentially may add even more information to the association of RAS and coronary atherosclerosis.

In this review, we will examine the evidence for benefit of RAS blockade in the secondary prevention of coronary atherosclerosis. Furthermore, there is increasing evidence of the importance of these agents in metabolic syndrome and insulin resistance, a growing risk factor for the development of cardiovascular disease. Thus, we

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will also examine the potential role of these agents prior to the overt development of coronary atherosclerosis.

Metabolic effects of the renin–angiotensin system

The importance of lipid and glucose metabolism in the pathogenesis of atherosclerosis is increasingly evident. Metabolic syndrome is a constellation of atherogenic risk factors including hypertension, dyslipidemia, and hyperglycemia that are associated with a pro-inflammatory and pro-thrombotic milieu. Definitions of this disorder have been controversial, but the most recent NCEP/ATPIII guidelines provide a list of criteria that have been the most widely accepted. Based on these definitions, the approximate prevalence of metabolic syndrome in the United States adult population may be as high as 25% (Prasad and Quyyumi 2004). The magnitude of this problem is amplified when we consider the potential risk this disease imposes on an individual. Estimates indicate that the metabolic syndrome increases the risk of stroke two to four fold and myocardial infarction three to four fold in comparison to general population (Lakka et al 2002).

The hallmark of the metabolic syndrome appears to be hyperinsulinemia and insulin resistance (Prasad and Quyyumi 2004). Insulin has been shown to have vasodilatory and anti-inflammatory effects (Cusi et al 2000; Montagnani et al 2002). Therefore, with the development of insulin resistance, the balance of these effects may be skewed to favor the development of atherosclerosis. Considerable evidence suggests that Ang II may modulate the action of insulin through inhibition of the phosphatidyl inositol pathway (PI3) and stimulation of the MAP kinase pathway (Velloso et al 1996). Likewise, both hyperglycemia and insulin activate the RAS by increasing expression of angiotensinogen, Ang II, and regulation and activity of the angiotensin type 1 (AT_1) receptor. In addition, insulin resistance is associated with increased NADPH oxidase (Rajagopalan et al 1996; Griendling et al 2000) and reactive oxygen species, another potential mechanism of vascular injury in these patients (Schmidt et al 1999). Another potential cause of reduced insulin sensitivity through RAS activation may be a result of vasoconstrictive effects, thereby reducing blood flow to skeletal muscle (Furuhashi et al 2003).

This interaction between the RAS and glucose metabolism has been further supported by analyzing the effects of RAS blockade on enhanced insulin sensitivity. It has been suggested that ACE inhibitors improve glycemic control in diabetic patients (Pollare et al 1989). This is evidenced through clinical studies showing the reduction in progression to overt diabetes mellitus. In the CAPPP study, captopril was found to reduce the incidence of type II diabetes mellitus (DM) by 14% (Hansson et al 1999). In addition, these findings were reproduced in the HOPE trial, which found a 34% reduction in new onset DM and a 16% reduction in complications from DM in patients treated with ramipril (HOPE 2000; Yusuf et al 2001).

Similar findings were also found in the PEACE trial, despite lack of efficacy in the primary outcome, when patients were treated with trandolapril (PEACE 2004). Additionally, in the SECURE trial, a substudy of the HOPE study, ramipril appeared to decrease fasting glucose levels in comparison to placebo (Lonn et al 2000). The improved insulin sensitivity seen with ACE inhibitors appears to results in an increased glucose uptake by skeletal muscles via enhanced synthesis and translocation of the glucose transporter 4 protein to the cell surface. This effect is facilitated by up-regulation of tyrosine phosphorylation of IRS-1 (insulin receptor substrate) and enhanced bradykinin and NO activity (Krutzfeldt et al 2000; Shiuchi et al 2002). The effect of RAS blockade via ARBs also has significant effects on glucose metabolism. In the LIFE study, a 25% reduction of new onset DM was seen in patients treated with losartan in comparison to atenolol (Dahlöf et al 2002; Lindholm et al 2002). In addition, the VALUE study has shown similar findings in patients treated with valsartan in comparison to amlodipine (Julius et al 2003).

A logical question raised by this clinical data is whether RAS blockade would be an appropriate treatment for patients with metabolic syndrome. It is conceivable that RAS blockade would not only prevent the progression to overt DM but would also ameliorate the documented risk of atherosclerosis in these patients. In experimental animal models, this hypothesis has been supported. In a study of mice with the metabolic syndrome, treatment with ARBs inhibited development of hyperinsulinemia, HTN, obesity, cardiac hypertrophy and atherosclerosis (Ortlepp et al 2002). While the clinical data in this field is limited, there is potential benefit of RAS blockade suggested through surrogate markers. Adiponectin is a adipocyte derived protein that has been found to have an important correlation to not only obesity, but coronary atherosclerosis. Adiponectin is believed to enhance insulin sensitivity, preserve endothelial function, reduce vascular smooth muscle proliferation and suppress macrophage foam cell formation (Lau et al 2005). It is thought that reduced circulating levels of this protein are associated with an increased risk of coronary artery disease (Pischon et al 2004). In this study, it was observed

that treatment with either temocapril or candesartan resulted in significant increases in adiponectin levels (Furuhashi et al 2003). In a small, clinical study (Nagamia et al 2007), treatment with quinapril in comparison to placebo resulted in an increase in adiponectin, decrease in serum leptins and positive improvement on insulin sensitivity.

The largest trial to date looking specifically at the effects of RAS blockade on insulin sensitivity was recently released. The DREAM trial randomized 5269 patients, with no cardiovascular disease but either impaired fasting glucose levels or impaired glucose tolerance, to either ramipril or placebo for a period of three years. Although there was no significant decrease in the primary outcome of death or new onset diabetes, patients on ramipril were likely to regress to normoglycemia and had improved glucose tolerance (DREAM 2006). We are currently awaiting the results of the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) which will be the largest randomized trial to date evaluating diabetes prevention. This study will compare the cardiovascular effects of valsartan and nateglinide, an oral hypoglycemic, in a population of patients with impaired glucose tolerance. While the primary outcome of this study will be a composite endpoint of cardiovascular events, there will also be an important secondary outcome of progression to diabetes mellitus (Prasad and Quyyumi 2004). The study is scheduled to be completed in 2007 and will provide useful information regarding inhibition of RAS with ARBs in patients with glucose intolerance and metabolic syndrome.

In summary, DM and metabolic syndrome are important cardiovascular risk factors that seem to have important links to the RAS. Perturbations of this abnormality in lipid and glucose metabolism can be achieved with blockade of the RAS system and may be a potential mechanism for their benefit in coronary atherosclerosis.

Clinical trials of ACE inhibitors in stable coronary artery disease

ACE inhibitors have now been definitively shown to reduce mortality and morbidity in patients with systolic heart failure, myocardial infarction (with or without left ventricular dysfunction), and those undergoing percutaneous coronary intervention (Al-Mallah et al 2006). In addition to their well-established role in the treatment of hypertension, ACE inhibitors also help to decrease cardiovascular events in patients with diabetes mellitus and renal dysfunction. However, controversy persists as to whether these agents are beneficial or not in patients with stable CAD and preserved left ventricular function.

Three large clinical trials have been performed to date that attempted to address this issue: HOPE, PEACE and EUROPA. We provide a comparison of the important aspects of these trials in Table 1. The HOPE trial enrolled 9297 patients with history of stroke, coronary atherosclerosis, peripheral vascular disease or DM plus at least one other cardiovascular risk factor, such as hypertension, dyslipidemia, smoking or documented microalbuminuria and excluded patients with systolic ventricular dysfunction. Over a 4.5 year period of follow-up, patients treated with ramipril (10 mg/day) were found to have a 22% relative reduction in the primary outcome of myocardial infarction, cardiovascular death and stroke compared to placebo (HOPE 2000). In addition, there was a significant decrease in secondary outcomes of revascularization, cardiac arrest, CHF, complications and diagnosis of new onset type II diabetes mellitus (as mentioned previously). This landmark trial seemingly advocated for the use of ACE inhibitors in all high risk patients with atherosclerosis and/or DM.

This study was followed by an even larger study, the EUROPA trial, which randomized 12218 patients with evidence of coronary artery disease but no systolic dysfunction to either perindopril 8 mg or placebo for a mean follow up of 4.2 years. In this study, there was a 20% reduction in the composite primary end point of cardiovascular event (Fox et al 2003). While the HOPE and EUROPA studies seemed to suggest the efficacy of ACE inhibitors in the secondary prevention of coronary disease, controversy was created with the release of the PEACE trial. This large-scale study randomized 8290 patients with coronary atherosclerosis and preserved ventricular function to either trandolapril 4 mg or placebo for a mean follow up of 4.8 years (PEACE 2004). However, unlike the HOPE and EUROPA trials, this trial found no statistical difference on the same composite end point used in the other trials (CV death, MI or revascularization).

In trying to hypothesize the mechanisms for these conflicting results, it is necessary to analyze the characteristics of each study (see Table 1). The main differences that could explain this discrepancy are the relative cardiovascular risk of each population, differences in mean blood pressure control and differences in ACE inhibitor dosing. The population in the HOPE study was a group of high risk patients with stringent inclusion criteria. Hence, this was an older population with significantly more cardiovascular risk based on traditional Framingham risk factors. This potentially explains the increase in revascularization needed when compared to the EUROPA and PEACE studies. In addition, if we compare PEACE and EUROPA, the former had a 72%

Table 1 Comparison of several major clinical trials of the effect of ACEI on pertinent cardiovascular events, onset of diabetes, inflammatory markers and flow mediated dilatation (FMD)

	HOPE	EUROPA	PEACE	LIFE	DREAM	Khan[1]
No. of patients	9297	12218	8290	9193	5269	112
Mean follow up (yrs)	4.5	4.2	4.8	4.8	3*	24 weeks
Primary end point	CV death, MI, stroke	CV death, MI, cardiac arrest	CV death, MI, revascularization	CV death, stroke, MI	Onset of diabetes or death	Inflammatory markers
Reduction in cardiovascular events (%)	22	20	None	13	None	44% decrease for IL-6; 53%–56% decrease for CD11bR
Reduction in new onset diabetes (%)	34	None	15	25	None	NR
Treatment	Ramipril	Perindopril	Trandolapril	Losartan	Ramipril	Quinapril, Irbesartan
Mean age (yrs)	66 ± 7	60 ± 9	64 ± 8	67 ± 7	55 ± 11	60 ± 9
Females (%)	25	15	18	54	59	43
HTN (%)	47	27	46	100	44	47
Mean BP	139/79	137/82	133/78	174/98	136/83	131/NR
SBP/DBP lowering (mmHg)	3/2	5/2	3/1	30/17	8/4	3/NR
Revascularization (%)	40	54	72	NR	NR	100
Diabetes (%)	38	12	17	13	9**	NR
Lipid lowering medications (%)	29	58	70	NR	15	100
Aspirin or other antiplatelets (%)	76	92	90	NR	14	100
BB (%)	40	62	60	NR	18	70

Notes: [1]Lauten et al 2003; *The DREAM trial reported median years of follow-up; **Previous gestational diabetes considered without overt diabetes at time of study enrollment.
Abbreviations: CV, cardiovascular; MI, myocardial infarction; NR, not reported in study; SBP, systolic blood pressure; DBP, diastolic blood pressure.

revascularization rate versus 55% in EUROPA and 40% in HOPE prior to enrollment in the study. Thus, this is a potentially important marker of patients whose coronary disease was not optimally treated. Looking through these three trials, it becomes evident that the PEACE population had the lowest cardiovascular risk. Since patients were more likely to be on optimum medical therapy in the PEACE trial, the study raised the important question of whether there is a level of risk at which there is benefit of ACE inhibition.

Another intriguing difference between these studies was the mean blood pressure of patients treated in each study. In the PEACE trial, mean BP was somewhat lower at 133/78 mmHg compared to EUROPA at 137/82 mmHg and HOPE at 139/79 mmHg. While this modest difference between blood pressures may seem to be trivial, one must consider the reduction of blood pressure that has been shown to reduce cardiovascular events (Collins et al 1990). With this in mind, these small differences in blood pressure may at least partially explain the negative results of the PEACE trial.

Another potential explanation for the negative results of the PEACE trial has been the relatively low dosing of trandolapril used in the study. The trandolapril dose used

in PEACE was based on dosing used in both the TRACE trial, the initial trial showing benefit of this agent after MI in patients with left ventricular dysfunction (Køber et al 1995) and the initial dosing studies showing the dose needed to decrease blood pressure in subjects with hypertension (Guay 2003). Despite the seemingly valid rationale for the trandolapril dosing, some critics have hypothesized that patients with stable coronary disease and preserved left ventricular function may need higher doses of ACE inhibitor than those with left ventricular dysfunction, as the latter group has increased secretion of growth factors, cytokines, signaling pathways and neurohormones (Pitt 2004). Additionally, while there has been concern about differences in different pharmacokinetics of ACE inhibitors, tissue versus non-tissue specific, it should be noted that all of the ACE-inhibitors used in these three trials were considered to be tissue-specific (Cushman et al 1989; Miyazaki et al 1995; Pitt et al 2001).

Given the potential of the differing medical therapies in these three studies, there has been some interest in further evaluating the interaction of RAS blockade and lipid lowering therapy. In the TREND study, 125 normotensive patients with stable coronary artery disease and LDL < 165 mg/dl

were randomized to quinapril or placebo for 6 months. Compared to placebo, patients treated with quinapril showed an improvement in endothelial function tested by coronary vasodilatory response to intracoronary infusion of acetylcholine. However, the benefit on endothelial function was only significant in those with an LDL > 125 mg/dl (Mancini et al 1996). The proposed reasoning behind this finding as been that ACE inhibitors share a common mechanism with statins on lectin–like oxidized LDL receptors and thus reduce oxidation of LDL cholesterol (Szmitko et al 2003). In another study, 112 patients with coronary atherosclerosis were initiated on atorvastatin for an average of 3.7 months to reach a target LDL < 100 mg/dL, then randomized to quinapril (20 mg/day), irbesartan (150 mg/day) or placebo for a period of 24 weeks. In patients treated with quinapril and irbesartan, but not placebo, there was a significant reduction in soluble interleukin-6 (sIL-6) and CD11b receptor (Lauten et al 2003). A recent study on patients with the metabolic syndrome treated with quinapril versus placebo for 4 weeks showed a significant reduction in the lag time to oxidation of LDL in the quinapril group (Khan et al 2004). It should be noted that the average LDL level in this study was 125 mg/dL. Another possibility is that statins could dampen the effects of RAS blockade through their known anti-inflammatory effect (Al-Mallah et al 2006) and inhibition of the formation of reactive oxygen species (Griendling et al 1994; Wagner et al 2000). Thus, as was seen in the PEACE trial, it seems plausible that lower levels of LDL from increased use of lipid lowering agents may negate the beneficial effect from ACE inhibitor treatment on atherosclerosis.

Another smaller study on ACE inhibition in stable coronary disease that had negative results was the QUIET trial (Pitt et al 2001). In this study, 1750 patients with documented CAD by angiography and LDL < 165 mg/dL were randomized to 20 mg of quinapril or placebo for a period of 27.0 ± 0.3 months. While they did not find patients treated with quinapril had a significant reduction in ischemic events, they did show a significant decrease in angioplasty for new previously unintervened vessels. Thus, despite some limitations to this study, including the lower dose of ACE inhibitor used than in the TREND trial (Mancini et al 1996), shorter duration of therapy, much lower mean blood pressure and inadequate power, there was still objective evidence of slowed progression of atherosclerosis in patients treated with ACE inhibitors.

Important clinical information on RAS blockade can also be extracted from the ALLHAT study, which evaluated the efficacy of ACE inhibitors over other anti-hypertensives in prevention of cardiovascular events (ALLHAT 2002). The ALLHAT trial randomized 33357 patients with stage 1 or 2 hypertension plus at least one risk factor for CHD to chlorthalidone, amlopdipine or lisinopril for a mean follow-up of 4.9 years. While there was no difference in the combined primary outcome (combined fatal CHD/non fatal MI) or secondary outcome of all cause mortality, it appears that the combined 6 year outcome of cardiovascular events was lower in the diuretic group. This has spurred tremendous debate about the utility of RAS blockade over traditional antihypertensive therapy. However, there are some important limitations that have been raised with this study. First of all, patients were treated with a multitude of "Step 2" drugs to achieve adequate BP control in addition to the study medication. The vascular effects of this additional therapy, which included reserpine, clonidine and atenolol, may have had some effect on the results. In addition, the lisinopril group had a systolic BP two mmHg higher than those on chlorthalidone, a potentially important difference given the large number of patients in the study. Furthermore, because of the study design, this was obviously a much lower risk population with a much lower incidence of cardiovascular disease. Most striking, however, may be the dosing and type of ACE inhibition used in this study. Not only does lisinopril have a lower tissue-specific ACE inhibition than agents like ramipril, perindopril and trandolapril, by the end of the study period, only 73% of patients in the lisinopril group were actually receiving an ACE inhibitor and only 60% were at the maximum dose of 40 mg/day. Thus, while there may be credence to the hypothesis that ACE inhibition may only be beneficial for those at higher cardiovascular risk, it must be noted that there are some limitations to these studies that may weaken any sweeping generalizations about superiority of alternative antihypertensive medications.

Another negative, albeit smaller, study that has brought into question the utility of ACE inhibitors in all patients with coronary atherosclerosis was the CAMELOT study (Nissen et al 2004). In this trial, 1997 normotensive patients with documented coronary disease by angiography were randomized to either amlodipine 10 mg, enalapril 20 mg or placebo for 24 months with a similar composite primary end point of cardiovascular event (cardiovascular death, non fatal MI, resuscitated cardiac arrest, coronary revascularization, fatal or non fatal stroke, TIA or new diagnosis of peripheral vascular disease). Despite similar reductions in blood pressure in both groups, it was found that amlodipine, but not enalapril, significantly reduced the primary outcome compared to placebo. In addition, in a subgroup analysis

using intravascular ultrasound, they found that amlodipine halted progression of atherosclerosis while there was a trend towards progression of atherosclerosis in the enalapril group compared to placebo. The neutral effects of ACE inhibition in this study can be explained through similar arguments to those in previous studies. This was a lower risk population and younger population than other studies. Once again, the use of a lower tissue-specific ACE inhibitor brings into question whether these agents may be less efficacious. In addition, there were a very high percentage of patients on statins (82%–83%), which was significantly more than in any of the other ACE inhibitor studies. Another unique limitation to this study was the duration of therapy used, two years, as the full effect of ACE inhibitors has been hypothesized to take up to three years.

Another smaller study that failed to find significant effects of ACE inhibitors on atherosclerosis was the PART 2 trial. In this study, 617 patients with coronary artery disease, peripheral vascular disease and carotid atherosclerosis were randomized to ramipril or placebo for four years with outcomes of carotid intima media thickness (CIMT) and left ventricular mass by echocardiography. While ramipril did produce a significant reduction in left ventricular mass, there was no significant difference in the carotid thickness progression between the two groups. However, this study was not powered to detect a difference in cardiovascular events (MacMahon et al 2000).

Despite a tremendous amount of heterogeneity between all of these studies, it should also be noted that there has been a meta-analysis of most of the pertinent trials with ACE inhibitors in patients with coronary atherosclerosis (HOPE, EUROPA, PEACE, QUIET, and PART-2 AND CAMELOT). From this meta-analysis, it was found that there was a favorable, modest benefit of ACE inhibitors in patients with CAD and preserved ventricular function on combined cardiovascular outcome used in these studies (Al-Mallah et al 2006).

Thus, the most important conclusion to draw from all of these studies is that ACE inhibitors seem to have beneficial effects in decreasing cardiovascular events in patients with high risk coronary atherosclerosis (as defined by the populations in HOPE and EUROPA). The benefit in other populations is unclear, as is evident from the conflicting results in the other mentioned trials. These conflicting results could have a variety of explanations, including variations in population characteristics, degree of blood pressure lowering, whether patients were on statins and/or had low LDL levels, use of tissue-specific ACE inhibitors, duration of the

treatment and the dosage of ACE inhibitor. This heterogeneity has to be taken into account when analyzing these studies and concluding if ACE inhibitors should be used in patients with or at high risk of developing coronary atherosclerosis.

Clinical trials on angiotensin receptor blockers in stable CAD

In addition to blockade of the RAS system via ACE inhibition, direct blockade of Ang II receptors has proven to be beneficial in patients with systolic dysfunction and myocardial infarction (Pfeffer, McMurray et al 2003; Pfeffer, Swedberg et al 2003). Given that there is a plethora of experimental data on the benefit of these agents in the atherosclerotic process, it would seem intuitive that ARBs could also have a potential role in this population. However, the clinical evidence for ARBs in stable coronary atherosclerosis is more limited than that for ACE inhibitors and has largely been confined to small clinical trials using surrogate markers.

Nonetheless, of the clinical trials that have addressed the efficacy of ARBs, there has been promise for the utility of these agents in this population. In one study examining patients following percutaneous coronary intervention, patients treated with candesartan for 24 months had a significant decrease in a composite cardiovascular endpoint (non fatal MI, cardiovascular death, and revascularization, with a secondary end point of hospitalization for cardiovascular causes) when compared to placebo (Kondo et al 2003). Interestingly, this effect was seen despite no difference in mean blood pressure during the course of the trial between the two groups. However, several additional conclusions were drawn from this study. First, there was no effect of ARBs on CRP levels during the study period, a finding supported by previously smaller clinical trials (Andersen et al 2000; Prasad et al 2001; Tan et al 2002). Second, there was achievement of the primary outcome without a significant change in blood pressure, once again confirming that the clinical benefit of these agents is likely independent of blood pressure effects. While it seems likely that the mechanism of this effect is related to the vasculoprotective effects of RAS blockade, this study did not definitively evaluate these issues.

The LIFE trial, another comparative trial evaluating the efficacy of ARBs in hypertension, also sheds some insight into the clinical benefit of these agents. This trial randomized 9193 patients with normal ventricular function and hypertension to either atenolol (50 or 100 mg/day) or losartan (50 or 100 mg/day) for a follow-up of four years (Dahlöf et al 2002). The primary end point was a similar composite end point of cardiovascular death, MI and stroke that has been used in

other studies. While both groups had a similar reduction in blood pressure, there was a significant decrease in the primary outcome in those patients treated with losartan. This clinical benefit of ARBs seemed to be driven by the reduction in the incidence of stroke, rather than a lower incidence of myocardial infarction, coronary revascularization and CV death. Once again, this study gives credence to the notion that there is clinical benefit to ARBs in cardiovascular disease and it is independent of blood pressure control. At present, there is an ongoing study, the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) study. This investigation is nearing completion, and the results should be reported shortly. This study investigates the role of the angiotensin II receptor blocker telmisartan and the ACE inhibitor ramipril alone or in combination in the prevention of stroke, myocardial infarction and cardiovascular death. A parallel study, the TRANSCEND study, which stands for Telmisartan Randomised AssessmeNt Study in ACE-iNtolerant subjects with cardiovascular Disease, compares telmisartan against placebo in patients who are intolerant to ACE inhibitors and is scheduled to be reported at about the same time (Yusuf 2002).

In conclusion, ARBs decrease mortality and morbidity in patients with CHF and MI, likely with similar efficacy to ACE inhibition. However, the clinical evidence in decreasing adverse cardiovascular outcomes in patients with coronary atherosclerosis remains limited. Hence, before judgments are made regarding their role in this population, we need both more clinical trials to assess their utility, in addition to better understanding of the mechanisms behind their efficacy.

Renin inhibitors: A look into the future

The potential for renin inhibition as a target for blockade of the RAS has been considered for more than 30 years, as renin is the initial and rate limiting step in the RAS system (Skegg et al 1957). To date, elucidation and release of an effective direct renin inhibitor have failed for multiple reasons, including achieving effective potency, poor oral bioavailability and high cost. With the advent of new technology using x-ray crystallography and reconstruction of the structure of the active site, there has been creation of novel agents that may overcome these shortcomings (Fisher and Hollenberg 2005).

The rationale for direct renin inhibition is multifaceted. It is known that renin is the rate limiting step in the RAS (Nussberger et al 2002). Furthermore, plasma renin active concentration is the most sensitive marker of RAS activity, with a striking relationship between onset of diabetic

micro vascular disease correlating well to elevated plasma concentrations of pro-renin (Franken et al 1990; Fisher and Hollenberg 2005). Renin inhibitors have a remarkable specificity for its substrate, which will reduce the likelihood of unwanted interactions and side effects. Additionally, blockade at the beginning of the pathway will lead to decreased levels of Ang I, bradykinin, Ang II and aldosterone (Nussberger et al 2002). Theoretically, direct renin inhibition should also eliminate the potential for bradykinin and substance P related side effects, such as cough and angioedema, seen with ACE inhibition. In addition, while direct renin inhibitors will decrease levels of Ang II, most ARBs lead to increased levels of Ang II. While they block the AT_1 receptor and negative many of the ill effects of Ang II, there is a paucity of information about the long term effects of elevated Ang II levels on the AT_2 receptors.

With this potential benefit, a direct renin inhibitor, aliskiren (SPP100) was recently approved by the Food and Drug Administration (FDA) for treatment of hypertension. In a double-blinded, crossover study, eighteen healthy volunteers were placed on a 100 mmol Na diet for a period of 6 weeks, then randomized to either placebo, enalapril (20 mg/day) or two dosing regimens of aliskiren. The results of this study have been encouraging, as the medication seems to be well-tolerated with similar adverse events in all groups. Aliskiren was found to inhibit RAS activity in a dose dependent manner, with a maximum reduction in Ang II levels by the first hour after administration of the dose and suppression up to six hours. This was in contrast to enalapril, which decreased its levels only after six hours. In addition to Ang II, plasma renin activity and Ang I were also decreased, while enalapril produced the expected increase in these levels by up to fifteen fold. Both drugs result in enhanced levels of renin. Thus, from a physiologic perspective, aliskiren seems a promising drug which shows effective blockade of the RAS (Nussberger et al 2002).

Furthermore, at least one study looking at patients with hypertension has shown that this agent effectively decreases blood pressure. In this safety and efficacy study, 226 hypertensive patients were randomized to receive variable doses of aliskiren or losartan (100 mg/day) for 4 weeks. There was a dose dependent reduction in daytime ambulatory systolic pressure of 11 mmHg with maximum dose of aliskerin (300 mg/day), which was comparable to the dose of losartan used in the study. Rates of side effects and adverse events were not significantly different between treatment groups (Stanton et al 2003). A more recent study compared the effects of aliskiren to valsartan, both separately

and in combination. While they were similar in tolerability and reduction in blood pressure, it is interesting to note that the combination was also found to be tolerable (Pool et al 2007).

Thus, direct renin inhibitors such as aliskerin hold further promise in elucidating the importance of the RAS in coronary atherosclerosis. Obviously, their efficacy is far from proven, but this drug opens the door for many more studies to answer a multitude of questions. Specifically, will this drug be useful in combination with other RAS-blocking agents? Will this drug more effectively reduce levels of the important pathophysiologic mediators of the RAS? Do these agents have a role beyond anti-hypertensives, in the prevention and treatment of diabetic micro vascular disease, atherosclerosis and systolic dysfunction?

Conclusion

The evidence for the renin angiotensin system as an important mediator of many pathologic cardiovascular processes has become overwhelming. However, while several classes of agents that block the RAS have shown clinical promise in preventing important cardiovascular outcomes, the exact mechanisms of these effects have not been fully realized. There does appear to be important effects on insulin resistance and lipid metabolism, two critical risk factors for cardiovascular disease. In addition, there are also important effects of the RAS on all steps in the atherosclerotic process, including endothelial dysfunction, inflammation, thrombosis and plaque stabilization, which we have not discussed in this review. While there have been multiple large-scale trials on the efficacy of ACE inhibitors in patients with stable coronary atherosclerosis, their benefit in this population remains unclear. The data for ARBs is even more limited, but certainly suggests promising benefit. We now also have direct renin inhibitors, which promise to add even further insights into our understanding of the RAS. Whether these agents that inhibit the RAS are useful in all patients with atherosclerosis remains to be seen and will certainly be the topic of future clinical studies.

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