Renin-angiotensin system and cardiovascular risk

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The renin-angiotensin system is a major regulatory system of cardiovascular and renal function. Basic research has revealed exciting new aspects, which could lead to novel or modified therapeutic approaches. Renin-angiotensin system blockade exerts potent antiatherosclerotic effects, which are mediated by their antihypertensive, anti-inflammatory, antiproliferative, and oxidative stress lowering properties. Inhibitors of the system—ie, angiotensin converting enzyme inhibitors and angiotensin receptor blockers, are now first-line treatments for hypertensive target organ damage and progressive renal disease. Their effects are greater than expected by their ability to lower blood pressure alone. Angiotensin receptor blockers reduce the frequency of atrial fibrillation and stroke. Renin-angiotensin system blockade delays or avoids the onset of type 2 diabetes and prevents cardiovascular and renal events in diabetic patients. Thus, blockade of this system will remain a cornerstone of our strategies to reduce cardiovascular risk.

The renin-angiotensin system has been at the centre of intensive research activities for several decades. As a result, our knowledge of cardiovascular, renal, and atherosclerotic diseases substantially increased and our therapeutic approaches became more tailored, taking into account comorbidities of the individual patients. Thus, in addition to controlling blood pressure in hypertension or optimising blood glucose concentration in diabetes, the preferential treatment strategy should aim at organ protection. Blockade of the renin-angiotensin system is now evidence based strategy for the protection of cardiovascular, cerebrovascular, and renal systems.

In this Review we draw attention to these conditions by focusing on the role of the renin-angiotensin system, blockade of this system, and the cardiovascular risk related to hypertension, atherosclerosis, and type 2 diabetes. We will not address the clinical role of the system in the pathophysiology and treatment of congestive heart failure or postmyocardial infarction. It is also beyond the scope of this Review to elucidate the importance of aldosterone and the interaction this steroid hormone has with the renin-angiotensin system.

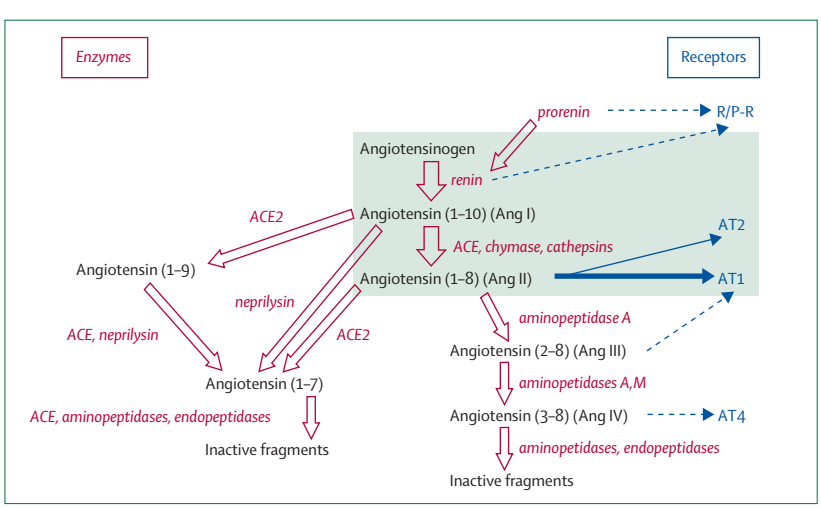

Figure 1: **Simplified overview of the proteins, peptides, enzymes, and receptors of the renin angiotensin system**
The classic pathway is shaded in grey. Renin cleaves the decapeptide angiotensin I from angiotensinogen. Angiotensin I is then converted to angiotensin II by the removal of the two carboxyterminal aminoacids. Angiotensin II binds two receptor subtypes, AT1, and AT2. See table 1 for details on the receptors. Ang=angiotensin. ACE=angiotensin converting enzyme. R/P-R=renin/prorenin receptor.

Biology of the renin-angiotensin system

Renin was described more than 100 years ago by Tigerstedt and Bergman.[1] Nevertheless, our understanding of the renin-angiotensin system is still not complete and has grown increasingly complex. The classic pathway is now textbook knowledge (figure 1). The generation of angiotensin I and II is not restricted to the systemic circulation but production also takes place in vascular and other tissues.[2] The extent to which local synthesis of renin-angiotensin system components[3] or uptake from the circulation contributes to angiotensin II tissue concentration is still debated.[4] Non-angiotensin converting enzymes (ACE) might account for part of the conversion of angiotensin I to II. Urata and colleagues'[5] identification of human heart chymase as the major angiotensin II generating enzyme in heart tissue homogenate has attracted particular attention. Chymase activity is present in heart and vascular tissue extracts of

Search strategy and selection criteria

We searched PubMed for publications with "renin-angiotensin" as a keyword and combinations with "cardiovascular disease", "atherosclerosis", "hypertension", "diabetes", and "therapy". We also searched all major relevant specialty journals in the areas of cardiology, hypertension, atherosclerosis, and diabetes, such as *The Lancet, New England Journal of Medicine, British Medical Journal, Circulation, Journal of the American College of Cardiology, Hypertension, Journal of Hypertension, Diabetes,* and *Diabetes Care* for similar or related articles. Furthermore, we searched PubMed for randomised controlled clinical trials and meta-analysis with keywords "RAS-blockade", "ACE-inhibitors", and "angiotensin receptor blockers". We also checked articles referenced in primary sources and their relevant citations.

many species, including rodents, but the enzyme's ability to generate angiotensin II in intact tissues is often barely detectable under physiological conditions.[6] However, the role of chymase can be more prominent in diseased or injured vascular tissue. The enzyme is upregulated in coronary vascular and kidney tissue in patients with diabetes.[7]

In 2000, a further enzyme associated with the generation of angiotensin peptides was identified—angiotensin converting enzyme 2 (ACE2), a carboxypeptidase with sequence similarity to ACE.[8] ACE2 does not generate angiotensin II but increases the formation of angiotensin (1–7) (figure 1). This heptapeptide causes vasodilatation and has growth inhibitory effects.[9] The effects of angiotensin (1–7) are not mediated by angiotensin receptors AT_1 or AT_2 but might be transmitted through the mas oncogene (table 1). ACE inhibitors and angiotensin receptor blockers (ARBs) increase the concentrations of angiotensin (1–7),[21] which is attributable to the rise of angiotensin I, and the heptapeptide's vasodilator effects could contribute to a lowering of blood pressure.[9] However, ACE2 has several additional functions that are not yet fully understood.[12,22,23] In patients with cardiovascular disorder, ACE2 is upregulated in failing hearts[24] and a haplotype of the ACE2 gene is associated with left ventricular hypertrophy.[25] Further research, including into specific inhibitors, is needed to understand the many functions of ACE2 inside and outside the renin-angiotensin system.

The effects of all angiotensin peptides are mediated through specific cell surface receptors (table 1). The AT_1 receptor mediates most of the effects usually associated with angiotensin II. The AT_2 receptor antagonises many effects of the AT_1 receptor—for example, cell proliferation.[26] This antagonism includes a direct binding of the AT_2 protein to the AT_1 receptor.[27] Stimulation of the AT_2 receptor can protect certain organs (eg, the brain against ischaemia).[28] The AT_4 receptor for angiotensin IV affects kidney tubular function and improves the memory of rodents.[15] Further, the ACE molecule itself could act as a cell surface receptor, mediating outside–in signalling in endothelial cells in vitro.[29] A receptor-mediated uptake of renin (and prorenin, or both) had long been suspected by many researchers[17,30] and such a renin/prorenin receptor was cloned by Nguyen and colleagues[31] in 2002. In cultured cells, the renin/prorenin receptor binds renin and prorenin, increasing the formation of angiotensin II, and exerts further profibrotic effects not mediated through angiotensin II.[17,31] Work in animals lend support to the notion that overexpression of the renin/prorenin receptor increases blood pressure.[32] The role of this receptor in human beings remains to be established[17] but might be of particular importance for the effects of renin inhibitors.

Our knowledge of the importance of the renin-angiotensin system for cardiovascular disease in individuals is partly attributable to the finding that renin activity predicts cardiovascular events.[33,34] However, substantial evidence is derived from clinical trials using inhibitors of the system. Several classes of drugs that inhibit the renin-angiotensin system are available. First, sympatholytic agents, (β blockers), suppress angiotensin II formation by inhibiting renin release from the kidney.[35] Second, ACE inhibitors reduce the formation of angiotensin II from angiotensin I by inhibiting ACE but not ACE2 or other angiotensin II forming enzymes (figure 1). Third, ARBs antagonise the binding of angiotensin II to the AT_1 receptor.

ACE inhibitors and ARBs are the most important renin-angiotensin system blockers in use. The biology of the system would suggest some differences between both types of drugs (figure 1 and table 1). For example, ACE inhibitors do not affect angiotensin II generation by non-ACE pathways, whereas ARBs antagonise all AT_1 receptor effects. Conversely, ACE inhibitors affect AT_1 and AT_2 receptors equally, whereas ARBs inhibit AT_1 receptors and stimulate AT_2 receptors. This notion might contribute to a different potential of both class of drug to protect patients from stroke.[28,36] Neither ACE inhibitors nor ARBs are solely renin-angiotensin system inhibitors. The contribution of bradykinin[37] to the effects of ACE inhibitors is well known, but less well known is that ARBs also increase bradykinin concentrations in human beings.[38] Nevertheless, ACE inhibitors affects the degradation of other bioactive peptides.[39] Renin inhibitors are under investigation and phase III trials have shown their effectiveness at lowering blood pressure.[40,41] From the point of view of the biology of the renin-angiotensin system, renin inhibitors offer the potential to inhibit the entire cascade of the system.[40]

	Full name	Ligand(s)	Function
AT_1	Angiotensin II type 1 receptor	Angiotensin II, Angiotensin III	Vasoconstriction, stimulation of aldosterone release and sympathetic nerve activity, promotion of cell growth, matrix deposition, inflammation[10]
AT_2	Angiotensin II type 2 receptor	Angiotensin II	Antagonism of the effects of AT1, promotion of apoptosis,[10,11] protection of neural tissue,[12] possible synergism with AT1 in promoting inflammation[13,14]
AT_4	Angiotensin IV receptor	Angiotensin IV, LVV-haemorphin 7	Vasodilatation, decreased tubular sodium transport, improved memory,[15] possibly promoting inflammation[16]
R/P-R	Renin/prorenin receptor	Renin and prorenin	Increase of angiotensin generation, further independent promotion of matrix deposition[17]
mas	*mas* oncogene	Angiotensin (1–7)	Antagonism of the effects of AT_1,[18] antidiuretic,[19] inhibits cell growth.[20] Not yet clear whether or not all actions of angiotensin (1–7) are mediated by *mas* oncogene

LVV=Leu-val-val-hemorphin.

Table 1: **Cell surface receptors of the renin-angiotensin system**

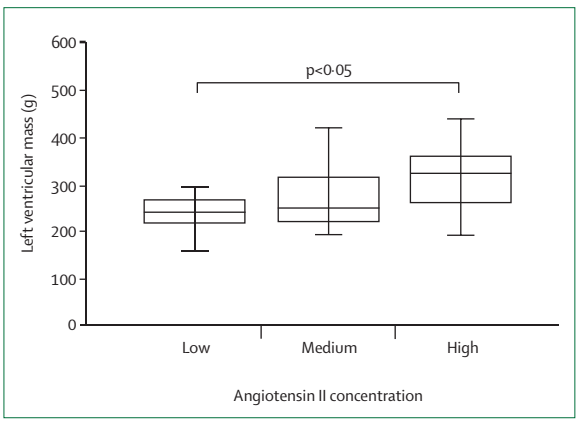

Figure 2: **Box plot of left ventricular mass in never treated patients, according to angiotensin II concentrations in relation to urinary sodium excretion**
Age, body-mass index, and 24 h ambulatory blood pressure were close in the three groups. Reproduced by permission from Schmieder et al. Angiotensin II related to sodium excretion modulates left ventricular structure in human essential hypertension. *Circulation* 1996; **94:** 1304–09.[46]

Renin-angiotensin system and arterial hypertension

Left ventricular hypertrophy

Evidence of early target organ damage in arterial hypertension, such as left ventricular hypertrophy, increases the risk of major cardiovascular events two-fold to five-fold.[42] In addition to the increased afterload—ie, raised blood pressure—the extent of vascular and cardiac damage, such as left ventricular hypertrophy, is greatly modulated by the activity of the renin-angiotensin system.[43,44] Left ventricular hypertrophy has proved to be heightened in patients with renal artery stenosis, a state characterised by the system activation, compared with patients with primary hypertension at similar levels of blood pressure.[45] In a homogeneous study cohort of never treated hypertensive people,[46] high angiotensin II concentrations were closely associated with high left ventricular mass (figure 2). Subsequent analysis revealed that increased activity and insufficient suppression of the renin-angiotensin system corresponds to inadequately high left ventricular mass in relation to the 24 h ambulatory blood pressure load.[47,48]

Many studies[11,13,28] have shown that various genotypes of the renin-angiotensin system alter the process of cardiac structural adaptation of the heart. Whereas growth stimulating effects of angiotensin II via the AT_1 receptor are widely accepted, effects of AT_2 receptor stimulation are controversial because of conflicting results that show both inhibitory and stimulating effects on growth and proliferation. Irrespective of this controversy, we and other groups[49,50] consistently reported that gene variants of the AT_2 receptor substantially modulated the degree of left ventricular hypertrophy in hypertensive male patients and predicted coronary heart disease events. Thus, renin-angiotensin system activation aggravates left ventricular hypertrophy in primary hypertensive patients independently of, and in addition to, the blood pressure load imposed on the left ventricle.[51]

Further evidence of an association between the renin-angiotensin system and left ventricular hypertrophy stems from therapeutic trials. Of the five antihypertensive agents recommended as first-line treatment, calcium antagonists, ACE inhibitors, and ARBs reduce left ventricular mass to a greater extent than do β blockers (including vasodilatory β blockers) and diuretics (figure 3).[52,53] This result has proved independent of other confounding factors. In a prospective trial (Losartan Intervention For Endpoint reduction in hypertension [LIFE] study)[54] with hypertensive patients who had left ventricular hypertrophy at baseline the investigators consistently reported that reduction of left ventricular hypertrophy was greater with the ARB losartan than with the β blocker atenolol, and this effect was maintained at similar blood pressure levels throughout the whole follow-up of 5 years.[55] Thus, it is not only a question of treatment duration or achieved blood pressure, but the choice of drug is also of clinical relevance for the treatment of left ventricular hypertrophy. Several clinical trials[56] have clearly indicated that reduction of left ventricular hypertrophy translates into a reduced rate of cardiovascular complications and improved prognosis. Thus, reduction of left ventricular hypertrophy emerges as a therapeutic goal in primary hypertension that should be adequately addressed.

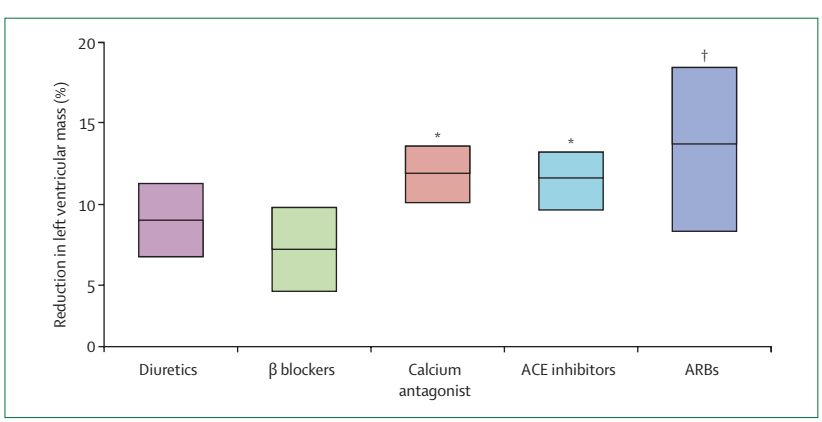

Figure 3: **Reduction of left ventricular mass stratified according to various antihypertensive regimens**
Mean (95% CI) fall in blood pressure, duration of treatment, and baseline values (including left ventricular mass) have been adjusted between the groups. Reproduced from Klingbeil et al. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. *Am J Med* 2003; **115:** 41–46[53] ©2003 with permission from Excerpta Media Inc. *= p<0·05, †=p<0·01 versus β blocker.

Atrial fibrillation

Atrial fibrillation is the most common cardiac arrhythmia, affecting roughly 1% of people younger than 65 years and 5% of individuals older than 65 years.[57] Atrial fibrillation heightens the risk of cardiovascular mortality by around two-fold and can be identified as the underlying cause for up to 15% of all strokes.[58] Hypertension is the most important risk factor for atrial fibrillation on a population basis. In hypertensive individuals, age, left atrial chamber diameter, and left ventricular mass have been identified as independent risk factors for the development of atrial fibrillation.[59]

In hypertensive patients with atrial fibrillation at baseline, the LIFE study[60] findings suggested that treatment based on ARBs was more effective than that based on β blockers in reducing the risk of the composite cardiovascular endpoint, stroke, and cardiovascular death. Similarly, treatment with ARBs reduced the frequency of atrial fibrillation in patients without atrial fibrillation at baseline by 21%.[61] In another large scale prospective study with hypertensive patients at high cardiovascular risk (the Valsartan Antihypertensive Long Term Use Evaluation [VALUE] study),[62] new atrial fibrillation onset was less frequent in those on ARBs than in those on calcium antagonists. However, in two trials,[63,64] treatment with ACE inhibitors seemed not to reduce the rate of new atrial fibrillation onset in hypertensive patients. Nevertheless, in patients with congestive heart failure, both ACE inhibitors and ARBs were effective in the reduction of the development of atrial fibrillation. Similarly, the combination of amiodarone with an ARB or an ACE inhibitor was more effective at maintaining sinus rhythm than was amidarone therapy alone.[63–65]

What could be the underlying pathogenic mechanism for renin-angiotensin system blockade prevention of atrial fibrillation? In animals, the system blockade has been reported not only to prevent left atrial dilation and atrial fibrosis but also to slow conduction velocity.[21,66–68] These ARB effects were not seen in animals treated to identical haemodynamic targets with hydralazine and isosorbide mononitrate.[21] Further potential mechanisms include increasing potassium concentrations, changing potassium currents and conduction, lowering end-diastolic left ventricular pressure, modifying the sympathetic tone, and direct antiarrythmic effects.[63] In addition to these mechanisms, there is now increasing evidence linking inflammation to atrial fibrillation.[66,69] Biopsies from patients with atrial fibrillation have shown evidence of inflammation in the left atrium,[70] and in a double blind randomised trial[71] low-dose glucocorticoide therapy reduced recurrence of atrial fibrillation. The renin-angiotensin system seems to have a key role in this process, since atrial fibrillation leads to altered AT_2 receptor expression and, conversely, blockade of the system decreases inflammatory processes. Furthermore, statins—also known to reduce the inflammatory state by their pleiotropic effects—reduced the rate of atrial fibrillation in four of five trials.[66] Thus, renin-angiotensin system blockade has emerged as a new preventive and therapeutic strategy for atrial fibrillation.

Stroke

From a patient perspective, stroke is the most debilitating result of cardiovascular disease. The incidence and prevalence of stroke increases linearly with age and blood pressure.[72] The most crucial factor in stroke prevention is best possible blood pressure control.[73] Meta-analyses suggest that ARBs, but possibly not ACE inhibitors, are effective in stroke prevention beyond blood pressure control.[73] How can this result be explained?

In animal studies,[74] treatment with ARBs improved neurological outcome of focal cerebral ischaemia and protected brain tissue against ischaemic injury. Stimulation of the AT_2 receptor induces vasodilatation, because it potentiates locally synthesised nitric oxide and prostacyclin, which in turn could improve cerebral blood flow by collateral circulation.[28] In the brain region adjacent to the infarct area, AT_1 receptor density remained unaltered but AT_2 receptors were upregulated in neurons,[28,75] and selective blockade of central AT_2 receptors abolished the neuroprotective effect of ARBs.[28] Thus, experiments have shown cerebral AT_2 receptors exert neuroprotective effects in response to ischemia induced neuronal injury.[28]

These new experimental findings might help to explain the results of several clinical trials. In a trial[76] of hypertensive patients aged 35–64 years, diuretics that activate the renin-angiotensin system prevented substantially more strokes than did β blockers, which suppress the system activity by equal blood pressure reductions. In hypertensive patients with stroke, the Perindopril Protection Against Recurrent Stroke Study[77] showed that the ACE inhibitor, perindopril, resulted in only a 5% stroke reduction, compared with a 43% stroke reduction if the diuretic indapamid was added to the ACE inhibitor. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),[78] treatment of hypertensive patients with lisinopril resulted in a 15% higher frequency of strokes in the whole study population and a 40% higher frequency of strokes in black patients, than treatment with the diuretic chlorthalidone.

In hypertensive patients with left ventricular hypertrophy but without previous stroke, the LIFE study showed a 25% reduction in strokes with ARB based regimen than the β blocker based regimen.[54] Similar results were reported in patients with isolated systolic hypertension (40% and 24% stroke reduction in LIFE study[79] and the Study on Cognition and Prognosis in the Elderly (SCOPE),[80] respectively). In these trials with ARBs, control of blood pressure was much the same, suggesting that the recorded difference in stroke frequency could be attributed specifically to treatment with ARBs. In a meta-analysis, calcium antagonists that do not affect the renin-angiotensin system reduced the risk of stroke better than did ACE inhibitors.[73] In patients with previous stroke, the Morbidity and Mortality after Stroke (MOSES) trial[81] reported reoccurrence of stroke was less frequent with ARB based treatment than with calcium antagonist based therapy at similar blood pressure control, throughout the whole follow-up (figure 4).

In summary, the most important factor in stroke prevention is good blood pressure control, and the control of aortic systolic blood pressure might be of particular importance.[82] The cerebroprotective effects of the AT_2 receptor stimulation by ARBs[83] have emerged as

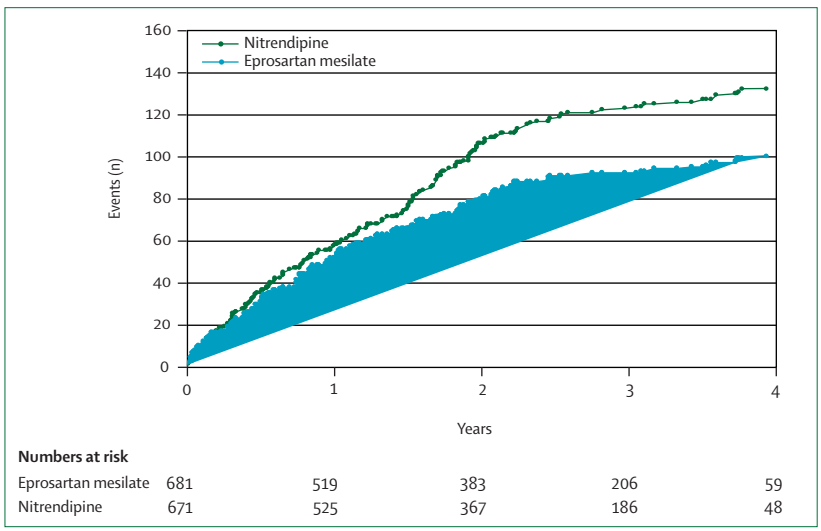

Figure 4: **Cumulative incidence of cerebrovascular events (secondary endpoint) in patients in the MOSES study**
Incidence density ratio was 0·75 (95%CI 0·58–0·97, p=0·026). Total events on eprosartan mesilate=102, on nitrendipine=134. Reproduced with permission from Prof Schrader.

a further important clinical means to address the serious target organ damage of hypertension—namely, ischaemic stroke.

Renin-angiotensin system and atherosclerosis

The importance of traditional cardiovascular risk factors, such as raised LDL cholesterol, hypertension, smoking, and diabetes for atherosclerotic vascular disease is well established. However, intensive research over the past few years has shown clear evidence for further important mechanisms that are critically connected with the atherosclerosis cascade. These mechanisms include vascular inflammation, generation of reactive oxygen species, and alterations of endothelial function. Furthermore, clinical and experimental evidence[36] clearly indicate that activation of the renin-angiotensin system, with angiotensin II binding to AT_1 receptors as the major effector, is central to almost all these pathways (figure 5).

Production of proinflammatory cytokines, such as interleukin 1, tumour necrosis factor α, and especially interleukin 6, play a major part in the pathogenesis of atherosclerosis.[84] The concentration of circulating cytokines is associated with an adverse outcome in patients with coronary atherosclerosis.[85,86] Both interleukin 6 and AT_1 receptors have been detected in stable and unstable atherosclerotic plaques and there is evidence for a bidirectional crosstalk—ie, interleukin 6 induced up-regulation of vascular AT_1 receptor expression[87] and enhanced interleukin 6 production in response to

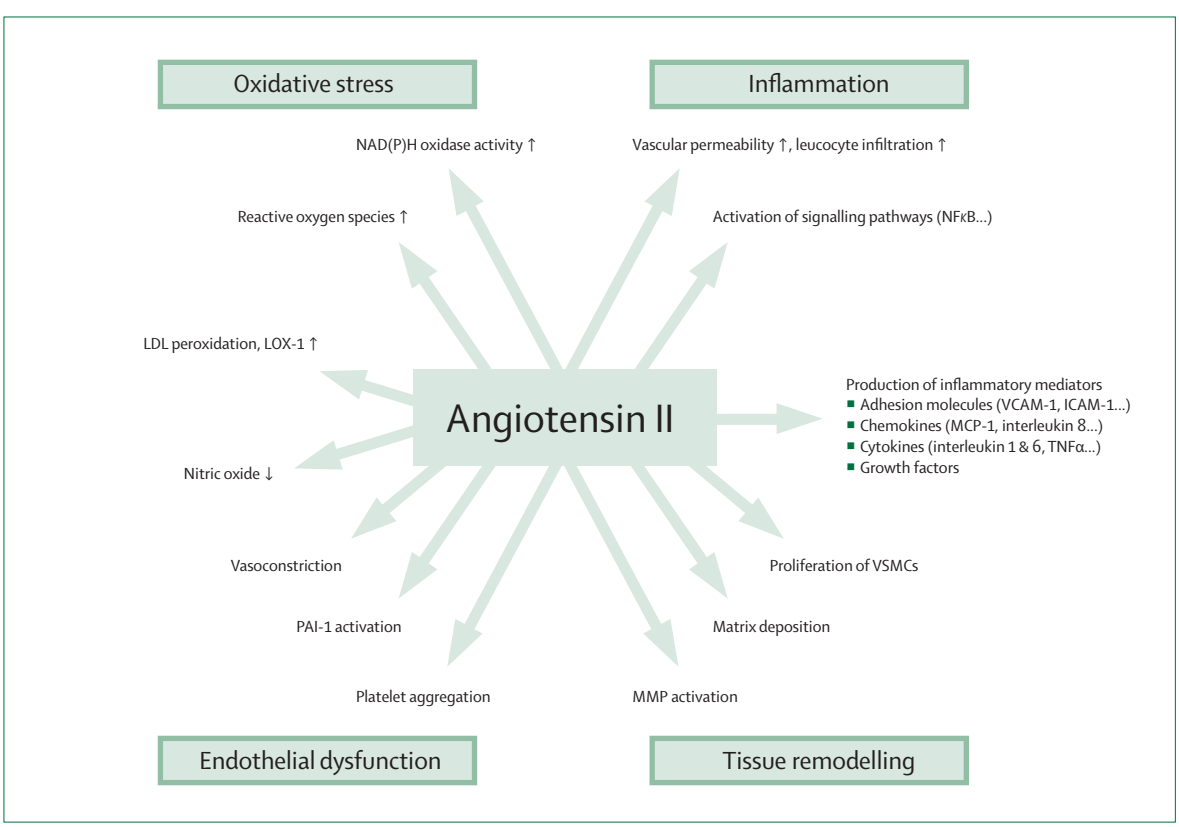

Figure 5: **Schematic illustration of important effects of angiotensin II on mechanisms associated with atherosclerosis**
The various interactions between several angiotensin II induced processes are not illustrated. ICAM-1=intercellular adhesion molecules. LOX-1=lectin-like oxidised LDL receptor. MCP-1=monocyte chemoattractant proteins. MMP=matrix metalloproteinases. PAI-1=plasminogen activator inhibitor. VSMCs=vascular smooth muscle cells. VCAM-1= vascular adhesion molecules.

activation of the AT_1 receptor.[88] Moreover, the sustained proinflammatory state seems to play an important part in the transformation of a stable atherosclerotic plaque into a vulnerable plaque prone to rupture.

Plaque rupture has been connected with activation of matrix metalloproteinases (MMP) in the fibrous cap of the atherosclerotic lesion[89] and there is evidence that angiotensin II is implicated in matrix metalloproteinases activation, both through direct actions and through induction of interleukin 6.[90] Furthermore, angiotensin II stimulates the redox sensitive transcription factor nuclear factor kappa B (NF-κB), which could serve as a unifying signalling system for inflammatory stimuli in atherogenesis,[91] through enhanced expression of adhesion molecules (intercellular and vascular adhesion molecules [ICAM-1 and VCAM-1], and E-selectin), monocyte chemoattractant proteins (MCP-1), and interleukin 8.[92,93] ARBs have been shown to prevent NF-κB activation and expression in response to angiotensin II,[13,14] even in healthy individuals.[94] Furthermore, both ACE inhibitors and ARBs decrease the expression of several adhesion molecules.[95,96] In a double blind, placebo controlled trial in hypertensive patients with increased levels of high-sensitivity C-reactive protein, administration of the ARB, olmesartan, greatly reduced vascular microinflammation after 6 weeks of therapy.[97] Thus, the chronic inflammatory response associated with atherosclerosis seems to be modulated by angiotensin II at every level and can be targeted therapeutically by inhibition of the renin-angiotensin system.

Generation of reactive oxygen species, such as superoxide and hydrogen peroxide, promotes and sustains the atherosclerotic process. Angiotensin II stimulates the activity of NADP(H) and xanthine oxidase, which are the major source of oxygen free radicals within the vascular wall.[98] Superoxide itself can directly react with nitric oxide derived from endothelium to form peroxynitrite, thereby scavenging nitric oxide.[99] Angiotensin II also promotes oxidation of LDL cholesterol and expression of lectin-like oxidised LDL receptors on endothelial cells.[85,100,101] Lectin-like oxidised LDL receptors in turn seem to be capable of upregulating AT_1 receptor expression, resulting in a detrimental positive feedback loop and increased uptake of oxidised LDL in endothelial cells. In hypercholesterolaemic animals, impaired endothelial function is associated with an upregulation of AT_1 receptor expression and an increased NADP(H) oxidase driven superoxide production in the diseased blood vessels, which can be returned to normal by treatment with an ARB.[102] The finding that the systemic and renal response to angiotensin II infusion in people is determined by LDL cholesterol concentrations[103] is in line with these animal data. Furthermore, oxidative stress induces tissue inflammation and damage by stimulating cytokine formation. By preventing angiotensin II from inducing oxidative stress through activation of NADP(H) oxidases, renin-angiotensin system blockade could improve nitric oxide activity in various conditions.

The endothelium plays an important part in the regulation of vascular function.[104] Several clinical studies[105–109] reported that both peripheral and coronary endothelial dysfunction contribute to an increased risk of cardiovascular events. Angiotensin II has been shown to initiate and sustain several mechanisms that contribute to impaired endothelial function—eg, accelerated degradation of nitric oxide and reduced endothelium dependent vasodilation, through increased formation of reactive oxygen species.[110] Activation of the renin-angiotensin system not only promotes vasoconstriction and exaggerated formation of extracellular matrix and matrix metalloproteinases, but also enhances migration and proliferation of vascular smooth muscle cells, increases synthesis of plasminogen activator inhibitor (PAI-1), and stimulates release of proinflammatory cytokines, such as interleukin 6.[111] An increased concentration of circulating endothelial progenitor cells, which are believed to maintain the integrity of the vascular endothelium, has been associated with a favourable cardiovascular outcome in patients with coronary artery disease.[112] A small study[113] in type 2 diabetic patients suggested that treatment with ARBs increases the number of regenerative endothelial progenitor cells, which could contribute to the beneficial cardiovascular effects seen with AT_1 receptor blockade.

As a result of these investigations, blockade of the renin-angiotensin system emerged as an obvious and attractive therapeutic target. Early evidence for a beneficial effect of inhibition of this system on impaired endothelial function was derived from the Trial on Reversing Endothelial Dysfunction study,[114] which showed that ACE inhibition in patients with coronary artery disease improves endothelial function. Similar beneficial effects of ACE inhibition on coronary endothelial function were shown in hypertensive patients.[115] By contrast with diuretics, AT_1 receptor blockade with valsartan improved basal nitric oxide production and release in hypertensive patients, despite similar blood pressure reduction.[116] In the peripheral circulation, therapy with the ACE inhibitor ramipril or the ARB losartan improved endothelium-dependent vasodilation in patients with coronary artery disease by increasing the bioavailability of nitric oxide.[117] Furthermore, a study in hypertensive, postmenopausal women[118] showed that the cardiovascular event rate was substantially lower in those patients with improved endothelial function in response to antihypertensive therapy than those without improvement, suggesting the prognostic effect of reversing endothelial dysfunction.

In high risk patients without evidence of heart failure, the Heart Outcome Prevention Evaluation (HOPE) trial[119] reported treatment with ramipril greatly reduced rates of death, myocardial infarction, and stroke (22% relative risk reduction for the primary composite endpoint). Similarly, the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA)

	Population	Intervention	Follow-up (years)	Composite primary endpoint *		Non-fatal myocardial infarction	
				Frequency	Relative risk reduction †	Frequency	Relative risk reduction †
HOPE	High risk (n=9297) (vascular disease or diabetes)	Ramipril 10 mg per day *vs* placebo	5·0	14·0% *vs* 17·8%	22% (14 to 30)	9·9% *vs* 12·3%	20% (10 to 30)
EUROPA	Low risk (n=12 218) (stable coronary artery disease)	Perindopril 8 mg per day *vs* placebo	4·2	8·0% *vs* 9·9%	20% (9 to 29)	4·8% *vs* 6·2%	22% (10 to 33)
PEACE	Low risk (n=8290) (stable coronary artery disease)	Trandolapril 4 mg per day *vs* placebo	4·8	21·9% *vs* 22·5%	4% (-6 to 12)	5·3% *vs* 5·3%	0% (-20 to 17)

*Primary composite endpoints: HOPE: cardiovascular death, non-fatal myocardial infarction, or stroke; EUROPA: cardiovascular death, non-fatal myocardial infarction, or cardiac arrest; PEACE: cardiovascular death, non-fatal myocardial infarction, or coronary revascularisation. †95% CI in brackets.

Table 2: **Comparison of three large scale clinical trials examining the effect of ACE inhibition on cardiovascular events**

trial[120] showed that perindopril treatment was associated with a 20% reduction of the relative risk for cardiovascular endpoints in a low risk population with stable coronary heart disease. However, the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial[121] could not show that patients with stable coronary artery disease and healthy or slightly reduced left ventricular function derive therapeutic benefit from the addition of ACE inhibitors to modern conventional therapy. The failure of ACE inhibitors to reduce the cardiovascular events in this trial was thought to be attributable to the low overall event rate of hard cardiovascular endpoints, such as cardiovascular death and myocardial infarction, and because of low plasma LDL concentrations of the participants, many of whom were taking statins (table 2).

Whether ARBs produce effects similar to those of ACE inhibitors in atherosclerotic vascular disease is unanswered, but large scale clinical trials are in progress. In hypertensive patients, the LIFE trial[54] reported treatment with losartan was associated with a 13% reduction of relative risk for the primary composite endpoint (death, myocardial infarction, or stroke), emphasising the notion that beneficial effects could also be seen in atherosclerotic vascular disease.

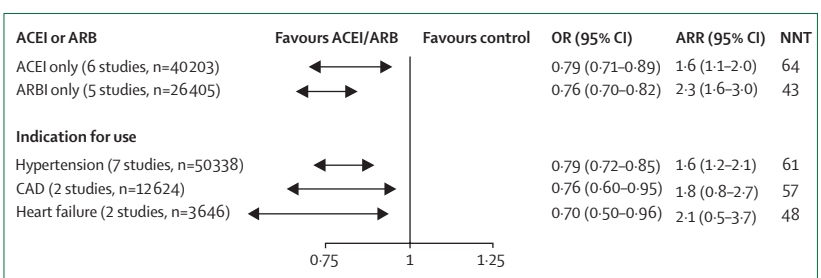

Figure 6: **Risk of developing type 2 diabetes with ACE inhibitors or ARBs compared with other antihypertensive treatment**

In this meta-analysis, ACE inhibitors lower the risk of developing type 2 diabetes by 21% and ARBs by 24%. The effect is independent from the indication for the use of the ACE inhibitor or ARB. In another meta-analysis,[127] ACE inhibitors and ARBs reduced the risk of onset of type 2 diabetes by 27% and by 23%, respectively. Reproduced from *The American Diabetes Association*. Gillespie et al. The impact of ACE inhibitors or angiotensin II type 1 receptor blockers on the development of new-onset type 2 diabetes. *Diabetes Care* 2005; **28:** 2261–66.[128] ©2005 The American Diabetes Association. ACEI=angiotensin converting enzyme inhibitor. ARB=angiotensin receptor blocker. ARR=adjusted relative risk. CAD=coronary artery disease. NNT=number needed to treat. OR=odds ratio.

Renin-angiotensin system and type 2 diabetes

Cardiovascular mortality and morbidity in patients with type 2 diabetes is very high. In view of the worldwide epidemic of the metabolic syndrome and obesity, the development and results of type 2 diabetes and the accompanying cardiovascular risk will be a major challenge of the future. The best strategy is prevention of diabetes itself, but measures to reduce the disease burden for diabetic patients are also important. The renin-angiotensin system blockade intervenes at different stages of this disease process.

Development of diabetes

Renin-angiotensin system blockade reduces insulin resistance, which is the pathophysiological hallmark of the metabolic syndrome and type 2 diabetes.[122] The proposed mechanisms by which insulin sensitivity is increased include better skeletal muscle perfusion, improvement of microvascular changes, and increased perfusion of the pancreatic islet cell. In addition to these haemodynamic effects, direct effects of angiotensin II on the pancreatic β cells from a local renin-angiotensin system in the islet might contribute to a loss of β cell function. Acute angiotensin II infusion in rats hinders the early phase of insulin secretion[123] and treatment with losartan[124] stimulates the early phase of insulin secretion in transplanted islets in mice. Furthermore, activation of renin-angiotensin system is associated with fibrosis of pancreatic islets in animals with type 2 diabetes.[122] In experimental models,[125,126] specific ARBs have modulated peroxisome proliferator-activated receptor γ (PPARγ) activity and thereby reduce insulin resistance, with the highest activity found with telmisartan. However, the clinical effect of renin-angiotensin system blockade on PPARγ activity remains to be proven.

Several clinical trials[127,128] have shown that the frequency of new onset of type 2 diabetes can be reduced by ACE inhibitors and ARBs (as opposed to β blockers and diuretics) (figure 6), which will certainly attract more attention in future guidelines. In the ALLHAT trial[78] of 33 357 hypertensive patients, the rate of new onset of diabetes over 4 years was 8·1% with lisinopril, 9·8%

with amlodipine besilate, and 11·6% with chlortalidone.[78] In patients with high cardiovascular risk, the VALUE study[129] showed that renin-angiotensin system blockade with valsartan was better than amlodipine besilate with respect to prevention of new onset of diabetes (13% versus 16·4%). These data lend support to the notion that diuretics stimulating the renin-angiotensin system are harmful, ACE inhibitors or ARBs that block the system are beneficial, and calcium antagonists that do not affect the system seem to be neutral.

We should note that the clinical evidence showing that renin-angiotensin system blockade prevents, or at least delays, the onset of type 2 diabetes has arisen from clinical studies, in which new onset of diabetes was not the primary endpoint. However, the uniformity of the result across all the various studies suggests that this is a true finding. The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication trial[130] produced mixed results in 5269 patients without cardiovascular disease but with impaired fasting glucose. Ramipril did not reduce the development of diabetes (primary endpoint) compared with placebo within the first 3 years. However, regression to normoglycaemia was increased and glucose concentrations in plasma 2 h after an oral glucose load were lower in the ramipril group than in placebo group. Therefore, in hypertensive patients at risk of developing type 2 diabetes—namely, patients who have a family history of type 2 diabetes, have a body-mass index greater than 30 kg/m², have impaired glucose tolerance (fasting plasma glucose 6·5 mmol/L or greater), or are of southeast Asian or African descent—ACE inhibitors or ARBs should be the first choice of antihypertensive therapy, with calcium antagonists being second-line treatments. Treatment with diuretics and β blockers should be avoided in these patients, unless other comorbidities (eg, volume overload or congestive heart failure) need the use of these agents.

Complications of diabetes

Blockade of the renin-angiotensin system reduced the frequency of various diabetic complications, including diabetic nephropathy. Furthermore, in the high risk group of diabetic patients, renin-angiotensin system blockade reduces cardiovascular mortality and morbidity.

Albuminuria is well known as an early sign of diabetic nephropathy, but it also represents a cardiovascular risk marker. Microalbuminuria predicts cardiovascular events in patients with diabetes, in those with hypertension, and in the general population.[131,132] This result leads to the idea that lowering albuminuria is an important goal of antihypertensive therapy, especially for patients with diabetes and impaired glucose tolerance.[133,134] Indeed, trials[135,136] now indicate that reduction of albuminuria is associated with better renal and cardiovascular outcome (figure 7).

Blockade of the renin-angiotensin system prevents the onset of microalbuminuria in diabetic patients and reduces proteinuria. Ruggenenti and colleagues[137] showed that in patients with type 2 diabetes, the ACE inhibitor trandolapril prevented the onset of microalbuminuria, whereas verapamil was not effective. A meta-analysis confirmed this result.[138] In patients with albuminuria, blockade of the renin-angiotensin system with the ARB irbesartan doses dependently reduced the occurrence of overt diabetic nephropathy.[139] In patients with such nephropathy, ARB treatment with losartan and irbesartan was associated with a reduction of proteinuria and better renal survival than placebo[140] or placebo and amlodipine besilate.[141]

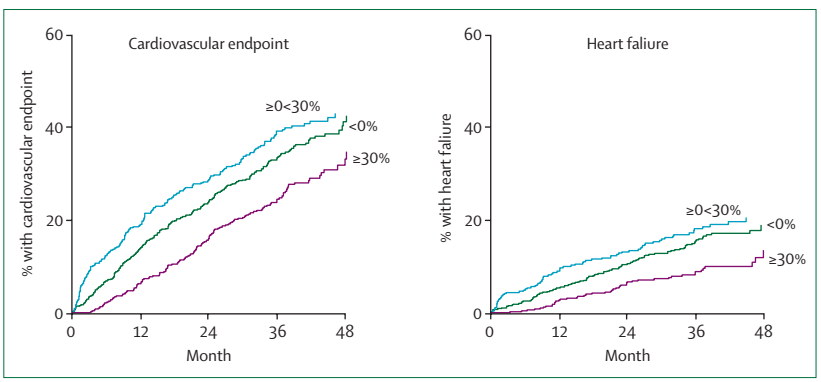

Figure 7: **Change of albuminuria predicts occurrence of cardiovascular events and heart failure in patients with overt diabetic nephropathy**
Reproduced with permission from de Zeeuw D et al. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. *Circulation* 2004; **110:** 921–27.[143]

In addition to being renoprotective, ACE inhibitors and ARBs have also been shown to reduce cardiovascular events in diabetic patients. Post-hoc analysis of these trials (Reduction of Events with Angiotensin Converting Enzyme Inhibition [RENAAL] and Irbesartan Diabetic Nephropathy Trial [IDNT])[142] showed a reduction of cardiovascular morbidity and mortality (figure 7).[143] In diabetic patients with atherosclerotic disease, the HOPE and substudy investigations[144] documented that ramipril lowered cardiovascular death by 37% and total mortality by 24%. Furthermore, in the subgroup of hypertensive patients with diabetes and left ventricular hypertrophy, the LIFE study[145] showed that losartan reduced cardiovascular mortality by 37% and total mortality by 39% compared with atenolol. In both studies, the effect of the renin-angiotensin system blockade was more pronounced in diabetics than in non-diabetics.

Patients with advanced renal failure, especially if diabetic, are at very high cardiovascular risk. Blockade of the renin-angiotensin system in these patients is safe and effective, as shown for the ACE inhibitor benazepril and the ARB losartan.[146,147] Although, for the early stages of diabetic nephropathy equivalence of ACE inhibitors and ARBs has been shown[148] there are some considerations favouring ARBs over ACE inhibitors in advanced diabetic nephropathy. Analyses from Italy and Canada examining the effectiveness of ACE inhibition according to the

underlying kidney disease, questioned whether ACE inhibition is effective in advanced diabetic nephropathy.[149,150] No clinical trial has shown a clear beneficial effect of ACE inhibitors in this situation.[151] However, other trials[140,141] using ARBs have shown efficacy of the renin-angiotensin system blockade in advanced renal failure. Experimental evidence suggests that the high degree of chymase expression in advanced diabetic nephropathy,[7] potentially leading to a highly activated renin-angiotensin system in local tissues, explains why blocking the converting enzyme with ACE inhibitors which are unable to block formation of angiotensin II by chymase, might be ineffective in these patients.

Conclusions

Improvement of the patient's cardiovascular risk by blockade of the renin-angiotensin system is caused by blood pressure reduction but includes additional non-haemodynamic effects. ARBs and ACE inhibitors are best proven interventions to reduce target organ damage in hypertension, atherosclerosis, and diabetes. New aspects of the renin-angiotensin system continue to emerge and could become targets for novel therapeutic strategies.

Conflict of interest statement

We have consulted for and lectured on behalf of MSD (RES), Novartis (RES, BMWS, KFH), Takeda (RES), AstraZeneca (RES, BMWS), Sanofi Aventis (RES, MPS, BMWS, KFH), Bristol Meyers-Squibb (RES, KFH), Sankyo (RES), Asche Chiesi (RES, MPS), Servier (RES, MPS), Boehringer Ingelheim (RES), Solvay (MPS), Abbott (BMWS), and Roche (KFH). RES has been involved in clinical trials, receiving research support from DFG, BMBF, MSD, Novartis, Takeda, AstraZeneca, Boehringer, Ingelheim, and Roche. MPS has received grant support from DFG and Servier. BMWS has received grant support from DFG, Altana, and Pfizer. KFH has received grant support from DFG, Sanofi Aventis, Novartis, and Amgen. We do not hold stocks, equity, contract of employment, or company board position.

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