



Stroke, high blood pressure and the renin–angiotensin–aldosterone system – new developments

Jeffrey Atkinson*

Pharmacology Laboratory, Pharmacy Faculty, Nancy University, Villers, France

Edited by:

Y. W. Kwan, Chinese University of Hong Kong, Hong Kong

Reviewed by:

Michel Félétou, Institut De Recherches Servier, France

Xiao Qiang Yao, Chinese University of Hong Kong, China

***Correspondence:**

Jeffrey Atkinson, Pharmacology Laboratory, Pharmacy faculty, Nancy University, 12 rue de Versigny, F-54600 Villers, France.
e-mail: jeffrey.atkinson@pharma.uhp-nancy.fr

This review considers whether a case can be made for a protective effect of inhibitors and blockers of the renin–angiotensin–aldosterone system (RAAS) on the cerebral circulation. It first looks at whether there exists a preferential effect on the cerebral circulation during a drug-induced lowering of high arterial blood pressure and cardiovascular morbi-mortality. It then goes on to consider background studies on the relationship between inhibition of the RAAS and stroke. This is followed by exploration of possible new directions in the inhibition of the RAAS and its effect on stroke.

Keywords: blood pressure, cerebral circulation, rat model, stroke, angiotensin I converting enzyme inhibitors, angiotensin AT1 receptor blockers

DRUG-INDUCED LOWERING OF HIGH ARTERIAL BLOOD PRESSURE AND CARDIOVASCULAR MORBI-MORTALITY – EXISTENCE OF A PREFERENTIAL EFFECT ON THE CEREBRAL CIRCULATION?

Once antihypertensive drugs that were reasonably well tolerated became available in the 1950s and 1960s, it became possible to evaluate whether chronically lowering high blood pressure [at first from moderately to severely elevated diastolic blood pressure (DBP) levels of 90–114 mmHg], would lower cardiovascular morbi-mortality (Freis, 1995). Thus the Veterans' Administration (VA) cooperative study, one of the first randomized, placebo-controlled, double blind, multi-institutional clinical trials of antihypertensive treatment demonstrated that target organ damage was lowered by 50% in treated groups and furthermore that the beneficial effect on stroke was greater than that on heart attacks (Veterans' Administration Cooperative Study Group on Antihypertensive Agents, 1970). This "preferential" effect of antihypertensive agents on the cerebral circulation was also seen in the Australian Therapeutic Trial in Mild Hypertension (The Management Committee, 1980) in which there were fewer cerebrovascular events in the treated group – but little overall difference in ischemic heart disease.

A similar result was obtained in the MRC trial (The Medical Research Council Working Party, 1985) on the treatment of mild hypertension (DBP 90–109 mmHg). In this trial stroke was lower on active treatment but there was no difference in overall rates of coronary events. Thus from an early date it appeared that antihypertensive treatment could have a beneficial effect on the cerebral circulation – and that this effect was (perhaps) greater than that on other circulations such as the coronary.

Abbreviations: ACEI, angiotensin I converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blocker; DBP, diastolic arterial blood pressure; RAAS, renin–angiotensin–aldosterone system; SHR, spontaneously hypertensive rats; SHR-SP, stroke-prone SHR; WKY, Wistar Kyoto normotensive rat.

The question then arose as to whether there was any difference amongst the different antihypertensive drugs.

The MRC trial was one of the few trials to compare the effects of two different drugs – benzofluazide, a diuretic, and propranolol, a beta-blocker. They reported that "...neither of the two drug regimens had any clear overall advantage over the other..." and yet "...the diuretic was perhaps better than the beta-blocker in preventing stroke". The latter observation was not confirmed however, in a comparison of 14 unconfounded randomized trials of antihypertensive drugs – with mainly diuretics and beta-blockers (Collins et al., 1990). They concluded that "...no consistent differences in stroke...were demonstrated in trials..."

The fact that lowering blood pressure with a wide range of drugs with very different mechanisms of action has a beneficial effect on stroke occurrence, would argue that the important factor is lowering blood pressure rather than the pharmacological way in which this is done (Figure 1). This is backed up by epidemiological data showing that stroke occurrence, survival and recurrence are all affected by high blood pressure (Sacco et al., 1982).

INHIBITION OF THE RAAS AND STROKE – BACKGROUND STUDIES

Although drugs such as diuretics and beta-blockers do impact on the renin–angiotensin–aldosterone system (RAAS), their effect on blood pressure is not primarily related to their effects on the RAAS.

Drugs that lower blood pressure by blocking the RAAS became available in the 1980s.

When the first inhibitor of the RAAS that was reasonably well tolerated – captopril an inhibitor of the angiotensin I converting enzyme (ACEI) – began to be more and more widely used in the early 1980s, several questions were asked. Were ACEIs safe drugs compared to the well-known conventional treatment available at the time (with diuretics and beta-blockers)? If

ACEIs were safe to use then was their effect on cardiovascular morbi-mortality as large as (or greater than) that obtained with conventional therapy?

The Nordic Captopril Prevention Project (CAPP; Hansson et al., 1999) was one of the few trials comparing “newer” to “older” treatment, *viz* captopril with conventional antihypertensive therapy with diuretics and beta-blockers. The two regimens did not differ in preventing cardiovascular morbi-mortality excepting that stroke was apparently more common with captopril. The authors suggested that the difference in stroke risk “...is probably due to the lower levels of blood pressure obtained initially in previously treated people randomized to conventional therapy.” Again in this trial blood pressure appeared to be the predominant factor.

Albeit in other trials the results on the relative risk for stroke were in favor of the ACEI. Thus in the HOPE trial (The Heart Outcomes Prevention Evaluation (HOPE) Study Investigators, 2000b) using the ACEI ramipril, the relative risk for stroke (0.68, $P < 0.01$) was in favor of the ACEI. The authors argued that the beneficial effect of ramipril was linked to inhibition of the RAAS or to some other effect of ramipril unrelated to lowering of blood pressure. In a related study – the microalbuminuria, cardiovascular and renal outcomes (MICRO) HOPE sub-study (The Heart Outcomes Prevention Evaluation (HOPE) Study Investigators, 2000a), the risk reduction of cardiovascular events was again greater than that to be expected from the difference in blood pressure, suggesting that ramipril, and perhaps ACEIs in general, have a “protective” effect on the vascular wall.

This could be brought about by inhibition of the RAAS and/or an increase in bradykinin (Unger, 2002). Regarding the latter however, it should be pointed out that stimulation of B2 receptors may produce brain damage (Schöller et al., 2011) and so offset any beneficial effect obtained with bradykinin-induced cerebral vasodilatation.

Following the establishment of ACEIs as effective and safe anti-hypertensive drugs with potential protective effects on the vasculature, angiotensin II type 1 receptor antagonists (ARB) were introduced. Losartan was the first ARB available clinically and in the LIFE trial (Dahlöf et al., 2002) its cardiovascular effects were compared to those of the beta-blocker, atenolol. The conclusion was that “...losartan prevents more cardiovascular morbidity... than atenolol for a similar reduction in blood pressure”. Once again a trial that showed a beneficial effect of RAAS blockade.

Debate continues over whether a certain mechanism of action (in this case blockade of the RAAS) confers additional beneficial impact on cardiovascular morbi-mortality over and above the reduction in blood pressure (Figure 1). Potential mechanisms involved – especially for ARBs – have been discussed in several reviews (Chrysant, 2005; Thöne-Reineke et al., 2006). These include the possibility that blockade of the angiotensin II type 1 receptor (vasoconstrictor) by ARB treatment, “uncovers” angiotensin II stimulation of the vasodilator angiotensin II type 2 receptor. Our group has shown that in the presence of the ARB, telmisartan, angiotensin II produces dilatation of cerebral arterioles in an animal model of hypertension, the spontaneously hypertensive rats (SHR; Vincent et al., 2005; Figure 2).

INHIBITION OF THE RAAS AND STROKE – NEW DIRECTIONS USE OF COMBINATIONS OF EXISTING DRUGS

Bi- and tri-therapy regimens have been used in the treatment of high arterial blood pressure for several decades. Regimens generally use drugs that act on different pharmacological pathways. Thus ACEIs or ARBs that block the RAAS are combined with diuretics that lower blood pressure by causing the body to rid itself of excess fluids and sodium (whilst at the same time activating the RAAS).

An original approach using combinations of drugs that act on the same pharmacological system has been proposed (Unger, 2002). Treatment with an ACEI may not completely block the RAAS as angiotensin I levels may rise due to interruption of the negative feedback control of renin release by angiotensin II, dissociation of the ACEI from the active sites of the enzyme and/or production of angiotensin II by other enzymatic pathways such as those involving chymase (Menard et al., 1997). When a combination of low doses of enalapril (ACEI) and losartan (ARB) was given to SHR, a synergistic effect on blood pressure and left ventricular hypertrophy was observed and this was attributed to more effective inhibition of the RAAS (Menard et al., 1997).

In the ONTARGET clinical trial (The ONTARGET Investigators, 2008) telmisartan (ARB) was combined with ramipril (ACEI) again on the basis that an ACEI does not completely block the RAAS so addition of an ARB may be beneficial. However no significant benefit was seen in the primary outcome and side effects such as the risk of hypotension and hyperkalemia were more marked. In the ONTARGET trial standard clinical doses of telmisartan and ramipril were used. This may have given an overall antihypertensive

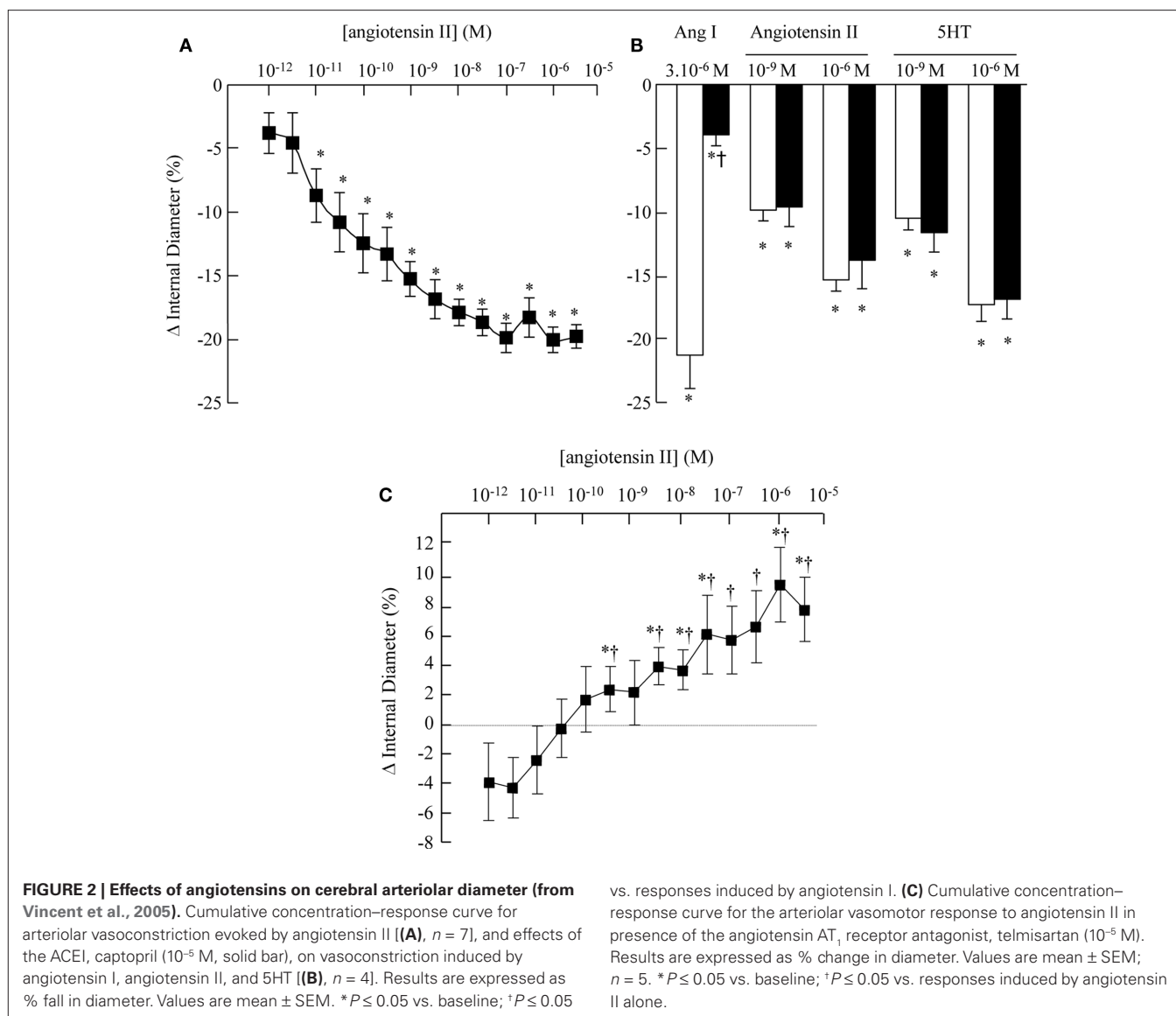
A Drug → lowers arterial blood pressure → lowers stroke risk

“Classical” view that high blood pressure is a risk factor for stroke so that lowering blood pressure will lower stroke risk.

B Drug → pressure-independent “vasculo-protective” effect → lowers stroke risk

“Recent” view that in addition to lowering blood pressure and thus lowering stroke risk, a given drug with a given mechanism of action can have a supplementary, pressure-independent effect on stroke risk.

FIGURE 1 | Possible pressure-dependent (A) and pressure-independent (B) effects of antihypertensive drugs on the cerebral circulation and stroke.



dose that was too high, thus producing side effects and masking the potentially beneficial synergism. Thus we carried out a study in the SHR similar to that of Menard et al. (1997) using a combination of suboptimal doses, i.e., doses that did not normalize blood pressure when given separately (Dupuis et al., 2010). The 0.8 mg/kg/day telmisartan plus 0.1 mg/kg/day ramipril combination (TEL8/RAM1) normalized cerebral arteriolar diameter ($62 \pm 18 \mu\text{m}$, $P < 0.05$ vs. untreated SHR 42 ± 16 and normotensive WKY rats 59 ± 16 , $n = 18$ or 19 per group) and the lower limit of cerebral blood flow autoregulation (50 ± 10 mmHg vs. 77 ± 28 for SHR and 53 ± 17 for WKY). TEL8/RAM1 reversed the effect of angiotensin II on cerebral arterioles to vasodilatation. Although the translation of such beneficial structural and functional effects in an animal model into a beneficial effect on stroke in man is debatable, on the basis of these results and those of Menard et al. (1997), quoted above, there may be a case for studying the effects of combinations of low doses of different inhibitors of the RAAS (Budzyn et al., 2010; see later).

NEW DRUGS

Renin inhibitors

The work of Goldblatt and others (Katz et al., 1939) in the early 1930s suggested that the link between renal ischemia provoked, for instance, by renal artery stenosis was renin. Building on this, the group of Page and Helmer at Lilly, USA provided evidence of the existence of an endogenous inhibitor for renin (Page and Helmer, 1940) and this stimulated research on the use of a renin inhibitor for the treatment of high blood pressure. Gross and others showed that renin inhibitors such as the *Streptomyces* pentapeptide, pepstatin, would lower blood pressure in animal models (Lazar et al., 1972).

At this time work was being carried out simultaneously on the first ACEI (teprotide, the peptide from the venom of the snake, *Bothrops jararaca*) and the first ARB (the peptide analog of angiotensin II, saralasin). All three – pepstatin, teprotide, and saralasin – are peptides presenting pharmacokinetic difficulties when used for daily oral treatment, as is the case for hypertension. In the pharmaco-chemical race to find therapeutically usable analogs,

ACEI research came in first with captopril, and from then on, interest waned in other forms of peptide research in the RAAS such as the research on renin inhibitors.

Albeit, research on renin inhibitors did not cease and in the 1990s Novartis, Switzerland developed an orally active renin inhibitor, aliskiren. The rationale behind this was the same as that of the research of the 1960s and 1970s: a “more complete” inhibition of the RAAS can be obtained by blocking the first rate-limiting enzyme (renin) at the summit of the metabolic cascade of production of active peptides (angiotensins; Paulis and Unger 2010; Riccioni, 2011). Recent clinical trials suggest that aliskiren may have beneficial cardiovascular and renal effects especially in diabetes (Parving et al., 2008); other trials are looking at the effect of aliskiren on stroke (Parving et al., 2009).

It is interesting to note that in the above trials on renin inhibition, dual RAAS blockade discussed previously is in fact being used: the renin inhibitor is added onto existing treatment with an ACEI or an ARB. Albeit, it has recently been concluded that for the time being: “...the use of dual RAAS blockade should be avoided unless ironclad data emerge to the contrary” (Messerli et al., 2010).

Specific aldosterone antagonists

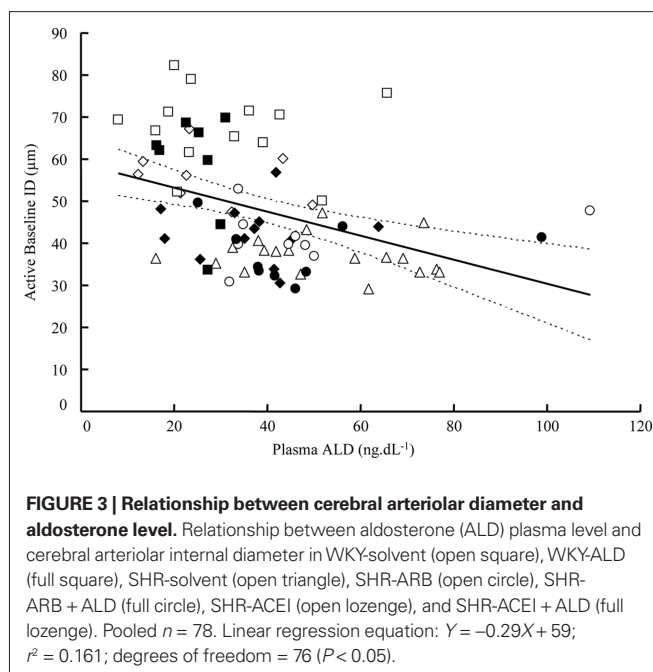
In parallel to blocking the RAAS cascade at the summit (with a renin inhibitor) there may be a case for blocking the system at the lowest level of the cascade of active products – aldosterone. The RAAS presents evolutionary duality with the appearance firstly of a blood pressure regulatory system (using angiotensins) followed by the evolution of a regulatory system for sodium metabolism (using aldosterone; Withers, 1992). Thus although the RAAS is absent in cyclostomes and elasmobranchs, juxtaglomerular cells are present in other chondrichthyan fish and all other vertebrates. The macula densa, however, appears later in some amphibia and higher tetrapods, suggesting that it evolved at a more advanced stage. Thus the RAAS may have evolved as a blood pressure regulatory system with sodium regulation developing later.

On the basis of the argument it has been postulated that aldosterone acts strictly as a mineralocorticoid hormone on renal and other epithelia, to maintain electrolytic homeostasis (Delyani et al., 2001). However, already in the 1970s it was suggested that aldosterone may play a negative role in vascular diseases such as stroke (Brunner et al., 1972). More recently evidence has revealed that aldosterone acts also on non-epithelial vascular sites; other results have shown that blocking the effects of aldosterone with antagonists such as spironolactone diminishes cerebrovascular lesions in the rat model of stroke (the SHR-SP; Rocha et al., 1998). Recently our group has detected an inverse linear relationship between plasma aldosterone levels and the diameter of the cerebral arteriole in SHR (Figure 3). Arguments are emerging therefore, that suggest the mineralocorticoid receptor as a potential therapeutic target for stroke prevention (Osmond et al., 2008).

NEW THERAPEUTIC INDICATIONS AND PATHWAYS

RAAS, neurological performance and cognition

In clinical trials on stroke, parameters such as occurrence, survival, and recurrence are measured. This contrasts with preclinical studies. Except in some rare species such as dogs, spontaneous stroke rarely occurs. In most laboratory animal models cerebral



ischemia is induced by various means such as surgical stenosis. Thus frequency of occurrence of stroke is by definition 100% and other parameters such as neurological performance are measured. Inhibitors of the RAAS are active in such models. Thus our group has shown that the ACEI captopril will improve neurological performance following induced ischemia in renovascular hypertensive rats (Capdeville et al., 1990). Again the translation of preclinical results into clinical reality is not assured. Recent clinical investigation into a possible beneficial effect of RAAS inhibition on neurological performance and cognition in the TRANSCEND trial (Anderson et al., 2011) came to the conclusion that “...blocking of the renin-angiotensin system had no clear effects of cognitive performance”. This question remains open.

RAAS inhibition in non-hypertensive patients

If it is hypothesized that inhibition of the RAAS can have beneficial effects that are not necessarily related to blood pressure then a case could be made for treating patients presenting cardiovascular risk, e.g., previous stroke or transient ischemic attacks, that are not necessarily hypertensive. This was investigated in the PROGRESS trial (MacMahon et al., 2001). In this trial treatment with an ACEI, perindopril, plus a diuretic, indapamide, reduced stroke risk in the non-hypertensive group.

Such observations raise another question regarding the risks and benefits of lowering blood pressure below classical normotensive goals. In the APRIL study, normotensive rats were treated from the age of 6 through 30 months with a hypotensive dose of the ACEI, perindopril, that lowered DBP from 90 to 80 mmHg (Lartaud et al. 1994). Cerebrovascular dysfunction in old rats as evaluated by an increase in the lower limit of autoregulation of cerebral blood flow, was corrected by ACEI treatment. Thus in this animal study, life-long ACEI treatment and/or systemic arterial hypotension improved cerebrovascular function.

There have been few clinical trials looking at the beneficial effects of arterial “hypotension.” In the HOT study with the calcium entry blocker, felodipine, lowering DBP below 90 mmHg had a beneficial effect on myocardial infarction but not on stroke incidence (Hansson et al., 1998). The question remains open.

RAAS and large artery stiffness

With aging and cardiovascular disease such as hypertension, the elastic properties of large central arteries change leading to stiffening of the wall. This leads to a decrease in compliance and an increase in pulse pressure. This can be important in vascular beds with low flow resistance and torrential flow such as that of the brain (O’Rourke and Safar, 2005). Exposure of small vessels to highly pulsatile pressure and flow can lead to structural modification and microvascular damage. This was shown for instance in the SHR rat by the group of Baumbach (1996) who found that an increase in pulse pressure – even in the absence of an increase in mean pressure – is enough to produce arteriolar wall hypertrophy.

Angiotensin I converting enzyme inhibitors may be useful in this context as they appear to protect the elastic fiber network of the arterial wall and reduced the age-related increase in wall stiffness (Figure 4).

RAAS genomics and stroke

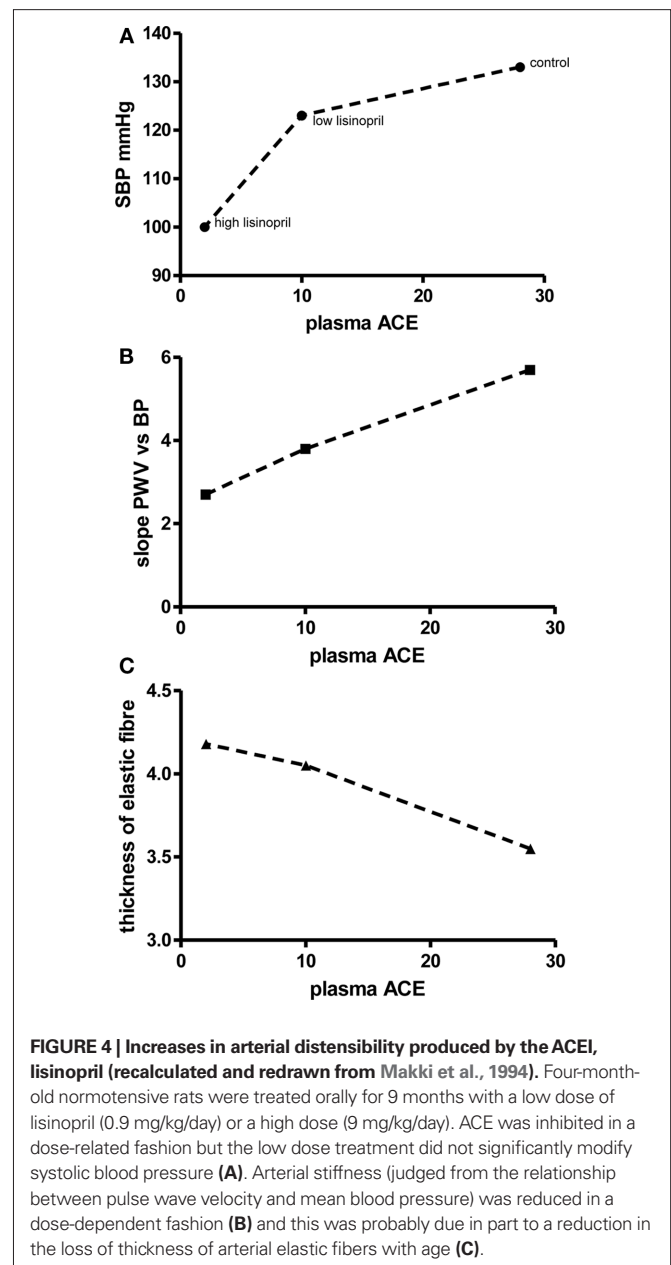
Analysis of RAAS gene polymorphisms may provide information for a targeted pharmaco-genomic approach to stroke prevention. The MOBILIZE Boston study (Hajjar et al., 2010) revealed that the angiotensinogen gene may be involved in cerebrovascular reactivity independently of blood pressure. Previous studies have also shown links between the RAAS gene polymorphisms and other forms of cerebrovascular dysfunction such as lacunar infarction (Takami et al., 2000) or cerebral white matter pathology (van Rijn et al., 2007) although the link to clinical stroke seems more tenuous (van Rijn et al., 2007). Again the question remains open as to whether future research will reveal RAAS gene polymorphism linked to stroke that could form the basis of pharmaco-genomic treatment with inhibitors and antagonists of the RAAS.

CONCLUDING REMARKS

The important issue in antihypertensive therapy is whether the latter prevents target organ damage in the brain, kidney, and other vascular beds. This review looks at the preclinical and clinical evidence suggesting that drugs acting *via* inhibition of the RAAS have a cerebrovascular protective effect. Whilst a case can be made for this hypothesis, the latter should be strengthened by further evidence

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from clinical trials. Furthermore a deeper investigation into the predictability of animal models of hypertension when used to test drugs and elaborate mechanisms is required.

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