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REVIEW ARTICLE

Angiotensin receptor blockers provide better stroke protection than angiotensin converting enzyme inhibitors - a hypothesis with clinical and experimental support

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Stroke is a major cause of death and disability and its incidence increases linearly with age and the level of systolic and diastolic blood pressure. Stroke, besides being a cause of long-term disability for the affected person, also imposes a significant burden on society and healthcare costs. Although good blood pressure control is very critical for stroke prevention, angiotensin receptor blockers (ARBs) may be superior to angiotensin converting enzyme inhibitors (ACEIs) for the same degree of blood pressure control. This hypothesis has clinical and experimental support. ARBs prevent stroke incidence by blocking the angiotensin II (AII), AT_1 receptors preventing brain ischemia and allowing AII to stimulate the unoccupied AT_2 receptors which improve brain ischemia. ACEIs, by reducing AII generation, are less effective in preventing stroke. This hypothesis provides evidence that AII plays an important role in the prevention of stroke. Certain ARBs like losartan and telmisartan possess additional properties which may play a role in stroke prevention, which is independent of AII. However, the most critical factor in stroke prevention is good blood pressure control irrespective of drug used. *Hippokratia 2005; 9 (3): 99-105*

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Stroke is a major cause of death and disability, and its incidence increases linearly with advancing age and level of blood pressure[1,2]. Lewington, et al have shown that incidence of stroke is directly related to the level of systolic and diastolic blood pressure for all age groups, but with higher prevalence in older than younger subjects[2]. Stroke, besides being a cause of long-term disability for the affected person, is also a significant burden on society and healthcare expenditures[3-5]. Stroke ranks as the third leading cause of death in the United States and accounts for 700,000 incident strokes annually and 4.4 million stroke survivors[5,6], with direct and indirect cost estimates for 2005 of $56.8 billion[7]. Disability from stroke accounts for significant healthcare expenditures in the European Union as well, and these expenditures are also projected to rise in the future, since the incidence of stroke will increase with the aging of the population[8]. In an analysis of 11 major randomized intervention trials for the treatment of hypertension, stroke emerged as more common than myocardial infarction among hypertensive patients[9]. Possible causes for this increase in stroke are the aging of the population and the poor control of hypertension[1,2]. Whether the choice of drugs for the treatment of hypertension could play a role, is debatable at present. Recently, has been reported that drugs which impair the production of AII, such as ACEIs and beta blockers, are less effective in preventing strokes than drugs which stimulate AII production, such as diuretics, calcium channel blockers, and angiotensin receptor blockers[10,11]. In this concise review, I will discuss the role of antihypertensive drugs on stroke prevention as it relates to their inhibitory or stimulatory action on AII release and present clinical and experimental evidence that ACEIs are less effective in stroke prevention than ARBs. Additionally, evidence will be presented about non-AII mediated mechanisms for cerebroprotection by ARBs.

Clinical evidence

a) *Angiotensin Converting Enzyme Inhibitors*

The hypothesis that AII might have a cerebroprotective effect was first advanced by Brown and Brown in 1986[12] based on the results of the first Medical Research Council (MRC) studies[13], where the diuretic bendrofluazide reduced the incidence of strokes by 70% versus a 27% reduction by propranolol, both compared to placebo, for a similar decrease in blood pressure. They proposed that the increased production of AII by the diuretic constricted the proximal cerebral arteries and prevented the rupture of the Charcot-Bouchard microaneurysms and the development of cerebral hemorrhage. Their original observations were duplicated by a subsequent study in elderly hypertensives, where the administration of hydrochlorothiazide/amiloride resulted in 33% stroke reduction versus 18% by atenolol compared to placebo for a similar decrease in blood pres-

sure[14], Similar results have been reported by other clinical trials using diuretics[15,16] or calcium channel blockers[17,18]. Contrary to the above presented results, are the findings from randomized clinical trials using ACEIs. In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), the initial treatment of post-stroke hypertensive patients with the ACEI perindopril, resulted in a meager 5% stroke reduction, compared to 43% stroke reduction, when the diuretic indapamide was added to the ACEI, for an additional systolic blood pressure (SBP) decrease of 7 mmHg[19]. The expected stroke reduction for a 10 mmHg SBP decrease would have been 28%. In the ALLHAT study[16], treatment of hypertensive patients with the ACEI lisinopril resulted in 15% higher incidence of strokes in the study population and in 40% higher incidence of strokes in blacks, compared to the diuretic chlorthalidone. It should be stressed, however, that the high incidence of strokes in blacks by lisinopril was partly due to the poorer control of blood pressure. Corroborating and enhancing these results are the findings from the Captopril Prevention Project (CAPP), where treatment of hypertensive patients with captopril showed a 43% higher incidence of strokes compared to conventional treatment[20]. This should be, somewhat, mitigated by the 3 mmHg higher SBP in the captopril group. The results on stroke incidence were equivocal in the second Australian National Blood Pressure Study (ANBP2) where elderly hypertensive patients treated with the ACEI enalapril showed a 9% higher incidence of fatal strokes, and a 7% lower incidence of nonfatal strokes compared to hydrochlorothiazide[21]. In a recently published, randomized double-blind, placebo controlled study of type 2 diabetic patients, treatment with low dose ramipril did not result in any significant decrease in the incidence of strokes compared to placebo, although it decreased the blood pressure by 2.43/1.06 mmHg and normalized micro-albuminuria and proteinuria[22]. Different findings from the above studies were reported from the Heart Outcomes Prevention Evaluation (HOPE) Study[23], which showed a 32% reduction in stroke incidence in patients treated with the ACEI ramipril compared to placebo. However, this study included mostly normotensive, high risk patients with pre-existing coronary artery disease, peripheral vascular disease and diabetes where the ACEIs are quite effective, more so when these results are compared to placebo-treated patients. Besides, the risk of stroke has been shown to be higher in patients with pre-existing coronary artery disease in whom prevention of myocardial infarction is associated with stroke prevention[24]. These studies are summarized in the Table 1.

b) ***Angiotensin Receptor Blockers***

Recently, several large clinical trials have shown that treatment of high risk hypertensive patients with ARBs results in significant reduction of strokes. The Losartan Intervention For Endpoint reduction (LIFE) study[25], showed that severely hypertensive patients with left ventricular hypertrophy (LVH) treated with a losartan based regiment, had a 25% reduction in strokes compared to those treated with an atenolol based regimen for the same reduction of blood pressure. A substudy of LIFE of patients with isolated systolic hypertension and LVH,

Table 1. *Stroke incidence from prostpective, randomized clinical trials using angiotensin converting enzyme inhibitors and angiotensin receptor blockers.*

STUDY (Ref)	SUBJECT PATHOLOGY	NUMBER PATIENTS	FOLLOW-UP Years	TREATMENT	INCIDENCE OF STROKE (%)
PROGRESS[19]	Post-Stroke	6,105	4.0	Perindopril vs Placebo	5.0% Decrease
CAPP[20]	Hypertensive	10,985	6.1	Captopril vs Diuretics, beta-blockers	25% Increase
ALLHAT[16]	Hypertensive	24,309	4.9	Lisinopril vs chlorthalidone	15% Increase
$ANBP_2$[21]	Elderly Hypertensive	6,083	4.1	Enalapril vs HCTZ	Total No Change
HOPE[23]	Mostly normotensive with CAD, PVD	9,297	1.5	Ramipril vs Palcebo	32% Decrease
DIABHYCAR[22]	Diabetic with MA	4,912	4.0	Ramipril vs Placebo	No Change
LIFE[25]	Hypertensive with LVH	9,193	4.5	Losartan vs Atenolol	25% Decrease
LIFE-ISH[26]	Elderly Hypertensive	1,326	4.7	Losartan vs Atenolol	40% Decrease
SCOPE[27]	Elderly Hypertensive	4,937	5.0	Candesartan vs. Conventional Drugs	28% Decrease
SCOPE-ISH[28]	Elderly Hypertensive	1,518	5.0	Candesartan vs Conventional Drugs	42% Decrease
ACCESS-PILOT[29]	Post-Stroke	33.9	1.0	Candesartan vs Placebo	52% Decrease
VALUE[31]	High Risk Hypertensive	15,245	4.2	Valsartan vs Amlodipine	25% Decrease*

LVH = Left ventricular hypertrophy - ISH = Isolated systolic hypertension
Valsartan decreased stroke by the end of study, but the overall stroke incidence was 15% higher.
Modified with permission from Chrysant SG[11]

treatment with the losartan based regimen, resulted in a 40% stroke reduction compared to those treated with the atenolol based regimen[26]. Complementary results to the LIFE study were subsequently reported from the Study on Cognition and Prognosis in the Elderly (SCOPE) study[27]. In this study, older patients with predominantly systolic hypertension, treated with a candesartan based regimen had a 27.8% reduction in nonfatal stroke and a 23.6% reduction in total stroke, compared with patients treated with conventional antihypertensive drugs for similar control of blood pressure. In a sub-study of the SCOPE trial of older patients with isolated systolic hypertension, treatment with the candesartan based regimen, resulted in a 40% stroke reduction compared with those patients treated with conventional antihypertensive drugs[29]. In addition, candesartan has been demonstrated to provide secondary protection in patients who have suffered a previous stroke. In the Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) pilot study[29], treatment of hypertensive patients with a previous stroke, with candesartan for 12 months, resulted in reduction of cumulative mortality and number of strokes by 52% compared to placebo treatment. This study was terminated prematurely due to the great disparity in outcomes between the two treatment arms, although there was no difference in systolic and diastolic blood pressure between the two treatment groups for the 12 month treatment period. Another small study in 24 post-stroke hypertensive patients without occlusive carotid disease, showed that administration of losartan 25-50mg, 2 to 7 days after an ischemic stroke, or transient ischemic attack did not cause any significant changes in cerebral blood flow autoregulation, or result in any serious side effects despite a decrease in mean arterial pressure by 18.1 mmHg[30]. The recently published Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study[31] in high risk hypertensive patients treated with either valsartan or amlodipine showed mixed results with respect to stroke prevention. Although this study was designed as a superiority study of valsartan against amlodipine for the same reduction of blood pressure, the results were mixed. In the first 6 months of treatment, the stroke incidence was 50% higher in the valsartan treated group compared to amlodipine treated patients. However, during this period, the blood pressure of the valsartan treated group was higher by 4.0 / 2.1 to 2.3 / 1.7 mmHg compared to amlodipine treated group. As the study progressed and the difference in blood pressure narrowed, the stroke incidence decreased and by the end of the study was 25% lower in the valsartan treated group compared to amlodipine treated group. Therefore, the superiority hypothesis for valsartan would have been true if valsartan would have reduced the blood pressure to the same degree with amlodipine throughout the study. Perhaps the administered dose of valsartan 160 mg/day was not sufficient and if a dose of 320 mg/day, as is currently approved by the FDA for the treatment of hypertension was given, the results might have been different. The major finding of this important study was that early blood pressure control is very critical for stroke prevention These studies are summarized in the table 1.

c) *Experimental Evidence Supporting A Possible Unique Role of AII and ARBs in Stroke Prevention*

1) AII Mediated Effects of ARBs. Subsequent to the original hypothesis by Brown and Brown[12] that AII could play a role in stroke prevention, several experimental studies have provided support for this hypothesis[32-34]. Fernandez, et al[32] showed that AII exerted a protective role against acute vascular ischemia and transitory paralysis of the hind limbs of the rat by applying an aortic ligature between the kidneys, thus rendering the left kidney ischemic and producing renovascular hypertension. Removal of the ischemic kidney reduced the level of plasma rennin activity and blood pressure to within normal values, but the limb's ischemia persisted for 24 hours. Exogenous administration of AII, increased the blood pressure and restored the limb ischemia by increasing the blood flow to the muscles of the hind limb. They concluded that the increased AII levels through renal ischemia, restored blood flow to the hind limb of the rat by stimulating the development of collateral circulation, an effect that was independent of its hypertensive action. In subsequent studies, Fernandez, et al[33] demonstrated that exogenous AII infusion decreased the mortality of gerbils after unilateral carotid occlusion. In these studies, gerbils were subjected to cerebral ischemia by unilateral carotid ligation. Immediately post ligation, some gerbils were infused with AII 50, 250 and 500 mcg/kg/min, whereas other gerbils were infused with either equipressor doses of metaraminol or normal saline. The AII infusion resulted in a dose-dependent decrease in mortality of the gerbils, whereas the infusion of metaraminol or normal saline had no effect on mortality. The authors postulated that the beneficial effects of AII on cerebral ischemia were independent of blood pressure and possibly due to the enhancement of preexisting collateral circulation and reduction of cerebral ischemia. In studies performed later, Fernandez, et al[34] showed that the protective effects of AII on the brain ischemia of gerbils was mediated through stimulation of the AT_2 receptors. Brain ischemic gerbils pretreated with either the selective AT_1 receptor blocker losartan, or the selective AT_2 receptor agonist PD-123319, had decreased mortality compared to gerbils pretreated with normal saline or the ACEI enalapril. Additionally, pretreatment of these animals with enalapril neutralized the brain protective effects of losartan. These experiments reinforced the hypothesis that AII exerts its cerebro-protective effects through AT_2 receptor stimulation and this effect is enhanced by selective blockade of the AT_1 receptors. Findings supporting the above hypothesis were reported by Dai, et al[35] in normotensive Wistar rats. Intracerebral administration of low-dose irbesartan that blocked the

cerebral but not the systemic AT_1 receptors for 5 days prior to induction of focal brain ischemia by occlusion of the middle cerebral artery for 90 minutes, improved the neurologic outcome of these rats in comparison to vehicle-treated rats. These experiments were reproduced and further extended by Dalmay, et al in gerbils[36]. These investigators induced acute cerebral ischemia in anesthetized adult gerbils by unilateral carotid ligation and tested the effect of treatment 2 hours post ligation with two different ARBs (losartan 50 mg/kg, candesartan 1 mg/kg), two different ACEIs (enalapril 10mg/kg, lisinopril 1 mg/kg), or their combination against a vehicle. They observed that the three day mortality of gerbils was not significantly decreased with the two ACEIs or their combination with the two ARBs compared to vehicle treated gerbils. In contrast, the three day mortality of gerbils treated with either ARB was significantly decreased compared to controls. In other studies, administration of losartan in high or low doses in spontaneously hypertensive stroke prone rats (SHR-SP) has been shown to have a cerebroprotective effect independent of its blood pressure lowering effect[37,38].

2) Non-angiotensin-Mediated Cerebro-Protective Effects of ARBs

Angiotensin receptor blockers like ACEIs exert favorable effects on glucose metabolism and prevent new onset diabetes mellitus[25,31,39]. This effect is very important because diabetes mellitus increases greatly the cardiovascular and stroke consequences of hypertension[5,40]. The beneficial effects of most ARBs on glucose metabolism and prevention of new onset diabetes mellitus have been attributed to their blockade of AII. Recent studies have suggested that AII may impair glucose metabolism through its adverse effects on insulin signaling pathways, tissue blood flow, oxidative stress, sympathetic activity and adipogenesis[41-44]. However, certain ARBs like telmisartan exert their beneficial effects on glucose metabolism independently of the renin-angiotensin system[45,46]. The molecule of telmisartan has a structural similarity to peroxisome proliferator-activated receptor-gamma (PPAR gamma) ligand pioglitazone, which has been approved for the treatment of type 2 diabetes mellitus. These drugs play an important role in regulating carbohydrate and lipid metabolism, by increasing insulin sensitivity[45,46]. In studies in rats fed a high carbohydrate, high fat diet, telmisartan given in doses similar to those used for the treatment of hypertension, reduced serum levels of glucose, insulin and triglycerides[46]. Other ARBs, like losartan exert their stroke preventive effects through their antiplatelet aggregating effects and serum uric acid lowering levels. Increased platelet aggregation and high uric acid levels, have been both associated with increased cardiovascular events and strokes. Platelet activation within the arterial lumen releases several substances including ADP, serotonin and thromboxane A_2 (TXA_2) and P-selectin, which all cause platelet aggregation. Recent experimental studies have shown that losartan interacts with the TXA_2/PGH_2 receptor in human platelets and also platelet activation by the TXA_2 agonist U46619 was significantly inhibited by losartan dose-dependently[47]. Losartan also blocks the action of P-selectin on platelet adhesion. P-selectin is an adhesion protein that is stored in the alpha granules of platelets, and platelets from SHR-SP have a higher expression of P-selectin and a higher ability to adhere to synthetic and endothelial surfaces than platelets from normotensive WKY rats. Treatment of platelets from these animals with losartan decreased their adhesiveness to surfaces, whereas treatment with candesartan or valsartan had no significant effect on platelet adhesiveness[48]. These studies indicated that the action of losartan on platelet adhesion was not mediated through the AT_1 receptor because neither the losartan's metabolite EXP 3174, nor the other ARBs, candesartan and valsartan were able to prevent platelet adhesion or significantly suppress the expression of P-selectin on platelet surface. The increased expression of P-selectin on the platelet surface of SHR-SP has been blamed for the increased thrombogenicity and the higher incidence of strokes seen in these animals[49,50]. Another mechanism, also independent of RAAS, by which certain ARBs could prevent the incidence of strokes, is their effect on serum uric acid. Although the role of uric acid as a risk factor for cardiovascular diseases and strokes has been widely debated over the years, recent studies have provided fresh evidence that high serum uric acid levels could be related to a higher incidence of cardiovascular diseases and strokes, especially in patients with hypertension, heart failure or diabetes mellitus[51-54]. Hypertensive patients, particularly with hyperuricemia have a higher risk of experiencing cardiovascular or cerebrovascular disease than patients with normal uric acid levels[51-54]. Although the mechanism by which uric acid exerts its pathogenetic effect on cardiovascular and cerebrovascular complications is still unclear, high uric acid levels have been shown to induce inflammation, endothelial dysfunction, oxidative metabolism and platelet adhesion and aggregation[55-59]. All these changes induced by high uric acid levels could conceivably lead to cardiovascular complications and stroke and therefore, drugs that lower uric acid levels have been shown to reverse these changes[57,58]. Losartan, in exception to other ARBs, lowers uric acid levels and its use for the treatment of hypertension has been shown to decrease the incidence of cardiovascular complications and strokes[60,61]. In fact, the results from the LIFE study showed that the baseline uric acid level was significantly associated with cardiovascular complications and strokes, especially in women, and that its lowering with losartan accounted for 29% of the reduction of strokes compared to atenolol[60].

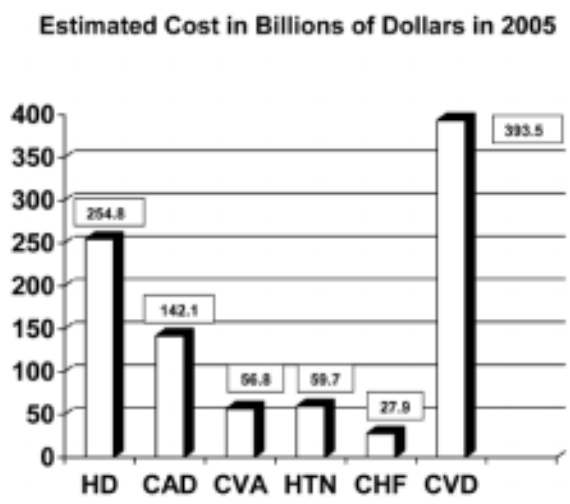
Discussion

Stroke is a major cause of death and disability, and a significant social and financial burden worldwide.[3-5] The incidence of stroke is directly related to blood pressure

and age,[1,2] and is expected to significantly rise in the future as the age of the population increases putting a great financial burden on society.[7] The direct and indirect costs of strokes in the US have been projected at $56.8 billion for 2005 and account for one third of the total health expenditure (Fig. 1). Successful blood pressure control is the most critical factor in stroke prevention and is shared by all antihypertensive drugs although certain drugs, such as diuretics, CCBs and ARBs, which stimulate AII production, may provide an additional benefit for the same blood pressure reduction, than drugs which suppress it, such as beta blockers and ACEIs. Several clinical and experimental studies presented earlier, have provided evidence that AII can be cerebroprotective and its effects on ischemic stroke are mediated through local stimulation of the AT_2 receptors[32-36]. Stimulation of AT_1 receptors in the brain by AII causes constriction of proximal arteries and could prevent the rupture of Charcot-Bouchard micro-aneurysms and the development of cerebral hemorrhage, as originally proposed by Brown and Brown[12]. It has been reported that AT_2 receptors are over expressed in areas of injury in the brain and counteract the undesirable effects of AT_1 receptor stimulation by AII. This could also explain the observations of Brown and Brown[12] that drugs that stimulate AII production are stroke protective. However, drugs that selectively block the AT_1 receptors, such as the ARBs, have additional advantages over drugs which only stimulate AII production, since by blocking the AT_1 receptors, they allow the free AII to stimulate the unoccupied AT_2 receptors leading to improvement of local ischemia through local vasodilation of pre-existing local collateral vessels. These are, perhaps, the reasons that losartan and candesartan have demonstrated a greater stroke reduction than other antihypertensive drugs[25,27] and especially in elderly patients with isolated systolic hypertension[26,28]. Two ARBs, losartan and telmisartan possess unique properties not shared by the other ARBs in their class. Telmisartan's molecule is similar to thiazolidinedione molecule of pioglitozone, a peroxisome proliferator-activated receptor gamma (PPAR-gamma), which improves insulin sensitivity and has been approved by FDA for the treatment of type 2 diabetes mellitus[45,46]. Rats fed a high carbohydrate, high fat diet, treated with telmisartan in doses used for the treatment of hypertension showed a significant decrease in serum glucose, insulin and triglycerides in comparison to vehicle treated rats[45,46]. On the other hand, losartan has been shown to decrease platelet aggregation by interfering with the binding of TXA_2 to its receptor on the platelet surface and by decreasing the concentration of P-selectin in the granules on the surface of platelets[47-50]. Losartan, also decreases serum uric acid levels and this could have a bearing on its stroke protective effects, since increased platelet aggregability and high uric acid levels are associated with high cardiovascular complications and strokes[51-54]. It should be stressed, however, that one should not rely on these special properties of ARBs compared to ACEIs and other antihypertensive drugs, because the most critical factor in stroke prevention is good blood pressure control of < 140/90 mmHg for uncomplicated hypertensives and < 120/80 mmHg for hypertensive patients with diabetes mellitus and impaired renal function[1]. However, selection of ARBs could provide an additional benefit for the same degree of blood pressure reduction, as it was clearly demonstrated in the LIFE and SCOPE studies[25-28]. In the VALUE study, valsartan was inferior to amlodipine, due to its failure for early blood pressure control compared to amlodipine. However, by the end of the study when the difference in blood pressure levels between the two treatment groups was significantly narrowed, then valsartan became superior to amlodipine by decreasing stroke incidence by 25% compared to amlodipine[31].

It should be stressed, though, that the hypothesis that ARBs are superior to ACEIs in stroke prevention, is not uniform. Other studies have shown that ACEIs reduced as well the incidence of strokes in high risk patients compared to placebo[23] or were equally effective in comparison to diuretics in elderly patients with hypertension[21]. Possibly, studies in progress at the time of this writing may approve or disprove this hypothesis. One study in particular will be very critical with respect to this hypothesis. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), is comparing the effects of telmisartan 80 mg/day, versus ramipril 10 mg/day, versus their combination on cardiovascular outcomes in 23,400 high risk hypertensive patients for 5 years and its results are expected with great interest[62]. So stay tuned for future developments.

Figure 1. *This figure shows the projected costs for all cardiovascular diseases in the US for the year 2005. HD = heart disease, CAD = coronary artery disease, CVA = cerebrovascular accident, HTN = Hypertension, CHF = congestive heart failure, CVD = cardiovascular diseases (total expenses). Adapted from American Heart Association.*[7]



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