Significant beneficial effect of AT-1 receptor blockers (sartans) in stroke

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ABSTRACT

يعد ارتفاع ضغط الدم من أكثر عوامل الخطر المسببة للسكتة الدماغية والتي يمكن السيطرة عليها، كما تعد العلاقة بين ضغط الدم والوفاة الناتجة عن السكتة الدماغية خطية وقوية. تعد مركبات سارتان التي تثبط فعالية هرمون أنجيوتنسين–2 من خلال تثبيط مستقبلات هرمون أنجيوتنسين من الأدوية السليمة في معالجة ارتفاع ضغط الدم، كما أن لها تأثيرات مضادة للالتهاب من خلال عملها في تثبيط المحركات الخلوية. تلعب هذه التأثيرات دوراً في تقليل الأذى الذي يلحق بالدماغ عقب السكتة الدماغية، وتحسن من عواقب السكتة الدماغية بتحسينها للوظائف الإدراكية للدماغ. تعد هذه المركبات سليمة في معالجة السكتة الدماغية بسبب ارتفاع ضغط الدم كما أن فوائدها تتعدى تحكمها بارتفاع ضغط الدم فحسب. وتعمل هذه المركبات على تكوين أوعية دموية حديثة المنشأ وبذلك تحمي الدماغ من خلال حمايتها للأوعية الدموية وتحسينها لإعادة تشكيل منشأ الأوعية الدموية. لقد قمنا في هذا المقال بمناقشة التأثيرات المفيدة لهذه المركبات في معالجة السكتة الدماغية مع الأخذ بعين الاعتبار لنتائج التجارب والدراسات السريرية.

Hypertension is the most important controllable and modifiable risk factor for stroke. The relationship between blood pressure and stroke mortality is strong and linear. Angiotensin receptor blockers (sartans) are competitive pharmacological antagonists of angiotensin II receptors, and some of them are approved for use in the treatment of hypertension. These drugs also show anti-inflammatory effects by reducing the cytokine levels. The anti-inflammatory effects of sartans play a role in reducing cerebral injury following stroke, and improve the outcome of stroke in terms of improving cognitive function. In humans, sartans are safe in hypertensive acute stroke patients and may offer advantages independent of blood pressure control. Sartans promote neovascularization and thereby provide long-term cerebro-protection in terms of vascular protection and enhancement of early angiogenic remodeling. In this review, the beneficial effects of sartans in the management of stroke are discussed, considering the results of experimental and clinical studies.

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Arterial blood pressure and cardiac output are controlled by the renin angiotensin aldosterone system (RAAS) via regulation of the blood volume and peripheral systemic vascular resistance.[1] Renin is a proteolytic enzyme, primarily released from juxtaglomerular cells into the circulation, acting upon a circulating alpha-2 globulin substrate angiotensinogen to form the decapeptide angiotensin I (Ang I). In the vascular endothelium, particularly in the lungs, angiotensin-converting enzyme (ACE) cleaves off 2 amino acids from Ang I to form the octapeptide, angiotensin II (Ang II) (**Figure 1**). Other tissues in the body, heart, brain, and blood vessels also can form Ang II. Angiotensin II is a powerful dipsogen acting as an endocrine, autocrine, paracrine, and intracrine hormone. It acts on angiotensin receptors (ATR), a class of G protein coupled receptors.[2] The subclass receptor AT1R is mainly expressed in vascular smooth muscle, liver, kidneys, lung, adrenal cortex, pituitary gland, and brain. The AT2R is expressed in fetal tissues, adult brain, adrenal gland (zona granulose), ovary, uterus, endothelium and heart.[2] The affinity of Ang II to AT1R and AT2R is similar.

Activation of AT1R by Ang II leads to:[3,4] 1. Increased peripheral vascular resistance (as a result of vasoconstriction) and thereby increased arterial blood pressure. 2. Enhanced sympathetic adrenergic function via facilitation of the release of norepinephrine from sympathetic nerve endings and inhibition of norepinephrine uptake by terminal nerve endings. 3. Cardiac and vascular cell proliferation (hypertrophy) 4. Increased cardiac contractility and thereby increased

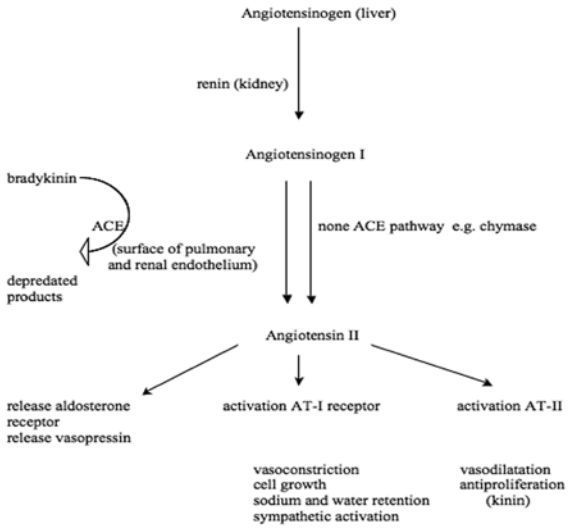

Figure 1 - The renin-angiotensin aldosterone system. ACE - angiotensin converting enzyme, AT-I - angiotensin-I, AT-II - angiotensin-II

cardiac output. 5. Decreased renal blood flow. 6. Synthesis and release of aldosterone, and thereby causing sodium, and water retention. 7. Release of vasopressin (antidiuretic hormone) from the posterior pituitary gland, which increases fluid retention by the kidneys. 8. Stimulation of the thirst center within the brain. 9. Increased extracellular matrix formation.

Activation of AT2R by Ang II leads to:[4] 1. Decreased cell growth. 2. Fetal tissue development. 3. Modulation of extracellular matrix. 4. Cell differentiation. 5. Neuronal regeneration. 6. Apoptosis. 7. Vasodilation.

Drugs that act on the RAAS include:[5,6] 1. Angiotensin converting enzyme inhibitors (ACEIs): they are classified, based on molecular structure, into: a) Sulfhydryl containing agents: for example, captopril, and zofenopril. b) Dicarboxylate containing agents: for example, enalapril, ramipril, quinapril, perindopril, lisinopril, and benazepril. c) Phosphonate containing agents: for example, fosinopril. 2. Angiotensin receptor blockers (ARBs). 3. Renin inhibitors: for example, aliskiren, remikiren, and enalkiren. 4. Aldosterone antagonists: for example, spironolactone, eplerenone, canrenone, prorenone, and mexrenone.

The purpose of this review is to highlight the beneficial effects of ARBs in the prevention and management of stroke, taking into consideration their anti-inflammatory effect.

The ARBs are competitive pharmacological antagonists of angiotensin II receptors (ATII). Most of the described actions of ATII, such as vasoconstriction, stimulation of cellular proliferation, and facilitation of sympathetic transmission are mediated by ATI receptors and blocked by ARBs.[7] The ARBs may block ATII and thereby disturb fetal growth and development, inhibition of neointima formation, and differentiation of neuronal cells.[8,9] The ARBs are similar in action and side effects (**Table 1**). They differ in how they are eliminated from the body and the extent to which they are distributed throughout the body. Some ARBs need to be converted to an active form (prodrug) in the body before they can lower blood pressure (BP). Some of them lower BP better than others, for example, irbesartan and candesartan reduced BP better than losartan. The main uses of ARBs include: treatment of systemic hypertension, treatment of heart failure, prevention of renal failure in diabetes mellitus and hypertension, reduction in the risk of stroke in hypertension and cardiomegaly, prevention of the recurrence of atrial fibrillation, and treatment of diabetic nephropathy. The ARBs do not inhibit bradykinin metabolism or enhance prostaglandin synthesis (**Figure 1**). Therefore, cough occurs much less often with those agents than with ACEIs. Also, ARBs do not adversely affect lipid profile or cause rebound hypertension after discontinuation. More than 10 drugs related to ARBs were launched and in addition to the differences in the pharmacokinetics (**Table 2**), they also show differences in pharmacodynamics and indications. Among these drugs:

Losartan. This was the first AT1R antagonist introduced in 1995 with the empirical formula $C_{22}H_{23}ClN_6O$. Its affinity for AT1R is around 1000 times greater than its affinity for AT2R. It is well tolerated, and as efficacious as enalapril and nifedipine for lowing BP.[10,11] The duration of its activity for a dose is 24 hours. It undergoes significant first pass metabolism to produce 5-carboxylic acid metabolite (EXP3174), which is a long acting non-competitive antagonist at

Table 1 - List of sartan drugs, mechanism of action, and adverse reactions.

Sarcosine-8-isoleucine angiotensin II	Irbesartan
Abitesartan	Losartan potassium
Azilsartan kamedoxomil	Losartan
Azilsartan medoxomil	Milfasartan
Azilsartan	Olmesartan medoxomil
Candesartan cilexetil	Olmesartan
Candesartan	Pomisartan
Elisartan	Pratosartan
Elisartan	Ripisartan
Embusartan	Saprisartan potassium
Enoltasosartan	Saprisartan
Eprosartan mesylate	Tasosartan
Eprosartan	Telmisartan
Fimasartan	Valsartan
Forasartan	Zolasartan

Mechanism of action: to block AT1 receptors

Adverse reactions: Dizziness, headache, hyperkalemia, first dose hypotension, myalgia, insomnia

AT1R and contributes to the pharmacological effects of losartan. It shows nephroprotective effects, due to its down-regulation of transforming growth factor (TGF-β) type I and type II receptors in the kidney.

Valsartan. This is a non-peptide orally active compound with the empirical formula $C_{24}H_{29}N_5O_3$ and its affinity for AT1R is around 20000 times greater than its affinity for AT2R. It is as effective as enalapril, lisinopril, and amlodipine in the treatment of mild-moderate hypertension.[12-14] Also, it is prescribed for congestive heart failure and post-myocardial infarction.

Irbesartan. The empirical formula of irbesartan is $C_{25}H_{28}N_6O$ and its affinity for AT1R is more than 8500 times greater than its affinity for AT2R. It has a higher bioavailability (60-80%). Besides its antihypertensive effect, it reduced microalbuminuria and proteinuria, and it may delay renal progression of diabetic or hypertensive nephropathy, while it does not improve the outcome of heart failure with normal ejection fraction.[15] It inhibits the advanced glycation end-products induced increase reactive oxygen species generation and subsequently blocks up-regulation of VCAM-1 mRNA in glomerular endothelial cells.[16]

Candesartan cilexetil. The empirical formula of candesartan is $C_{33}H_{34}N_6O_6$ and it is a prodrug, which is metabolized completely by esterases in the intestinal wall during absorption to the active candesartan moiety. Candesartan itself is poorly absorbed after oral administration while candesartan cilexetil improves the bioavailability (15%). Its affinity for AT1R is more than 10000 times greater than for AT2R. It has vasodilatory effects within the renal circulation due to decreased renal vascular resistance.[17] It significantly reduced the innate immune response and the activation of the nuclear factor kappa B pathway, the tumor necrosis factor alpha, and interleukin-6 secretion, and the reactive oxygen species formation induced to lipopolysaccharide in human circulating monocytes.[18] It is approved for treatment of high blood pressure (less effective in black patients) and congestive heart failure.

Eprosartan. The empirical formula of eprosartan is $C_{23}H_{24}N_2O_4S$. It blocks AT1R in vascular smooth muscle and adrenal glands producing vasodilation, and it inhibits sympathetic noradrenaline production. The bioavailability is approximately 13% after a 300 mg oral dose. Food delays absorption, and causes non-clinically significant variable changes (<25%) in peak plasma concentration (Cmax) and area under the plasma concentration–time curve. Administration of eprosartan during the second and third trimesters can cause fetal and neonatal morbidity and mortality (neonatal skull hypoplasia, oligohydramnios, deterioration in fetal renal function, fetal limb contractures, craniofacial deformities, hypoplastic lung, prematurity, intrauterine growth retardation, and patent ductus arteriosus).

Tasosartan. A new long acting non-peptide AT1R antagonist, with the empirical formula $C_{23}H_{21}N_7O$ developed for the treatment of hypertension in a worldwide clinical program that began in 1992. It is well absorbed orally and has absolute bioavailability of 60%. The pharmacokinetic profile is similar in fed and fasted patients. The long duration of antihypertensive activity is due to 2 metabolites that have a half-life of 60 and 70 hours. Tasosartan was superior to losartan in controlling the trough sitting diastolic blood pressure, the mean 24-hour diastolic blood pressure, and systolic blood pressure response to strenuous exercise. After 2 days of missed doses, losartan lost its antihypertensive effect, while tasosartan's antihypertensive effects remained constant.

Olmesartan medoxomil. This is a prodrug with the empirical formula $C_{29}H_{30}N_6O_6$ indicated for hypertension. It improves endothelial function in hypertensive patients independent of its lowering blood pressure, which was due, at least in part, to its antioxidant property.[19]

Telmisartan. The empirical formula of telmisartan is $C_{33}H_{30}N_4O_2$ and its affinity for AT1R receptor is more than 3000 times greater than its affinity for AT2R. The inhibitory effect of telmisartan on vasoconstriction in resistance vessels is mediated through a peroxisome proliferators-activated receptor gamma (PPAR-γ) dependent increase in endothelial nitric oxide synthase expression and activity, which is unrelated to AT1R blockade.[20]

Azilsartan medoxomil potassium. The empirical formula is $C_{30}H_{24}N_4O_8$ and this is a highly potent and

Table 2 - Pharmacokinetic profile of selected angiotensin receptor blockers and their dosage regimen in controlling blood pressure.

Drug	Time to peak concentration (hours)	Bioavailability (%)	Half life (hours)	Dosage range (mg/d)	Recommended initial dose (mg/single dose/day)
Losartan	1	33	2	25-100 once or twice	50
Valsartan	2-4	25	6	80-320 once	80
Irbesartan	1.5-2	60-80	11-15	75-300 once	150
Candesartan	3-4	15	9	8-32 once or twice	16
Telmisartan	0.5-1	42-58	24	40-160 once	40

slowly dissociating AT1R blocker. Its tight receptor binding might be expected to produce potent and long-lasting antihypertensive effects.[21]

Saprisartan. This is a selective, potent, orally active, and long-acting nonpeptide AT1R antagonist. It binds reversibly to the AT1R in vascular smooth muscle and the adrenal gland. The mode of (functional) AT1 receptor antagonism is characterized as surmountable/noncompetitive like losartan, tasosartan, and eposartan, or insurmountable/noncompetitive like candesartan, saprisartan, and irbesartan. Therefore, the slow dissociation kinetics from the AT1 receptor underlie the insurmountable antagonism of saprisartan.[22]

Advantages of ARBs. The Federal Drug Association has labeled losartan, valsartan, irbesartan, candesartan, and telmisartan for use in the treatment of hypertension. The antihypertensive effect of these drugs should become apparent within 2-4 weeks after initiation of therapy, and they show the following advantages: 1. Good efficacy with once daily dosing. 2. Safety and tolerability profile. 3. They are lipid neutral. Olmesartan and irbesartan improved the lipid level (reduced total cholesterol and low density lipoprotein-cholesterol) in obese women.[23] 4. They do not differ substantially with regard to blood pressure effects, and they have a somewhat flat-response curve. 5. First dose hypotension seldom occurs, does not change heart rate, with no rebound hypertension occurring after they are discontinued. 6. Better blood pressure lowering effects are achieved when combined with hydrochlorthiazide.[24] 7. Olmesartan and irbesartan reduced insulin levels in obese women with mild-moderate hypertension.[23]

Some troublesome adverse reactions are reported with ARBs, these are: a) Non-significant cough. b) Life threatening angioedema, but its incidence is lower than that reported with ACEIs. c) Dizziness (2-4%). d) Fetal and neonatal injury or death when administered during the second and third trimesters. e) Renal effect. The AT-I receptor is found throughout the kidneys including renal vessels, afferent and efferent arterioles, tubules and juxtaglomerular cells. Blockade AT1R causes changes in renal hemodynamics and sodium excretion. Therefore, AT1R receptor blockade should be used cautiously in patients with renal dysfunction, and potassium levels should be monitored. The ARBs should not be used in patients with bilateral renal artery stenosis. f) Recently, the analysis of 70 randomized controlled trials found that the increased risk of cancer with the combination of ACEIs and ARBs cannot be ruled out.[25] The combination of ACEIs and ARBs carried an at least 10% relative increase in cancer risk. A meta-analysis combining cancer-related findings from several clinical trials reported the frequencies of cancer occurrence to be 7.2% for patients receiving ARBs compared with 6% for those not receiving ARBs (risk ratio 1.08, 95% confidence interval [CI] 1.01-1.15).

Anti-inflammatory property of ARBs. Cytokines are a group of small proteins and polypeptides produced and secreted throughout the body. They are involved in immune function, inflammation, tissue repair, cell growth, and normal physiologic processes such as sleep regulation.[26,27] As a common rule, cytokines have either proinflammatory or anti-inflammatory properties. However, they cannot be clearly divided into distinct categories because their effects overlap.[19] The cytokines; interleleukin-1(IL-1), IL-2, IL-12, tumor necrosis factor-α [TNF-α] and interferon-γ [INF-γ] are generally considered proinflammatory, whereas IL-4 and IL-10 are typically anti-inflammatory.[26,28] Increasing evidence suggests that the proinflammatory effect of Ang II is directly involved in atherosclerosis development and thrombus formation. Accumulating evidence indicates that AT1R activation has proinflammatory effects; in term of activation of NFκB,[29] which results in production of various cytokines and adhesion molecules.[30,31] Moreover, Ang II induces aldosterone release, a hormone that plays a role in cardiac remodeling, induction of vascular lesions, and recruitment of leucocytes to atherosclerotic lesions.[32] Thus, aldosterone can amplify the proinflammatory process. Also, Ang II is involved in the production of reactive oxygen species, which impaired the endothelial vascular relaxation via destroying nitric oxide.[33,34] The anti-inflammatory property of ARBs has been studied in a number of in vitro and animal studies. Valsartan reduced TNF-α production in a rat model of diabetes, which was correlated with a renal protective effect.[35] Also, valsartan has shown a 40% reduction in generation reactive oxygen species as well as reduced NFκB activation.[36] In a rat model of endotoxemia, ARBs significantly reduced IL-6 and TNF-α.[37] Candesartan reversed adhesion molecular expression and macrophage accumulation in hypertensive rats.[38]

Stroke. Stroke is the second leading cause of death and the sixth most common cause of disability worldwide in adults.[39,40] Silent or subclinical stroke is likely to occur with even greater frequency than clinical stroke and increases the risk of subsequent cerebrovascular accident. Hypertension is the most important controllable and modifiable risk factor for stroke, regardless of geographic location and ethnicity,[41] causing a population-attributable risk for up to 40%.[42,43] The relationship between BP and stroke mortality is strong, linear, and continues in subjects with levels of BP higher than 115/75 mm Hg. In the Framingham cohort,[44] BPs of greater than 160/95 mm Hg were associated with relative-risk increases for stroke of 3.1

for males and 2.9 for females. Blood pressure reduction by antihypertensive treatment is clearly efficacious in the prevention of stroke (primary and secondary). Accordingly, BP reduction of 10-12 mm Hg in systolic BP and 6 mm Hg in diastolic BP led to 38% fewer strokes.[45] Blood pressure reduction, per se, is the most important determinant for stoke risk reduction. A small reduction in BP results in substantial reduction of both ischemic and hemorrhagic stroke. Blood pressure therapy in patients with a history of stroke was associated with an odds ratio [OR] of 0.76 for recurrence.[46]

MacMahon et al's study[47] indicated that prolonged differences in diastolic blood pressure of 5, 7.5, and 10 mm Hg was associated with differences in stroke risk of at least 34, 36, and 56%. Approximately 54% of strokes worldwide can be attributed to elevated BP.[48] Such is the association that people with hypertension are 3-4 times more likely to suffer a stroke than those without hypertension.[49] The relationship between BP and risk of first stroke is direct, continuous, and independent, with the risk of increasing continuously above a BP 115/75 mm Hg.[41] Hypertension also increases the risk of stroke recurrence and it has been shown that approximately 25-30% of patients recovering from stroke have raised BP at the time of discharge from hospital.[50] There is strong and consistent evidence that lowering elevated BP is an important therapeutic target in the primary and secondary prevention of stroke regardless of age, gender, or ethnicity (Asian or white).[51] A meta-analysis of 9 randomized comparative trials found that a reduction in systolic BP of just 1-3 mm Hg led to a reduction in risk of stroke of 20-30%.[52] Moreover, in an age-specific analysis from 2 cohort study overviews (the prospective studies collaboration and the Asia Pacific cohort studies collaboration)[53] a 10 mm Hg reduction in systolic blood pressure was associated with a 35% reduction in the risk of stroke in subjects aged 60-69 years.[54] Early discontinuation of antihypertensives was associated with a 28% increase in the risk of stroke.[55] Drugs that increase plasma levels of Ang II such as diuretics, ARBs, all seem to prevent cerebrovascular accidents more efficiently than therapeutic modalities that lower Ang II levels such as ACEIs and beta blockers. In 1986, Fernandez et al[56] showed that administration of an intravenous Ang II in gerbils reduced cerebral infarct size and decreased mortality [35%] after acute unilateral carotid ligation. Stimulation of AT2R by using ligand PD-1233 and the administration of an ARB, on the other hand, both resulted in a reduction in infarct size and in improvement survival.[56,57] Currently, there is evidence supporting the use of either ARBs or ACEIs in the primary prevention of stroke. In the secondary prevention of stroke, the choice of agent is less clear.

The rational use of sartans in the management of stoke is related to these facts: 1. Angiotensin II stimulates tissue factor, which is the physiologic initiator of blood coagulation, and may contribute to the increased risk of thrombotic complications that characterize arterial hypertension. Both ACEIs and ARBs abolished that effect.[58] Therefore, the use of ARBs may reduce the thrombo-embolic events. 2. In addition to BP lowering, ARBs have a vascular protective effect (pleiotropic), namely, improving the regeneration of vascular cells.

Evidence supporting the beneficial effect of 'sartans' in stroke. i) Experimental studies. In spontaneously hypertensive stroke prone rats, ARBs increased survival, delayed brain damage, and significantly reduced kidney expression of monocyte chemoattractant protein-1, IL-1β and TGF-β without a significant decrease in BP.[59] Pretreatment of mice with telmisartan reduced stroke volume 72 hours after transient ischemic insult in a dose dependent manner, but it did not reduce stroke volume due to permanent ischemia.[60] The most likely mechanism of cerebral protection is related to the inhibition of proinflammatory adhesion molecules such as ICAM-1 and P-selectin, which are involved in transient ischemia, due to the selective PPAR-γ agonist activity of telmisartan.[60] The administration of telmisartan or losartan to KK-Ay mice before middle cerebral artery occlusion (MCAO), reduced the ischemia area, and improved the neurological score compared with non-treated group with an increase in blood flow and a reduction in superoxide anion and expression of inflammatory cytokines.[46] Telmisartan, but not losartan, has a beneficial effect on stroke partly due to activation of PPAR-γ receptors as well as angiotensin receptor antagonists.[61]

There are reports that Ang II levels are increased bilaterally in the cortex following stroke, and systemic treatment of spontaneously hypertensive rats (SHR) with ARBs reduces the occurrence of stroke.[62,63] Stier et al[62] found that oral losartan (30 mg/kg/d) delayed the development of severe hypertension and prevented stroke in saline-drinking spontaneous hypertensive rats stroke prone (SHRSP). Losartan at a dose of 10 mg/kg/d did not affect systolic BP elevation, but prevented the occurrence of cerebrovascular lesions. Inada et al's study[63] indicated that candesartan cilexetil reduces the incidence of stroke without affecting the blood pressure in SHRSP in a dose of 0.1 mg/kg/d. The ARBs provide a 40-50% reduction of infarct volume, and reduce the neurological deficit in normotensive rats and SHR.[57] Irbesartan significantly improved the neurological outcome of cerebral ischemia induced by MCAO in rats.[64] Candesartan pretreatment of SHR prevented the decrease in the blood flow in the marginal zone of ischemia and reduced the volume of total and cortical

infarcts after MCAO.[65] Ito et al,[66] found that candesartan pretreatment (0.1 mg/kg) decreased the infarct area by 31% and improved the cerebral blood flow followed MCAO. Moreover, Groth et al[67] found that candesartan pretreatment (0.1 mg/kg) decreased mean arterial pressure before, during, and after ischemic injury, but did not improve recovery from brain ischemia in rats subjected to MCAO. Li et al's[68] data indicate that cerebral AT2R exert neuroprotection in response to ischemia-induced neuronal injury, possibly by supporting neuronal survival and neurite outgrowth in peri-ischemic brain areas. Also, Lu et al's study[69] indicates that candesartan appears to provide beneficial effects against stroke in SHR in 3 ways: AT1R antagonism, down-regulation of AT1R expression, and up-regulation of AT2R receptors. The suitable experimental model of cerebral ischemia that closely mimics an embolic stroke is to occlude the MCA by endothelin-1.[63] This model produced rapid occlusion of the MCA and induced significant neurological impairment with cerebral infarct size of 30%. Candesartan (0.2 mg/kg/d for 7 days) attenuates both the infarct size and the neurological impairment without altering BP.[70] Therapy with valsartan restores cerebral flow modulation, and furthermore it decreases superoxide production, ischemic area, and neurological deficit after MCAO in the mice that have Ang II AT2R. Iwai et al[71] reported that AT2R stimulation has protective effects on ischemic brain lesions. Therefore, the actions of ARBs are at least in part, independent of their BP lowering action.[64,68] Increased levels of Ang II in response to ARB treatment may have a role in cerebral protection.[68,72] The AT2R often mediate the effects of Ang II that are exactly opposite to that mediated by AT1R,[73] and tissue levels of AT2R are dramatically increased in the peri-infarct region in the brain following ischemia.[68,74] Moreover, Ang II acts via AT2R in neurons to elicit differentiation, regeneration, and neurotrophic actions.[75-77] The beneficial actions of ARBs after MCAO induced cerebral ischemia prevented by specific AT2R blockers.

ii. Clinical studies. Experimental evidence has linked the RAAS to the development and progression of cerebrovascular disease. The Acute Candesartan Cilexetil Evaluation in Stroke Survivors (ACCESS), however, suggested that ARBs are safe in hypertensive acute stroke patients and may offer advantages independent of BP control.[78] Eprosartan can be differentiated from other ARBs due to its noradrenergic effects. It acts to decrease total peripheral resistance, and also acts at vascular AT-1 receptors (postsynaptic) as well as at presynaptic AT-1 receptors where it inhibits noradrenaline release. It represents a useful therapeutic option in the management of patients with hypertension including those with a history of stroke or with co-morbid type 2 diabetes mellitus.[79] It significantly reduced systolic BP with a significant reduction in pulse pressure in elderly patients with isolated systolic hypertension. This reduction in BP is associated with improvement in cognitive function.[80] In the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET), investigators demonstrated the non inferiority of the ARB telmisartan compared with the ACEI ramipril for the primary prevention of vascular events in high risk cardiovascular population.[81] The ONTARGET program reported no significant difference between ramipril and telmisartan for reducing stroke in patients at high risk of cerebrovascular disease.[82] In a meta-analysis covering 49924 patients in 6 trials, the ARBs were associated with an 8% lower risk of stroke compared to the ACEIs (OR 0.92, CI 0.85-0.99). The Telmisartan Randomized Study in ACE intolerant subjects with cardiovascular disease (TRANSCEND) study reported a non significant 17% reduction in stroke with telmisartan compared with placebo in high risk patients who were intolerant to ACEIs.[83] In the MOSES trial (a multicenter, prospective, randomized, open, blinded endpoint design that began enrollment in October 1998 and closed in February 2002), the comparison of eprosartan versus nifedipine in patients with a previous stroke resulted, despite similar BP reduction, in a significant reduction in the primary composite endpoint of total mortality plus cardiovascular end cerebrovascular events, including recurrent events.[84,85] The VALUE trial (Valsartan Antihypertensive Long term Use Evaluation) found that BP was reduced by both eprosartan and nitrendipine, but eprosartan reduced all cardiovascular and cerebrovascular events to a greater extent than nitrendipine.[86] In one retrospective study, stroke patients that received ARBs showed better outcome upon discharge than non-ARB groups upon discharge as assessed by the modified Rankin scale (mRS) and Barthel index (BI).[87] The LIFE (losartan intervention for endpoint) study demonstrated that ARBs are more effective as anti-stroke agents than the traditionally used beta-adrenoceptor blockers in patients with hypertension and left ventricular hypertrophy.[88] In this study, losartan substantially reduced the rate of fetal and non-fetal stroke by 25% versus atenolol in 9139 patients with hypertension and left ventricular hypertrophy.[81] A small (1.1 mm Hg) but significant difference in the reduction in systolic BP was observed between treatments in favor of losartan. In the LIFE study, they found a 40% stroke reduction in patients with left ventricular hypertrophy and isolated systolic blood pressure.[89] Also, the LIFE study data indicated that losartan reduced the incidence of stroke in patients with new onset atrial fibrillation.[57] The Study on Cognition and Prognosis in the Elderly (SCOPE) data indicates the importance of AT1R

blockade for stroke prevention.[90] In the SCOPE study, candesartan-based treatment reduced nonfatal stroke by 27.8% and all stroke by 23.6% compared with placebo in 4964 elderly patients.[91] In the CASE-J study there was no significant difference in cerebrovascular events between amlodipine and candesartan based regimen in Japanese high risk patients with hypertension.[92] A significant reduction in 12-month mortality and vascular events with candesartan was reported in the ACCESS study (Acute Candesartan Cilexetil therapy in Stroke Survivors) that assessed the safety of a modest BP reduction by candesartan in the early treatment of stroke.[93] The ARBs provide particularly robust protection of the cerebral vasculature.[93,94] Delayed acute treatment with candesartan, in an experimental model of stroke in rats, resulted in neurovascular protection and improved function at 24 hours after stroke,[95] which was beyond that of BP lowering alone.[96] After stroke, lowering BP with a combination of ACEIs and diuretics reduced rates or recurrent stroke in the perindopril protection against recurrent stroke study (PROGRESS).[97] Schrader et al[93] reported that candesartan cilexetil soon after a stroke reduced the rate of death and cardiovascular events despite no BP reduction. Telmisartan (80 mg/day) initiated soon after an ischemic stroke did not significantly reduce the risk of subsequent stroke, of the composite outcome of major cardiovascular events or new onset of diabetes over 2.5 years follow up.[97]

The possible mechanism of long term ARBs is promoting the neovascularization.[98] Kozak et al's[99] results indicate that candesartan provides long-term cerebro-protection that may involve vascular protection and enhancement of early angiogenic remodeling. Long term ARB administration (irbesartan) reduces the expression of c-Fos and c-Jun (Fos and Jun), AP-1 transcription factors, are induced after focal brain ischemia, and are associated with programmed cell death and neurodegeneration, and correlated with neurological outcome in brain ischemia,[64] which suggests less apoptosis and degeneration. Boutitie et al[100] proposed that ARBs, in addition to lowering BP, inhibit the negative effect of AT1R in cerebral circulation, and allow Ang II to mediate potentially stroke protective effects through AT2R. Conclusive evidence has been presented indicating that the angiotensin type-2 receptor mediates vasodilatation in small resistance arterioles, in the coronary microcirculation and dilates large capacitance vessels, including the aorta, subjected to pressure-overload.

Angiotensin receptor blockers and dementia. Previous studies suggest that ARBs offer an important advantage over ACEIs and other antihypertensive agents in improving outcomes from stroke.[101-104] Animal studies report that ARBs elicit neuroprotective responses that are independent of decreases in BP and are apparent even in cell culture.[103,105] The strong association of stroke with dementia and nursing home admission was observed, suggesting the importance of vascular factors in progression of cognitive loss.[106-108] An increasing number of studies have shown a relation between ARBs and preservation of cognitive function.[109] Studies in both animals and humans found that ARBs help to preserve cognitive function through a mechanism that is independent of the antihypertensive effects.[110-114]

In conclusion, it appears that not all members of the sartans achieve cerebro-protection and improve the outcome of stoke, therefore, appropriate sartan selection is needed. The mechanism of cerebro-protection of sartans in animal studies and human studies differ, and further studies are necessary to elucidate the mechanism of cerebro-protection.

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