

Cerebral White Matter Lesions, Risk of Stroke and Cerebrovascular Protection with Angiotensin Receptor Blockers

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Abstract: The pathogenesis and clinical significance of cerebral white matter lesions (WML) remain controversial. Various studies have shown that age, hypertension, diabetes mellitus and a history of stroke or heart disease are the most important factors related to cerebral WML. Other studies suggest that WML are closely related to the development of future strokes and other forms of cerebrovascular disease, such as cognitive impairment, in elderly patients with vascular risk factors, particularly hypertension.

Angiotensin receptor blockers are antihypertensive drugs useful for the treatment of hypertension and cardiovascular diseases. Recent data from experimental studies and clinical trials suggest that they could be superior to other antihypertensive therapies in preventing the development of cerebrovascular disease and in reducing the risk of death and recurrences in patients with a previous stroke.

This paper reviews the clinical importance of cerebral WML, their relationship with stroke development and data concerning cerebrovascular protection with angiotensin receptor blockers.

Key Words: Cerebral white matter lesions, stroke, angiotensin receptor blockers, hypertension, cerebrovascular disease.

CEREBRAL WHITE MATTER LESIONS: PREVALENCE, PATHOGENESIS AND RELATION TO ARTERIOSCLEROSIS AND STROKE

Since the introduction, more than 25 years ago, of brain magnetic resonance imaging (MRI) with its high sensitivity and resolution capacity, the presence of cerebral hyperintensities in the deep and subcortical white matter has been a common finding in elderly people [1]. During the last few years, exhaustive research has tried to identify risk factors for the presence and progression of white matter lesions (WML) both in healthy individuals and in hypertensives or people with a history of stroke or dementia. However, methodological differences among studies have generated numerous discrepancies and unresolved questions remain. The pathogenesis of WML is poorly understood, although the majority of studies have found that age, hypertension, diabetes mellitus and a history of stroke or heart disease are the most important factors related to WML [1]. Indeed, besides age, hypertension is constantly reported to be the main risk factor for cerebral WML. The association between WML and hypertension may be mediated through several different pathogenic pathways, with WML being associated with the severity of high blood pressure (BP) values [2], lack of BP control in treated hypertensive patients [3,4] and nocturnal BP dip [5,6] in various reports. In addition, a relationship between some genetic polymorphisms and WML has also been reported in hypertensive patients [7,8].

The main hypothesis regarding the association between high BP and ischaemic WML is that long-standing hypertension causes lipohyalinosis of the media and thickening of

the vessel walls with narrowing of the lumen of the small perforating arteries and arterioles which nourish the deep white matter [1]. The perforating vessels, which originate in the cortical and leptomeningeal arteries, have a relatively poor anastomotic system, which makes the white matter vulnerable to cerebral ischaemia. In fact, low BP has also been reported to be a risk factor for WML [1]. Hypertension may also cause disturbances in the blood-brain barrier, which may lead to lesions in the white matter caused by cerebral oedema, activation of astrocytes or the passage of destructive enzymes or other poisons through the damaged vessel walls [1].

Postmortem studies have indicated that WML seen on MRI scans are associated with atherosclerosis-related degenerative changes in arterioles, suggesting that cerebral arteriosclerosis of the penetrating vessels is the main factor in the pathogenesis of ischaemic WML [1]. Bots *et al.* [9] reported that WML are related to atherosclerosis, indicated by increased common carotid intima-media thickness and carotid plaques. Manolio *et al.* [10] reported an association between WML and atherosclerosis severity (measured by carotid intima-media thickness and degree of stenosis) but found no significant association with specific plaque characteristics, suggesting a relationship with more generalized vascular disease rather than an etiological role for a specific form of carotid disease. Similarly, de Leeuw *et al.* [11] showed that aortic atherosclerosis during midlife, assessed on abdominal radiographs, was significantly associated with periventricular WML twenty years later.

Several vascular risk factors have been related to WML, and it seems that the greater the number of vascular risk factors for cerebrovascular disease, the higher the presence and severity of WML. A review by Pantoni and Garcia [1] of more than 160 publications about WML found that studies

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with multivariate analysis showed that diabetes mellitus and hypertension were associated with WML. However, the relationship with lipid abnormalities and smoking status remains controversial.

Other studies have also reported that WML are associated with a history of stroke, lacunar infarcts, heart disease and atrial fibrillation, which are frequently associated with both hypertension and vascular risk factors [1].

Insulin resistance syndrome and haemostatic abnormalities (imbalance between coagulation and fibrinolysis) have been proposed as new risk factors for cardiovascular disease. Breteler *et al.* [12] reported an association between elevated factor VIIc activity and fibrinogen levels and the presence of WML. Kario *et al.* [13] studied the relationship between hyperinsulinaemia and haemostatic abnormalities (plasminogen activator inhibitor-1, d-dimer, von Willebrand factor, prothrombin fragment 1+2 and thrombin-antithrombin complexes) and WML in older hypertensive patients. They found an association between hyperinsulinemia and subcortical WML but did not find a relationship with haemostatic abnormalities.

High BP has been reported to clearly influence the presence and severity of WML in most studies. Some studies have shown that treated and controlled hypertensive patients have a lower prevalence of WML than both untreated hypertensives and treated, but not controlled hypertensive patients [3,4]. Most of these studies were cross-sectional, but de Leeuw *et al.* [14] conducted a prospective study which found that diastolic and systolic BP levels assessed 20 years previously were significantly associated with WML. Similarly, van Dijk *et al.* [15] found that patients with poorly controlled hypertension had a higher risk of severe WML than those without hypertension or those with controlled hypertension. This study was performed in 1805 subjects aged 65 to 75 years from 10 European ongoing community-based studies that were initiated 5 to 20 years before the MRI.

Several studies have examined the prevalence of WML in both normotensive and hypertensive subjects. The ARIC study [4] reported a prevalence of WML of 24.6% among individuals aged 55-72 years (49% were hypertensive patients). The Cardiovascular Health Study [16] found a prevalence of 33.3% in individuals aged 65 years or older (44% were hypertensive patients). The prevalence was 27% in the Rotterdam Study [12], which included individuals aged 65-84 years (39% were hypertensives). Shimada *et al.* [2] studied 28 normotensives and 20 hypertensives aged 59-83 years and found a prevalence of advanced WML of 25% and 40%, respectively. Finally, Lee *et al.* [17] have recently reported an age-adjusted prevalence of silent cerebral infarction (which includes WML) of 5.1% in a large population of normal adults of all ages (994 individuals aged 20 to 78 years, 42.8% were hypertensive patients). In a cohort of 66 untreated hypertensives aged 50-60 years, a prevalence of WML of 40.9% was found [18]. Differences in the prevalence of WML between studies may be due to subtle variations in WML assessment, but especially to the different impact of risk factors such as age and hypertension, which are influenced by the subject selection criteria. Thus,

different studies included both normotensive and hypertensive patients (untreated and treated), and subjects with a wide range of ages, or only elderly people.

Cerebral WML are an important prognostic factor for the development of stroke [19,20] or stroke recurrence [21-23], cognitive impairment [12,16, 24] and dementia [25]. Kuller *et al.* [20] have recently shown that the relative risk of stroke increased significantly as the WML increased in 3293 participants in the Cardiovascular Health Study followed-up for an average of 7 years. The authors postulated that assessment of WML may be useful in identifying patients at high risk for stroke and that measurement of WML progression may serve as a marker for the efficacy of various pharmacological therapies. Fu *et al.* [23], in a study of 228 stroke patients, found that the three year cumulative incidence of recurrent stroke (43.7%) in patients with severe WML was more than fourfold than that of patients with mild (9.3%) or no WML (7.8%).

Conversely, stroke patients have significantly more WML than healthy controls, and those with lacunar infarcts are particularly affected [26]. It is known that lacunar infarcts are the most frequent cerebrovascular lesions observed in hypertensive patients. Thus, the role of high blood pressure on the presence, severity and progression of all of these lesions are important. The reduction of stroke incidence and recurrence after antihypertensive therapy has been established in several clinical trials. It may be useful to consider WML progression as a surrogate endpoint for trials in cerebral small-vessel disease in order to prevent stroke.

Data concerning the impact of antihypertensive treatment on WML or cognitive impairment are scarce and indirect. Van Dijk *et al.* [15] showed that blood pressure control obtained by means of antihypertensive therapy was inversely associated with the presence and severity of WML. Furthermore, in the Syst-Eur trial [27], active treatment was associated with a decrease in new cases of dementia in old patients with isolated systolic hypertension. Finally, a recent paper suggests that patients taking angiotensin receptor blockers improved cognitive scores in comparison with other antihypertensive therapies [28]. All these data must be viewed with caution waiting for clinical trials specifically designed for measuring the impact of antihypertensive treatment on WML progression

ANGIOTENSIN RECEPTOR BLOCKERS AND CEREBROVASCULAR PROTECTION

Angiotensin receptor blockers (ARB) are the newest class of antihypertensive agents marketed for the treatment of hypertension. The effect of various ARB on cardiac and cerebrovascular disease has been investigated in several clinical trials, both placebo controlled and face to face comparison against other antihypertensive drugs. Whereas most studies conducted in cardiac patients (those with left ventricular dysfunction after a myocardial infarction or with congestive heart failure) have failed to show a superiority of ARB against usual treatment with angiotensin converting enzyme inhibitors, the effect of ARB on stroke prevention (both primary and secondary) has been demonstrated to be superior to other antihypertensive drug classes, suggesting

these drugs have a special effect on cerebrovascular protection. In fact, 3 of the 4 trials that compared ARB with other antihypertensive drugs demonstrated a significant reduction in strokes with these agents.

The LIFE Trial

The LIFE (Losartan Intervention For Endpoint reduction in hypertension) study [29] compared the ARB losartan and the betablocker atenolol in 9193 hypertensive patients older than 55 with electrocardiographically demonstrated left ventricular hypertrophy. The primary endpoint (a combination of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) was significantly reduced in losartan treated patients. The relative risk for losartan compared to atenolol was 0.87 (95% CI: 0.77-0.98; $p=0.021$). A separate analysis for each component of the primary endpoint revealed that almost all the differences were due to stroke prevention (fatal and non-fatal). The relative risk for losartan compared to atenolol for stroke was 0.75 (0.63-0.89; $p=0.001$), whereas the reductions in myocardial infarction or cardiovascular death were not statistically significant.

A subgroup analysis of the LIFE trial that included 1326 patients with isolated systolic hypertension [30] (a condition clearly associated with a high-risk of stroke) also demonstrated that losartan was superior to atenolol in preventing stroke (relative risk for losartan: 0.56; 0.36-0.86; $p=0.008$).

LIFE was the first comparative trial with an ARB in hypertensive patients. The favourable results observed with losartan can be related to beneficial effect of this drug, and extensively to other ARBs, or can reflect a deleterious effect of atenolol in hypertensive patients. In this sense, a recent review suggested that atenolol was unable to prevent cerebrovascular events in hypertensive patients [31]. However, other trials with ARBs suggest a beneficial effect of this class of drugs.

The SCOPE Study

The Study on Cognition and Prognosis in the Elderly (SCOPE) [32] compared the ARB candesartan against placebo in 4964 elderly patients (70-89 years) with mild to moderate hypertension (systolic BP 160-179 and diastolic BP 90-99 mmHg). Open-label antihypertensive drugs were allowed to achieve BP control. As a consequence, most patients (75% in the candesartan group and 84% in the placebo group) received antihypertensive therapy apart from study drugs. The authors claimed that this study was a comparison of a candesartan-based therapy against conventional treatment. However, there were clear differences in BP reduction between treatments that favoured candesartan (3.2/1.6 for systolic and diastolic BP, respectively, at the end of the study).

The SCOPE trial failed to demonstrate a significant beneficial effect of candesartan on the primary objective (a composite of cardiovascular death, stroke and myocardial infarction). However, as in the LIFE trial, whereas no effect was observed on cardiac events, the candesartan treatment regimen reduced stroke (24%; $p=0.056$) and, in particular, non-fatal stroke (28%; $p=0.04$).

A subgroup analysis of patients with isolated systolic hypertension included in the SCOPE trial (1518) also demonstrated a reduction in the number of strokes (fatal and nonfatal) that was at the limit of statistical significance (relative risk reduction 42%; $p=0.049$) [33].

The VALUE Trial

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial [34] is the largest trial with ARB conducted until now. The study included 15 245 high-risk hypertensives older than 50 who were randomised to valsartan or amlodipine. The primary endpoint was a composite of cardiac morbidity and mortality that showed no differences between treatment groups. One of the pre-specified secondary endpoints was stroke. The total number of strokes was 322 in valsartan treated patients and 281 in the amlodipine group. The relative risk for valsartan was 1.15 (0.98-1.35; $p=0.08$). Another secondary endpoint, the rate of myocardial infarction, also occurred more frequently in valsartan treated patients (19%; $p=0.02$).

The results of the VALUE trial were greatly affected by differences in BP control between treatments. In fact, the main difference in stroke prevention occurred during the first three months of follow-up when differences in BP reached 4 mmHg for systolic BP in favour of amlodipine.

In an attempt to overcome this BP influence, the VALUE investigators carried out a special case-control analysis, choosing more than 5000 pairs of patients matched for age, sex, risk and, especially, for systolic BP [35]. Using this approach, differences in the cardiovascular endpoints that favoured amlodipine in the main analysis disappeared. In fact, the relative risk of stroke for valsartan compared to amlodipine was 1.02 (0.81-1.28; $p=0.899$).

The MOSES Trial

The most recent trial on stroke prevention using ARB is the MOSES (Morbidity and mortality after Stroke, Eprosartan compared with nitrendipine for Secondary prevention) trial [36]. In this study, 1405 hypertensive stroke survivors were randomised to the ARB eprosartan or the calcium channel blocker nitrendipine during a mean follow-up of 2.5 years. Open antihypertensive treatments were allowed in order to achieve target BP and both BP control and mean BP values were essentially the same between groups. Despite this, differences in the primary composite endpoint (total mortality and cerebrovascular and cardiovascular events) occurred between groups. The hazard ratio for eprosartan compared to nitrendipine was 0.79 (0.66-0.96; $p=0.014$). Once more, these differences were due to better prevention of stroke and related cerebrovascular events in the eprosartan group (25%).

In summary, three large trials of primary prevention in hypertensive patients have examined the effect of ARB on cardiovascular protection. In two of these large trials, losartan and candesartan were superior to atenolol or conventional treatment in preventing stroke. The third trial did not show a better outcome with valsartan compared to amlodipine, although the important differences in BP control

may have influenced the results. Finally, in a smaller study of secondary prevention in hypertensive patients with a previous stroke, another ARB, eprosartan was superior to nitrendipine in cerebrovascular protection (Fig. 1). Although it is always difficult to draw definite conclusions from different trials involving different types of patients and different drug comparisons, it seems that a picture of better cerebrovascular protection with ARB may be suggested by these trials.

POSSIBLE MECHANISMS OF CEREBROVASCULAR PROTECTION WITH ARB

Several different (and probably complementary) mechanisms have been proposed to explain better cerebrovascular outcomes in patients treated with ARB, including left ventricular hypertrophy regression, protection against atrial enlargement and supraventricular arrhythmias, effects on endothelial function, risk biomarkers and vascular remodeling, and specific neuroprotection mediated through angiotensin II and the AT-2 receptor.

Left Ventricular Mass Regression

In the LIFE trial, the cardiovascular protection observed independently of treatment allocation was related to left ventricular hypertrophy regression [37]. Patients in whom both the Cornell product and Sokolow-Lyon voltage, the electrocardiographic criteria used for definition of left ventricular hypertrophy, were reduced, had a better outcome. Losartan induced changes in these parameters that were significantly more pronounced than those observed in

atenolol-treated patients. These results are in agreement with previous observations showing that left ventricular mass regression, measured by echocardiography is associated with a better prognosis in hypertensive patients [38]. Furthermore, in a meta-analysis of randomised studies, the left ventricular mass regression induced by ARB was clearly superior to that observed with diuretics or betablockers and slightly better than that promoted by ACE inhibitors or calcium channel blockers [39].

Supraventricular Arrhythmias

This effect on the regression of left ventricular hypertrophy can be linked with protection against atrial fibrillation. Supraventricular arrhythmias are frequent in hypertensive patients with diastolic dysfunction related to the increase in ventricular mass, which promotes atrial enlargement. It is recognised that atrial fibrillation is one of the main risk factors for stroke, especially when accompanied by hypertension, older age or left ventricular dysfunction.

A post-hoc analysis of the LIFE trial revealed that rates of new onset atrial fibrillation were significantly reduced in losartan-treated patients compared to those who received atenolol [40]. Furthermore, in a study of patients suffering paroxysmic atrial fibrillation, complementary treatment with another ARB, irbesartan, added to baseline amiodarone, was superior to amiodarone alone in preventing recurrences [41]. These data suggest a specific effect of this class of drugs on myocardium that is not dependent on BP. In this sense, the greater effect of ARBs on LVH regression, as stated above, can help to understand a specific antiarrhythmic effect.

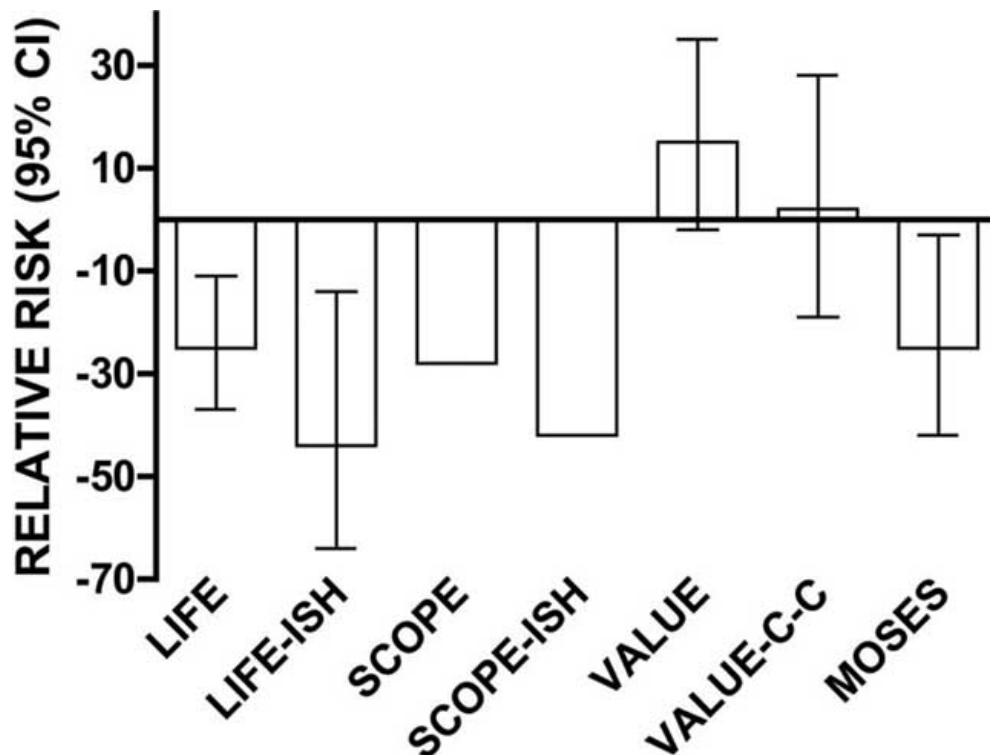


Fig. (1). Effects of angiotensin receptor blockers on cerebrovascular protection (reduction in the relative risk of stroke) in clinical trials comparing ARBs with other antihypertensive treatments (relative risk reduction and 95% confidence interval). VALUE C-C refers to the special case-control study derived from the VALUE trial that examined blood pressure dependent and independent effects of treatment.

Moreover, experimental data suggest that ARBs can have a direct effect of atrial electrical remodelling [42].

Endothelial Function

Endothelial dysfunction is one of the most important mechanisms involved in the development of atherosclerosis and is present in patients with various cardiovascular risk factors, including hypertension, hypercholesterolaemia and type 2 diabetes, as well as in patients with coronary artery disease. Endothelial dysfunction has important prognostic implications in these groups of patients [43,44].

Blocking the renin-angiotensin system with ARB clearly ameliorates endothelial dysfunction, an effect that is not totally dependent on BP reduction. In an elegant study by Schiffrin *et al.* [45], a small group of hypertensive patients and normotensive controls was studied. Resistance arteries obtained from gluteus subcutaneous biopsies were analysed by measuring the endothelium-dependent and independent responses and the cross-sectional area. Patients were then randomised to losartan or atenolol for one year and the procedures were repeated. The results showed that patients treated with losartan normalised acetylcholine-dependent vasorelaxation and also reduced the ratio of the media/lumen diameter. No changes were observed in atenolol-treated patients, despite a similar reduction in BP. In another study with irbesartan [46], an amelioration of endothelium-dependent and independent vasodilation in the forearm of a group of hypertensive patients we also found. Moreover, the effect of L-NMMA (a selective nitric oxide synthase inhibitor) on the acetylcholine-dependent response was clearly enhanced after 6 months of irbesartan treatment, suggesting that nitric oxide bioavailability in the vasculature was restored with irbesartan treatment.

Risk Biomarkers

There is growing interest in the effect of treatment on atherosclerosis biomarkers. Several of these biomarkers, including acute-phase reactants such as C-reactive protein and adhesion molecules and selectins that mediate vascular inflammation, have been implicated in the prognosis of patients at risk of or with cardiovascular diseases, especially coronary artery disease [47,48]. Experimental studies have shown that angiotensin II accelerates the development of atherosclerosis, and the plausible mechanisms are that angiotensin II promotes superoxide anion generation, endothelial dysfunction, inflammation, and impaired fibrinolysis [49]. Various studies have shown an improvement in these parameters by blocking the effects of angiotensin II. Two months of candesartan therapy promoted reductions in oxidative stress (malondialdehyde), inflammatory biomarkers (monocyte chemoattractant protein, tumor necrosis factor- α) and thrombotic factors (plasminogen activator inhibitor type-1) in 45 hypertensive patients independently of BP changes [50]. In a recent study [51], C-reactive protein, interleukin-6, and monocyte chemoattractant protein-1 (MCP-1) were reduced in patients treated with olmesartan. These results were in agreement with another study comparing eprosartan and hydrochlorothiazide [52], which showed that despite similar BP reductions, decreases in MCP-1, soluble vascular cell

adhesion molecule-1 (sVCAM-1) and superoxide anion generation were only observed in patients treated with eprosartan. Treatment with valsartan has also shown an inhibition of reactive oxygen species generation by both polymorphonuclear and mononuclear cells, with a concomitant suppression of nuclear factor κ B, thus reducing oxidative load [53]. In this study, quinapril and simvastatin did not share the effects observed with valsartan.

Vascular Remodelling

Another important mechanism leading to stroke protection is the effect on small-artery remodelling, which seems to be the earliest form of organ damage in hypertension [54]. Structural alterations of subcutaneous small resistance arteries are associated with a worse clinical prognosis in patients with hypertension and/or type 2 diabetes mellitus [55]. As mentioned above, Schiffrin *et al.* [45] showed that losartan induced regression of vascular structural alterations in hypertensive patients, whereas atenolol did not. A recent study [56] evaluated indices of subcutaneous small resistance artery structure using micromyography. Hypertensive patients with type 2 diabetes mellitus underwent a biopsy of the subcutaneous fat from the gluteal region at baseline and after 1 year of treatment with candesartan (n=8) and enalapril (n=7). The results showed that enalapril and candesartan proved to be equally effective in correcting small resistance artery remodelling, but that vascular collagen content was reduced and metalloproteinase-9 was increased by candesartan, but not by enalapril. These differences may be related to a more extensive inhibition of the RAS with ARB, particularly of angiotensin II-mediated effects.

Another study [57] performed in hypertensive patients with LVH has shown that treatment for 36 weeks with losartan (n=111) decreases myocardial collagen content (assessed by echoreflectivity and serum markers of collagen synthesis and degradation), whereas atenolol (n=99) does not, despite a comparable decrease in BP. The authors suggest that the reduction in fibrosis in myocardium with losartan may have contributed to the protective action that losartan exerted in the LIFE study.

Neuroprotection Mediated by Angiotensin II and the AT-2 Receptor

There is growing experimental evidence suggesting that some actions directly related to the increase in angiotensin II and other angiotensins or the stimulation of the AT-2 receptor may be involved in the cerebroprotection of ARB.

Several angiotensin receptors mediate angiotensin II actions. Most of the deleterious effects of angiotensin II are mediated by the AT-1 receptor, which is selectively blocked by ARB. Conversely, stimulation of the AT-2 receptor by the same angiotensin II seems to promote vasodilation, natriuresis and apoptosis and impairs cellular hyperplasia [58,59]. Some preliminary data support the idea that the AT-2 receptor is expressed more intensively in the brain than in the heart and that this expression is enhanced in patients with target organ damage, especially when cerebral ischaemia occurs [60]. In experimental models, the AT-2 receptor stimulation protects brain tissue from ischaemia [61,62]. Treatment with ARB

would increase angiotensin II concentration locally, thus promoting the availability of this angiotensin II to bind the AT-2 receptor and to mediate the mentioned beneficial actions. Other forms of RAS blockade, such as treatment with ACE inhibitors, would decrease angiotensin II and thus would not share the beneficial effects mediated through the AT-2 receptor stimulation.

In addition to a neuroprotective effect mediated by the AT-2 receptor, the increase in angiotensin II observed with treatment with ARBs may also lead to a parallel increase in other angiotensins such as angiotensin III and angiotensin (1-7). These recently discovered peptides may also contribute to better organ protection when AT-1 is blocked with ARBs [63-65].

CLOSING REMARKS

Hypertension is associated with silent organ damage that precedes the development of clinical events related to cardiovascular disease. Like left ventricular hypertrophy in the heart, microalbuminuria in the kidney or endothelial dysfunction and intima-media thickness in the vascular wall, white matter lesions constitute the early process of brain damage in hypertension. Patients with cerebral white matter lesions are at a high risk of stroke and specific neuroprotection must be considered. One class of antihypertensive drugs, the ARB, is specifically indicated for stroke prevention in these high-risk patients or in those who have had a previous stroke. This indication comes from well controlled intervention studies showing a clear reduction in strokes when hypertensive patients were treated with ARB in comparison with other forms of antihypertensive treatment. This better outcome is supported by some particular mechanisms related not only to the renin-angiotensin system blockade, but to the specific AT-1 receptor antagonism, the increase in angiotensin II and the stimulation of the AT-2 receptor. The fact that some of these actions are not shared by angiotensin converting enzyme inhibitors helps to explain why this latter class of drugs has failed to provide significantly better protection against stroke than other conventional antihypertensive treatments, whereas trials based on ARB therapy have consistently shown better cerebrovascular protection.

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