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Scientific Update™

The cerebroprotective effects of AT_1-receptor blockade

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Clinical trials of hypertension have established the benefit of antihypertensive therapy for primary and secondary prevention of cerebrovascular events, and multiple studies have elucidated the crucial role of the renin-angiotensin system (RAS) in the pathogenesis of cardiovascular (CV) disease. Indeed, clinical trials of agents that interfere with the RAS (eg, angiotensin-converting enzyme [ACE] inhibitors and angiotensin receptor blockers [ARBs]) suggest benefits beyond blood pressure reduction alone. Recent studies with the ARB, candesartan, in hypertensive patients suffering an acute stroke suggest that it is safe and beneficial. Additionally, results from the Study of Cognition and Prognosis in the Elderly (SCOPE) showed that candesartan had beneficial effects on cerebrovascular events and cognitive function in selected groups of elderly, mildly hypertensive patients. Because the RAS is important in modulating vascular function, there has been interest in evaluating ARBs in migraine prevention. A recent randomized clinical trial suggested a benefit that could extend the role of RAS antagonism to other cerebrovascular disorders. This issue of *Cardiology Scientific Update* reviews the evidence from these recent experimental and clinical studies.

Inhibition of the RAS in the brain

All major components of the RAS are found in the brain,[1,2] including the angiotensin II-receptor subtypes AT-1 and AT-2. Experimental studies have evaluated the blockade of AT-1 receptors in animal models of stroke. Inada et al established that low doses of candesartan that do not decrease blood pressure help prevent stroke in spontaneously hypertensive rats (SHR), suggesting that the RAS is involved in the pathogenesis of stroke.[3] In another rat model, the ARB irbesartan was infused directly into the lateral ventricle of the brain. On day 6, the middle cerebral artery was occluded, followed by reperfusion. A neurologic assessment performed the following day revealed that there was a reduced neurological deficit. In other studies, the ARB losartan and a separate compound, PD-123177, was used to block the AT-2 receptors. Losartan attenuated the neurological deficit by a magnitude similar to irbesartan, while the AT-2 antagonist had no effect. Simultaneous treatment with both antagonists negated the beneficial effects of losartan, suggesting that an intact AT-2 receptor is necessary for protection by the AT-1 antagonist.

As patients do not receive ARBs by intracranial infusion, additional studies were needed to determine whether ARBs can penetrate the brain when given systemically. Studies revealed that IV irbesartan, given for 6 days, had no significant effect on neurological deficits in contrast to infusion into the lateral ventricle of the brain. Candesartan administered subcutaneously, however, resulted in markedly improved neurological deficits and reduced stroke size. This result was surprising since candesartan is more hydrophilic and was expected to be less effective in crossing the blood-brain barrier. However, other mechanisms such as active transport of candesartan across the blood-brain barrier may explain its ability to inhibit brain AT_1 receptors.[4] Similar protective effects have been observed with the oral administration of candesartan.[5-10]

ACCESS: acute candesartan therapy in stroke survivors

Abundant experimental data suggest that blockade of the RAS is beneficial in humans. Wada et al, like Inada,[3] using a rat hypertension model, demonstrated that ischemic brain damage is limited by the ACE inhibitor, enalapril, and the ARB, candesartan, in doses that decrease blood pressure only slightly.[11,12] Although it has been demonstrated that arterial hypertension is important in the pathogenesis of stroke, data about antihypertensive treatment in acute stroke patients were not available. In addition, there were marked discrepancies between different therapeutic guidelines for stroke (eg, the German Hypertension League recommends treatment when BP is >200/100 mm Hg, while EUSI recommends treatment if BP is >220/110).[13,14] These facts underscored the importance of conducting randomized controlled trials in acute stroke in humans and led to the ACCESS Study.

The Acute Candesartan Cilexetil Evaluation in Stroke Survivors (ACCESS) study was the first clinical trial of an ARB in humans suffering a stroke. Its objective was to investigate whether patients treated with candesartan during the acute phase of cerebral ischemia had better

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Figure 1: ACCESS – Study course[15]

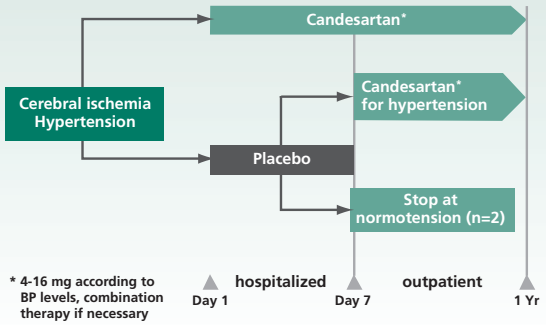
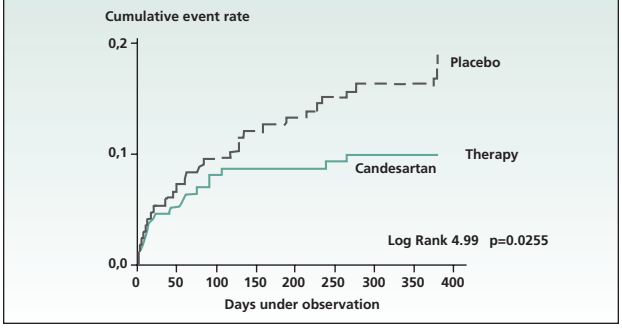


Figure 2: ACCESS – Cumulative event rate (Kaplan-Meier curve)[15]



outcomes than those receiving standard stroke therapy. The primary endpoint was a composite of total CV and cerebrovascular events and total mortality. The trial was prospective, randomized, double-blind, placebo-controlled and conducted in 53 study centres in Germany.[15] Inclusion criteria were a motor deficit and hypertension (ie, occasional BP values ≥200/110 mm Hg or a mean of at least 2 measurements within 30 minutes of ≥180/105 mm Hg). Patients were included on the basis of either systolic blood pressure (SBP) or diastolic blood pressure (DBP), or both, and were eligible within 72 hours of the stroke. The main exclusion criteria were age >85 years, disorders in consciousness, internal carotid artery stenosis >70%, and contraindications to candesartan use.

All patients were hospitalized (day 1 of the study) and randomized to candesartan (4 mg daily and increasing to 16 mg if BP remained >160/100 mm Hg) or placebo. On day 7, combination therapy with diuretics, calcium channel blockers, or ß-blockers could be introduced if BP remained above the target. Patients randomized to placebo received standard stroke therapy including low-dose heparin and aspirin. If still hypertensive after 1 week, patients were started on candesartan (Figure 1). Only 2 patients in the placebo group achieved normotension at day 7 and excluded from the study. A total of 173 patients (87 women) were randomized to candesartan and 166 were randomized to placebo (79 women). The mean time of inclusion from onset of the stroke was 29.9 hours and 29.7 hours, respectively. The study population was well-matched and high-risk with fairly high percentages of patients with diabetes mellitus, hyperlipidemia, and coronary artery disease.

On April 1st 2001, the Safety and Steering Committee recommended study discontinuation because a significant difference in vascular events was evident between groups, ie, there was a 47.5% reduction in primary events with candesartan (p=0.0255) after only 20 days that became quite obvious by 3-4 months. In the placebo group, 18.7% of the patients suffered a primary event compared to 9.8% in the candesartan group (Figure 2). It must be emphasized that the benefit started from week 1 since, after day 7, the medications were the same in both arms of the study. Analysis of the secondary endpoints revealed only 5 deaths in the candesartan group compared to 12 in the placebo arm. Similar trends were observed for cerebrovascular events (12 versus 19) and CV events (2 versus 10). There were no differences in non-CV mortality. BP reduction in the early and late phases of the study was similar in both arms. The use of other antihypertensive drugs was similar between the 2 groups, with approximately 20% receiving ß-blockers, 25%-30% diuretics, and 20% calcium channel blockers.

In conclusion, in the ACCESS study, early therapy with candesartan after acute cerebral ischemia (mean <30 hours) decreased total cerebrovascular and CV events and total mortality in hypertensive patients by 47.5%. The efficacy of the intervention was independent of BP control and administration during the first week appeared to have the greatest impact on preventing vascular events.

SCOPE: management of hypertension in the elderly

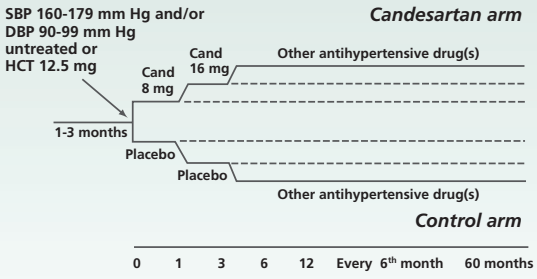
If present demographic trends continue, in a few decades the majority of people in developed countries will belong to higher age groups. Elderly people have a high prevalence of hypertension, a well-characterized risk factor for CV disease and dementia. Antihypertensive therapy reduces CV risk and may reduce the risk of dementia; however, these data are inconclusive in elderly patients with mild hypertension. Indeed, most trials in the elderly included patients with SBPs of 219-239 mm Hg.

The Study on Cognition and Prognosis in the Elderly (SCOPE) was conducted at 527 sites in 15 countries. It included 4937 elderly hypertensive patients followed for 3-5 years. The primary objective was to assess the effect of candesartan on major CV events, a composite endpoint consisting of CV deaths, non-fatal myocardial infarction (MI) and nonfatal stroke. There were multiple secondary objectives, including cognitive function, dementia, total mortality, CV mortality, fatal, and nonfatal MI, and fatal and nonfatal stroke.[16]

The study included men and women, aged 70-89 years, with previously treated or untreated hypertension. Only patients with SBP160-179 mm Hg or DBP 90-99 mm Hg were included (Figure 3). Baseline characteristics were well-matched between the 2 groups: mean age 76.4 years (21.2% >80 years), 64% women, mean Mini-Mental State Examination (MMSE) score of 28.5,[17,18] and BP 166/90 mm Hg. At the start, patients previously treated for hypertension had their medications stopped and their treatment standardized to 12.5 mg of hydrochlorothiazide (HCTZ) once daily. Subsequently, patients were randomized into the first step (candesartan 8 mg daily or placebo). If BP remained >160/85 mm Hg one month later, patients moved to the second step (candesartan 16 mg or corresponding placebo). At 3 months, if BP remained ≥160/90 mm Hg, step 3 was implemented (the addition of other antihypertensive, excluding ARB and ACE inhibitors).

SCOPE was originally planned to compare candesartan and placebo; however, as the results of other antihypertensive studies were published, the guidelines changed because investigators felt that patients randomized to placebo had to be treated due to ethical considerations. Thus, SCOPE became a comparison of a candesartan group and a control group receiving other antihypertensive drugs. In the candesartan group, 25% received only the ARB, 26% received candesartan plus HCTZ 12.5 mg, and the rest received candesartan plus other drugs. In the placebo group, only 16% were on placebo, while the rest (84%) were actively treated with antihypertensive medications (18% on placebo +12.5 mg of hydrochlorothiazide, and 66% on placebo + add-on drugs, eg, diuretics, calcium channel blockers, and ß-blockers).

Figure 3: SCOPE – Study design[16]



Step 1: Candesartan 8 mg or placebo
Step 2: If SBP >160 mm Hg or DBP >85 mm Hg double dose
Step 3: If SBP remains ≥160 mm Hg or DBP remains ≥90 mm Hg, add other antihypertensive drug (ARB or ACEI not allowed)

HCT = hydrochlorothiazide

At study end, mean BP was only 3.2/1.6 mm Hg higher in the placebo group than in the candesartan group. The primary endpoint (a composite of CV death, nonfatal MI, and nonfatal stroke) was reduced in the candesartan group by 10.9% (p=0.19). Various secondary endpoints favoured candesartan: nonfatal stroke was decreased by 28% (p=0.04) and there was a strong trend toward the reduction of all stroke of 24% (p=0.056, Figure 4). These reductions are noteworthy given the change in the study design and the fact that SCOPE was not powered to make an active comparison. In addition, although SCOPE had a lower number of relatively healthy elderly patients, the magnitude of benefit or positive trends observed with candesartan are consistent with larger trials of ARBs (ie, the Losartan Intervention for Endpoint Reduction in Hypertension [LIFE] study that utilized losartan to treat high-risk hypertensive patients with left ventricular hypertrophy).[20]

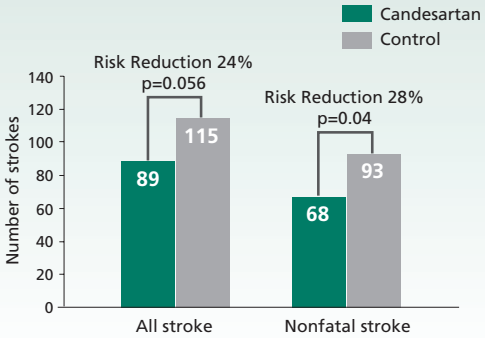
A subgroup analysis of SCOPE revealed that patients with a previous stroke and smokers were most likely to benefit from candesartan compared to other drugs used in the placebo group. Another secondary endpoint demonstrating a strong trend in favour of candesartan was reduction in new cases of type 2 diabetes mellitus (20% lower, p=0.08), which is consistent with studies of ACE inhibitors (ie, HOPE)[19] or ARBs (ie, LIFE).[20] The event reduction, mainly nonfatal stroke, observed in the candesartan group, may be due in part to the small BP difference between the treatment arms, but a more specific effect related to the blockade of the RAS with candesartan cannot be ruled-out.

The cognitive endpoints evaluated in SCOPE were cognitive decline, dementia, and mean change in the MMSE score from baseline. There was no difference in cognitive decline in the first 2 years of the study, but then the curves began to separate rapidly. At study conclusion, candesartan reduced the risk of significant cognitive decline by 11%. In a post-hoc analysis, no difference was found in the MMSE of patients with a baseline score of >28, whereas a marked protective effect was observed with candesartan treatment in patients with a baseline score of ≤28. There was no decline in MMSE during the study in patients randomized to candesartan, whereas a significant decline occurred in the control group (Figure 5).[21,22]

Potential role of AT-1 receptor blockade in migraine prevention

Migraine is a common episodic headache affecting up to 18% of women and 6% of men. Current prophylactic drugs have limited efficacy and possible side effects that may be quite severe. As the RAS is important in regulating vasomotor function and because of anecdotal reports suggesting migraine improvement in hypertensive patients

Figure 4: SCOPE – Total and non-fatal stroke



taking ACE inhibitors,[23] a study with lisinopril was conducted that demonstrated a clinically important effect of lisinopril on migraine prophylaxis.[24] Blockade of the AT-1 receptor could potentially be even more helpful, given the ability of ARBs to block angiotensin II. As well, the better side-effect profile of ARBs could make them a preferred form of prophylaxis, taking into account the incidence of cough with ACE inhibitors.

The vascular benefits of candesartan beyond BP reduction were recently demonstrated by Tronvik et al in a double-blind, randomized, placebo-controlled, crossover study of migraine prophylaxis.[25] After a 4-week placebo run-in period, patients (n=60) were randomized to candesartan 16 mg daily or matching placebo. Treatments were administered for 12 weeks, after which a 4-week placebo washout ensued. Patients then crossed over to the alternative treatment arm for 12 weeks. Study patients were aged 18-65 years, had migraine according to the International Headache Society criteria, a history of migraine for at least 1 year, and suffered 2-6 attacks monthly. A total of 57 patients (12 men, 45 women) were included in the analysis, their mean age was 43.8 years, their mean age at onset was 19.2 years, and they averaged 4 attacks per month. The primary endpoint was the number of days with headache and the multiple secondary endpoints included number of days with migraine and a headache severity index.

Based on the intention-to-treat analysis over a treatment period of 12-weeks, with candesartan there was a relative reduction in headache days of 26% (p=.001). The mean migraine days were 9.0 versus 12.6, respectively (p<0.001; Figure 6). For the secondary endpoints (mean headache hours, mean migraine hours, mean doses of triptans and

Figure 5: SCOPE – Change in MMSE Score[21]

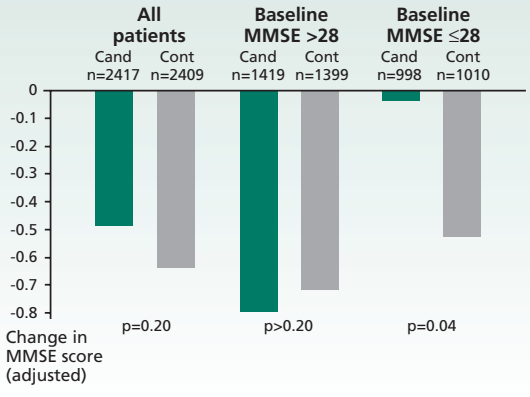
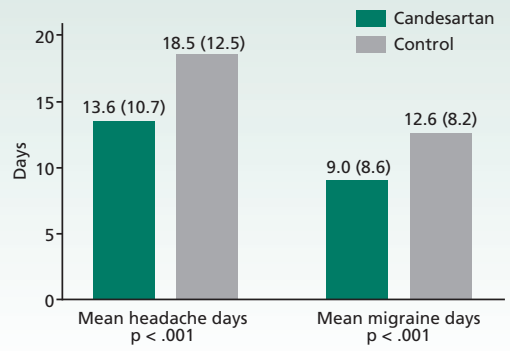


Figure 6: Effects on headache and migraine with candesartan vs placebo – Treatment period of 12 weeks[25]



analgesics, number of days of sick leave [reduced by a highly significant 64%], level of disability, and headache severity index), there were significant benefits with candesartan. There was also a significant reduction in the mean BP in the candesartan group (115/70 mm Hg) compared to placebo (126/77 mm Hg, p<0.001).

Responders were defined as patients who had a ≥50% reduction in efficacy measures compared to placebo. For the primary endpoint of mean headache days, the response rate was 32% and it reached as high as 46% for the secondary endpoint of mean migraine hours. There were no differences in adverse events between the 2 treatment arms, consistent with the well-characterized placebo-like tolerability profile of the ARB.

The mechanisms of action of candesartan on migraine are unknown. Angiotensin II has effects that may be relevant to migraine (ie, direct vasoconstriction, increased sympathetic discharge, and medullary catecholamine release) and, through its action on cerebral AT-1 receptors, angiotensin II modulates cerebrovascular flow and has effects on fluid and electrolyte homeostasis, autonomic pathways, and neuroendocrine systems. In this small trial, candesartan exhibited significant benefits as potential migraine prophylaxis. It had very few and mild side effects and an adverse event profile identical to placebo. Additionally, candesartan has no significant dose-dependent side effects, no significant drug interactions, and is administered as a single daily dose.

Conclusion

All the major components of the RAS are present in the brain. Experimental studies have shown that blockade of the brain RAS can prevent ischemic cerebral injury in animal models of stroke. All ARBs have exhibited protective properties when administered locally into the brain; however, there are potentially important differences between the ARBs in their ability to prevent ischemic brain damage when administered systemically. Additional studies are needed to elucidate this issue. Recent clinical trials have demonstrated protective effects with the early acute intervention of the ARB candesartan in hypertensive stroke patients, as well as in the protection of cognitive function in elderly hypertensives with mild baseline levels of cognitive impairment. ARBs such as candesartan may emerge as important agents in the prophylaxis of migraine headaches with the added benefit of their excellent tolerability. All of these novel developments in angiotensin II blockade will require additional randomized clinical trials before they are fully incorporated into clinical practice, but they are likely to extend the benefits of AT-1 antagonism beyond the currently known CV and renal protective effects.

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