

FOR STROKE PREVENTION, AT1 ANTAGONISTS ARE THE BEST CHOICE FOR HYPERTENSIVE TREATMENT

D. Russell

Department of Neurology, Rikshospitalet, University of Oslo, Oslo, Norway

Stroke is a major cause of death and disability, and a significant social and financial burden worldwide. The incidence of stroke is directly related to blood pressure and age, and is expected to rise significantly in the future as the age of the population increases putting a great financial burden on society.

Large hypertension treatment studies have revealed that various blood-pressure-lowering drugs have similar effects in terms of reduction in cardiovascular morbidity (1), stressing the importance of blood pressure control. The introduction of selective angiotensin II AT1 receptor antagonists (ARB) changed this picture.

Several clinical trials have shown that treatment of high-risk hypertensive patients with ARBs resulted in a more significant reduction of strokes. The Losartan Intervention for Endpoint reduction (LIFE) study, (2) showed that severely hypertensive patients with left ventricular hypertrophy (LVH) who were treated with a losartan-based regimen had a 25% reduction in strokes compared to those treated with an atenolol-based regimen for the same decrease of blood pressure. In a sub-study of LIFE of patients with isolated systolic hypertension and LVH, treatment with the losartan-based regimen, resulted in a 40% stroke reduction compared to those treated with the atenolol-based regimen(3). Confirmatory results to the LIFE study were subsequently reported from the Study on Cognition and Prognosis in the Elderly (SCOPE) study.(4) In this study, older patients with predominantly systolic hypertension who were treated with a candesartan-based regimen, had a 27.8% reduction in non-fatal strokes and a 23.6% reduction in total strokes, compared with patients treated with conventional antihypertensive drugs for similar control of blood pressure. In this study, placebo was given for the first 3 months to the group that was treated with conventional drugs. 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 (5).Candesartan has also been demonstrated to provide secondary protection in patients who have suffered a previous stroke. In the Acute Candesartan Cilxetil Therapy in Stroke Survivors (ACCESS) pilot study (6), 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 large difference in outcomes between the two treatment arms, although there was no difference in SBP and DBP 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 25–50 mg, 2–7 days after an ischaemic stroke, or transient ischaemic 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 18.1mmHg (7). The Morbidity and mortality after Stroke, Eprosartan Study (MOSES), provided additional evidence for superior stroke protection by ARBs (8). This study compared the stroke protective effects of eprosartan vs nitrendipine in post-stroke hypertensive patients. After 2.5 years of follow-up, eprosartan decreased the incidence of recurrent stroke by 25% compared to nitrendipine for the same reduction of blood pressure. Supporting evidence for improved stroke protection by ARBs was also provided by the meta-analysis carried out by the Blood Pressure Lowering Treatment Trialists (BPLTC).This showed that ARBs were better than ACEIs in stroke prevention for equal blood pressure reductions.(9)

Several reasons may explain the additional benefit of ARBs in stroke prevention. Experimental evidence indicates that blockage of the AT1 receptors leads to the upregulation of the AT2 receptors in endothelial cells through a complex mechanism of cross regulation between the AT1 and AT2 receptors (10).This leads to blood pressure-lowering, cardiovascular remodelling and stroke prevention.Other mechanisms by which ARBs may reduce the incidence of new or recurrent stroke include their beneficial effects on blood glucose control by increasing insulin sensitivity (11),their platelet anti-aggregating effects (12),their hypouricemic effects (13), and their atrial antifibrillatory effects.(14-15)These positive effects of ARBs on stroke protection should not, however exclude the critical role of blood pressure control on stroke prevention, since the blood pressure levels (systolic and diastolic) have a continuous and direct effect on stroke incidence for all age groups.(1) However, selection of ARBs may provide an additional benefit in stroke reduction for the same degree of blood pressure decrease.

References

- Chobanian AV et al. Seventh Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC-7). *Hypertension* 2003; 42: 1206–1252.
- Dahlof B et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint (LIFE) reduction in hypertension: a randomized trial against atenolol. *Lancet* 2002; 359: 995–1003.
- Kjeldsen SE et al. Effects of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy: a Losartan Intervention For Endpoint reduction (LIFE) sub-study. *JAMA* 2002; 288: 1491–1498.
- Lithell H et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens* 2003; 21: 875–886.
- Papademitriou V et al. Stroke prevention with the angiotensin II type-1 receptor blocker candesartan in elderly patients with isolated systolic hypertension: The Study on Cognition and Prognosis in the Elderly (SCOPE). *J Am Coll Cardiol* 2004; 44: 1175–1180.
- Schrader J, et al, on behalf of the ACCESS study group. The ACCESS Study: evaluation of acute candesartan cilxetil therapy in stroke survivors. *Stroke* 2003; 34: 1699–1703.
- Nazir FS et al. The effects of losartan on global and focal cerebral perfusion and on renal function in hypertensives with mild early ischemic stroke. *J Hypertens* 2004; 22: 989–995.
- Schrader J et al. Morbidity and Mortality after Stroke, Eprosartan compared with Nitrendipine for Secondary Prevention. Principal results of a prospective randomized controlled study (MOSES). *Stroke* 2005; 36: 1218–1226.
- Blood Pressure lowering Treatment Trialists Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomized trials. *Lancet* 2003; 362: 1527–1535.
- DePaolis P et al. Modulation of the AT2 subtype receptor gene activation and expression by the AT1 receptor in endothelial cells. *J Hypertens* 1999; 17: 1873–1877.