Sartans for hypertension – implications of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial

Angiotensin receptor blockers (ARBs), also known as sartans, block the activation of angiotensin type 1 receptors and have a recognised role in the treatment of heart failure and nephropathy. The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study[1] and the Study on Cognition and Prognosis in the Elderly (SCOPE)[2] were two large clinical trials of ARBs in the treatment of hypertension.

The LIFE study showed that a losartan-based regimen was superior to an atenolol-based regimen in preventing cardiovascular events (mainly strokes) in hypertensive patients with electrographic left ventricular hypertrophy. The favourable results in LIFE study have led to claims that ARBs are especially beneficial in patients with left ventricular hypertrophy and especially good at preventing strokes. The SCOPE study randomised elderly hypertensive patients into two groups: one group was given candesartan and the other, a placebo.[2] Additional medications were allowed for blood pressure control, so the difference in blood pressure in the two randomised groups was minimal. Unlike the LIFE study, the SCOPE study showed no statistically significant differences in the main endpoints in the two groups. Thus, the results of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial—in which valsartan was compared with amlodipine, a calcium channel blocker—were eagerly anticipated. A positive result would propel ARBs to become the preferred treatment for hypertension.

The results of VALUE have just been announced at the 14th European Meeting on Hypertension in Paris and published.[3] In terms of the primary composite endpoint, there was no significant difference between the treatments. In fact, when comparing the two groups, the patients treated with valsartan suffered more cases of myocardial infarction and stroke (P=0.02 and P=0.08, respectively), instead of receiving greater protection from those diseases. On the plus side, there were fewer cases of new-onset diabetes in the valsartan-treated group than in the amlodipine-treated group (13.1% versus 16.4%, P<0.0001).

The findings in VALUE do not support claims that ARBs are particularly good for the heart or the brain. Instead, they emphasise the importance of good blood pressure control. In the valsartan-treated group, the average blood pressure was about 2.0 mm Hg/1.6 mm Hg higher in the valsartan-treated group over the course of the trial. The difference was even greater in the first 6 months. The investigators attributed the negative results of the study to this blood pressure difference and devised a new statistical test called serial median matching to support their interpretation. Ironically, a similar mismatch of blood pressure in the treatment groups in the LIFE study[1] and the Heart Outcomes Prevention Evaluation (HOPE) study[4] had not undermined the positive interpretation of these studies. Favourable results in large clinical trials comparing antihypertensive drugs increasingly depend on small and inconspicuous blood pressure differences.

It now seems clearer than ever that meticulous control of blood pressure is important and worthwhile. A good antihypertensive agent must at least do that. Hypertension affects about 20% of the general population and more than half of the elderly.[5] Unfortunately, just over half of the hypertensive patients are on treatment, and good control is achieved in fewer than half of those being treated.[6] The priority must surely be the detection of hypertension and other risk factors in the community, and achieving good blood pressure control. For the majority of hypertensive patients, good control requires the use of more than one class of antihypertensive drugs. Angiotensin receptor blockers are well tolerated and may reduce new-onset diabetes, whilst calcium channel blockers lower blood pressure highly effectively in the Chinese. Both have a place in the formulary. Debating which antihypertensive drug is the best is only of commercial, and not academic, interest.

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