Valsartan treatment of hypertension—does VALUE add value?

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Less than a decade ago, three randomised studies were designed to test whether antihypertensive regimens based on angiotensin-receptor blockers would have a different effect on cardiovascular disease than other types of treatment that lower blood pressure: the Losartan Intervention For Endpoint reduction in hypertension study (LIFE), the Study on Cognition and Prognosis in the Elderly (SCOPE), and the Valsartan Antihypertensive Long-term Use Evaluation trial (VALUE), which is presented in The Lancet today. All three trials included large numbers of patients. However, they included different types of hypertensive patient, and had different primary endpoints.

LIFE reported in 2002. 9193 hypertensive patients with left ventricular hypertrophy (mean age 67 years, 46% men, mean blood pressure on placebo at baseline 174/98 mm Hg, 13% had diabetes) were randomised to losartan or atenolol in a double-masked design, and were followed up for a mean of 4·8 years. About 70% of patients in both groups were also given a diuretic (double-masked) as supplementary treatment. Blood pressure was lowered similarly in the two groups, with a systolic difference at the end of follow-up of about 1 mm Hg.

The primary endpoint in LIFE (non-fatal and fatal cardiovascular disease) occurred in 508 patients on losartan (23·8 per 1000 patient-years) and in 588 patients on atenolol (27·9 per 1000 patient-years, p=0·02). 232 and 309 patients, respectively, had a fatal or non-fatal stroke (p=0·001); and 198 and 188 patients, respectively, had myocardial infarction (non-fatal and fatal; not statistically significant). New-onset diabetes mellitus was less frequent in the losartan than in the atenolol group (6·0% vs 8·0%, p=0·001). It cannot be determined whether the lower frequency of cardiovascular events in the losartan-treated patients reflects only an effect of this drug or whether a weak cardiovascular effect of atenolol contributed.

SCOPE included 4964 elderly patients with hypertension (mean age 76 years, 36% men, mean blood pressure at baseline 166/90 mm Hg, 12% had diabetes). They were randomised to candesartan or placebo in a double-masked design with open-label treatment with an active antihypertensive added as needed. As a consequence, active antihypertensive therapy was extensively used in the control (“placebo”) group, with 84% of the patients on such drugs. Mean follow-up was 3·7 years. The mean difference in reduction of blood pressure between the two groups was large: 3·2/1·6 mm Hg.

The primary endpoint in SCOPE (fatal and non-fatal cardiovascular disease) occurred in 242 patients on candesartan (26·7 per 1000 patient-years) and 268 patients on control (30·0 per 1000 patient-years, not statistically significant); 89 and 115 patients, respectively, had a stroke (non-fatal or fatal, p=0·06). Myocardial infarction (non-fatal or fatal) occurred in 70 and 63 patients, respectively (not statistically significant). 4·3% and 5·3% of patients in the candesartan and control groups, respectively, had new-onset diabetes mellitus (p=0·09). Moreover, the proportions of patients with cognitive decline or who developed dementia did not differ between the two groups.

The results of the VALUE trial, presented in this week’s issue of The Lancet as an article and research letter, have been awaited with great interest, because the two previously reported trials on angiotensin-receptor blockers differed in outcome, and because valsartan was compared with a calcium antagonist in VALUE. The investigators, Stevo Julius, Michael Weber, and their colleagues, deserve praise for having completed the largest trial with an angiotensin-receptor blocker in hypertension to date, with few patients lost to follow-up. In VALUE, 15 245 hypertensive patients with high cardiovascular risk (mean age 67 years, 58% men, mean blood pressure at baseline 155/87 mm Hg, 32% with diabetes) were randomised to valsartan or amlodipine in a double-masked design with the aim of achieving the same control of blood pressure. The patients were followed up for a mean of 4·2 years. Many patients in both groups were given open-label concomitant treatment; more patients in the valsartan group received the highest dose of study drug plus hydrochlorothiazide plus add-on therapy than in the amlodipine group.

Blood pressure was reduced in both groups in VALUE, but the trial failed to achieve the same control of blood pressure in the two groups. Blood pressure in the amlodipine group was lowered more than in the valsartan group, especially in the early period of the trial when the difference in blood pressure was 4·0/2·1 mm Hg in favour of amlodipine. At 6 months the difference was 2·1/1·6 mm Hg, in favour of amlodipine, and remained at about that level during the rest of the trial. The doses of the study drugs in VALUE, valsartan 80–160 mg and amlodipine 5–10 mg, are the currently recommended ones.

The primary endpoint in VALUE (cardiac morbidity and mortality) occurred in 810 patients on valsartan (25·5 per 1000 patient-years) and in 789 patients on amlodipine (24·7 per 1000 patient-years, not statistically significant). 369 and 313 patients, respectively, had myocardial infarction (non-fatal and fatal; p=0·02). The corresponding figures for stroke (non-fatal and fatal), which was a secondary endpoint in VALUE, were 322 and 281 (p=0·08). When the primary endpoint data were analysed for different periods, the odds in favour of amlodipine...
were higher during the first 6 months when differences in blood pressure between the treatment groups were greatest. In the following months, when the difference in blood pressure was less, there was an attenuation in the odds ratios.

New-onset diabetes mellitus (type 2) was less frequent in the patients on valsartan than in those on amlodipine (13·1% vs 16·4%, p<0·0001). This result is especially interesting because the comparison group in VALUE was a calcium antagonist, considered to be metabolically neutral. Also, the LIFE1 and SCOPE2 trials showed a lower incidence of new-onset diabetes in the sartan groups. Moreover, a lower incidence of diabetes was seen in the Heart Outcomes Prevention Evaluation study3 with ramipril, an angiotensin-converting enzyme inhibitor, than with placebo. Hence blockade of the renin-angiotensin system might exert preventive effects on diabetes development.

The inequalities in blood pressure in VALUE in favour of amlodipine throughout the trial make the comparison of cardiovascular outcome difficult. In a post-hoc attempt to overcome this result, the investigators used serial median-matching at 6 months to create about 5000 valsartan-amlodipine patient-pairs who were well matched for systolic blood pressure and other variables. In an analysis of subsequent combined cardiovascular events, no difference in outcome was seen between the two regimens. There was also no difference for myocardial infarction. Moreover, reaching control of systolic blood pressure (<140 mm Hg) by 6 months, independently of drug type, was associated with significant benefits for subsequent major outcomes. This method of analysing the data is interesting but its reliability remains to be proven.

So what can we learn from these three trials of angiotensin-receptor blockers? First, this group of drugs seems to be at least as effective as other types of antihypertensives in preventing cardiovascular events, provided blood pressure is equally well lowered. Second, the degree of lowering of blood pressure—and especially early control of blood pressure—is very important for the cardiovascular outcome. Third, the incidence of new-onset diabetes is lower in the patients treated with an angiotensin-receptor blocker than in the control groups of these trials. This finding is especially interesting in the VALUE trial in which the comparison was made with a regimen based on a calcium antagonist.

What we do not know for sure, however, is whether there are any differences between the preventive effects of losartan, candesartan, and valsartan. To answer that question, we need a new randomised trial that compares them. I suspect, however, that we will have to wait a very long time for the results of such a trial, if it is ever carried out.

I chair the Working Group on High Blood Pressure of the Swedish Council on Technology Assessment. I have received a research grant from AstraZeneca for the ALPINE study, and I was on the Steering Committee of the LIFE trial.

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Statins in rheumatoid arthritis—two birds with one stone?

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Rheumatoid arthritis is one of several inflammatory diseases that is associated with an increased risk of morbidity and mortality from cardiovascular disease.1 In fact, cardiovascular disease is the main single cause of the significantly shortened life-span of patients with rheumatoid arthritis,2,3 and inflammatory activity seems to be a major risk factor for this comorbidity.2 Reduction of inflammatory activity by conventional disease-modifying agents, such as methotrexate, may reduce the mortality from cardiovascular disease,4 whereas the effect of agents blocking tumour necrosis factor on cardiovascular morbidity remains unknown. Considerable uncertainty thus persists on how to handle and reduce the risk of future cardiovascular disease in patients with rheumatoid arthritis.

Therefore, interest has prevailed in whether agents such as statins, which are widely used for prevention of cardiovascular disease, can be recommended for use in patients with rheumatoid arthritis.5,6 By definition, a high risk of cardiovascular disease. This question has become even more important with the recognition that statins do not only affect lipid metabolism via their 3-hydroxy-3methylglutaryl-CoA reductase inhibitory activity, but may also affect inflammatory mechanisms in several ways.7

It is against this background that the report in this week’s issue of The Lancet by Carey and colleagues is so interesting. These researchers have done the first controlled trial with a statin (atorvastatin) in rheumatoid arthritis, evaluating the effects of the statin compared with placebo, on clinical signs of disease and biochemical markers related to future risk of cardiovascular disease. The setting was that of a clinical practice study—ie, atorvastatin or placebo was added to therapy with an existing disease-modifying anti-rheumatic drug in patients recruited from a single clinical centre (in Glasgow), where the investigators completed a 6-month study on 116 patients. Here they report an effect, albeit modest, on certain clinical measures (mainly swollen-joint count) and on the composite disease activity score that is routinely used for evaluation of clinical effects in rheumatoid arthritis. Equally interesting were the beneficial effects of atorvastatin on inflammatory markers, such as erythrocyte sedimentation rate, fibrinogen, C-reactive protein, and interleukin 6, which were both statistically significant and of a magnitude that may affect the risk of future cardiovascular disease along with the cholesterol-lowering effects that were confirmed in the patients. Also, atorvastatin was well tolerated.

McCary and colleagues’ data might seem almost too good to be true—hitting both the inflammation in rheumatoid arthritis and one of the major traditional risk factors for cardiovascular disease, especially because atorvastatin, and other statins that may have similar effects, are already on the market. But there are caveats that should be considered before statins can be generally recommended for rheumatoid arthritis in clinical practice. First, the
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