Angiotensin blockade for hypertension: a promise fulfilled

See pages 999, 1004

Many years ago we proposed that angiotensin II might exert detrimental effects beyond the mechanical damage of high blood pressure.1,2 There was evidence that angiotensin excess produced myocardial necrosis and renal parenchymal damage independent of blood pressure rise.3,4 There was epidemiological evidence that hypertensive patients with low concentrations of renin, although older, were less likely to have heart attacks, strokes, or renal complications than those with higher plasma renin activity.5 And there was evidence that an angiotensin II antagonist would not only normalise blood pressure6 and reverse the signs and symptoms of heart failure,7 but also selectively improve perfusion of vital organs. Yet the idea that inhibiting the renin-angiotensin system might have benefits beyond lowering of blood pressure was received sceptically.

The value of effectively lowering blood pressure was firmly established in the 1970s. When the two latest classes of antihypertensive drugs that interfere with the renin-angiotensin system (angiotensin-converting enzyme [ACE] inhibitors and selective angiotensin-type-1-receptor blockers [ARBs]) came along, their proposed value as more than just antihypertensives became hotly debated. What was missing was hard evidence from randomised trials. As late as 1997, the JNC VI report8 stated that there was no advantage with the newer agents because thiazides and β-blockers had been proven to lower morbidity and mortality compared with placebo.

Obviously, the era of placebo-controlled trials for antihypertensives is past and any new agents can only be compared against the gold-standard of diuretics or β-blockers. Outcome trials comparing two antihypertensives require large groups of patients, because the risk in patients with mild-to-moderate essential hypertension is low, and intervention trials are usually limited to a duration of 5 years. It is only when patients with higher absolute cardiovascular risk are studied that differences between drug classes are seen. Thus, β-blockers were shown to provide unique (compared with other drug classes) protection in secondary prevention of myocardial infarction and heart failure. Subsequently, ACE inhibitors were found to reduce morbidity and mortality more than comparators in patients with coronary heart disease,10 congestive heart failure,10 diabetic nephropathy,11 and stroke.11 Even more recently, studies in patients with type 2 diabetes and nephropathy showed that ARBs provided renal protection beyond the reduction of blood pressure.12-14

The LIFE trial results reported in this issue of The Lancet add further evidence to the concept that blockade of the renin-angiotensin system may provide cardiovascular protection beyond the blood-pressure-lowering effect. 9222 patients with primary hypertension and electrocardiographic evidence of left ventricular hypertrophy were randomly assigned to losartan or atenolol at equal doses (both at 50 or 100 mg), to which diuretics and other antihypertensive drugs could be added as needed to normalise blood pressure. In the main trial, blood pressure was reduced similarly in the two groups, although at the end of the follow-up, sitting systolic blood pressure was reduced by 1 mm Hg more with losartan than with atenolol. The primary composite endpoint of cardiovascular mortality, stroke, and myocardial infarction was reached at a rate of 23·8 per 1000 patient-years of follow-up in the losartan group versus 27·9 in the atenolol group, a significant decrease in relative risk of 13%. The difference was due mainly to a significant reduction in frequency of stroke by 25% in the losartan group; the rates of myocardial infarction and cardiovascular mortality were not significantly different between groups.

In a separate analysis of the 1195 diabetic hypertensive patients from that cohort, however, the results favouring losartan were more impressive: in these patients with inherently higher risk at baseline, there was a significant 24% reduction in risk in the primary composite endpoint. Furthermore, among the secondary endpoints, all-cause mortality was reduced by 39%, cardiovascular mortality by 37%, and admission for heart failure by 40% in the losartan group, whereas strokes and heart attacks occurred in small numbers that did not reach statistical difference. Whether the small (2 mm Hg) difference in systolic blood pressure between the two groups at endpoint may also have contributed to these differences will undoubtedly be debated.

Unlike other large trials that have been criticised for unbalanced distribution of risk at baseline favouring the study drug (eg, the HOPE trial15 was accused of having patients with more risk factors in the control group), the LIFE study groups were generally well balanced. Inspection of baseline characteristics shows that, if
the deck was stacked against losartan: 84 more losartan than atenolol patients had coronary heart disease and 32 more had peripheral vascular disease, which would place them at higher overall risk. Despite this and despite the advantage of slower heart rate in the atenolol arm, the overall frequency of cardiovascular events was either neutral or in favour of losartan. In keeping with earlier observations, there was also more regression of left ventricular hypertrophy in the losartan group, a fact which must have contributed to these benefits.

The highly significant difference in the frequency of stroke deserves comment. Diuretics are more effective in preventing stroke than β-blockers. In the LIFE study, most patients in both groups were also receiving hydrochlorothiazide. Although at baseline there were more patients with atrial fibrillation (25%) in the atenolol group, the large difference in absolute numbers that had a stroke (77 more with atenolol) suggests that additional factors were involved.

Interestingly, among patients without diabetes at randomisation, the losartan group had fewer new cases of diabetes at the end of the study than the atenolol group. Many patients with essential hypertension have some degree of insulin resistance, which is usually progressive with age and explains the higher rate of development of type 2 diabetes than that observed in the general population. As there is no obvious reason why angiotensin-receptor blockade should alter this course, the results suggest that atenolol aggravates glucose intolerance. Indeed, β-blockade decreases insulin sensitivity and thus contributes to the development of the metabolic syndrome.

These favourable results were obtained with less than 50% of the patients receiving 100 mg of the study drugs. Even 100 mg losartan hardly blocks the renin-angiotensin system for a full 24 h. In a recent trial testing an ARB in patients with diabetic nephropathy, dose had an important role in outcome, with 300 mg irbesartan providing better protection than 150 mg. Perhaps even higher doses of losartan administered twice daily would have enhanced the difference between losartan and atenolol.

Even in the losartan group, the rate at which a primary endpoint was reached is still considerable, which leaves room for further improvement. At the end of the study more than 20% of all patients were off study drug, which must have further reduced the advantage of losartan in outcome. For the patients, potentially of much greater importance is the fact that losartan caused significantly fewer adverse events than atenolol.

To normalise blood pressure, more than one drug is generally needed. The LIFE trial design can therefore be considered close to the way antihypertensive therapy is provided. The combination of an ARB with low-dose hydrochlorothiazide does not produce more side-effects than placebo. Thus a treatment strategy based on this combination provides at least equal cardioprotection to β-blockers and more protection from strokes with the further benefit of fewer side-effects. Hopefully, in 2004, results of the VALUE trial will become available, comparing in high-risk hypertensive patients an ARB-based strategy (valsartan) with one using the calcium-channel blocker amlopidine. To date, all evidence suggests that the beneficial effects of ACE inhibition can be duplicated with ARBs, without the nuisance of side-effects. Can the LIFE trial results be extrapolated to hypertensive patients with a lower risk profile? Blood pressure regulation and pathogenesis of stroke, heart attack, and other cardiovascular complications are the same for all patients. With the available evidence, an ARB-based strategy is probably reasonable for any hypertensive patient. Is it also fair to extrapolate these findings obtained with losartan to any ARB? The more specific the therapeutic target (eg, the angiotensin receptor), the more difficult it is to differentiate one agent from another, not only in terms of pharmacokinetics and potency. However, losartan has one unique feature different from other ARBs, unrelated to antagonism at the angiotensin receptor: it is uricosuric, which is a desirable feature, especially for patients who require combination with a thiazide diuretic. Indeed, in the LIFE study, serum uric acid concentrations at the end of the trial were significantly lower in the patients treated with losartan. Nevertheless, it seems unlikely and difficult to understand how this small difference in uric acid could be responsible for the protection from stroke. Therefore, it seems appropriate to postulate that the observed effect could probably be obtained by any ARB.

The LIFE trial has added one more piece of evidence to support our claim that angiotensin II is an important risk factor in cardiovascular disease.

HRB and HG are consultants to almost all the major pharmaceutical companies that are active in the cardiovascular area. They have received funding for studies, seminars, and travel from such companies.

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Vertical HIV transmission in South Africa: translating research into policy and practice

Vertical (mother-to-child) transmission of HIV in South Africa ranges from 19 to 36%, depending on whether the child is breastfed or not. In 2000, the prevalence of HIV infection in antenatal clinic attendees in public health services was 24.5%, and the government estimated that about 75,000 infants were born with HIV-1 infection in South Africa. About half these infections could have been prevented if short-course antiretroviral treatment had been available. The South African Government has claimed these interventions cannot be universally implemented because of cost, toxicity, drug resistance, breastfeeding, and the capacity of the health service to implement programmes. Antiretroviral drugs have become much cheaper over the past few years because of lobbying by activist groups, including those in South Africa. The manufacturers of nevirapine have offered the drug free over the next 5 years to countries in Africa to reduce vertical transmission. The costs to be incurred would therefore be the costs of establishing voluntary counselling and testing at antenatal clinics, including staff training and extra counsellors. Such costs may be considerable but need to be weighed against those of not providing this intervention (lives lost and treatment of HIV-infected children). Widespread counselling and testing would have additional benefits such as informing individuals about their infection status, which may prevent further sexual or perinatal transmissions. Counselling and testing is cost effective. Costing studies in South Africa have shown that antiretroviral therapy to prevent vertical transmission is cost effective. Short-course regimens used to prevent vertical transmission have been shown in several studies to be safe with minimum side-effects. Follow-up of mothers and children many years after receiving zidovudine showed an acceptable safety profile. A decision analysis model has shown that nevirapine is beneficial even if its toxicity was up to 42 times that observed in clinical trials, and concluded that implementation of nevirapine should not be delayed by toxicity concerns.

Drug-resistance mutations in some mothers after a single dose of nevirapine are usually variants present at low frequency before the use of antiretroviral drugs, which are then selected and expanded when nevirapine is introduced. However, resistance does not affect the efficacy of antiretroviral prophylaxis to prevent vertical transmission, since these variants are not transmitted to the child, and they wane over time with absence of drug pressure. Drug resistance is not unique to HIV. As with tuberculosis and other infectious diseases, there needs to be good surveillance and monitoring for drug resistance.

Breastfeeding is a route of HIV transmission, but several strategies can minimise this risk. One solution is to replace breastfeeding with formula feeding. However, in the settings where many HIV-infected women live, formula feeding is not a safe alternative and the risk of HIV transmission is exchanged for the risk of mortality from diarrhoea and pneumonia. Counsellors need to advise mothers to understand the risks and benefits of breastfeeding and formula feeding so that they can make an informed choice. Women who choose to breastfeed can be assisted to make breastfeeding safer.

The argument that nevirapine can only be used if women are not breastfeeding is not valid. Nevirapine used according to the HIVNET 012 regimen has its effect intrapartum and the reduction in transmission is obtained regardless of whether the mother is breastfeeding or formula feeding. The HIVNET 012 trial in Uganda showed that the acquisition of new infections due to breastfeeding at age 6 weeks to 12 months was not increased in the babies of mothers receiving nevirapine, the rate being similar to that in those of mothers who did not receive nevirapine.

The operational capacity to implement use of nevirapine already exists in several health-care facilities. It is ethically and morally unacceptable for government policy to preclude them from providing nevirapine in the best interests of their patients or instructing them to hold back until research at pilot sites is completed, since these pilot studies merely add to the substantial South African data already available on the experience of implementing antiretroviral prophylaxis to reduce vertical transmission. In settings with less capacity, less resource-intensive alternatives could be considered while resources and training are provided to address operational inadequacies. For example, although not universally accepted, the option of nevirapine for all pregnant women without HIV testing has been suggested, especially in high-prevalence settings.

Screening all pregnant women for anaemia, weight gain, syphilis, and rhesus factor is routine in the public health service. This capability serves as a foundation for a national programme to prevent HIV vertical transmission. Short-course antiretroviral therapies to prevent vertical transmission are being used successfully.