Angiotensin II receptor blockers: a new lease of LIFE?

Professor Mike Kirby and Dr Rubin Minhas review recent studies in hypertension and the role of angiotensin II receptor blockers in the primary care management of hypertension and prevention of stroke.

Abstract

Hypertension is a significant risk factor for both coronary artery disease and cerebrovascular disease. Isolated systolic hypertension and left ventricular hypertrophy are well-recognised risk factors for cardiovascular mortality. The management of hypertension in elderly patients, patients with isolated systolic hypertension or left ventricular hypertrophy is discussed in the context of recent British Hypertension Society guidelines, recent trial evidence and an appraisal of the LIFE study results. Compelling indications for the use of angiotensin II receptor blockers in the management of hypertension are examined and the need for combination therapy in achieving satisfactory blood pressure control is established through examination of the trial evidence.

Key words: hypertension, stroke, angiotensin II receptor blockers, losartan, LIFE, left ventricular hypertrophy, isolated systolic hypertension, combination therapy.

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Introduction

Hypertension is one of the most prevalent and commonly managed conditions in primary care. Recent data indicate that the prevalence of hypertension may be as high as 40% for men and 39% in women[1] in the general population. Primary prevention of cardiovascular disease, and cerebrovascular disease in particular, have not been fully addressed in practice partly because of implicit recognition that the associated resource implications, workload and costs attached to primary prevention are considerable.

Against this background, approximately 110,000 people every year in England and Wales have their first stroke. Some 30,000 go on to have further strokes. Stroke is the third most common cause of death in the UK but is ranked as the number one cause of severe disability. Certain population groups appear to be at higher risk of stroke than others. Afro-Caribbean and South Asian men, for example, have a prevalence of stroke between 40–70% higher than that of the general population after adjusting for age. The elderly are a well recognised risk group and there is also a social class gradient which indicates that people in socio-economic group V (unskilled manual workers) have a 60% higher chance of having a stroke than those in socio-economic group I (professionals). The mortality rates from stroke are 50% higher in socio-economic group V than in socio-economic group I.[2]

> ***'Until recently there was little trial evidence that any particular therapeutic class of drug might have a differential positive effect on stroke incidence in the hypertensive population'***

In recognition of this significant morbidity and mortality, the National Service Framework for Older People[2] has recognised the prevention and treatment of stroke as a priority for all those involved in the planning and delivery of services affecting older people. Hypertension and its adequate management are highlighted as specific areas that require attention.

The secondary prevention of coronary heart disease (CHD) is well ingrained in the clinical psyche but prevention and management of stroke has received less widespread recognition. That hypertension is a major risk factor for stroke is well established and it is thought that lowering diastolic blood pressure by 5–6 mmHg and systolic blood pressure by 10–12 mmHg for three years could reduce the annual stroke risk from 7% to 4.8%. In practical terms, approximately 45 people would require treatment at this level to prevent one stroke.[3]

Hypertension is a risk factor for both ischaemic and haemorrhagic stroke. Its presence in an individual signifies an approximate doubling of risk. The Framingham study indicated that systolic hypertension was a better predictor of risk in individuals over the age of 45 and characterisation of the benefits of treating isolated systolic hypertension (ISH)[4] have since led to recognition that both diastolic and systolic hypertension should be regarded as important targets for treatment.

Epidemiological studies suggest that isolated systolic hypertension may be a distinct hypertension subgroup where ISH may reflect an increased rigidity of the major arteries over the peripheral circulation.[5] Data from statistical analy-

ses suggest that systolic hypertension may be a more potent contributor to cardiovascular mortality than diastolic hypertension[6] and a better predictor of stroke.[7] The prevalence of ISH is estimated at around 15% in men and women over the age of 60.[4] The age-adjusted prevalence of ISH is higher in men than women by up to 100% and higher in Afro-Caribbeans by up to 30%.[5]

Recent trials in hypertension

Until recently there was little trial evidence that any particular therapeutic class of drug might have a differential positive effect on stroke incidence in the hypertensive population. The STOP-2 (Swedish Trial in Old Patients with Hypertension-2)[8] study compared newer antihypertensive drugs (angiotensin-converting enzyme [ACE] inhibitors and calcium channel antagonists) against older drugs, i.e. diuretics and beta blockers, among 6,614 patients who were aged between 70 to 84 years. The results demonstrated no significant difference in the prevention of cardiovascular mortality or major events between the three groups. CAPP (Captopril Prevention Project)[9] and NORDIL (Nordic Diltiazem Study)[10] compared beta blocker and diuretics against ACE inhibitors and calcium channel antagonists, respectively, and found no significant reduction in the primary end point of myocardial infarction (MI), stroke or cardiovascular death. Table 1 compares the results from these three studies.

HOPE (Heart Outcomes Prevention Evaluation Study)[11] provided an initial indication that ramipril, an ACE inhibitor, might offer additional benefits with respect to stroke prevention over and above its effect on blood pressure lowering – a benefit that was reported in both hypertensive and non-hypertensive patients. Analysis of a small sub-study examining ambulatory blood pressure has led some clinicians to suggest that larger blood pressure differences in those patients taking ramipril might account for the findings in this study.[12] ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial)[13] compared diuretics, ACE inhibitors, alpha blockers and calcium channel antagonists. The results indicated that diuretics were as effective as the newer and more expensive treatments. Another observation from ALLHAT was that lisinopril treatment without a diuretic was less effective in preventing stroke.

Table 1. Results in recent studies in hypertension

	CAPP n=10,985	NORDIL n=10,881	STOP-2 n=6,614
Comparative drugs	ACEI *vs.* BB/diuretics	CCB *vs.* BB/diuretics	ACEI/CCB *vs.* BB/diuretics
Number of primary end points (CV death, stroke, MI)	736	845	1,481
Differences between drugs	None	None	None

Key: CAPP = Captopril Prevention Project; NORDIL = Nordil Diltiazem Study; STOP-2 = Swedish Trial in Old Patients with Hypertension-2; ACEI = angiotensin-converting enzyme inhibitors; CCB = calcium channel blockers; BB = beta blockers; CV = cardiovascular; MI = myocardial infarction

Another study, SCOPE (Study on Cognition and Prognosis in the Elderly),[14] was undertaken in 4,964 patients aged 70–89 years. Patients had a systolic blood pressure of 160–179 mmHg and/or a diastolic blood pressure of 90–99 mmHg and a Mini Mental State Examination (MMSE) test score greater than 24. This study looked at the angiotensin II receptor blocker (ARB) candesartan. Patients were randomly assigned to receive this or placebo, with open-label active, antihypertensive therapy added as needed. As a consequence, active antihypertensive therapy was extensively used in the control group (84% of patients).

The conclusions from the study were that there was slightly more effective blood pressure reduction in those receiving candesartan compared with the control therapy and this was associated with a statistically significant reduction in non-fatal stroke of 27.8% (95% CI, 1.3 to 47.2, p=0.04) but a non-significant reduction in all stroke by 23.6% (95% CI, -0.7 to 42.1, p=0.056). There were no significant differences in MI and cardiovascular mortality. Cognitive function was similar in both treatment groups in the presence of substantial blood pressure reductions.

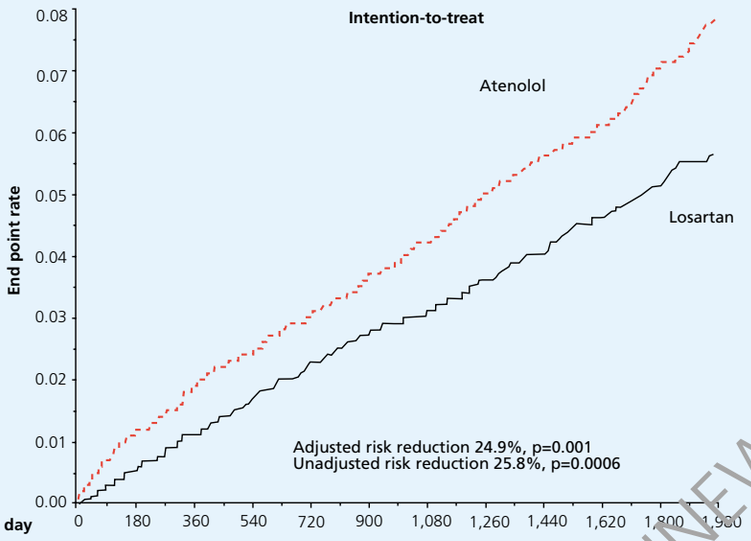
The meaning of LIFE?

The LIFE (Losartan Intervention For Endpoint reduction in hypertension) study[15] was a multi-centre, double-blind, randomised, prospective, active controlled, parallel group study designed to compare the effects of another ARB, losartan, against the effects of the beta blocker, atenolol, on the reduction of cardiovascular morbidity and mortality (stroke, MI and death) in 9,193 patients. The patients enrolled in this study had blood pressures between 160–200/95–115 mmHg and all patients had documented electrocardiogram evidence of left ventricular hypertrophy (LVH). Nearly one third of patients had been untreated for their hypertension for six months prior to the study.

LVH is an independent risk factor for cardiovascular disease and it substantially increases the risk of stroke, MI, heart failure and sudden death.[16] In one study one third of men and one fifth of women did not survive beyond five years of appearance of LVH on an ECG.[17] The patients in LIFE were therefore a very high-risk group. The major hypothesis examined in the LIFE study was that losartan would reduce the incidence of cardiovascular morbidity and mortality to a greater extent than atenolol.

Patients in LIFE were followed up for

Figure 1. Reduction in fatal and non-fatal stroke in the LIFE study



Key: LIFE = Losartan Intervention For Endpoint reduction in hypertension

Adapted from Dahlof B *et al.*[15]

over four years (mean 4.8 years) and a broadly similar 30/16 mmHg blood pressure reduction was observed in both of the treatment groups. In addition to the study drugs, hydrochlorothiazide was used as an add-on drug to both treatment arms. The composite end point of cardiovascular morbidity and mortality was reduced by 13% (p=0.021), while the incidence of stroke was reduced by a larger and more statistically robust 24.9% (p=0.001) (see figure 1). A 25% reduction in the onset of diabetes was observed while no significant difference in the incidence of MI was observed between the atenolol and losartan arms of the study. The finding that losartan appeared equivalent to atenolol in its effect on the incidence of MI is surprising as beta blockers are known to have a beneficial effect on reducing mortality following MI.

The LIFE study replicated the real world observation that few patients will reach satisfactory levels of blood pressure control with monotherapy. Only around 10% of patients in each of the treatment groups achieved this, with the others requiring the addition of hydrochlorothiazide (which was therefore also validated in this study). A significant reduction in the rate of drug discontinuations was seen in patients taking losartan as opposed to atenolol, demonstrating the superior tolerability of ARBs.

Careful interpretation of the study results requires a critical assessment of any factors that mitigate the benefits observed. Blood pressure measurements revealed a small disparity, particularly with respect to systolic pressure in favour of losartan (mean systolic blood pressure for losartan and atenolol during year four was 144.1 mmHg and 145.4 mmHg, respectively). It is thought that the beneficial effects of beta blockers on cardiovascular mortality are partly mediated through a reduction in fatal arrhythmias and the observed heart rate amongst patients taking atenolol in LIFE has been criticised as suboptimal.[18] Favourable differences with respect to baseline characteristics such as Framingham risk scores, smoking prevalence, diabetic control and isolated systolic hypertension have also been invoked in accounting for the benefit observed with losartan.[19] The shorter half-life of atenolol and resultant possibility of greater swings in ambulatory blood pressure have also been advanced as possible explanations.[20] It has been widely suggested that the differential effect on new onset diabetes could be attributed to a negative effect of atenolol rather than a favourable effect of losartan. This interpretation of the evidence is reflected in the most recent recommendations from the BHS.[20]

The LIFE study investigators should be commended on adopting an active comparator as a benchmark rather than placebo. Furthermore, few studies are ever immune from this kind of criticism mainly because near perfect matching of patient characteristics and drug effects between different treatment arms is very difficult to achieve.

In favour of the study hypothesis is the observation that in LIFE, left ventricular mass regressed more with losartan than with atenolol. There is also a possibility that differential effects of atenolol and losartan on central pressure, theoretically thought to reflect cardiovascular risk more accurately than peripheral blood pressure, may account for the benefit seen with losartan. It has previously been shown that treatment with losartan provided greater reduction in small arterial wall thickness than did atenolol for equal peripheral blood pressure control.[21]

> ***'The incidence of stroke was reduced by a statistically robust 24.9% in the LIFE study'***

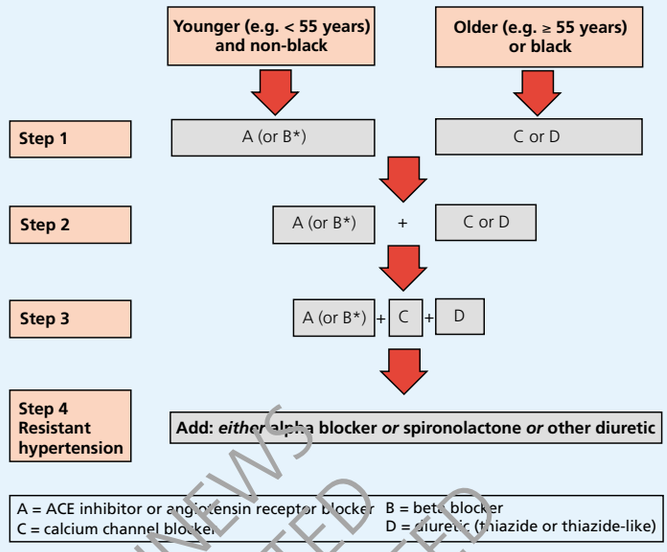
Subgroup analysis of the predefined ISH (≥ 160 / < 90 mmHg) subgroup demonstrated even greater reductions in stroke incidence. In the 1,326 patients in LIFE diagnosed with ISH (660 randomised to losartan and 666 to atenolol), there was a relative risk reduction of 46% (p=0.011) for cardio-

vascular mortality, 41% (p=0.020) for stroke, and 28% (p=0.048) for total mortality in those on losartan compared to those on atenolol.

BHS guidelines: compelling indications

Many of the national and international guidelines recommend that drug therapy should be initiated with a diuretic or beta blocker, assuming these drugs are not contraindicated or if there are compelling reasons for the use of other agents. The rationale for this recommendation is that in almost all of the long-term morbidity and mortality trials hitherto, these were the two principal drug groups used. The most recent guidelines from the US, the World Health Organisation and the British Hypertension Society (BHS), while acknowledging that most trial data relate to diuretics, the least expensive agents available, have all moved towards the approach of tailoring treatment to the individual profile of the patient. The most recent BHS guidelines[22] acknowledge that the degree of blood-pressure lowering is the key consideration. But they also introduce the concept of 'compelling reasons' for initiating particular classes of drugs in specific scenarios. The rationale for this approach is based on both therapeutic and mechanistic considerations.

Figure 2. AB/CD algorithm



Key: * Combination therapy involving B and D may induce more new onset diabetes compared with other combination therapies

Adapted from Williams B *et al*.[22]

Therapeutic considerations

- The prognosis of patients with hypertension is greatly influenced by the presence of other risk factors, which commonly co-exist with hypertension, and by target organ damage.
- Different drug groups exert differential effects on the frequently co-existent risk factors and target organ damage.
- Trial-based evidence has expanded recently and newer agents have been shown to be at least as effective as diuretics or beta blockers in certain types of patients.

Whatever the theory, the place for ARBs in therapy can only be ascertained through large randomised controlled trials, assessing their efficacy in terms of clinically important outcomes such as cardiovascular morbidity and mortality. Evidence is also slowly accumulating for the use of ARBs in the treatment of hypertension, diabetic nephropathy and heart failure.

Mechanistic considerations

It is most unlikely that hypertension is the result of a single pathological process. While the cellular and molecular mechanisms that underlie the pathogenic process have not been identified, it appears from the available evidence that a multiplicity of environmental and genetic factors may contribute to blood pressure elevation in the population at large. Similarly, it seems unlikely that a single preferred drug will cover the broad spectrum of people with hypertension, anymore than one antibiotic can be used for all types of infections.

The following factors may affect the initial choice of therapy:

- lifestyle
- age
- sex
- race
- lipids
- diabetes
- coronary heart disease
- left ventricular failure
- co-existing disease (asthma, gout, BPH or intermittent claudication).

Looking to the future, it seems reasonable that the use of low doses of two currently available agents in combination may become a preferred first-line therapeutic approach following satisfactory clinical trial evaluation. This approach has the potential advantage of producing at least additive and, in certain cases, synergistic effects on blood pressure lowering. At the same time, because of the low doses used, it also results in fewer side effects, leading to increased tolerability and concordance and hence greater efficacy. It is known that 50% of hypertensive patients require more than one drug for the control of blood pressure. One third require more than two drugs.[23-25] In the LIFE study, the number of patients in both arms who required additional

Key messages

- Hypertension is a prevalent and modifiable risk factor for stroke
- Patients with left ventricular hypertrophy (LVH) represent a particularly high-risk group
- Angiotensin II receptor blockers (ARBs) are well tolerated
- ARBs have been shown to have a beneficial effect on stroke incidence in patients with LVH when compared against atenolol

drugs for blood pressure control was identical: only 11% in the losartan arm and 12% in the atenolol arm were on a single drug. As the patients in this study had long-standing hypertension and as all had to have LVH in order to enter the trial, the need for more drugs might be anticipated.

The AB/CD guidelines[26] published by the BHS suggest combinations where A stands for ACE inhibitor or ARB, B for beta blocker, C for calcium channel blocker, D for diuretic. Where hypertension is resistant, an alpha blocker, spironolactone or other diuretic may be added (see figure 2).

Screening for hypertension is recommended at least once every five years in apparently normotensive patients although the increasing prevalence of systolic hypertension requires more rigorous surveillance in the elderly. The BHS Guidelines[22] recommend that in the elderly, treatment of confirmed systolic blood pressure when greater than 160 mmHg should be implemented irrespective of diastolic blood pressure. The guidelines recommend that in patients with ISH, calcium channel blockers or thiazide/thiazide-like diuretics should be viewed as preferential therapy. The AB/CD recommendations from the BHS suggest calcium channel blockers or diuretics as initial therapy in the elderly or in Afro-Caribbeans, which can then be combined with ACE inhibitors, ARBs or beta blockers if further add-on therapy is required. It should be noted that the LIFE study did not demonstrate the superior efficacy of losartan in Afro-Caribbeans.

Drug formularies in Primary Care Trusts (PCTs) have tended to reflect both official guidelines and local consensus. In practice ARBs have often been recommended as 'ACE alternatives' when patients experience troublesome side effects from ACE inhibitors. The LIFE study results have led to an increased recognition of the role of ARBs within hypertension management. Evidence of the benefits of ARBs, their superior tolerability and potential effect on stroke incidence have established a compelling indication for their use in preference to other classes of therapy in patients with hypertension and LVH. In primary care there will be reasonably small numbers of patients in this category – in the ALLHAT study, for example, 16% of patients had ECG-detected LVH.[13]

The targeting of hypertensives is an important component of an overall approach to risk factor reduction. As more strokes are observed in patients with a systolic blood pressure of less than 160 mmHg (rather than above this figure), some commentators have pointed out that if a small reduction in blood pressure is achieved across the population, this will prevent more strokes than will be achieved by targeting those most at risk. Most clinicians, however, manage their patients as individuals and most patients would prefer to be treated as individuals. Thus, in reality, both approaches are necessary.

The emphasis on targeting hypertension should not detract from the importance of tackling other major risk factors for stroke. Examples of these include cholesterol, smoking, alcohol intake, ischaemic heart disease, atrial fibrillation, previous transient ischaemic attack, diabetes and various medications. In clinical practice an assessment of the entire risk profile is required, particularly as risks interact in a synergistic fashion to contribute to the probability and the too often seen reality of a cerebrovascular event.

Conflict of interest

None declared.

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References

1. British Heart Foundation. *CHD statistics 2003.* British Heart Foundation Statistics Database. (www.heartstats.org).
2. Department of Health. *National Service Framework for Older People.* London: Department of Health, 2001.
3. Department of Health. *Our healthier nation: a contract for health.* London: The Stationery Office, 1997.
4. Staessen JA, Fagard R, Thijs L *et al*. The Systolic Hypertension Europe (Syst-Eur) Trial Investigators. Morbidity and mortality in the placebo controlled European trial on isolated systolic hypertension in the elderly. *Lancet* 1997;**360**:757-64.
5. Wing S, Aubert RE, Hansen JP *et al*. Isolated systolic hypertension in Evans County - I. Prevalence and screening considerations. *J Chron Dis* 1982;**35**:735-42.
6. Kannel WB, Dawber TR, McGee DL. Perspectives on systolic hypertension. The Framingham study. *Circulation* 1980;**61**: 1179-82.
7. Nielson WB, Vestbo J, Jenson GB. Isolated systolic hypertension as a major risk factor for stroke and myocardial infarction and an unexploited source of cardiovascular prevention: a prospective population-based study. *J Hum Hypertens* 1995;**9**:175-80.

8. Hansson L, Lindholm LH, Ekbom T *et al*. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity in the Swedish trial in Old Patients with Hypertension-2 study. *Lancet* 1999;**354**:1751-6.
9. Hansson L, Lindholm LH, Niskanen L *et al*. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPP) randomised trial. *Lancet* 1999;**353**:611-16.
10. Hansson L, Hedner T, Lund-Johansen P *et al*. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. *Lancet* 2000;**356**: 359-65.
11. The HOPE Investigators. Effects of angiotensin-converting enzyme inhibitor ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;**342**:145-53.
12. Svenson P, de Faire U, Sleight P, Yusuf S, Ostergen J. Comparative effects of ramipril on ambulatory and office blood pressures; a HOPE substudy. *Hypertension* 2001;**38**:e28.
13. ALLHAT Collaborative Research Group: Major cardiovascular events in hypertensive patients randomized to doxazosin versus chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA* 2000;**283**:1967-75.
14. Lithell H, Hansson L, Skoog I *et al*. The study on cognition and prognosis in the elderly (SCOPE): principal results of a randomised double blind intervention trial. *J Hypertens* 2003;**21**:875-86.
15. Dahlof B, Devereux RB, Kjeldsen SE *et al*. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;**359**:995-1003.
16. Kannel WB. Potency of vascular risk factors as the basis for antihypertensive therapy. *Eur Heart J* 1992;**13**:34-42.
17. Kannel WB. Prevalence and natural history of electrocardiographic left ventricular hypertrophy. *Am J Med* 1983;**75**(3A):4-11.
18. Hamonn M. Letter to the editor. *Lancet* 2002; **359**:2199-200.
19. Bloom M. Letter to the editor. *Lancet* 2002; **359**:2200-01.
20. Cockroft JR, Brown MJ. Letter to the editor. *Lancet* 2002;**359**:2202.
21. Schiffrin EL, Park JB, Intengan HD *et al*. Correction of arterial structure and endothelial dysfunction in human essential hypertension by the angiotensin receptor antagonist losartan. *Circulation* 2000;**101**:1653-9.
22. Williams B, Poulter NR, Brown MJ *et al*. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004 - BHS IV. *J Hum Hypertens* 2004;**18**:139-85.
23. Lip GY. Losartan and the meaning of life. *J Hum Hypertens* 2002;**16**:289-91.
24. Hackam DG, Ashcroft JS. Drug treatment of hypertension. *BMJ* 2003;**326**:764.
25. Ruzicka M, Leenen FH. Combination therapy as first line treatment of arterial hypertension. *Can J Cardiol* 2002;**18**:1317-27.
26. Brown MJ, Cruickshank JK, Dominiczak AF *et al.* Better blood pressure control: How to combine drugs. *J Hum Hypertens* 2003;**17**: 81-6.