Prevention of cardiovascular disease in clinical practice

Emerging concerns about the effectiveness of beta-blockers in hypertension and the publication of clinical trials such as ASCOT prompted the National Institute for Health and Clinical Excellence to bring forward a partial review of the 2004 hypertension guidelines. This review concluded beta-blockers should not be the preferred agent in routine management, particularly for older people as **Dr Mark Davis** explains.

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In preventing cardiovascular disease (CVD) the Health Survey for England in 2003 shows us the scale of the challenge: 9.1 per cent of men and 4.5 per cent of women have established CVD[1]. The prevalence of CVD rises with age –for example, it affects 26 per cent of men between the ages of 65 and 74. Individual risk factors are common – 29 per cent of men and 27 per cent of women have hypertension (>140/90mmHg) and 68 per cent of men and 67 per cent of women have an elevated cholesterol (>5mmol/L).

When the National Service Framework for Coronary Heart Disease was published in 2000, it was a major step in driving the agenda forward for CVD prevention. For pragmatic reasons it suggested primary care should prioritise secondary prevention and, when this had been addressed, we should turn our attention to high risk primary prevention. The British Hypertension Society guidelines (BHS IV)[2] and the recently published Joint British Societies (JBS2) guidelines[3] have built on this foundation and suggest a strategy more appropriate to 2006, and give the key role in CVD prevention to primary care.

The biology of atherosclerotic disease makes the separation of 'secondary' and 'primary' prevention arbitrary as they share the same underlying disease process. JBS2 suggests the following patient groups should be regarded as having equal priority when considering lifestyle and therapeutic interventions to reduce their risk:

- clinical evidence of atherosclerotic CVD;
- diabetes mellitus (types 1 or 2);
- a total CVD risk > 20 per cent over 10 years.

Some patients have a single risk factor elevated to such a degree it requires modification regardless of absolute risk. Examples of this would be blood pressure (BP) greater than systolic 160mmHg, a diastolic greater than 100mmHg, a familial hypercholesterolaemia or a total cholesterol to high-density lipoprotein (HDL) cholesterol ratio greater than six.

To calculate this, the Framingham risk equation was used to produce new charts estimating CVD risk using the classical risk factors of age, sex, smoking habit, systolic blood pressure and total cholesterol to HDL cholesterol ratio. There are now three age bands. This does something to address the criticism levelled at previous risk charts, which ignored the potential life-years to be gained by treating earlier those on track to becoming high risk later in life. For example, someone of 50 is considered to be 59. The final age band is >60. From aged 70 the CVD risk, particularly in men, is usually >20 per cent and using the charts will underestimate the risk. There is no chart for people with diabetes. This reinforces

the widely held belief that risk calculation in diabetics is rarely, if ever, needed as they usually have a 10-year risk of >20 per cent[1,2].

The object of high risk CVD prevention is to reduce the incidence of non-fatal or fatal cardiovascular events, and therefore to improve the quality and length of life. To do this we should offer lifestyle and risk factor interventions using appropriate drug therapies to lower BP, modify lipids and reduce glycaemia. Therapeutic targets for blood pressure, lipids and glycaemia are given and the audit standards are the same as JBS2 as those in the new General Medical Services contract, which is of great importance to GPs. Rigorous blood pressure control is required in all high risk individuals. The optimal target is 140mmHg systolic and 85mmHg diastolic. In secondary prevention patients and those with diabetes and renal impairment, the target should be 130mmHg systolic and 80mmHg diastolic. The ABCD treatment algorithm[4] suggested in BHS IV provided useful advice on the use of drugs to help us achieve these targets. As detailed later this has now been superseded by the NICE/BHS updated treatment algorithm ACD[4].

In this high risk group, statins should be used to reduce low-density lipoprotein (LDL) cholesterol. The evidence-based targets the BHS have adopted are to reduce the total cholesterol to 4.0mmol/L and the LDL cholesterol to 2.0mmol/L. Although the statins are the mainstay of treatment, other treatment modalities, such as cholesterol absorption inhibitors, may be needed in some patients.

Does recent evidence support this guidance?

The ASCOT[5] study trial was designed to address and whether the 'newer' drugs – the calcium channel blockers (CCBs) and the angiotensin-converting-enzyme inhibitors (ACEIs), would confer cardiovascular disease outcome advantages, particularly on CHD, over the older antihypertensive treatments – the diuretics and beta-blockers. Additionally, it was designed to establish whether or not lipid lowering with a statin would confer protection against CHD events in hypertensive patients with 'normal' or modestly raised cholesterol levels. The patients in ASCOT had an average CVD risk on treatment of 16 per cent, which is likely to translate into a CVD risk >20 per cent over 10 years pre-treatment. Thus, they would be eligible for interventions under JBS2.

The trial involved the randomisation of over 19,000 patients to one of two antihypertensives strategies – a 'newer' regimen of a CCB (amlodipine) with or without an ACE inhibitor (perindopril) and an older regimen of a beta-blocker (atenolol) with or without a thiazide diuretic (bendroflumethiazide-K). The progression to second-line, third-line (doxazosin-GITS) and to other drugs was designed by way of a prescribed algorithm to achieve blood pressure targets of <140/90mmHg, or <130/80mmHg in those with diabetes.

Of those recruited into the main blood pressure trial (ASCOT-BPLA), approximately half the patients (about 10,000) with total cholesterol levels <6.5mmol/L were re-randomised to atorvastatin, 10mg or placebo. ASCOT, unlike many recently reported trials in hypertensive patients, was a 'primary' prevention trial in that a history of prior myocardial infarction or concurrent coronary heart disease would exclude patients from entry. The lipid-lowering arm of ASCOT (ASCOT-LLA)[5] was stopped prematurely in 2003 due to substantial benefits in favour of atorvastatin over placebo. CHD events were reduced by 36 per cent and stroke by 27 per cent. The benefits on CHD events occurred within three months and probably earlier.

In December 2004, the Data Safety Monitoring Board (DSMB) recommended stopping the blood pressure arm of the trial[6] – prematurely – on the grounds that those in the beta-blocker based treatment limb were being disadvantaged and that there was a difference in all cause mortality (11 per cent) and cardiovascular mortality (24 per cent) between the two blood pressure treatment arms. The Steering Committee had no alternative other than to accept the recommendations of the DSMB, but in closing the trial early recognised the number of primary (non-fatal myocardial infarction and fatal CHD) events (903) was less than the number (1,150) on which the power calculations for the trial were based.

However, after all the final visits of patients and analysis of the complete data base, it was evident that most CV endpoints were substantially and significantly reduced in the amlodipine +/- perindopril regimen. The reduction in the primary endpoint (10 per cent) of non-fatal myocardial infarction of fatal CHD did not achieve statistical significance. On the other hand, all the other coronary endpoints were significantly reduced compared with the atenolol +/- thiazide regimen. Other endpoints were reduced, including stroke (23 per cent), new onset peripheral

Key points

> Calcium channel blockers or thiazide type diuretics are the drugs most likely to confer benefit as first-line treatment for most patients 55 years or older.

> If a further drug is needed adding an ACE inhibitor is a logical combination.

> In the presence of a compelling indication bet-blockers are no longer considered part of routine therapy in hypertension.

> Statin therapy should be considered in all patients with hypertension whose CVD risk is ≥20 per cent in 10 years

vascular disease (35 per cent) development of renal impairment (15 per cent) and the development on new onset diabetes (30 per cent) in favour of the 'newer' treatment strategy.

There were, however, BP differences between the two regimens in the trial, with amlodipine+/- perindopril more effective than atenolol+/- thiazide. These differences were maximal in the first six months but differed by 1.6mmHg at the end. Average differences over the course of the trial were 2.7/1.9mmHg. Detailed posthoc analyses, including Cox regression techniques and multivariate adjustment, suggested that only about half of the stroke benefit – and none of the CHD benefits – could be explained on the basis of the BP differences between the two treatment arms. It seems the adverse effect of the beta-blocker-based regimen on certain lipid parameters, notably HDL-cholesterol, could have contributed to some of the observed differences in CHD outcome.

This trial is supportive of the ACD rule suggested by NICE and the BHS in their algorithm. For the untreated patient aged over 55 and black people of any age, ACD suggests a C or D drug as first-line treatment. Dose-up titration and add-on therapy should be followed according to the BHS guidelines (ie, C or D + A). Further support for ACD comes from the relatively poor BP responses to ACE inhibitors (and beta-blockers) in patients of Afro-Caribbean origin, which should persuade physicians to avoid these classes of drugs as first-line agents. To what extent the disadvantages of the beta-blocker-based regimen reported from ASCOT were due to atenolol, rather than the class of beta-blocker drugs is, of course, unknown.

The result of the lipid-lowering arm of ASCOT together with recent meta-analyses of lipid-lowering trials, provide an overwhelming evidence base for the benefits of statins in hypertensive patients. Irrespective of baseline cholesterol levels, a relative risk reduction of about one-third of CHD events and in excess of one-quarter of stroke events will result from the addition of a statin to BP lowering therapy. Probably the most important messages from the ASCOT trials are that good BP control combined with lipid-lowering with a statin – and the preference for a newer BP treatment strategy involving a CCB and an ACE inhibitor – can reduce the incidence of CV morbidity and mortality in hypertensive patients by 60–70 per cent compared with poor control, no statin and older antihypertensive drugs.

Conflict of interest: Dr Davis is on the executive committee of the BHS and served in the Guideline Development Group for the NICE/BHS management of hypertension update. He lectures on hypertension and cardiovascular risk reduction.

References

1. Department of Health. The health survey for England 2004. Summary of key findings. DoH, 2003:8
2. Williams B, *et a*l. British Hypertension Society. Guidelines for the management of hypertension; report of the fourth working party of the British Hypertension Society, 2004 - BHS IV. *J Hun Hypertens* 2004; 28:139-185
3. British Cardiac Society, British Hypertension Society, Diabetes UK, Heart UK, Primary Care Cardiovascular Society, The Stroke Association. JBS2: Joint British Societies' Guidelines on Prevention of Carciovascular Disease in clinical practice. *Heart* 2005;**91**:v1-v52
4. The National Institute for Health and Clinical Excellence. Hypertension: management of hypertension in adults in primary care. http://www.nice.org.uk/CG034
5. Dahlof B, Sever PS, Poulter NR, *et a*l; Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required *versus* atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005; **366**: 895-906.
6. Sever PS, Dahlof B, Poulter NR, *et al*. ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial –Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003; **361**:1149-1158.