The continuing role of beta-blockers in hypertension

The publication of the ASCOT and Lindholm studies last year led many physicians to believe that the era of beta-blockers for hypertension was over. Updated guidelines from the National Institute for Health and Clinical Excellence and the British Hypertension Society are expected later this year and should help to clear up any confusion. In this article, **Dr Ahmet Fuat** discusses the future of beta-blockers in the management of hypertension in the elderly.

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WHEN a joint collaboration was announced last year between the *National Institute for Health and Clinical Excellence* (NICE) and the *British Hypertension Society* (BHS) to produce updated guidelines on blood pressure control, many within the medical profession breathed a huge sigh of relief. The move brought an end to almost a year of confusion over their differing recommendations after they launched contradictory guidelines in 2004[1,2].

The collaboration also promised to help interpret the results of the Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm (ASCOT-BPLA) trial whose conclusions have been reported as sounding the death knell for many widely used anti-hypertensive treatments[3]. Indeed, with ASCOT swiftly followed by Lars Lindholm's highly critical meta-analysis of beta-blocker (ß-blocker) therapy[4], it has been a confusing time for those of us trying to offer the best possible therapy for our hypertensive patients.

The question many have been asking is whether we should continue prescribing ß-blockers in the light of the ASCOT and Lindholm studies as both recommend that ß-blocker should no longer be considered first-line treatments for hypertension. This article will look at the results of these studies and assess the future for ß-blocker use in the management of hypertension in the elderly and also the likely impact on future guidelines.

ASCOT study

ASCOT included more than 19,000 men and women with high blood pressure who were at a moderate risk of strokes and heart attacks. To control their blood pressure, they received either the newer drugs – a calcium antagonist, amlodipine and the ACE inhibitor, perindopril – or a traditional combination of a ß-blocker, atenolol and a diuretic. Additionally, 10,000 patients were also treated with the cholesterol lowering drug atorvastatin or a placebo. This is the only major European study to-date to combine these two treatment strategies.

The final results of ASCOT, which was conducted in the UK, Ireland and the Nordic countries, showed that the combination of newer blood pressure lowering drugs reduced the risk of strokes by about 25 per cent, coronaries by 15 per cent, cardiovascular deaths by 25 per cent and new cases of diabetes by 30 per cent compared with the standard treatment. Clearly its findings cannot be ignored.

Of the 25 per cent of patients in both groups who stopped therapy early because of adverse events, significantly fewer did so because of serious adverse events in the amlodipine group compared to the atenolol group (1.7 per cent *versus* 2.6 per cent, p<0.0001) but numbers were few and there was no significant difference in cessation from non-serious adverse events.

Lars Lindholm's meta-analysis

In their meta-analysis, Lars Lindholm and colleagues included 13 randomised controlled trials (n=105 951) comparing treatment with ß-blockers with other antihypertensive drugs. They also included seven studies (n=27 433), which compared ß-blockers with placebo or no treatment[4].

The meta-analysis found that the relative risk of stroke was 16 per cent higher for ß-blockers (95 per cent CI 4–30 per cent) than for other drugs. There was no difference for myocardial infarction. When the effect of ß-blockers was compared with that of placebo or no treatment, the relative risk of stroke was reduced by 19 per cent for all ß-blockers (seven to 29 per cent), about half that expected from previous hypertension trials. There was no difference for myocardial infarction or mortality.

It concluded that in comparison with other antihypertensive drugs, the effect of ß-blockers is less than optimum, with a raised risk of stroke. The investigators added that ß-blockers should not therefore remain first choice in the treatment of primary hypertension and should not be used as reference drugs in future randomised controlled trials of hypertension.

The future?

Beta-blockade has long been regarded as a safe and effective therapy for hypertension. It has been clearly established that, after myocardial infarction and in patients with heart failure, treatment with selected ß-blocker prevents re-infarction, reduces hospitalisation for heart failure, and cuts the risk of premature death[5-8]. Both the guidelines from NICE and, to a lesser extent from the BHS, recommend ß-blocker as a first or second line therapy in patients with hypertension.

NICE/BHS guidelines

Whether the NICE/BHS Expert Advisory Group, set up to produce the updated guidelines, and chaired by past-BHS President Professor Bryan Williams, agrees with this interpretation remains to be seen. A number of meetings are planned and it is hoped that draft recommendations will be available for consultation by stakeholders soon with publication of the final joint NICE/BHS document by June. However, before we abandon what has, after all, been a tried and trusted approach to anti-hypertension therapy for many years, it is important that we ensure that these new findings are truly applicable to our own patients and the treatments we currently prescribe.

The first thing to point out is that atenolol, as used in ASCOT and in many of the Lindholm trials, can no longer be considered a typical ß-blocker. It is now 30 years old and lacks the cardioselectivity and vasodilatory properties of more modern ß-blockers such as nebivolol and carvedilol.

This distinction is especially important when we consider that many of our hypertensive patients, and especially our more elderly patients, present with considerable cardiovascular co-morbidity. These patients require careful risk assessment and management so that their overall risk of a major coronary event is not increased and their quality of life is maintained. Many elderly patients with hypertension have overt coronary heart disease. Others may have underlying coronary disease that is not clinically evident because they are taking a ß-blocker. Sudden discontinuation of a ß-blocker, particularly from high doses, could cause rebound hypertension, rebound angina or even precipitate a myocardial infarction.

Trial data for ß-blockers

The potential benefits of using ß-blockers in elderly patients with chronic heart failure have been clearly demonstrated. Sin-Don D, *et al* observed in a retrospective study of 11,942 patients over 65 years with heart failure (1,162 taking ß-blockers), that ß-blocker use was associated with substantial reductions in all-cause mortality, heart failure mortality and hospitalisations due to heart failure[9].

These endpoints were less frequent in patients treated with ß-blockers than in untreated patients in all examined subgroups. In the study, all doses of ß-blockers were associated with benefit, but there was a trend towards greater benefit in patients prescribed higher doses.

Furthermore, in the SENIORS trial, the randomisation of over 2,000 patients, with a mean age of 76.1 years and a clinical diagnosis of chronic heart failure, to receive either nebivolol or placebo showed a significantly reduced all-cause mortality or rate of hospitalisation for cardiovascular events among the nebivolol-treated patients[10].

The primary outcome was a composite of all cause mortality or cardiovascular hospital admission (time to first event). This occurred in 332 patients (31.1 per cent) on nebivolol compared with 375 (35.3 per cent) on placebo (hazard ratio (HR) 0.86, 95 per cent CI 0.74-0.99; P=0.039). There was no significant influence of age, gender, or ejection fraction on the effect of nebivolol on this primary outcome. Death (all causes) occurred in 169 (15.8 per cent) on nebivolol and 192 (18.1 per cent) on placebo (HR 0.88, 95 per cent CI 0.71-1.08; P=0.21). The study, therefore, concluded that nebivolol, a beta-blocker with vasodilating properties, is an effective and well-tolerated treatment for heart failure in the elderly.

Results such as this demonstrate that there remains a place for modern, cardioselective ß-blockers within the management of hypertension. While the results of ASCOT and the Lindholm meta-analysis are likely to change the guidance on first-line use of ß-blocker, we should recognise that many patients will continue to need ß-blocker therapy and that rapid discontinuation could be particularly dangerous for patients with cardiovascular co-morbidities.

Conclusion

We must remember that successful treatment of hypertension frequently requires the use of several types of drugs. For reasons of effectiveness and tolerability (indeed 25 per cent of patients in the ASCOT trial did not tolerate the drugs), a variety of alternative and adjunctive treatments are needed to effectively manage hypertension, including ß-blockers ■ GM

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Key points

- A joint collaboration between NICE and the BHS will produce updated guidelines on blood pressure control.
- It will help interpret the results of the ASCOT-BPLA trial and the Lindholm studies.
- Both trials recommend that ß-blocker should no longer be considered first-line treatments for hypertension.
- Beta-blockade has long been regarded as a safe and effective therapy for hypertension.
- The potential benefits of using ß-blockers in elderly patients with chronic heart failure have been clearly demonstrated.
- We must remember that successful treatment of hypertension frequently requires the use of several types of drugs.