Role of beta-blockers in hypertension and heart failure.

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Abbreviations  

Background

Worldwide, arterial hypertension is one of the most important modifiable risk factors for cardiovascular disease. Realistic and affordable treatment began in the 1960s with oral diuretics followed by the beta-blockers, calcium-channel blocking agents, alpha-receptor blockers and, later, the angiotensin converting enzyme inhibitors (ACEI) and, most recently, angiotensin-receptor blockers (ARB). All have been shown to reduce blood pressure and consequential cardiovascular events.

However, one of the central issues that has been argued over the past 50 years is whether any of these classes of medicines brings added benefit over and above the reduction in blood pressure itself (so-called ‘pleiotropic’ effects). Clearly, the pharmaceutical industry has an interest in promoting products which might have extra advantages over competitors and many clinical trials have been conducted (and funded by industry) to find these extra benefits which might have big marketing implications. This must always be kept in mind when reviewing clinical trial data and especially the commentaries of ‘experts’ on the implications of the latest data set.

Hypertension in LMICs is increasing and it is estimated that over 600 million people, almost three quarters of all people with this condition, live in developing countries with limited health resources and where awareness of hypertension is low and blood pressure control poor(1). It is important therefore that advice about preferred medicines should focus not only on comparative efficacy and safety (and convenience which may determine adherence to the treatment) but also comparative cost/cost-effectiveness.

Clinical trials and meta-analyses

This Section is not based on an exhaustive literature search but includes key trials and meta-analyses since 2000.

The 2003 WHO-ISH statement on the management of hypertension (2) adopted the stance that reduction of blood pressure per se was the mechanism of cardiovascular benefit and endorsed the
view that all primary groups of medicines were equi-effective and could be used to initiate treatment.

In the same year the Blood Pressure Trialists Collaboration published overviews of data from 29 randomised trials (n=162,341) concluding that treatment with any ‘commonly-used regimen’ reduces the risk of major cardiovascular events. ‘Larger reductions in blood pressure produce larger reductions in risk’ (3).

This analysis did not incorporate the first RCT of the decade to re-ignite debate over the place of atenolol in hypertension, the LIFE study 2002 (4). This ran into the problem, facing all larger prospective studies, of sufficient duration to generate firm CV end-points. A majority of patients will require more than one medicine to achieve control of blood pressure and the need to introduce a second or third agent potentially confounds cause and effect relationships. Atenolol-based treatment was compared with losartan-based. Initial add-on therapy was with hydrochlorothiazide 12.5 mg in both groups but if further medicines were needed they could be chosen from any group apart from those modifying angiotensin’s action or beta-blockers. The text states that ‘the distribution of additional drugs on top of the masked study drug and hydrochlorothiazide did not differ between groups’. Details are not provided. The dominant effect of losartan vs. atenolol was a greater incidence of stroke with the beta-blocker (RR 0.75; 95% CI 0.63-0.89) which contributed to the composite end-point and overall CV mortality.

(Study funded by Merck. No conflicts of interest are declared by the authors and the data analysis was conducted by Merck Research Laboratories).

A sub-group analysis of 1195 pre-specified patients with diabetes and hypertension from the LIFE trial (5) produced similar findings, with greater stroke incidence in the atenolol group (HR 0.79: 0.55-1.14).

(Study funded by Merck. Three employees of the company were co-authors).

In 2003, the INVEST study reported (6). This was a multicentre study of hypertension in 22,576 patients with confirmed coronary artery disease treated with verapamil (add-on trandolapril) or atenolol (add-on hydrochlorothiazide). At 24 months, blood pressure control was similar in both groups as were all clinical outcomes –including nonfatal stroke. The authors concluded that the two treatments were equi-effective.

(No conflict of interest declarations or funding source acknowledgement)

The third large trial (7) was the 2005 ASCOT-BPLA multicentre RCT of 19,257 patients (aged 49-75) with hypertension and at least three other CV risk factors. These were randomised to either amlodipine with perindopril as add-on or to atenolol with bendroflumethiazide and potassium as add-ons. The trial was stopped ahead of the predicted time as the mortality rate in the atenolol group was significantly higher than the amlodipine group as was the incidence of fatal and non-fatal stroke (HR 0.77; 95% CI 0.66-0.89) and total CV events and procedures. However, the study needs to be read in conjunction with the next paper (8) in the same issue of the ‘Lancet’ which is a detailed analysis of the outcomes. With multivariate adjustment of the data half of the differences in coronary events and about 40% of the difference in stroke events were accounted for and the
differences were no longer statistically significant. (The group systolic pressures were systematically lower in the amlodipine patients, throughout the study period)*

(Both studies were funded by Pfizer and Servier Laboratories: conflict of interest declared)

One response to both ASCOT-BPLA and the earlier LIFE study was a meta-analysis of 12 beta-blocker RCTs in hypertension by Lindholm et al. which claimed the ‘effect of beta-blockers is less than optimum with a raised risk of stroke’ (RR 1.16; 95% CI 1.04-1.30 favouring medicine other than atenolol) while demonstrating no detriment as far as all-cause total mortality and myocardial infarction were concerned (10).

An accompanying editorial—admittedly from an investigator in the ASCOT trial (a declared conflict) suggested this was the ‘end of beta-blockers for uncomplicated hypertension’ (11).

Others looked at different ways of addressing the problem. Two observational studies have been presented. Blackburn et al in Canada (12) linked administrative databases to demonstrate very similar 2 year rates of myocardial infarction, unstable angina, stroke or death in cohorts receiving atenolol, ACEI, thiazide diuretics or calcium blockers in a total population of 19,249 people with average age of 60.6 yrs.

Secondly, the long-term follow-up of the UK-Prospective Diabetes Study, difficult to interpret though it is, did not show any detrimental effect in those who had been initially randomised to beta-blockers - especially no excess in stroke (13).

Nadia and McAlister performed a meta-analysis in 2006 (14) of 21 hypertension trials with data from 145,811 participants which showed similar efficacy in reduction of cardiovascular events in younger patients treated with beta-blocker compared to other agents but more composite endpoints (death, stroke, myocardial infarction) in patients over 60 years of age (RR 1.12; 95% CI 1.02-1.24). Refining the analysis (by excluding the three studies excluded by Lindholm et al, 10) generated an excess, composite risk in patients over 60 which was largely driven by excess risk of stroke (RR 1.18; 95% CI 1.07-1.30). They suggested incorporating this age distinction in the (Canadian) guidelines (see below).

A meta-analysis published in 2009 (15) aimed to determine the quantitative efficacy of different classes of blood pressure lowering drugs in preventing coronary heart disease and stroke and who should receive treatment. Included were 46 trials comparing medicines. In the blood pressure difference trials beta-blockers had an extra effect over and above blood pressure reduction in preventing recurrent coronary heart events in people with a recent history of CHD. This effect was limited to a ‘few years’ after a myocardial event. (Fig. 1)

All classes of blood pressure lowering drugs had a similar effect in reducing new CHD and stroke for a given reduction in blood pressure ‘so excluding material pleiotropic effects’.

*Rothwell et al performed further analyses demonstrating that smaller within-individual visit-to-visit differences in blood pressure could account completely for the lower risk of stroke in the amlodipine group (9)
A thoughtful analysis published in 2009 gave a reappraisal of the European guidelines on hypertension management (16). The authors point out the variability of individual patients and the need to tailor management but endorse the Guidelines in accepting that reduction in blood pressure is the prime factor in reducing CV morbidity and mortality. They recommend all classes of medicine as first-line therapy.

**Response of Guideline Committees to the debate on atenolol**

Four sets of Guidelines have been published since 2011 giving their authors time to reflect on the case for and against beta-blockers in primary hypertension in the light of the newer evidence.

**NICE 2011 Recommendation for initial treatment of primary hypertension**

Step 1. <55 years old ACEI or ARB. ‘Consider beta-blocker in younger patients’

>55 years calcium blocker

Step 2 if inadequate response add diuretic

Step 3 if response not optimal consider alpha or beta-receptor blocker

These recommendations to be reviewed in 2015
ESH/ESC Guidelines for the management of arterial hypertension 2013 (17)

Page 2189: ‘Once it is agreed that (i) the major mechanism of the benefits of antihypertensive therapy is lowering of b.p. per se, (ii) the effects on cause-specific outcomes of the various agents are similar or differ by only a minor degree, (iii) the type of outcome in a given patient is unpredictable, and (iv) all classes of antihypertensive agents have their indications but also contra-indications...it is obvious that any all-purpose ranking of drugs for general antihypertensive usage is not evidence-based’

Table 14 Compelling and possible contraindications –to beta-blockers - Asthma, Grade 2 or 3 AV block

Table 15. Preferred conditions for beta-blockers –hypertension with previous myocardial infarction; angina pectoris; heart failure; atrial fibrillation (controlling ventricular rate).

Evidence-based guideline for the management of high blood pressure in adults, Joint National Committee (USA) 2014 (18)

‘The panel did not recommend beta-blockers for the initial treatment of hypertension because in one study use of beta- blockers resulted in higher rate of the primary composite outcome of cardiovascular death, myocardial infarction or stroke compared to use of an ARB, a finding that was driven largely by an increase in stroke’.

(the study referred to is the LIFE trial (4))

The 2014 Canadian Hypertension Education Program, Recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention and treatment of hypertension (19)

‘Initial therapy should be a single agent thiazide/thiazide-like diuretic, a beta-blocker (in patients younger than 60 years), an ACE inhibitor .......

‘Beta-blockers are not recommended as first-line treatment for uncomplicated hypertension in patients 60 years of age or older.....

(clearly, they have adopted the implication of the meta-analysis conducted in Canada by Nadia and McAlister (14))

The place of atenolol in treatment of hypertension

Despite the influence of the two trials reporting lesser preventive effects on stroke incidence, the balance of evidence does not support the call to banish beta-blockers altogether as first-line agents in primary hypertension. Differences of opinion exist even between guideline committees but beta-blockade and, specifically he use of atenolol as a primary choice, is supported by most commentators.
There needs to be an acknowledgement of a possible difference in effects between the young and the elderly which is captured in the recent Canadian guidelines. There are also very positive reasons for preferring beta-blockers as initial treatment of hypertension in those with CHD and especially in post-infarct patients in whom substantial benefit has been demonstrated, at least for the first two post-infarct years (15, Fig 1). Patients with hypertension and risk of supraventricular arrhythmias are also candidates for beta-blockade.

Beta-blockers are not an homogeneous group and the added pharmacological properties of vasodilatation and/or alpha-blockade might have an advantage in hypertension. However, only short-term studies in hypertension have been done with agents with these actions, all showing hypotensive effects. However, there are no outcome studies in hypertension- as opposed to chronic heart failure in which there is clear evidence of overall benefit for metoprolol, carvedilol and bisoprolol (large RCTs conducted mainly in the mid-1990s).

**Atenolol and LMICs**

Atenolol is a water soluble, beta1-receptor blocker with a prolonged half-life enabling once daily dosing which should enhance compliance/adherence. It is not significantly metabolised (and is therefore not a target for interactions through metabolic pathways) and is lost to the body by renal excretion (caution in use in renal impairment). It is in all the EMLs that I am familiar with in the countries of the Western-Pacific Region and, as a generic medicine, is very cheap to buy (below).

Most of the beta-blockers other than atenolol are not registered in these countries and certainly not for hypertension. They are slowly getting into the EMLs for chronic heart failure.

<table>
<thead>
<tr>
<th>Beta-blocker</th>
<th>Price to patient (expressed as US $/cents)</th>
</tr>
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<tbody>
<tr>
<td>Atenolol 50mg</td>
<td>8.8c</td>
</tr>
<tr>
<td>Bisoprolol 5mg</td>
<td>18.8c</td>
</tr>
<tr>
<td>Carvedilol 12.5mg</td>
<td>$1.88</td>
</tr>
<tr>
<td>Metoprolol 100 mg</td>
<td>21.9c</td>
</tr>
</tbody>
</table>

**Table:** Comparative prices for four beta-blockers, Ghana, November 2014 (courtesy of Brian Asare)

**Conclusion and summary of responses to the questions I was asked to address**

1. **What is the role of atenolol in the management of hypertension? Are there particular patient populations where atenolol could be recommended?**

Based on the evidence reviewed, atenolol should be considered as a first–line agent in hypertension associated with coronary heart disease, especially treatment initiated after a myocardial infarct, and in patients with angina and supraventricular arrhythmias.

It is reasonable and concordant with the evidence to list it as a first-line antihypertensive in younger hypertensive patients (perhaps with a cut-off at 60 years, in line with the Canadian evidence and NICE Recommendations) – but it should not be listed as first-line treatment in age groups over 60 years.
Atenolol retains a place as add-on/second or third-line treatment if blood pressure control is not obtained with other antihypertensive agents.

2. Is there any need to differentiate between beta-blockers for the four main indications for use in hypertension, angina/post-MI, arrhythmias and heart failure?

The distinctions between available beta-blockers are less pharmacological than derived from the way clinical trials have been undertaken over a long period. Atenolol and propranolol were early representatives of the class and many more studies have been done in hypertension with these two medicines than with the others.

However, while there are short-term (a few weeks) studies with either bisoprolol or carvedilol in hypertension there are no CV outcome studies and neither should be regarded as a first-line agent for hypertension if the EML is to remain evidence-based.

The retention of bisoprolol, carvedilol and metoprolol for the management of chronic cardiac failure is in line with the evidence. While atenolol has been used in heart failure, the major outcome studies (not reviewed here) have been conducted with these three compounds.

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