

# Prevention of risk factors: beta-blockade and hypertension

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Some national guidelines on hypertension have demoted beta-blockers from a first-choice to a fourth-choice treatment. In contrast, the 2007 guidelines of the European Society of Hypertension/European Society of Cardiology (ESH/ESC) retain them among the drug classes used to initiate and maintain antihypertensive treatment, together with diuretics, angiotensin-converting enzyme (ACE)-inhibitors, calcium antagonists, and angiotensin receptor antagonists. The reasons are as follows. First, in most trials beta-blockers were used with thiazide diuretics, making it illogical to drop one and save the other. Secondly, individual trials and meta-analyses conflict regarding whether beta-blockers are less effective in preventing cardiovascular events than other drugs. Thirdly, a reduced protective effect of beta-blockers against stroke has been reported in some but not all trials; blood pressure reduction *per se* is probably the most important factor in protecting patients against stroke. Rationally, therefore, it seems appropriate for the ESH/ESC guidelines to recommend that no available drug class should be generically prescribed or proscribed. Beta-blockers should be avoided in patients with a high risk of incident diabetes, and in those with contraindications. However, they remain drugs of crucial importance in other common clinical situations, e.g. in hypertensive patients with angina pectoris, post-myocardial infarction, and heart failure.

**Keywords** Antihypertensive agents • Hypertension • Guidelines • Beta-blockers • Evidence-based medicine • Coronary artery disease • Ischaemic heart disease • Clinical trials

## Introduction

Over the last three decades, national and international guidelines on the management of hypertension have sought to rank the available drugs in order of preference, as first, second, third, and fourth-choice therapies. This 'step care' approach began with the US Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure in 1977<sup>1</sup> and is still maintained today in some national guidelines such as those published in 2006 in the UK.<sup>2</sup> A rigid ranking of antihypertensives certainly had merits at a time when some drugs in routine use (e.g. centrally acting agents) ran a substantial risk of serious adverse events, or could only be administered in combination (e.g. hydralazine).

However, today's clinicians have access to a range of generally well-tolerated modern agents, with differing modes of action but similar antihypertensive efficacy. Thus, it seems less logical nowadays to insist on a global ranking system for antihypertensives. Accordingly, the most recent guidelines of the European Society of Hypertension/European Society of Cardiology (ESH/ESC)<sup>3</sup> have decisively moved away from the step care approach. Instead, they recommend that evidence-based antihypertensive treatment should be adapted to a patient's clinical characteristics.

The difference between this individualized approach and that of the step care strategy is particularly marked when it comes

to the role of beta-blockers. Despite their long history as a cornerstone of antihypertensive treatment, the 2006 UK national guidelines downgraded beta-blockers to a fourth-choice treatment after diuretics, ACE-inhibitors/angiotensin receptor antagonists, and calcium antagonists.<sup>2</sup> In contrast, the 2007 ESH/ESC guidelines maintain beta-blockers among the drug classes that can be used to initiate and maintain antihypertensive treatment, together with diuretics, ACE-inhibitors, calcium antagonists, and angiotensin receptor antagonists.<sup>3</sup> This review considers the evidence underlying these contrasting recommendations, and argues that, in selected individuals, there is still a place for beta-blockers among the first-choice agents for hypertension.

## Beta-blockers and prevention of cardiovascular events

Why were beta-blockers downgraded to a fourth-choice treatment in the UK 2006 guidelines?<sup>2</sup> One important factor was the publication of trials and meta-analyses suggesting that beta-blockers might have less effect on mortality and morbidity than other antihypertensives. However, as we shall see, the evidence is far from conclusive.

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## Cardiovascular risk reduction: individual trials

Key trials often mentioned in support of the argument for downgrading beta-blockers include the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA)<sup>4</sup> and the Losartan Intervention For Endpoint (LIFE) study.<sup>5</sup> ASCOT was a 5-year randomized controlled trial in more than 19 000 hypertensive patients aged 40–79 years, all of whom had at least three other cardiovascular risk factors. Patients received either an amlodipine/perindopril-based or an atenolol/bendroflumethiazide-based regimen. The primary endpoint was non-fatal myocardial infarction (MI; including silent MI) and fatal coronary heart disease (CHD). A non-significant difference was found for the primary endpoint in favour of the amlodipine/perindopril-based regimen. Significant differences were found in favour of amlodipine/perindopril for fatal and non-fatal stroke, total cardiovascular events and procedures and all-cause mortality. Moreover, the incidence of diabetes was less on the amlodipine-based regimen. It should be mentioned, however, that reduction in blood pressure was also greater in the amlodipine-based arm.

LIFE was a 4-year randomized controlled trial in nearly 10 000 patients aged 55–80 years with hypertension and left ventricular hypertrophy (LVH).<sup>5</sup> Participants received losartan-based or atenolol-based therapy; as in ASCOT, a thiazide diuretic was commonly prescribed alongside both losartan and atenolol. The effects of the two regimens on blood pressure were similar. However, the primary composite endpoint (death, MI, or stroke) was significantly more common in the atenolol group, as was fatal or non-fatal stroke. There were also non-significant differences in favour of losartan for cardiovascular death and MI, and new-onset diabetes was less frequent with losartan.

One may readily understand why these two trials were influential in the decision of the UK guidelines to downgrade beta-blockers.<sup>2</sup> However, it is less easy to understand why thiazide diuretics retained their place, as most atenolol-treated patients in ASCOT and LIFE were also receiving thiazide diuretics. This makes it difficult to distinguish the favourable or adverse contribution of each class and illogical to drop one and save the other.

Nonetheless, it must be acknowledged that ASCOT and LIFE were large, well-controlled trials that showed a clear advantage for a calcium antagonist (with an ACE-inhibitor) or an angiotensin receptor antagonist, compared with an atenolol-based regimen. However, some other large trials comparing beta-blockers with other agents have shown no difference. For example, in the Heart Attack Primary Prevention in Hypertension trial (HAPPHY),<sup>6</sup> the International Prospective Primary Prevention Study in Hypertension (IPPPSH),<sup>7</sup> the second Swedish Trial in Old Patients with Hypertension (STOP-2),<sup>8</sup> and the International Verapamil-Trandolapril Study (INVEST)<sup>9</sup> the incidence of cardiovascular events was superimposable for patients treated with beta-blockers or other drugs.

The contrast between the results of ASCOT and INVEST is notable. INVEST was a greater size than ASCOT, including more than 22 500 patients aged at least 50 years. Like ASCOT, INVEST was conducted in relatively high-risk hypertensive patients [all had known coronary artery disease (CAD)] and it compared a

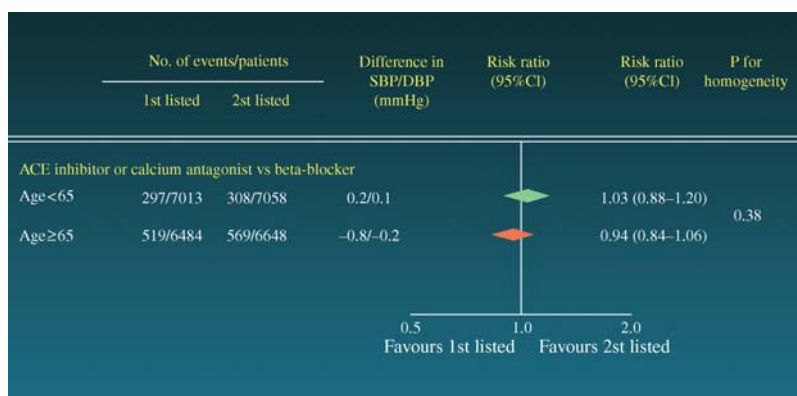
calcium antagonist/ACE-inhibitor-based regimen with a beta-blocker/thiazide diuretic regimen. In INVEST, the drugs used were verapamil sustained release/trandolapril and atenolol/hydrochlorothiazide. A similar percentage of patients in each group achieved target blood pressure control. In contrast to ASCOT, 2-year results from INVEST showed no difference between the groups for the primary endpoint (the combination of all-cause mortality and non-fatal MI or stroke). Nor were there any significant differences between the groups for other outcomes such as cardiovascular death, angina, or hospitalizations.

Further evidence suggesting that successful control of blood pressure (rather than the use of any particular drug class) may be the key to event reduction comes from the United Kingdom Prospective Diabetes Study (UKPDS). This trial showed that tight blood pressure control in patients with hypertension and type 2 diabetes significantly reduced the risk of diabetes-related death and both macrovascular and microvascular diabetic complications.<sup>10</sup> Importantly, it also revealed that the beta-blocker atenolol and the ACE-inhibitor captopril were equally effective in reducing the risk of non-fatal and fatal diabetic complications, death related to diabetes, heart failure, and progression of retinopathy.<sup>11</sup> If anything, there was a trend towards fewer events with atenolol than with captopril, though the difference was not significant.

## Cardiovascular risk reduction: meta-analyses

To gain an overview of the effects of different antihypertensive agents on mortality and morbidity, a number of meta-analyses have also been conducted. However, as with individual trials, the findings of meta-analyses are inconsistent. A 2004 meta-analysis by Carlberg *et al.*<sup>12</sup> included four studies in which atenolol was compared with placebo ( $n = 6825$ ). Despite the fact that atenolol was successful in lowering blood pressure, there were no significant differences between atenolol and placebo for all-cause mortality, cardiovascular mortality, or MI, although atenolol did appear to reduce the risk of stroke. The same meta-analysis also included five studies comparing atenolol with other agents ( $n = 17\,671$ ). Total mortality was significantly higher with atenolol than with other antihypertensives, and there was a trend towards higher cardiovascular mortality. Stroke was also more frequent with atenolol. These findings certainly cast doubt on the role of atenolol, but may not be assumed to apply to beta-blockers in general.

A 2006 meta-analysis by Khan *et al.*<sup>13</sup> incorporated data from 21 trials including a total of 145 811 participants. In placebo-controlled trials, beta-blockers significantly reduced major cardiovascular outcomes in patients younger than 60 years, but in older patients there was no significant benefit. In active-comparator trials, beta-blockers demonstrated similar efficacy to other antihypertensive agents in younger patients but not in older patients. The excess risk of beta-blockers in older patients was particularly marked for stroke. The authors concluded that 'beta-blockers should not be considered first-line therapy for older hypertensive patients without another indication for these agents [such as chronic heart failure (CHF), post-MI, or symptomatic CHD];



**Figure 1** The Blood Pressure-Lowering Treatment Trialists' Collaboration meta-analysis of 31 trials in 190 606 patients found that beta-blockers have similar efficacy to other agents in preventing major cardiovascular events in both elderly and younger patients. Reproduced with permission from Turnbull *et al.*<sup>15</sup>

however, in younger patients beta-blockers are associated with a significant reduction in cardiovascular morbidity and mortality.'

The most recent and largest meta-analysis in this area is that by the Blood Pressure-Lowering Treatment Trialists' Collaboration (BPLTTC).<sup>14,15</sup> This included 31 trials ( $n = 190\,606$ ), and showed no difference between the effects of different drug classes (ACE-inhibitors, calcium antagonists, or beta-blockers) on major cardiovascular events.<sup>15</sup> Nor were there any differences between the effects of different drug classes in different age groups (older or younger than 65 years) (Figure 1).

Thus, there is only limited and controversial evidence for the contention that beta-blockers have any less effect on overall cardiovascular morbidity and mortality than other agents (for a similar degree of blood pressure reduction). Nor is there any conclusive evidence that they are less protective in older than in younger patients.

## Beta-blockers and stroke

The next controversy that should be considered is whether beta-blockers are any less protective against stroke than other agents. This concern has been raised by both individual studies and by meta-analyses.

### Stroke prevention: individual trials

For example, LIFE showed a lower risk of stroke with a losartan-based regimen than an atenolol-based regimen, for a similar reduction in blood pressure.<sup>5</sup> On the other hand, INVEST found no evidence that a calcium antagonist-based regimen was better at reducing the risk of stroke than a non-calcium antagonist-based regimen.<sup>9</sup> In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial in more than 33 000 hypertensive patients, those receiving a thiazide diuretic (usually combined with a beta-blocker) were just as well protected against stroke as patients receiving a calcium antagonist or an ACE-inhibitor.<sup>16</sup>

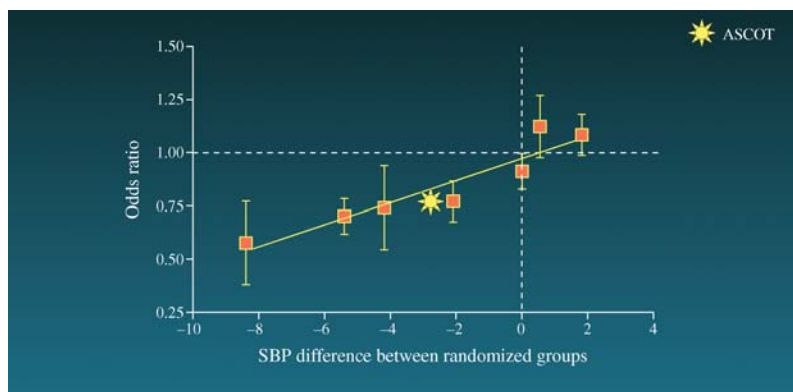
### Stroke prevention: meta-analyses

Several meta-analyses have also suggested that beta-blockers may be less protective against stroke than other antihypertensives, and have doubtless influenced guidelines.<sup>12,17,18</sup> For example, Lindholm *et al.* analysed 13 randomized controlled trials ( $n = 105\,951$ ) comparing treatment with beta-blockers to other antihypertensive drugs, and 7 ( $n = 27\,433$ ) comparing beta-blockers with placebo or no treatment. Although beta-blockers reduced the risk of stroke by 19% compared with placebo or no treatment, the relative risk of stroke was 16% higher for beta-blockers than with other antihypertensive agents.

However, such analyses should be seen in the context of convincing evidence that reducing blood pressure is probably the most important means of protecting patients against stroke regardless of how the reduction is achieved.<sup>14,19</sup> A meta-analysis by the BPLTTC shows that the greater the reduction in blood pressure, the greater the reduction in the risk of stroke (Figure 2).<sup>14</sup> The data from ASCOT fit closely when interpolated into this regression analysis.<sup>20</sup> This suggests that the fact that the amlodipine/perindopril-based regimen lowered systolic blood pressure by 2.7 mmHg more than the atenolol/bendroflumethiazide-based regimen may largely account for the difference in stroke between the two groups. In other words, blood pressure reduction appears to play a fundamental cerebrovascular protective role that far outweighs any drug-related effect.

### Tailoring treatment to the individual

Even though controversy continues, it is clear that beta-blockers retain an important place in the management of hypertension. When formulating their 2007 guidelines, the ESH/ESC took the view that when the results are not consistent (but in fact highly heterogeneous) straightforward step-care recommendations should be avoided.<sup>3</sup> They argue that the choice of antihypertensive agents should be tailored to an individual's concomitant conditions



**Figure 2** Relationship between the reduction in systolic blood pressure (SBP) and the risk of stroke in a Blood-Pressure Lowering Treatment Trialists' meta-regression analysis of data from trials of different drug treatments vs. placebo. Note that when data from ASCOT are interpolated, they fall close to the predicted position. Thus, the reduced protection against stroke reported in ASCOT may be due to a difference in blood pressure-lowering effect between treatments. Reproduced with permission from Turnbull<sup>14</sup> and Mancia, Zanchetti<sup>20</sup>

and medications, age, race, and risk. The ESH/ESC guidelines state that each of the recommended classes of antihypertensive drugs may have specific properties, advantages, and limitations. They list pros and cons for the different agents in specific conditions rather than for general usage. No single agent is generally prescribed, but each agent can be preferentially prescribed in specific conditions (Table 1).

### When are beta-blockers preferred?

Hypertensive patients who also have CAD and/or CHF are among those in whom beta-blockers may be a first-choice option. Beta-blockers may also be particularly appropriate in patients with tachyarrhythmias, glaucoma, and in pregnancy.

Numerous trials and meta-analyses have demonstrated a clear and consistent benefit of beta-blockade in angina pectoris, after MI,<sup>21</sup> and in CHF.<sup>22</sup> Indeed, beta-blockers are recommended by current guidelines as part of standard treatment for post-MI patients,<sup>23</sup> those with stable angina pectoris,<sup>24</sup> and in CHF.<sup>25,26</sup> Thus, many patients with hypertension already have a clear indication for beta-blockers because of their co-existing CHD or CHF.

Even trials and meta-analyses suggesting that beta-blockers may not be as effective as other agents against stroke demonstrate that they are at least as effective as other agents in protecting against MI and other coronary disease endpoints. For example, in LIFE there was a similar incidence of coronary events in patients receiving losartan-based or atenolol-based therapy.<sup>5</sup> In ASCOT, fatal and non-fatal MI were the only outcomes for which no difference could be demonstrated between the amlodipine/perindopril-based and the atenolol/bendroflumethiazide-based regimen.<sup>4</sup> This was despite the finding that, in this study, blood pressure reduction was less with the beta-blockers. Similarly, the meta-analyses by Lindholm *et al.*<sup>17</sup> and Bradley *et al.*,<sup>18</sup> found that beta-blockers had comparable efficacy with other agents in protecting against coronary events.

### When are beta-blockers inappropriate?

Beta-blockers are clearly contraindicated in a minority of patients, e.g. in asthma and in grade 2 or 3 atrioventricular block. Although they are not specifically contraindicated in patients with chronic obstructive pulmonary disease (COPD), caution is needed in such patients because of the possibility of concomitant reversible airway obstruction that is masked by the COPD. Caution is also recommended when prescribing beta-blockers to athletes because of possible effects on exercise capacity. There is some evidence that atenolol produces less regression of LVH than other agents, but little comparative data are available for other beta-blockers.<sup>3</sup>

The ESH/ESC Guidelines<sup>3</sup> also recommend that beta-blockers, especially in combination with a diuretic, should be avoided in patients with the metabolic syndrome, or who have impaired glucose tolerance. This is based on evidence that inhibitors of the renin-angiotensin system and calcium-channel blockers are less likely to be associated with new-onset diabetes than beta-blockers and diuretics.<sup>27,28</sup> A recent network meta-analysis of 22 clinical trials including more than 140 000 patients found that, in rank order, the association of antihypertensive drugs with incident diabetes was lowest for angiotensin-receptor blockers and ACE-inhibitors, followed by calcium antagonists and placebo, beta-blockers, and diuretics.<sup>29</sup>

It is not clear, however, whether the increased risk of developing diabetes with diuretics and beta-blockers is simply a matter of speeding-up the onset of diabetes in individuals who would have developed the condition anyway, or whether the risk of developing diabetes increases with continued treatment.<sup>28</sup> Nor is it absolutely certain whether long-term drug-induced diabetes increases cardiovascular risk in the same way as non-drug-induced diabetes, though indirect evidence suggests that this may be the case.<sup>28</sup> A further factor complicating the situation is that most studies indicating an increased risk of new-onset diabetes with beta-blockade have used atenolol. Other agents may not have the same effect—for

**Table 1** Conditions favouring the use of some antihypertensive drugs vs. others: European Society of Hypertension/ European Society of Cardiology guidelines

Thiazide diuretics	Beta-blockers	Calcium antagonists (dihydropyridines)	Calcium antagonists (verapamil/diltiazem)
Isolated systolic hypertension (elderly)	Angina pectoris	Isolated systolic hypertension (elderly)	Angina pectoris
Heart failure	Post-MI	Angina pectoris	Carotid atherosclerosis
Hypertension in blacks	Heart failure	Left ventricular hypertrophy	Supraventricular tachycardia
	Tachyarrhythmias	Carotid/coronary atherosclerosis	
	Glaucoma	Pregnancy	
	Pregnancy	Hypertension in blacks	
ACE-inhibitors	Angiotensin receptor antagonists	Diuretics (antialdosterone)	Loop diuretics
Heart failure	Heart failure	Heart failure	End-stage renal disease
Left ventricular dysfunction	Post-MI	Post-MI	Heart failure
Post-MI	Diabetic nephropathy		
Diabetic nephropathy	Proteinuria/microalbuminuria		
Non-diabetic nephropathy	Left ventricular hypertrophy		
Left ventricular hypertrophy	Atrial fibrillation		
Carotid atherosclerosis	Metabolic syndrome		
Proteinuria/microalbuminuria	ACE inhibitor-induced cough		
Atrial fibrillation			
Metabolic syndrome			

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example—the beta<sub>1</sub>-selective agent bisoprolol or the vasodilating beta-blocker carvedilol have not been reported to increase insulin resistance or new-onset diabetes. However, in the light of current knowledge, it seems prudent where possible to avoid the use of both diuretics and beta-blockers in hypertensive patients at high-risk of incident diabetes (i.e. those with the metabolic syndrome or impaired glucose tolerance).<sup>3</sup>

## Conclusions

Given that all the antihypertensive drug classes in current widespread use have a similar ability to lower blood pressure and are in general well-tolerated, nowadays it seems inappropriate to specify a priority order for antihypertensives across the whole range of patients. A more rational evidence-based approach, espoused by current ESH/ESC guidelines is to list the conditions in which some drugs should be preferred, and others in which they should be avoided. According to this perspective no available drug class should be generically prescribed, but no available drug classes should be generally proscribed. Many patients will require more than one drug, and it is useful for physicians to have as wide a choice as possible when attempting to tailor treatment to each patient's unique clinical profile. Beta-blockers should not be preferred in individuals in whom there is a high risk of incident diabetes (e.g. in patients with the metabolic syndrome or impaired glucose tolerance). However, they remain drugs of crucial importance in many other clinical pictures frequently associated with hypertension, such as angina pectoris, post-MI, and CHF. Their place as an important treatment option in the management of hypertension therefore remains assured.

**Conflict of interest:** none declared.

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