Beta-Blockers in the Treatment of Hypertension: Latest Data and Opinions

DANAI TSALTA, EMMANUEL ANASTASAKIS, DIMITRIOS E. PAPADOGIANNIS

1st Propedeutic Department of Internal Medicine, University of Athens, Laiko Hospital, Athens, Greece

Beta-adrenergic blockers have been widely used as first-line drugs in the treatment of idiopathic arteriolar hypertension for around 40 years. Recent meta-analyses, however, suggest that they are significantly inferior to other categories of drugs (thiazide diuretics, calcium channel blockers, angiotensin converting enzyme [ACE] inhibitors, angiotensin II receptor blockers).1,2 This observation has led to the demotion of beta-blockers to fourth-line drugs in the latest guidelines of the British Hypertension Society.3 The aim of this review is to illuminate the historical course of the use of beta-blockers in the treatment of hypertension up to the present day, to present the most recent data from meta-analyses that have downgraded them from antihypertensive drugs of first choice, and to discuss the different views expressed in the most recent guidelines for the treatment of hypertension issued by the European Society of Hypertension and the European Society of Cardiology.

Historical data

The theory of adrenergic blockade dates back to the deduction by Ahlquist in 1948 that there are two discrete types of adrenergic receptors, classified as alpha- and beta-receptors.4 Theories about adrenergic receptors were received with scepticism and doubt until the discovery of dichloroisoproterenol by Powell and Slater in 1958.5 This substance selectively inhibits the action of isoproterenol, which according to Ahlquist acted via the beta-receptors, and gave proof that those receptors existed. James Black showed that inhibition of the sympathetic nervous system using a suitable agent could benefit patients with cardiac arrhythmias and angina.6,7 Black’s work resulted in two new non-selective beta-blockers—pronethalol,8 with an endogenous sympathomimetic action, and propranolol,7 without such action—as well as in his receiving the Nobel Prize for Medicine and Physiology in 1988.6 Pronethalol was soon abandoned as carcinogenic,9 but propranolol went on to become the standard medication in clinical practice for patients with angina and arrhythmias.

Prichard and Gillam10 established that propranolol had antihypertensive properties and the drug became accepted as an oral antihypertensive medication. Later, it also came to be used as supplementary therapy to phentolamine in the treatment of phaeochromocytoma. Subsequently, labetalol, with its combined action on the alpha and beta-receptors, proved useful in the treatment of cases with emergency hypertension.11

In 1967, Lands et al12 described two types of beta-receptors, beta1 and beta2, and beta-blockers were classified as beta1-selective or non-selective according to their ability to oppose the action of sym-
pathomimetic amines in low doses in some tissues but not in others. Practolol came on to the scene in 1970, as the first beta1-selective blocker, but after four years’ clinical use it was found to be extremely toxic. In the following years, agents with various pharmacological profiles were approved for the treatment of systemic hypertension, among which were the non-selective beta-blockers propranolol, nadolol and timolol, the beta1-selective blockers metoprolol, atenolol, betaxolol and bisoprolol, the beta-blockers with an endogenous sympathomimetic action pindolol, oxprenolol and celiprolol, and the alpha/beta-blocker labetalol.

The latest trend in hypertension as far as beta-blockers are concerned is represented by the newest vasodilatory agents carvedilol and nebivolol. Carvedilol is an adrenergic blocker with an antagonistic action towards both alpha1 and beta1,2 receptors and a direct vasodilatory effect. Carvedilol has less of a relation with the alpha1-adrenergic receptors than does labetalol (carvedilol ratio alpha1:beta1:10; labetalol ratio alpha1:beta1:4) and has been studied especially in patients with symptomatic heart failure. In contrast to labetalol, carvedilol has a proven antioxidative, anti-inflammatory and antiplatelet action. Data from the GEMINI study also showed that carvedilol has a particularly beneficial pharmacological profile for glycaemic and metabolic control in patients with diabetes and hypertension.

Nebivolol is a beta-blocker with high selectivity for beta1-adrenergic receptors, with no endogenous sympathomimetic action and with the ability to promote the endothelial production of nitric oxide (NO), thus causing vasodilation. NO is synthesised by the amino acid L-arginine in the vascular endothelium. Reduced bioavailability of NO is associated with arterial stiffness, hypertension, atherosclerosis, and cardiovascular disease. Based on these data, nebivolol has become an invaluable antihypertensive agent that is widely used in clinical practice.

### Latest data from large meta-analyses: beta-blockers versus placebo

Beta-blockers have long been used as a first-line treatment for hypertension, based on a well-founded conviction that they improved life expectancy and cardiovascular mortality. Comparisons with placebo established their use in the treatment of hypertension. Seven such controlled studies were carried out, five of which used atenolol. The studies found differing degrees of blood pressure reduction (Table 1).

Two recent meta-analyses by Lindholm et al and Bradley et al which focused on the use of beta-blockers as first-line therapy, investigated, among other things, the effect of beta-blockers compared with placebo (Table 1). Lindholm et al carried out a meta-analysis of 18 clinical trials, including seven placebo-controlled studies. The endpoints were stroke, myocardial infarction, and overall mortality. The relative risk (RR) for stroke with beta-blockers was reduced by 19% (RR 0.81, 95% confidence interval [CI] 0.71-0.93). When the atenolol studies were analysed separately, the reduction in RR was only 15% (RR 0.85, 95% CI 0.72-1.01). The reduction for the other beta-blockers was 16% (RR 0.84, 95% CI 0.64-1.10) (Table 2). The STOP trial was the only study to compare the combination of beta-blockers and thiazide diuretics with placebo and found a 45% reduction in RR for stroke (95% CI 0.35-0.85) and a

### Table 1. Studies comparing beta-blockers with placebo. Change in blood pressure (BP, mmHg).

<table>
<thead>
<tr>
<th>Study</th>
<th>Beta-blocker</th>
<th>Comparison</th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPPPSH (1985)</td>
<td>Oxprenolol</td>
<td>Placebo</td>
<td>-4.1</td>
<td>-1.5*†</td>
</tr>
<tr>
<td>MRC (1985)</td>
<td>Propranolol</td>
<td>Placebo</td>
<td>-9.5</td>
<td>-5.0*†</td>
</tr>
<tr>
<td>HEP (1986)</td>
<td>Atenolol</td>
<td>No treatment</td>
<td>-18.0</td>
<td>-11.0*†</td>
</tr>
<tr>
<td>STOP (1991)</td>
<td>Atenolol</td>
<td>Placebo</td>
<td>-19.5</td>
<td>-8.1*</td>
</tr>
<tr>
<td>MRCOA (1992)</td>
<td>Metoprolol</td>
<td>Placebo</td>
<td>-13.0</td>
<td>-7.0*†</td>
</tr>
<tr>
<td>Dutch TIA (1993)</td>
<td>Atenolol</td>
<td>Placebo</td>
<td>-5.8</td>
<td>-2.9*</td>
</tr>
<tr>
<td>TEST (1995)</td>
<td>Atenolol</td>
<td>Placebo</td>
<td>-4.0</td>
<td>-3.0*</td>
</tr>
</tbody>
</table>

*Studies included in the meta-analysis of Lindholm et al. †Studies included in the meta-analysis of Bradley et al.
43% reduction in RR for all-cause mortality (95% CI 0.39-0.85). In the Hypertension in Elderly Patients (HEP) trial, which compared atenolol with placebo, the mean reduction in RR for stroke was an equally satisfactory 42% (95% CI 0.36-0.94) and was probably due to the fact that these patients were taking additional medication from early on, mainly thiazide diuretics.

Bradley et al., in a meta-analysis of 13 randomised clinical trials, included four placebo-controlled studies (Table 1). The endpoints of the meta-analysis were overall mortality, coronary artery disease, stroke, cardiovascular mortality, total cardiovascular events, and cessation or withdrawal of therapy (Table 3). The results showed a clear reduction in the risk of stroke by 20% (RR 0.80, 95% CI 0.66-0.96), and in total cardiovascular events by 12% (RR 0.88, 95% CI 0.79-0.97). These results confirm the findings of Lindholm et al. There was no proof that the action of beta-blockers reduced the risk of overall mortality, coronary artery disease, or cardiovascular mortality. The meta-analysis showed that the probability of therapy discontinuation was the same for beta-blockers and placebo. However, there was significant heterogeneity among the studies as regards the latter parameter ($I^2=99.5\%$). There was no difference in the probability of therapy discontinuation as regards oxprenolol (results of one study, RR 0.95, 95% CI 0.87-1.04), whereas there was a higher probability of interruption in the case of propranolol and atenolol (two studies, RR 3.67, 95% CI 1.99-6.79).

### Latest data from large meta-analyses: beta-blockers versus other categories of antihypertensive drug

Starting antihypertensive therapy with beta-blockers has recently been called strongly into question. The two meta-analyses by Lindholm et al. and Bradley et al. played a fundamental role in this, while a third meta-analysis carried out by the British Hypertension Society as part of a review of their guidelines, focusing on the comparison between various categories of antihypertensive drugs, highlighted the deficiencies of beta-blockers and especially atenolol. The three meta-analyses included randomised, controlled, clinical trials published until the end of 2005. The ASCOT trial was thus included in all three.

Lindholm et al., as mentioned above, examined a total of 18 clinical trials in which beta-blockers were used as first-line antihypertensive therapy in at least 50% of patients in one arm. This criterion allowed the inclusion of studies that either had one arm without initiation of monotherapy with beta-blockers or were not randomised. The latter studies were reported by the authors separately, as “mixed” studies. Studies that had a placebo arm were also included (Table 1). All the studies included data concerning overall mortality, stroke, and myocardial infarction. Heart failure was not included as an endpoint since many studies did not provide adequate data.

The analysis had two components: comparison of beta-blockers with all other hypertensive drugs and comparison with placebo (the latter findings have been discussed above). The authors also analysed the data in three other categories: beta-blockers apart from atenolol, beta-blockers together with diuretics where more than 50% of patients began with a beta-blocker (“mixed” studies), and atenolol.

The results of this meta-analysis showed that in all the studies where beta-blockers were compared...
with other antihypertensive drugs, the RR for stroke was 16% greater with beta-blockers (95% CI 1.04-1.30, p=0.009). For overall mortality the RR was 3% greater with beta-blockers (95% CI 0.99-1.08, p=0.14), while there was no significant difference as regards myocardial infarction (Table 4).

When the studies were analysed separately by category, the most significant difference was for atenolol, which showed an increase in RR of 26% for stroke (95% CI 1.15-1.38, p<0.0001), whereas for the other beta-blockers in the “mixed” studies the RR was increased by 9% (95% CI 0.98-1.21, p=0.13). For beta-blockers apart from atenolol only a small number of clinical events were recorded (just 77 strokes in 9004 cases) and the results were unclear (Table 4).

The meta-analysis published by Bradley et al included 13 randomised clinical trials in which monotherapy with beta-blockers was initiated. Overall mortality was the primary endpoint, while secondary endpoints were coronary artery disease, stroke, cardiovascular mortality, total cardiovascular events, and discontinuation of therapy because of side effects (Table 5). Studies with placebo were also included. In contrast to Lindholm et al, Bradley et al did not compare beta-blockers with all other antihypertensive drugs together, but made comparisons by category (thiazide diuretics, renin-angiotensin inhibitors, calcium channel blockers) as well as comparing beta-blockers with placebo, as discussed above. The comparison of beta-blockers with diuretics showed no difference as regards overall mortality, coronary artery disease, stroke, cardiovascular mortality, and the total number of cardiovascular events. However, the authors had reservations about these findings because there was considerable heterogeneity among the studies involved. This lack of homogeneity (in the case of stroke it reached I²=72.9%,

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Beta-blockers</th>
<th>Atenolol</th>
<th>Non-atenolol</th>
<th>BB + diuretic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>1.16 (1.04-1.30)</td>
<td>1.26 (1.15-1.38)</td>
<td>1.20 (0.30-4.71)*</td>
<td>1.09 (0.98-1.21)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.02 (0.93-1.12)</td>
<td>1.05 (0.91-1.21)</td>
<td>0.86 (0.67-1.11)</td>
<td>1.00 (0.81-1.22)</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>1.03 (0.99-1.08)</td>
<td>1.08 (1.02-1.14)</td>
<td>0.89 (0.70-1.12)</td>
<td>0.97 (0.89-1.05)</td>
</tr>
</tbody>
</table>

*n=77,904.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Thiazides</th>
<th>Ca-channel blockers</th>
<th>RAS inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mortality</td>
<td>1.04 (0.91-1.19), I² 22.4%</td>
<td>1.07 (1.00-1.14), I² 2.2%</td>
<td>1.08 (0.95-1.23), I² 53.4%</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.12 (0.82-1.54), I² 66.3%</td>
<td>1.05 (0.96-1.15), I² 32.2%</td>
<td>0.90 (0.76-1.06), I² 42.2%</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.17 (0.65-2.09), I² 72.9%</td>
<td>1.24 (1.11-1.40), I² 0%</td>
<td>1.30 (1.11-1.53), I² 29.1%</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>1.09 (0.90-1.32), I² 54.7%</td>
<td>1.15 (0.92-1.46), I² 60.3%</td>
<td>1.00 (0.92-1.29), I² 43.8%</td>
</tr>
<tr>
<td>Total cardiovascular events</td>
<td>1.13 (0.99-1.28), I² 45.2%</td>
<td>1.18 (1.08-1.29), I² 0%</td>
<td>1.00 (0.72-1.38), I² 73.8%</td>
</tr>
<tr>
<td>Withdrawal/cessation of treatment</td>
<td>1.86 (1.39-2.50), I² 78.2%</td>
<td>1.20 (0.71-2.04), I² 93.4%</td>
<td>1.41 (1.29-1.54), I² 12.1%</td>
</tr>
</tbody>
</table>

RAS – renin-angiotensin system.
p=0.01) was probably related to the type of beta-blocker. There was an increased risk of stroke when non-selective beta-blockers were used (propranolol) (RR 2.28, 95% CI 1.31-3.95), but there was no difference in the case of cardioselective beta-blockers (atenolol or metoprolol) (RR 1.00, 95% CI 0.74-1.33). It is significant that in comparison with those who were taking diuretics, patients under beta-blocker treatment were more likely to stop treatment because of side effects (RR 1.86, 95% CI 1.39-2.50) (Table 5).

Compared with calcium channel blockers, beta-blockers were 7% less effective in reducing all-cause mortality (RR 1.07, 95% CI 1.00-1.14), and were associated with a 24% greater risk of stroke (RR 1.24, 95% CI 1.11-1.40), and an 18% greater risk of all cardiovascular events (RR 1.18, 95% CI 1.08-1.29) (Table 5).

Bradley et al\textsuperscript{2} combined the data from two classes of renin-angiotensin inhibitors (ACE inhibitors and angiotensin II receptor blockers). Beta-blockers failed to reduce the risk of stroke to the same level as the latter drugs (RR 1.30, 95% CI 1.11-1.53) and entailed a higher risk of discontinuation of therapy (RR 1.41, 95% CI 1.29-1.54); however, there was no significant difference as regards overall mortality, coronary artery disease, cardiovascular mortality, and total cardiovascular events. Despite this, there was significant heterogeneity in the risk of cardiovascular events ($\Gamma^2=73.8\%$, $p=0.02$) with the effect of beta-blockers being similar to that of ACE inhibitors but less than that of angiotensin II receptor blockers (Table 5).

On the basis of the above findings, the British Hypertension Society reviewed its guidelines for the pharmaceutical treatment of hypertension.\textsuperscript{3} As part of this review, 20 randomised, controlled trials were analysed for a combination of antihypertensive agents in five basic categories. Placebo studies were not included, since the object was to review the guidelines for the treatment of hypertension. However, placebo studies of isolated systolic hypertension were included because of a lack of comparable trials. Where available, data were recorded concerning overall mortality, stroke (ischaemic or haemorrhagic), myocardial infarction including silent infarction, heart failure, new-onset diabetes mellitus, reperfusion interventions (coronary and carotid arteries), unstable angina, and exclusion from the study. A total of seven randomised clinical trials that compared beta-blockers with other hypertensive medication were included.\textsuperscript{24,27,34,35,37,41,44} The meta-analysis, naturally, was not limited to beta-blockers but extended to all categories.

Beta-blockers and diuretics did not differ significantly as regards mortality. The heterogeneity among the studies ($\Gamma>75\%$) did not allow this study to draw conclusions for stroke and myocardial infarction (Table 6).

The only study that included a comparison with angiotensin II receptor blockers, was the LIFE trial\textsuperscript{35} (losartan compared with atenolol). This included more than 9000 hypertensive patients with electrocardiographically documented left ventricular hypertrophy and demonstrated the same degree of blood pressure reduction in both the losartan and atenolol arms. The follow up showed that angiotensin II receptor blockers were associated with a 25% lower incidence of stroke (RR 0.75, 95% CI 0.63-0.88), a 25% lower rate of new-onset diabetes mellitus (RR 0.75, 95% CI 0.64-0.88), as well as a 14% lower rate of discontinuation of treatment (RR 0.86, 95% CI 0.82-0.91). There was no difference between the two types of treatment as regards heart failure or angina. Mortality was lower in the losartan group, but the difference was not statistically significant. In patients with isolated systolic hypertension and left ventricular hypertrophy losartan therapy reduced the incidence of stroke by 40% (RR 0.60, 95% CI 0.38-0.92) and mortality by

\begin{table}[h]
\centering
\caption{Beta-blockers compared with other antihypertensive agents. Relative risk (95\% confidence interval). Study by British Hypertension Society.\textsuperscript{3}}
\begin{tabular}{|l|l|l|l|}
\hline
Endpoint & Thiazides & Ca-channel blockers & RAS inhibitors \\
\hline
Overall mortality & 1.04 (0.91-1.19) & 1.06 (1.00-1.12) & 1.11 (0.99-1.22) \\
Stroke & 1.27 (0.73-2.23) & 1.23 (1.12-1.33) & 1.25 (1.22-1.37) \\
Coronary artery disease & 1.15 (0.82-1.60) & 1.09 (0.98-1.19) & 0.95 (0.72-1.14) \\
Heart failure & 1.04 (0.74-1.26) & 1.04 (0.74-1.26) & 1.05 (0.82-1.24) \\
New-onset diabetes & 1.29 (1.22-1.36) & 1.25 (1.12-1.36) & \\
Withdrawal & 1.20 (0.71-2.04) & 1.14 (1.09-1.18) & \\
\hline
\end{tabular}
\end{table}
46% (RR 0.54, 95% CI 0.34-0.87). On the other hand, the same study showed that in black patients with hypertension and left ventricular hypertrophy losartan therapy was associated with an increased risk of stroke compared with atenolol (RR 2.18, 95% CI 1.08-4.40).

A comparison of calcium channel blockers with beta-blockers showed that the former drugs were associated with a 23% lower risk of stroke (RR 0.77, 95% CI 0.67-0.88), whereas there was no significant difference regarding mortality or myocardial infarction (Table 6).

**Discussion**

The three meta-analyses agree on one thing: beta-blockers are inferior to other available first-choice antihypertensive drugs in the treatment of hypertension and for that reason they should no longer be considered as a first-line medication. Lindholm et al compared beta-blockers with other categories of antihypertensive medication taken together and concluded that they are deficient as regards the incidence of stroke. This approach, however, could lead to false conclusions, since beta-blockers could be superior or inferior to an individual category of antihypertensive drugs with respect to a specific endpoint. The study by Bradley et al filled this gap, by comparing other medications with beta-blockers on a category by category basis. This meta-analysis revealed the superiority of calcium channel blockers and inhibitors of the renin-angiotensin system as regards overall mortality and stroke. The British Hypertension Society corroborated these findings and in its new guidelines recommends starting antihypertensive therapy with calcium channel blockers or thiazide diuretics in patients aged over 55 years and with ACE inhibitors in patients aged below 55 years.

Of great importance is the analysis of data with respect to the involvement of atenolol in the studies and the results this drug achieved. In the meta-analysis of Lindholm et al the studies that used atenolol were analysed separately and the impressive 26% greater risk of stroke casts serious doubt upon its role. In another meta-analysis, Karagiannis et al analysed the data from 10 randomised clinical studies that used atenolol (4 comparing atenolol with placebo, 5 comparing atenolol with another antihypertensive drug, and 1 that compared atenolol with both placebo and a drug from another category). They found no statistically significant difference between atenolol and placebo in any of the endpoints (stroke, acute myocardial infarction, cardiovascular or overall mortality), whereas in comparison with drugs of other categories atenolol was associated with an increased risk of stroke (RR 1.27, 95% CI 1.16-1.38), and increased cardiovascular and overall mortality (RR 1.13, 95% CI 1.03-1.23 and RR 1.07, 95% CI 1.01-1.14, respectively). There was no statistically significant difference between atenolol and other drugs with respect to myocardial infarction (RR 1.02, 95% CI 0.95-1.11, p=0.55).

It should be noted, however, that in the meta-analyses mentioned above, the number of studies that did not involve atenolol was very small, with few clinical events. There were only three such studies in Lindholm’s meta-analysis of which two provided data concerning stroke), five in the analysis of Bradley et al, and just one in the British Hypertension Society’s analysis. Further investigation is needed into the effect of beta-blockers apart from atenolol on blood pressure and cardiovascular events and appropriately designed trials should be carried out.

In all the meta-analyses, the studies that were included used combined therapy to a large degree for the attainment of the target blood pressure, and this should be taken into consideration when conclusions are drawn. We should also keep in mind Zanchetti’s pertinent remark, that hypertension studies focused on cardiovascular events are generally limited to older age groups and do not include the whole picture.

As the British Hypertension Society’s report pointed out, the patient population under 55 years of age is represented only to a very small degree in clinical trials, and limited data are available concerning the achievement of target blood pressure in young patients. The report goes on to say that initial treatment with a beta-blocker or renin system inhibitor can provide a more ideal blood pressure reduction than can a calcium channel blocker or thiazide diuretic, and concludes with the recommendation that, in young patients who have intolerance or contraindications for ACE inhibitors or angiotensin II receptor blockers, beta-blockers should be kept in mind. Women who are trying to become pregnant and patients with elevated sympathetic tone should also be considered candidates for initial beta-blocker therapy. Finally, in patients with well controlled blood pressure who are under treatment that already includes beta-blockers there is no need for the substitution of an alternative agent.

The European Society of Hypertension, in its recently issued guidelines, treats this matter circum-

---

**Table 6**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Category</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>Calcium channel blockers</td>
<td>0.77</td>
<td>0.67-0.88</td>
</tr>
<tr>
<td>Stroke</td>
<td>Other antihypertensive drugs</td>
<td>0.77</td>
<td>0.67-0.88</td>
</tr>
<tr>
<td>Stroke</td>
<td>Atenolol</td>
<td>1.27</td>
<td>1.16-1.38</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Calcium channel blockers</td>
<td>1.13</td>
<td>1.03-1.23</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Other antihypertensive drugs</td>
<td>1.07</td>
<td>1.01-1.14</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Atenolol</td>
<td>1.02</td>
<td>0.95-1.11</td>
</tr>
</tbody>
</table>
spects, stating that the conclusions from the meta-analyses of Lindholm et al.\(^1\) and Bradley et al.\(^2\) as well as the guidelines of the British Hypertension Society, should be viewed with reservation and caution. It notes that beta-blockers have proved beneficial in patients with angina, heart failure, and recent myocardial infarction, which are significant complications related to hypertension.\(^{33-35}\) With regard to the climate of doubt concerning the efficacy of beta-blockers that arose from the above meta-analyses, the European Society of Hypertension comments that the two main studies on which the meta-analyses were based, namely the LIFE\(^3\) and ASCOT\(^3\) trials, demonstrated the superiority of an angiotensin II receptor blocker and a calcium channel inhibitor, respectively, over atenolol with regard to stroke (LIFE), and stroke and mortality (ASCOT). However, both trials were designed in such a way that combination therapy was used at an early stage, and a large majority of patients who were under beta-blocker treatment ended up receiving the combination of beta-blocker and thiazide diuretic. On the other hand, in the INVEST trial,\(^4\) where the initial beta-blocker therapy was followed in most patients by administration of thiazide diuretic, the incidence of cardiovascular events was similar in the arm where initial verapamil therapy went on to be combined with the ACE inhibitortrandolapril. Moreover, beta-blockers significantly reduced the risk of stroke compared with placebo.\(^1,2\) This shows that at least a part of the shortcomings shown by the combination of beta-blocker and thiazide diuretic in the ASCOT trial\(^3\) could have been due to the smaller degree of reduction in blood pressure, especially central blood pressure.\(^56\)

One mechanism that could explain the deficiencies of beta-blockers is the small degree of regression in left ventricular hypertrophy they achieve.\(^57\) A number of studies\(^58-60\) have shown more regression with various angiotensin II receptor blockers (valsartan, irbesartan, losartan) than with atenolol. This conclusion is reinforced significantly by the results of an echocardiographic sub-study of LIFE,\(^61\) which involved 960 patients and confirmed a significantly greater regression of left ventricular hypertrophy with losartan than with atenolol. The same study showed that regression of left ventricular hypertrophy was maintained over time, but reached its greatest extent after two or three years of therapy. The sub-study also revealed that the reduction in left ventricular hypertrophy as a result of treatment was a significant and independent factor correlated with a reduction in cardiovascular risk, stroke, and cardiovascular and overall mortality, reinforcing the findings of other long-term, prospective studies.\(^62-64\)

Newer data from the LIFE study showed that over a mean 4.5-year follow up, sudden cardiac death\(^65\) and incidence of new-onset diabetes mellitus\(^66\) were correlated with the regression of left ventricular hypertrophy (using echocardiographic indexes), regardless of the kind of therapy (losartan or atenolol), with other cardiovascular risk factors, and with the reduction in blood pressure. However, losartan had better results with respect to regression of electrocardiographic indexes of left ventricular hypertrophy.\(^67\)

In a smaller study,\(^68\) another angiotensin II receptor blocker, irbesartan, was also found to be more effective than atenolol in improving electrocardiographic indexes of left ventricular hypertrophy. The REASON study compared a standard combination of ACE inhibitor and diuretic (perindopril, indapamide) with atenolol, but the greater reduction in left ventricular mass was correlated with a greater reduction in blood pressure and a satisfactory reduction in central blood pressure.\(^69\)

In a small study that investigated the effect of telmisartan compared with carvedilol using cardiac ultrasound and magnetic resonance imaging, there was significantly greater regression of left ventricular hypertrophy with the former drug for the same degree of reduction in 24-hour blood pressure.\(^70\)

In contrast to the British guidelines, the recent guidelines of the European Society of Hypertension\(^52\) include beta-blockers among the options for first-line antihypertensive therapy. On the other hand, they stress the fact that beta-blockers promote weight gain,\(^71\) have a negative effect on lipid metabolism, and (in comparison with other drugs) increase the incidence of new-onset diabetes mellitus.\(^72,73\)

For these reasons, they should not be preferred for hypertensive patients with a compromised metabolic profile and risk factors such as metabolic syndrome and its component elements (abdominal obesity, high normal or impaired fasting glucose level, and glucose intolerance) — i.e., conditions that increase the risk of diabetes mellitus. The same applies to thiazide diuretics, which in large doses have a negative effect on lipid profile and the occurrence of diabetes mellitus.\(^74\)

In research studies thiazides have often been used in combination with beta-blockers, thus making it difficult to distinguish the extent to which each drug contributes to the appearance of new-onset diabetes.

The above conclusions, however, probably do not apply to the newer, vasodilatory beta-blockers,
carvedilol and nebivolol, which have little or no effect on the metabolic profile, as well as a lower incidence of new-onset diabetes compared with the older, standard beta-blockers.\(^{75,76}\) The role of newer, vasodilatory beta-blockers is still in question, since there are no studies that demonstrate the effect of these agents in hypertensive patients. According to Bradley et al,\(^{2}\) the mechanism by which beta-blockers fail to reduce stroke is a dual one: first, the increased risk of new-onset diabetes,\(^{72-76}\) and second, the failure to reduce central aortic pressure to the same degree as brachial.\(^{56}\) Since diabetes takes years to develop cardiovascular complications, the authors consider the second mechanism to be more probable, namely the failure of beta-blockers to reduce central pressure. Theoretically, the vasodilatory agents carvedilol and nebivolol are better placed to reduce central pressures than are conventional beta-blockers. Vasodilation is likely to have a beneficial effect on the pulse wave reflected from the periphery, in this way reducing central pressures. Nevertheless, the bradycardia caused by beta-blockers is probably related with their inability to reduce central pressures, as shown by the comparisons of atenolol with thiazide and amlodipine with perindopril in the CAFE study.\(^{56}\)

The fruitful discussion that was prompted by the conflicting views presented above has been fuelled further by newer data concerning the effect of beta-blockers on atheromatous lesions in the coronary arteries. More specifically, Sipahi et al reported that beta-blocker therapy reduced to a statistically significant degree the rate of development of atherosclerosis in the coronary vessels of patients with diabetes mellitus.\(^{77}\) The study included 1515 diabetic patients who were under hypolipidaemic medication and monitored the degree of regression of the volume of atherosclerotic plaque using intravascular ultrasound, comparing patients who were taking beta-blockers with those who were not.

Conclusions

Beta-blockers as a class of antihypertensive agents have come under serious scrutiny, mainly as regards their inability to provide the same degree of protection against stroke as do other agents. Most studies, however, involved atenolol and included patients of advanced age. Taking an objective look at the existing data, we consider that beta-blockers comprise a class of drugs with different pharmacological profiles and properties; thus any generalisation of conclusions could be inaccurate. The newer vasodilatory agents and their effect on the reduction of central pressure have not yet been investigated. The knowledge that a reduction in blood pressure in itself, independently of the antihypertensive agent, is beneficial for all cardiovascular events remains at the core of any therapeutic approach.\(^{78,79}\) Therefore, beta-blockers can be considered as first-choice drugs for the treatment of hypertension, as recommended in the recent guidelines of the European Society of Hypertension and the European Society of Cardiology.\(^{52}\) However, the unfavourable effect of beta-blockers on the metabolic profile of patients with certain risk factors (metabolic syndrome, abdominal obesity, glucose intolerance, familial history of diabetes mellitus), as well as their lower efficacy in the regression of left ventricular hypertrophy, must always be taken into account when the treating physician is called upon to treat coexistent hypertension.

References

13. Wright P: Untoward effect associated with practolol adminis-
B-Blockers and Hypertension


Veterans Administration Cooperative Study Group on Antihypertensive Agents: Comparison of propranolol and hydrochlorothiazide for the initial treatment of hypertension.

(Continued on next page)

