DEBATE

Beta Blockers Should Not be Used as First Line Antihypertensive Agent

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Introduction

Hypertension is an important public health problem in both industrialized and low and middle income countries due to its high prevalence (1) and associated morbidity and mortality (2). Beta blockers have been widely prescribed to treat hypertension over the years (3). While the benefits of these agents in reducing cardiovascular events in people with preexisting heart disease are clear (4), their clinical benefits in individuals with uncomplicated hypertension are less well-defined. Questions have been raised about beta blockers as first-line treatment options in hypertension (5).

Beta Blockers and Prevention of Cardiovascular Events

The concept of cardiovascular protection mediated by beta blockers was born in the 1970s from several prospective randomized trials in patients with previous myocardial infarctions, in whom mortality of about 25% was observed (6). This observation was then uncritically translated from secondary to primary prevention of the broad spectrum of cardiovascular diseases, including uncomplicated hypertension. On the basis of this extrapolation, and the common idea that reducing blood pressure (BP) automatically reduces cardiovascular morbidity and mortality, even most recent international guidelines (7,8) recommend beta blockers as first-line agents in uncomplicated hypertension.

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Cardiovascular risk reduction: individual trials

The robustness of the evidence for use of beta blockers as first line therapy for uncomplicated hypertension was first challenged by the results of two of the latest large hypertension trials: the Losartan Intervention for End Point Reduction in Hypertension (LIFE) study (9) and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)–Blood Pressure Lowering Arm (BPLA) (10).

LIFE was a 4-year randomized controlled trial in nearly 10,000 patients aged 55–80 years with hypertension and left ventricular hypertrophy (LVH) (9). 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 favor of losartan for cardiovascular death and MI, and new-onset diabetes was less frequent with losartan.

ASCOT (10) 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. A non-significant difference was found for the primary endpoint in favor of the amlodipine/erindopril based regimen. Significant differences were found in favor 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 BP was also greater in the amlodipine based arm.

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.

A 2004 meta-analysis by Carlberg *et al.* (11) included four studies in which atenolol was compared with placebo (n=6,825). Despite the fact that atenolol was successful in lowering BP, 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.* (12) 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, post-MI, or symptomatic coronary heart disease); however, in younger patients beta blockers are associated with a significant reduction in cardiovascular morbidity and mortality.'

Even a recent Cochrane review, the most complete and comprehensive document analyzing the available research regarding beta blockers in primary hypertension, concluded that beta blockers (a) exert a relatively weak effect in reducing stroke compared to placebo or no treatment, (b) do not have any protective effect with regard to coronary artery disease, and (c) compared to other drugs, such as calcium channel blockers and renin-angiotensin-aldosterone system (RAAS) inhibitors, show evidence of worse outcomes, particularly with regard to stroke. The final message was categorical: "The available evidence does not support the use of beta blockers as first-line drugs in the treatment of hypertension (13)."

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 trials

LIFE study showed a lower risk of stroke with a losartan based regimen than an atenolol based regimen, for a similar reduction in blood pressure (9).

Lindholm *et al*. (14) analyzed 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.

The Reasons for the Lack of Cardiovascular Protection

Why beta blockers do not confer similar cardiovascular protection to other classes of agents despite their proven efficacy in lowering BP? Several mechanisms could be responsible for this reduced or lack of efficacy of beta blockers in uncomplicated hypertension.

Problems with Atenolol

Most of the trials in the meta-analyses discussed above used atenolol and other beta blockers that had no vasodilatory properties. Further, in most of the trials atenolol was used in a once-daily dosage, whereas ideally it needs to be taken more frequently, based on its pharmacokinetic and pharmacodynamics properties (a half-life of 6–9 hours) (15). Neutel *et al.* (16) confirmed that atenolol, when taken once daily, leaves the patient unprotected in the last 6 hours of a 24-hour period, as demonstrated by 24-hour ambulatory BP monitoring. It is possible that this short duration of action of atenolol may have contributed to the results observed in clinical trials that used atenolol to treat hypertension.

Reduced efficacy of beta blockers in lowering blood pressure

The efficacy of beta blockers in lowering BP involves various mechanisms, such as antagonism of catecholamine mediated cardiotoxic effects and of hyperactivity of the sympathetic system, a decrease in cardiac output, the inhibition of renin release and angiotensin II production, the blockade of presynaptic alpha–adrenoceptors that increase the release of norepinephrine from sympathetic nerve terminals, and a decrease in central vasomotor activity (17,18). In contrast, blockade is known to determine a vasoconstrictive effect in arteries and veins through beta 2 receptor antagonism, thus antagonizing the antihypertensive effect of beta blockers. Moreover, it should not be forgotten that beta blockers are a complex class of drugs involving several compounds that differ from one another in terms of pharmacologic characteristics, such as beta 1/beta 2-selectivity, intrinsic sympathomimetic activity, and vasodilatory capabilities. Thus, it is clear that the effect of blockade in BP control is complex and not yet completely understood. Furthermore, the BP lowering efficacy of beta blockers is suboptimal. This was first observed in older trials, in which beta blocker therapy resulted in small decreases in BP values, requiring the addition of second drugs in most patients (19). Even in more recent trials, such as LIFE, BP control was achieved in 50% of patients assigned to the beta blockers group, and only 10% of patients continued receiving beta blocker monotherapy (9). In ASCOT-BPLA, compared to the atenolol based arm, an amlodipine based regimen conferred a small but statistically significantly higher effect in BP lowering (1.7 mmHg mean lower systolic BP and 2.0 mmHg mean lower diastolic BP) (10).

Pulse-wave dyssynchrony

Bangalore *et al*. (20) offer an interesting hypothesis to explain the probable adverse effect of beta blockers. Their theory concerns the effect of these drugs on the arterial pulse wave.

Normally, with each contraction of the left ventricle during systole, an arterial pulse wave is generated and propagated forward to the peripheral arteries. This wave is then reflected back to the heart from the branching points of peripheral arteries. The final form of the pressure wave at the aortic root is a synchronized summation of the forward-traveling wave and the backward-reflected wave.

In healthy people with normal arteries, the reflected wave merges with the forward traveling wave in diastole and augments coronary blood flow. In patients whose arteries are stiff due to aging or vascular comorbidities, the reflected wave returns faster and merges with the incident wave in systole, resulting in higher left ventricular afterload and less coronary perfusion (21).

Bangalore *et al.* (20) propose that artificially reducing the heart rate with beta blockers may further dyssynchronize the pulse wave, adversely affecting coronary perfusion and leading to an increased risk of cardiovascular events and death

Unfavorable hemodynamic effect

In the elderly, the hemodynamic profile is typically characterized by low cardiac output and high peripheral resistance. Focusing on their pure pharmacodynamics effects, most beta blockers lower BP by further decreasing cardiac output and increasing systemic vascular resistance. The difference pattern of hypertension, such as mainly systolic or diastolic, also might affect beta blockers efficacy. Because of their negative chronotropic effect, beta blockers should not be prescribed to patients with predominantly systolic hypertension. In fact, the decrease in heart rate tends to be compensated by a parallel increase in stroke volume, which will elevate systolic BP and decrease diastolic BP, resulting in an unfavorable increase in pulse pressure.

Reduced efficacy in reducing central aortic pressure (Pseudo antihypertensive effect)

Although beta blockers reduce peripheral BP, which is commonly measured and considered a reference in everyday clinical practice, beta blockers have been shown to be less efficacious in reducing central aortic BP compared with RAAS blockers, diuretics, and calcium channel blockers, a phenomenon commonly called the pseudoantihypertensive effect.

The CAFE (Conduit Artery Function Evaluation) trial (22), a substudy of the main ASCOT trial (10), indicated that beta blocker based therapy was less effective in reducing central aortic pressure than were regimens based on an ACE inhibitor or a calcium channel blocker.

The CAFE researchers recruited 2,073 patients from five ASCOT centers and used radial artery applanation tonometry and pulse-wave analysis to derive central aortic pressures and hemodynamic indices during study visits up to a period of 4 years. Although the two treatment groups achieved similar brachial systolic BPs, the central aortic systolic pressure was 4.3 mmHg lower in the amlodipine group (95% CI 3.3–5.4; $p<0.0001$), and the central aortic pulse pressure was 3.0 mmHg lower (95% CI 2.1–3.9; $p<0.0001$).

This increase in central aortic systolic BP should be more predictive of cardiovascular events, such as stroke and MI, than the traditional peripheral (brachial) BP measurements. The pseudoantihypertensive effect thus might explain the increased risk for stroke seen in clinical trials (14).

Reduced adherence to therapy due to undesirable adverse effects

Beta blockers considered as a class have many undesirable adverse effects, including drowsiness, lethargy, sleep disturbance, visual hallucinations, depression, blurring of vision, dreams or nightmares, pulmonary side effects such as increased airway resistance in asthmatics, and peripheral vascular side effects such as cold extremities, Raynaud's phenomenon, and erectile and orgasmic dysfunction. It is common experience that beta blockers are often less tolerated in elderly patients than other drugs.

Reduced left ventricular hypertrophy (LVH) regression

The regression of LVH has been shown to lower cardiovascular risk independently of other risk factors (23). In the LIFE study, antihypertensive treatment with losartan based therapy resulted in greater LVH regression than conventional atenolol based therapy (9). Moreover, a meta-analysis of 109 studies of more than 2,000 patients comparing the effects of various antihypertensive strategies on LVH regression, beta blocker-based therapy induced a significantly lower LVH regression compared to other drugs, especially RAAS blockers (24).

Adverse metabolic profile

Traditional beta blockers, in fact, have been shown to increase insulin resistance and predispose patients to diabetes Bangalore *et al.* (25) evaluated the effect of beta-blockers in a meta-analysis of 12 studies in 94,492 patients followed up for more than 1 year. Beta blocker therapy resulted in a 22% higher risk of new-onset diabetes mellitus (RR 1.22, 95% CI 1.12–1.33) than with other nondiuretic antihypertensive agents. Possible mechanisms by which beta blockers may contribute to the development of diabetes include weight gain, attenuation of the beta-receptor-mediated release of insulin from pancreatic beta cells and decreased blood flow through the microcirculation in skeletal-muscle tissue, leading to decreased glucose uptake and increased insulin-resistance. Second, beta blockers can worsen the blood lipid profile. In fact, the long-term administration of beta blockers has been shown to increase triglyceride levels by 20% to 50% and decrease high-density lipoprotein cholesterol by 10% to 20% (26).

What Recent Guidelines Say About Beta Blockers?

The 2007 European Society of Hypertension and European Society of Cardiology recommended beta blockers as an option in both initial and subsequent antihypertensive treatment strategies (7). But based on the results of recent studies (20,27) and meta-analysis (28-30), European Society of Hypertension and European Society of Cardiology gave the reappraisal document (31) in 2009 which concluded that beta blockers have pros and cons, as do other antihypertensive drugs. This means that there is no reason for a *priori* banning but rather a need to consider the circumstances in which they may offer more or less disadvantages, compared with other therapeutic options.

Recently the 2012 NICE (British Hypertension Society) guidelines (32) for the treatment of hypertension have been published that no longer include beta blockers as first-line or even second- or third-line drugs for patients with uncomplicated hypertension. Beta blockers are, however, still recommended for patients with compelling indications.

Newer Beta Blockers: Are They Better?

Most of the data regarding the efficacy of beta blocker therapy in primary hypertension derive from studies conducted with older agents, such as propranolol, atenolol, and metoprolol. Newer beta blockers showing

vasodilatory properties, such as carvedilol and nebivolol, show a much better hemodynamic and metabolic profile than older compounds. But whether these vasodilating agents such as carvedilol and nebivolol, which show a more favorable hemodynamic and metabolic profile, will be more efficacious in reducing cardiovascular morbidity and mortality remains to be determined

Conclusion

In conclusion, beta blockers should not be the first drugs of choice in the management of uncomplicated hypertension. Beta blockers, in particular, atenolol is associated with a higher rate of stroke and significant adverse effects. They may be used in addition to other antihypertensive agents to achieve BP goals. The use of beta-blockers still remains appropriate in patients with compelling indications such as angina pectoris, heart failure or post-myocardial infarction.

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