CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will prescribe beta-blockers as antihypertensive therapy only when there are compelling indications for them or as add-on treatment

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Beta-blockers for hypertension: Are they going out of style?

ABSTRACT

Although beta-blockers lower blood pressure in most patients, the outcomes of clinical hypertension trials of these drugs have been disappointing, and the value of beta-blockers in treating hypertensive patients who do not have compelling indications for them has been questioned. Until these drugs are proved beneficial, they should be used as antihypertensive therapy only in patients with compelling cardiac indications for them or as add-on agents in those with uncontrolled or resistant hypertension.

KEY POINTS

No evidence exists that beta-blockers prevent first episodes of cardiovascular events in patients with hypertension, and in some trials, outcomes were worse with beta-blockers than with antihypertensive drugs of other classes.

Younger hypertensive patients have hemodynamic characteristics that would seem to be amenable to beta-blocker therapy. However, most clinical trials of beta-blockers did not stratify patients by age.

Most trials of the antihypertensive effects of beta-blockers used atenolol (Tenormin), which is not an ideal representative of this class of drugs.

Newer beta-blockers with vasodilatory properties may overcome the adverse effect of increased peripheral vascular resistance that occurs with older agents such as atenolol.

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In recent years the role of beta-blockers as a primary tool to treat hypertension has come under question. These drugs have shown disappointing results when used as antihypertensive therapy in patients without heart disease, ie, when used as primary prevention. At the same time, beta-blockers clearly reduce the risk of future cardiovascular events in patients who already have heart disease, eg, who already have had a myocardial infarction or who have congestive heart failure.

Several meta-analyses and a few clinical trials have shown that beta-blockers may have no advantage over other antihypertensive drugs, and in fact may not reduce the risk of stroke as effectively as other classes of blood pressure medications.

Why should this be? Is it that the patients in the antihypertensive trials were mostly older, and that beta-blockers do not work as well in older patients as in younger ones? Or does it have to do with the fact that atenolol (Tenormin) was the drug most often used in the trials? Would newer, different beta-blockers be better?

Hypertension experts currently disagree on how to interpret the available data, and this has led to conflict and confusion among clinicians as to the role of beta-blockers in managing hypertension. Current evidence suggests that older beta-blockers may not be the preferred first-line antihypertensive drugs for hypertensive patients who have no compelling indications for them (eg, heart failure, myocardial infarction, diabetes, high risk of coronary heart disease). However, newer beta-blockers with vasodilatory properties should be considered in cases of uncontrolled or resistant hypertension, especially in younger patients.

Further, while controversy and debate continue over the benefits and adverse effects of one class of antihypertensive drugs vs another, it is indisputable that controlling arterial blood pressure to the recommended goal offers major protection against cardiovascular and renal events in patients with hypertension.[1,2]

MECHANISM OF ACTION OF BETA-BLOCKERS

Beta-blockers effectively reduce blood pressure in both systolic-diastolic hypertension and isolated systolic hypertension.[3–5] Exactly how is not known, but it has been proposed that they may do so by:

Reducing the heart rate and cardiac output. When catecholamines activate beta-1 receptors in the heart, the heart rate and myocardial contractility increase. By blocking beta-1 receptors, beta-blockers reduce the heart rate and myocardial contractility, thus lowering cardiac output and arterial blood pressure.[6]

Inhibiting renin release. Activation of the renin-angiotensin system is another major pathway that can lead to elevated arterial blood pressure. Renin release is mediated through the sympathetic nervous system via beta-1 receptors on the juxtaglomerular cells of the kidney. Beta-blockers can therefore lower blood pressure by inhibiting renin release.[7]

Inhibiting central nervous sympathetic outflow, thereby inducing presynaptic blockade, which in turn reduces the release of catecholamines.

Reducing venous return and plasma volume.

Generating nitric oxide, thus reducing peripheral vascular resistance (some agents).[8]

Reducing vasomotor tone.

Reducing vascular tone.

Improving vascular compliance.

Resetting baroreceptor levels.

Attenuating the pressor response to catecholamines with exercise and stress.

The lipid solubility and water solubility of each beta-blocker determine its bioavailability and side-effect profile

HETEROGENEITY OF BETA-BLOCKERS

Selectivity

Beta-blockers are not all the same. They can be classified into three categories.

Nonselective beta-blockers block both beta-1 and beta-2 adrenergic receptors. It is generally accepted that beta-blockers exert their primary antihypertensive effect by blocking beta-1 adrenergic receptors.[6] Of interest, nonselective beta-blockers inhibit beta-2 receptors on arteries and thus cause an unopposed alpha-adrenergic effect, leading to increased peripheral vascular resistance.[9] Examples of this category:

- Nadolol (Corgard)
- Pindolol (Visken)
- Propranolol (Inderal)
- Timolol (Blocadren).

Selective beta-blockers specifically block beta-1 receptors alone, although they are known to be nonselective at higher doses. Examples:

- Atenolol (Tenormin)
- Betaxolol (Kerlone)
- Bisoprolol (Zebeta)
- Esmolol (Brevibloc)
- Metoprolol (Lopressor, Toprol).

Beta-blockers with peripheral vasodilatatory effects act either via antagonism of the alpha-1 receptor, as with labetolol (Normodyne) and carvedilol (Coreg),[10] or via enhanced release of nitric oxide, as with nebivolol (Bystolic).[8]

Lipid and water solubility

The lipid solubility and water solubility of each beta-blocker determine its bioavailability and side-effect profile.

Lipid solubility determines the degree to which a beta-blocker penetrates the blood-brain barrier and thereby leads to central nervous system side effects such as lethargy, nightmares, confusion, and depression. Propranolol is highly lipid-soluble; metoprolol and labetalol are moderately so.

Water-soluble beta-blockers such as atenolol have less tissue permeation, have a longer half-life, and cause fewer central nervous system effects and symptoms.[11]

Routes of elimination

Beta-blockers also differ in their route of elimination.

Atenolol and nadolol are eliminated by the kidney and require dose adjustment in patients with impaired renal function.[12,13]

On the other hand, propranolol, meto-

prolol, labetalol, carvedilol, and nebivolol are excreted primarily via hepatic metabolism.[13]

BETA-BLOCKERS IN THE MANAGEMENT OF HYPERTENSION

Beta-blockers were initially used to treat arrhythmias, but by the early 1970s they were also widely accepted for managing hypertension.[14] Their initial acceptance as one of the first-line classes of drugs for hypertension was based on their better side-effect profile compared with other antihypertensive drugs available at that time.

In the 1980s and 1990s, beta-blockers were listed as preferred first-line antihypertensive drugs along with diuretics in national hypertension guidelines.[15] Subsequent updates of the guidelines favored diuretics as initial therapy and relegated all other classes of antihypertensive medications to be alternatives to diuretics.[16] Although beta-blockers remain alternative first-line drugs in the latest guidelines (published in 2003; see reference 66), they are the preferred antihypertensive agents for patients with cardiac disease.

The current recommendations reflect the findings from hypertension trials in which patients with myocardial infarction and congestive heart failure had better cardiovascular outcomes if they received these drugs,[17–19] including a lower risk of death.[20,21] It was widely assumed that beta-blockers would also prevent first episodes of cardiovascular events.

However, to date, there is no evidence that beta-blockers are effective as primary prevention. Several large randomized controlled trials showed no benefit with beta-blockers compared with other antihypertensive drugs—in fact, there were more cardiovascular events with beta-blockers (see below).

Beta-blockers are well tolerated in clinical practice, although they can have side effects that include fatigue, depression, impaired exercise tolerance, sexual dysfunction, and asthma attacks.

Wiysonge et al[22] analyzed how many patients withdrew from randomized trials of antihypertensive treatment because of drug-related adverse events. There was no significant difference in the incidence of fatigue, depressive symptoms, or sexual dysfunction with beta-blockers compared with placebo, and trial participants on a beta-blocker were not statistically significantly more likely to discontinue treatment than those receiving a placebo in three trials with 22,729 participants (relative risk [RR] 2.34, 95% confidence interval [CI] 0.84–6.52).

THE CONTROVERSY: WHAT THE TRIALS SHOWED

Messerli et al[23] performed a meta-analysis published in 1998 that suggested that beta-blockers may not be as effective as diuretics in preventing cardiovascular events when used as first-line antihypertensive therapy in elderly patients. In 10 randomized controlled trials in 16,164 patients who were treated with either a diuretic or a beta-blocker (atenolol), blood pressure was normalized in two-thirds of diuretic-treated patients but only one-third of patients treated with atenolol as monotherapy. Diuretic therapy was superior with regard to all end points, and beta-blockers were found to be ineffective except in reducing cerebrovascular events.

The LIFE study (Losartan Intervention for Endpoint Reduction in Hypertension)[24] compared the angiotensin-receptor blocker losartan (Cozaar) and atenolol in 9,193 patients with hypertension and left ventricular hypertrophy. At 4 years of follow-up, the rate of primary cardiovascular events (death, myocardial infarction, or stroke) was lower in the losartan group than in the atenolol group. The difference was mainly due to a 25% lower incidence of stroke, which was statistically significant. The rates of myocardial infarction and death from cardiovascular causes were not significantly different between the two treatment groups. The systolic blood pressure was 1 mm Hg lower in the losartan group than in the atenolol group, which was statistically significant.

Atenolol and nadolol are eliminated by the kidney and need dose adjustment in patients with impaired renal function

Carlberg et al[25] performed another important meta-analysis that questioned whether atenolol reduces rates of cardiovascular morbidity and death in hypertensive patients. The results were surprising: eight randomized controlled trials including more than 6,000 patients and comparing atenolol with placebo or no treatment showed no dif-

ferences between the treatment groups with regard to the outcomes of all-cause mortality (RR 1.01, 95% CI 0.89–1.15), cardiovascular mortality (RR 0.99, 95% CI 0.83–1.18), or myocardial infarction (RR 0.99, 95% CI 0.83–1.19).

In addition, when atenolol was compared with other antihypertensives in five other randomized controlled trials that included more than 14,000 patients, those treated with atenolol had a higher risk of stroke (RR 1.30, 95% CI 1.12–1.50) and death (RR 1.13, 95% CI 1.02–1.25).

The ASCOT-BPLA trial (Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm)[26] had similar results. This trial compared the combination of atenolol plus the diuretic bendroflumethiazide against the combination of the calcium channel blocker amlodipine (Norvasc) plus the angiotensin-converting enzyme (ACE) inhibitor perindopril (Aceon). Although no significant difference was seen in the primary outcome of nonfatal myocardial infarction or fatal coronary heart disease (unadjusted hazard ratio [HR] with amlodipine-perindopril 0.90, 95% CI 0.79–1.02, $P = .1052$), the amlodipine-plus-perindopril group had significantly fewer strokes (327 vs 422, HR 0.77, 95% CI 0.66–0.89, $P = .0003$), fewer total cardiovascular events (1,362 vs 1,602, HR 0.84, 95% CI 0.78–0.90, $P = .0001$), and fewer deaths from any cause (738 vs 820; HR 0.89, 95% CI 0.81–0.99, $P = .025$).

Once-daily atenolol leaves the patient unprotected for the last 6 hours

Lindholm et al[27] performed a meta-analysis that included studies of selective beta-blockers (including atenolol) and nonselective beta-blockers, with a follow-up time of more than 2 years. Compared with placebo or no treatment, beta-blockers reduced the risk of stroke by 19% but had no effect on myocardial infarction or all-cause mortality. Compared with other antihypertensive drugs, beta-blockers were less than optimum, and the relative risk of stroke was 16% higher. Atenolol was the beta-blocker used in most of the randomized clinical trials included in this meta-analysis.

The Cochrane group[22] found beta-blockers to be inferior to all other antihypertensive drugs with respect to the ability to lower the risk of stroke.

WHY WERE THE RESULTS SO DISAPPOINTING?

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 pharmacodynamic properties (a half-life of 6–9 hours).[3] Neutel et al[28] 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 blood pressure 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.

Differences between older and younger patients

Another possible reason for the disappointing results is that the trials included many elderly patients, in whom beta-blockers may not be as effective. The pathophysiology of hypertension in younger people is different from that in older patients.[29] Hemodynamic characteristics of younger hypertensive patients include a high cardiac output and hyperdynamic circulation with a low pulse pressure, while older patients have lower arterial compliance with an elevated vascular resistance.

The notion of choosing antihypertensive medications on the basis of age and age-related pathophysiology is supported by several clinical studies. Randomized controlled trials appear to show that beta-blockers are effective in younger hypertensive patients.[30]

Conversely, the CAFE (Conduit Artery Function Evaluation) trial,[31] a substudy of the main ASCOT trial,[26] 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

Beta-blockers are better than placebo in younger patients but not older patients

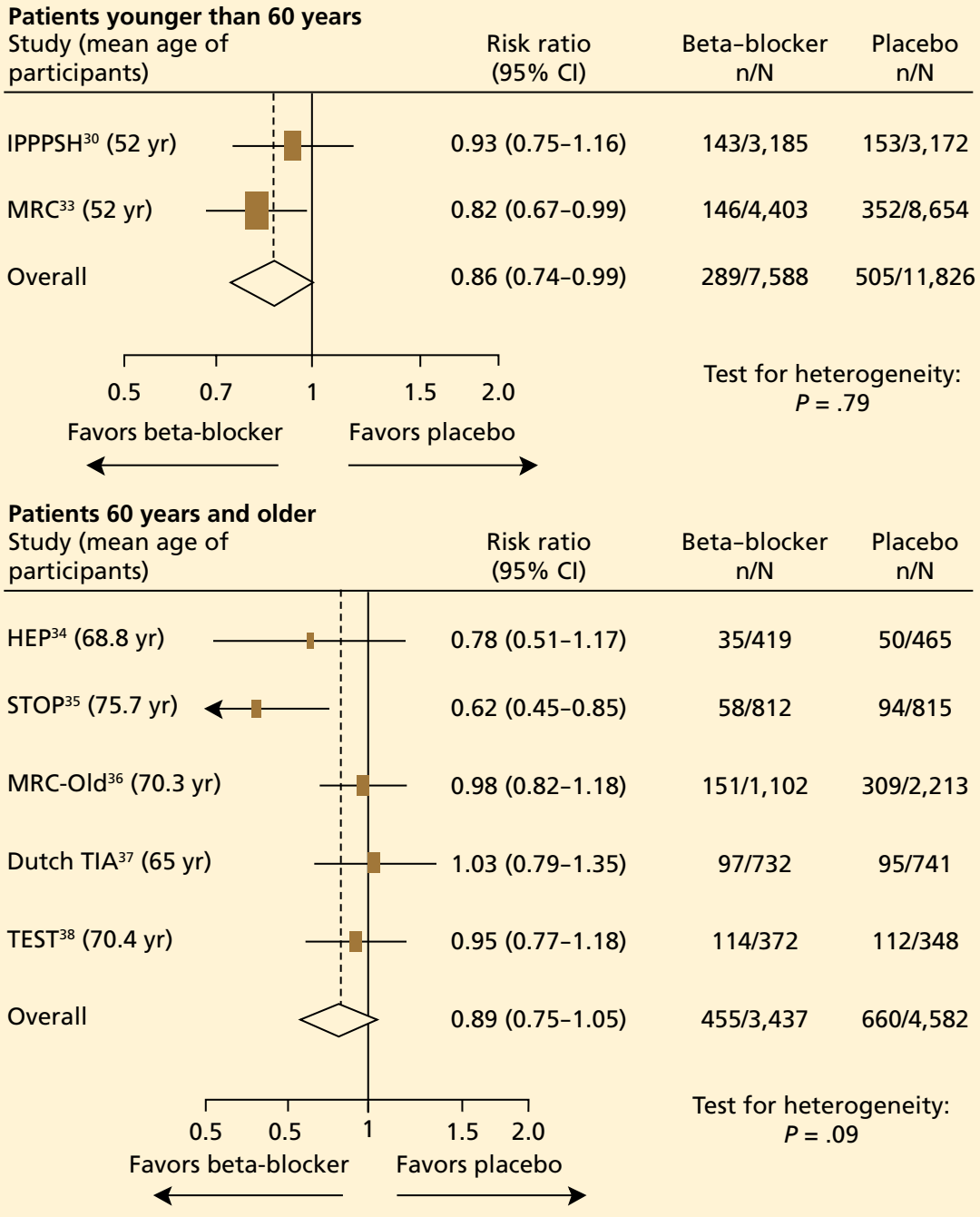

FIGURE 1. Risk ratios for the composite outcome (death, stroke, or myocardial infarction) in patients under age 60 (top) and patients age 60 and older (bottom) receiving beta-blockers or placebo. The size of the boxes represents the number of participants who experienced a cardiovascular event. Trials are listed in order of publication. CI = confidence interval.

Beta-blockers are as good as other classes in younger patients but not older patients

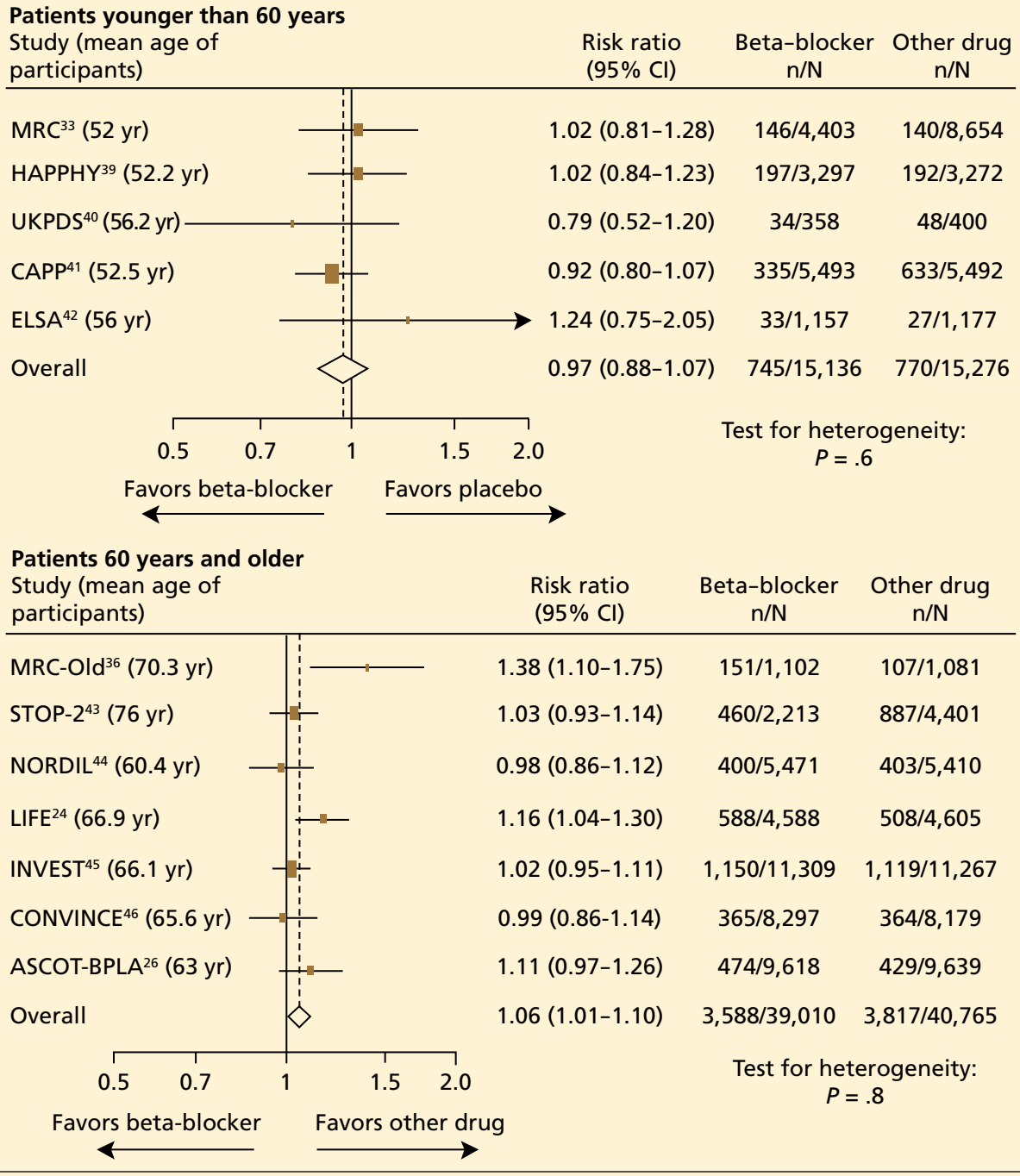

FIGURE 2. Risk ratios for the composite outcome (death, stroke, or myocardial infarction) in patients under age 60 (top) and patients age 60 and older (bottom) receiving beta-blockers or other antihypertensive drugs. The size of the boxes represents the number of participants who experienced a cardiovascular event. Trials are listed in order of publication. CI = confidence interval.

study visits up to a period of 4 years. Although the two treatment groups achieved similar brachial systolic blood pressures, the central aortic systolic pressure was 4.3 mm Hg lower in the amlodipine group (95% CI 3.3–5.4; $P < .0001$), and the central aortic pulse pressure was 3.0 mm Hg lower (95% CI 2.1–3.9; $P < .0001$).

Khan and McAlister[32] performed a meta-analysis in which they stratified clinical trials by the age of the study participants: those enrolling patients younger than 60 years and those enrolling patients 60 years and older. Included were 145,811 patients from 21 hypertension trials. In placebo-controlled trials,[30,33–38] beta-blockers reduced the risk of major cardiovascular events in younger patients (RR 0.86, 95% CI 0.74–0.99, based on 794 events in 19,414 patients) but not in older patients (RR 0.89, 95% CI 0.75–1.05, based on 1,115 events in 8,019 patients) (FIGURE 1). In active comparator trials,[24,33,36,39–46] beta-blockers were similar in efficacy to other antihypertensive agents in younger patients (1,515 events in 30,412 patients, RR 0.97, 95% CI 0.88–1.07) but not in older patients (7,405 events in 79,775 patients, RR 1.06, 95% CI 1.01–1.10) (FIGURE 2), with the excess risk being particularly marked for strokes (RR 1.18, 95% CI 1.07–1.30).

In view of these findings, Khan and McAlister[32] proposed that beta-blockers should not be the first-line drugs for elderly hypertensive patients who do not have any other compelling indications for this class of drugs.

Pulse-wave dyssynchrony

Bangalore et al[47] 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.[48]

Bangalore et al[47] 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.

Metabolic side effects

Older beta-blockers, and especially atenolol, have well-known metabolic adverse effects, particularly impairment of glycemic control. This adverse effect appears to occur only with beta-blockers that do not possess vasodilatory properties and thus increase peripheral vascular resistance, which results in lower glucose availability and reduced uptake by skeletal muscles.[49]

Bangalore et al[50] 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.

Beta-blockers are well tolerated in clinical practice, despite their side effects

Of note, however, the meta-analysis did not show a significantly higher risk of the onset of diabetes with propranolol or metoprolol than with other nondiuretic antihypertensives when studies of these beta-blockers were separated from atenolol-based studies.

Further, the United Kingdom Prospective Diabetes Study[40] found that cardiovascular outcomes in patients with good blood pressure control were similar when atenolol-based therapy was compared with therapy with the ACE inhibitor captopril (Capoten).

A meta-analysis conducted by Balamuthusamy et al[51] in 2009 found no higher risk of stroke in patients with hypertension and diabetes mellitus who received beta-blockers than in those who received other antihypertensive medications. However, beta-blockers were associated with a higher risk of death from cardiovascular causes (RR 1.39, 95% CI 1.07–1.804; $P < .01$) compared with renin-angiotensin blockade.

NEWER BETA-BLOCKERS MAY BE BETTER

In the United States, more than 40 million prescriptions for atenolol are written every year, making it by far the most commonly used beta-blocker for the treatment of hypertension.[52] It is clear, however, that atenolol is not an ideal representative of this class of antihypertensive medications.

Preliminary data from studies of newer beta-blockers that possess beneficial vasodilatory properties are encouraging. Animal studies and preliminary human studies find that these new-generation beta-blockers cause fewer adverse metabolic effects and improve endothelial function, measures of arterial stiffness, and cardiovascular outcomes.

Carvedilol

Carvedilol is a nonselective beta-blocker with vasodilatory effects that are thought to be due to its ability to concurrently block alpha-1 receptors in addition to beta receptors.[53] In experiments in vitro and in trials in patients with diabetes and hypertension, carvedilol increased endothelial vasodilation and reduced inflammation and platelet aggregation. These effects may be achieved though antioxidant actions, thereby preserving nitric oxide bioactivity.[54,55]

Preliminary data on newer beta-blockers are encouraging

In the Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial,[56] carvedilol was associated with better maintenance of glycemic control in diabetic hypertensive patients than was metoprolol. Insulin sensitivity improved with carvedilol but not with metoprolol, and fewer patients on carvedilol progressed to microalbuminuria.

Nebivolol

Nebivolol is a novel selective beta-blocker with a much higher affinity for beta-1 adrenergic receptors than for beta-2 adrenergic receptors. Among all the beta-blockers in clinical use today, nebivolol has the highest selectivity for beta-1 receptors.[8]

Nebivolol causes vasodilation through activation of the L-arginine/nitric oxide pathway.[57–59] Blockade of synthesis of nitric oxide leads to local arterial stiffness. Endothelial dysfunction is characterized by decreased bioavailability of nitric oxide and has been shown to be a strong predictor of cardiovascular outcomes. By generating nitric oxide, nebivolol reduces peripheral vascular resistance, overcoming a significant side effect of earlier beta-blockers that lowered blood pressure but ultimately increased peripheral vascular tone and resistance.[8]

In an experiment in a bovine model,[60] nebivolol significantly reduced the pulse-wave velocity (a measure of arterial stiffness), while atenolol had no effect. Moreover, evidence for the role of the L-arginine/nitric oxide pathway in the vasodilatory effect of nebivolol was demonstrated by co-infusion of N^G-monomethyl-L-arginine, a specific endothelial nitric oxide synthetase inhibitor that attenuated the reduction of pulse-wave velocity by nebivolol.

In studies in hypertensive patients, nebivolol was associated with a better metabolic profile than atenolol, with none of the adverse effects on insulin sensitivity that atenolol had.[61] In the Study of Effects of Nebivolol Interventions on Outcomes and Rehospitalization in Seniors With Heart Failure (SENIORS) trial, significantly fewer patients receiving nebivolol died or were admitted to the hospital for cardiovascular reasons compared with those receiving placebo.[62]

Although these findings are encouraging, we do not yet know if these effects will translate into a significant reduction in cardiovascular outcomes in clinical trials. Large, prospective hypertension outcome trials, particularly to evaluate primary prevention of cardiovascular outcomes, are needed for an evidence-based approach to using the newer beta-blockers as preferred first-line therapy for hypertension.

WHAT RECENT GUIDELINES SAY ABOUT BETA-BLOCKERS

The British National Institute for Health and Clinical Excellence and the British Hypertension Society, in their 2004 guidelines, recommended beta-blockers as one of several first-line antihypertensive medications in young, nonblack patients.[63] On the other hand, they advised clinicians to be aware of the reported increase in onset of diabetes mellitus in patients treated with these medications. After

the LIFE[24] and ASCOT[26] study results were published, these guidelines were amended to exclude beta-blockers as preferred routine initial therapy for hypertension.[64]

More recently, the 2007 European Society of Hypertension and European Society of Cardiology reconsidered the role of beta-blockers, recommending them as an option in both initial and subsequent antihypertensive treatment strategies.[65]

The current guidelines from the National Heart, Lung, and Blood Institute,[66] which were published in 2003, were highly influenced by the results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),[2] and favor diuretics as the first-line therapy. However, they indicate that beta-blockers are a suitable alternative, particularly when a compelling cardiac indication is present.[53] We hope that the next update, expected late in 2009, will re-address this issue in the light of more recent data.

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