Is the Relationship Between Beta-Blocker–Induced Heart Rate Lowering and Cardiovascular Outcomes the Result of Confounding by Indication?

In a meta-analysis of beta-blocker trials for the treatment of hypertension, Bangalore et al. (1) report that there is an inverse relationship between achieved heart rate at the end of the trials and risk of myocardial infarction and cardiovascular death. The authors suggest that the heart rate decrease associated with beta-blockers leads to increased central aortic pressure, and that this phenomenon is the cause of increased adverse events associated with lower heart rate. However, this study and conclusion are subject to several sources of residual confounding, including indication bias. It is well known in cardiovascular trials that patients who require higher doses of medication are almost always those with the worst cardiovascular disease; the converse is also true. In their limitation section, the authors note that they were unable to determine the dose of beta-blocker used. However, based on the pharmacology of beta-blockers, it is highly likely that the achieved heart rate is closely correlated with the dose of beta-blocker that was required to achieve blood pressure control. In addition, many of the trials that the authors included in their meta-analysis were conducted before the era of ambulatory blood pressure monitoring, and therefore included patients with white coat hypertension, who are at low risk for cardiovascular events. In these low-risk patients, blood pressure would most likely have been controlled with a low dose of beta-blockers, and therefore they would have had higher heart rates and few cardiovascular events.

Although these potential confounding factors are difficult to test in a post-hoc fashion, the authors should have the data to answer the question of the relationship between achieved heart rate and achieved blood pressure, as well as the relationship between achieved heart rate and percentage of patients achieving goal blood pressure. If these analyses demonstrate an inverse relationship between heart rate and measures of blood pressure control, then it would suggest that the authors’ findings simply reflect the fact that more difficult to control patients require higher doses of antihypertensive medication—in this case, a beta-blocker.

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Atenolol Versus Other Beta-Adrenergic Blockers

The question is: Does atenolol differ from other beta-adrenergic blockers in clinical outcome? Bangalore et al. (1) nicely related unfavorable trial outcomes to the degree of pulse rate reduction induced by beta-adrenergic blockers. But is it not a mistake to include the HAPPHY (Heart Attack Primary Prevention in Hypertension) trial without considering that the 2 beta-adrenergic blockers arms differed as to outcome (2)? Patients on atenolol showed higher death rates and patients on metoprolol showed lower death rates than did patients taking diuretics. The difference between the 2 outcomes was not by itself statistically significant (results with other end points were neither reported nor provided on request). But together with a borderline significant difference between atenolol and other beta-adrenergic blockers in a meta-analysis of beta-adrenergic blockers in hypertension using a Bayesian approach (3) without including the HAPPHY trial, we do think that atenolol is inferior to other beta-adrenergic blockers. It should be underscored that atenolol differs markedly from most other beta-adrenergic blockers by being water soluble and thus almost unable to enter the central nervous system. This seems to explain why atenolol did not stimulate the vagal nerves by an action in the central nervous system, as metoprolol did (4).

We therefore suggest that the conclusion drawn by Bangalore et al. (1) should be restricted to atenolol only. Atenolol does not seem to be an appropriate representative for the whole class of beta-adrenergic blockers, although unfortunately it is widely used. This should be considered when interpreting results from clinical trials on beta-adrenergic blockers and when designing new trials.

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Atenolol Is Dead: Long Live Beta-Blockade

Bangalore et al. (1) recently reported that a lower heart rate was associated with a greater risk for all-cause mortality ($r = -0.51$, $p < 0.0001$), cardiovascular mortality ($r = -0.61$, $p < 0.0001$), myocardial infarction (MI) ($r = -0.85$, $p < 0.0001$), stroke ($r = -0.20$, $p = 0.06$), or heart failure ($r = -0.64$, $p < 0.0001$). They concluded that beta-blocker–associated reduction in heart rate increased the risk of cardiovascular events and death in hypertensive patients, in contrast to patients with MI and heart failure. In an accompanying editorial, Kaplan (2) stated that beta-blockers will continue to be indicated for heart failure, tachyarrhythmias, and secondary prevention post-MI, but not for treatment of hypertension in patients without these compelling indications. However, as the authors wrote, care should be taken in extrapolating these findings to newer beta-blockers, especially the vasodilating agents (e.g., nebivolol and carvedilol) (3). It should be emphasized that the studies included in this review used atenolol almost exclusively: 78% of patients received atenolol; 12%, atenolol/metoprolol/pindolol or hydrochlorothiazide; 9%, oxprenolol; and 1%, propranolol. Thus, it is difficult to extrapolate the findings to newer vasodilating beta-blockers. Future studies should strive to determine whether atenolol per se or the reduction of heart rate is responsible for increased cardiovascular risk. This issue needs to be resolved, because the findings would have major clinical implications (3).

Another important issue to resolve is the effect of drugs on central pressure. The benefits of heart rate reduction may be negated by a drug that lowers heart rate while simultaneously increasing central pressure (4). Different drugs, especially beta-blockers, have differential effects on peripheral and central pressure, and a number of studies have now shown that central pressure is a better predictor of outcome than pressure in the arm (5,6). As demonstrated in the CAFE (Conduit Artery Function Evaluation) study, antihypertensive medications can have substantially different effects on central aortic pressure and hemodynamics, despite a similar impact on brachial blood pressure (7). Vasodilatory beta-blockers may well offset any deleterious hemodynamic effects of heart rate reduction by decreasing wave reflection from the periphery. In a study by Dhakam et al. (8), the central hemodynamic effects of nebivolol and atenolol were compared in patients with systolic hypertension. Despite similar reductions in peripheral blood pressure, nebivolol reduced central pulse pressure more than atenolol. Both drugs reduced aortic stiffness, but nebivolol had less impact on the aortic augmentation index. These findings suggest that important differences may exist among drugs in the beta-blocker class.

Finally, beta-blockade remains very important in the treatment of cardiovascular disease, and in hypertensive patients with coexisting angina. Further, hypertensive patients younger than 50 years old may benefit more from beta-blockade than older patients, as they have a different hemodynamic form of hypertension (9). However, all evidence to date (4) suggests that a beta-blocker other than atenolol should be chosen when beta-blockade is required.

It is premature to sound the death knell for all beta-blockers in the treatment of hypertension based upon the Bangalore et al. (1) review, but it is high time to stop prescribing atenolol.

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REFERENCES


Beta-Blocks, Hypertension, and Randomized Controlled Trials: Science and Sensibility

Bangalore et al. (1) suggest that beta-blocker–induced reduction of heart rate increases the risk for cardiovascular events and death for