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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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Beta-Blockers, 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

hypertensive patients. Results of meta-analyses should be viewed with circumspection, especially when clinical practice might be influenced (2). With one-fifth of the general population susceptible to migraine (and other primary vascular headaches) and with nonvasodilating beta-blockers still regarded as first-line preventive agents, the conclusions of this study (1) raise concern. The authors admittedly ignore the dose of atenolol (1), a critical variable that limits this analysis. Besides, biologically, in no 2 patients can the evolution of atherosclerosis or its complications be strictly comparable. Statistics do permit such mathematical comparisons in randomized controlled trials (RCTs), but they can extract a hidden biological price (3).

First, contrary to the assertion that the "slower the heart rate, the greater the benefit" (1), heart rates below 50 beats/min cannot generally be claimed to promote overall cardiovascular integrity. Second, the negative inotropic action of beta-blockers has been ignored in this study (1) as well as in the CAFE (Conduit Artery Functional End Point) study (4). Any rise in central aortic pressure/pulse pressure by nonvasodilating beta-blockers would be intrinsically countered by their negative inotropic action. A pharmacologically reduced stroke volume would maximally affect central conduit vessels to reduce central vessel wall stress. Not surprisingly, atenolol reduces the elevated augmentation index in hypertensive patients compared with that in normotensive subjects (5). Third, the investigators (1) did not stratify their results according to age. An aging cohort is likely to have stiffer conduit arteries that, in turn, would exacerbate any differential drug effects on central aortic pressure (4). Fourth, the concept of dyssynchrony or uncoupling between outgoing and reflected aortic waves consequent to pharmacologically induced bradycardia (1) is purely speculative.

Cardiovascular morbidity and mortality are too complex to be resolved through multiple mathematics-based comparisons of diverse pharmacologic agents, particularly when polytherapy with several drugs might be involved. Moreover, all vasodilators usually worsen migraine headache; among antihypertensive agents, beta-blockers, however, do not generally aggravate headache. Regardless of age or race, hypertension is commonly associated with headache that has several features of migraine (6). Proscription of beta-blockers for initial or primary management of hypertension will increase the incidence of associated vascular headaches including migraine and make their management more complex. Next, beta-blockers hold center stage in management of predominantly systolic hypertension as well as the anxiety-related white coat hypertension/effect. Weight gain and precipitation of diabetes mellitus by beta-blockers is a relative risk unrelated to pancreatic islet cell damage.

In essence, this study (1) and the accompanying editorial (7) seek to convert a small-to-moderate statistical relative risk into an absolute biological risk with important practical implications. RCTs allow scientists to carry out credible research without having to discern crucial clinical phenomena or diminishing the need for the same (3). While using research tools such as RCTs or meta-analysis involving RCTs, we must remain cognizant of the intrinsic biological limitations of mathematical data mining. To seek or force a clinical/therapeutic consensus in the face of biological uncertainty cannot be commended as the best scientific/research practice.

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Beta-Blocker–Induced Heart Rate Reduction

Too Simplistic to Explain the Deleterious Effects of Beta-Blockers

In their recently published article, Bangalore et al. (1) concluded, from a meta-regression analysis of 9 studies including a total of 34,096 patients taking beta-blockers as first-line therapy and 30,139 patients taking other antihypertensive agents, that beta-blocker–associated reduction in heart rate increased the risk of myocardial infarction, cardiovascular events, and death for hypertensive patients. The authors suggested, as a mechanism, that "pharmacologically induced bradycardia leads to dyssynchrony or uncoupling between outgoing and reflected wave, thereby elevating central aortic pressure." They referred to the CAFE (Conduit Artery Functional End Point) study, which showed a higher central aortic systolic blood pressure after atenolol-based treatment than after amlodipine-based treatment, and to the main ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) study showing a better predictive value for cardiovascular events of amlodipine-based treatment than atenolol-based treatment. Although appealing, their conclusion that beta-blockers are deleterious through the reduction in heart rate, thus increasing central pulse pressure, may be too simplistic and not supported by data.

Indeed, although the authors pointed out that resting heart rate was an independent risk factor for cardiovascular morbidity and