Different Metabolic Effects of Selective and Nonselective Beta-Blockers Rather Than Mere Heart Rate Reduction May Be the Mechanisms by Which Beta-Blockade Prevents Cardiovascular Events

We read with interest the article by Bangalore et al. (1), who analyzed in 9 trials the role of pharmacologic reduction of heart rate (HR) using beta-blockers in preventing cardiovascular events in patients with hypertension. Beta-blocker–induced lower HR was associated with greater mortality and morbidity risk. As the basis of worse outcomes with “beta-blockers,” the authors recognize only an increase in central aortic/pulse pressure with pharmacologic HR lowering. Even though they acknowledge that the beta-blocker used in the studies was mainly atenolol, and hence, any extrapolation of these results to other beta-blockers should be done with caution, the whole paper and the accompanying editorial just generically refer to “beta-blockade.” In fact, the mechanisms by which beta-blockers improve prognosis in different cardiac contexts are probably multiple. Improved energy efficiency seen with some beta-blockers (2) could be one of the reasons for better survival observed with their use (3). Additionally, central inhibition of sympathetic activity with moxonidine in heart failure, despite a significant reduction of HR, has been associated with increased mortality (4). In fact, moxonidine has been shown to alter myocardial metabolism (5). This could be the reason for the failure of central sympathetic inhibition to prevent deaths in patients with heart failure and also indicates that the predominant mechanism of action of “effective” beta-blockers is probably related to mechanisms other than mere HR reduction. In fact, apart from reducing HR, atenolol and most selective beta-blockers impair endothelial function, decrease insulin sensitivity, and increase lipid levels (6), all conditions that may worsen the global risk profile. Conversely, new generation beta-blockers have been seen to improve metabolism and endothelial function (7). Therefore, HR reduction in itself, especially if associated with a bulk of deleterious metabolic and vascular effects, is definitely not enough to improve prognosis. The alarm created by the Bangalore et al. (1) paper should be clearly confined to selective beta-blockers and not generically extended to the whole drug class.

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REFERENCES


Beta-Blockers and Hypertension

Bangalore et al. (1) state that unlike results from post-myocardial infarction and congestive heart failure studies, a beta-blocker–induced low heart rate (HR) in hypertension is associated with an increase in death rate and cardiovascular (CV) events. This conclusion is highly misleading.

In post-myocardial infarction and congestive heart failure studies, the benefit from beta-1 blockade arises from decreased work of the heart (via reduced HR and blood pressure), reduced ventricular fibrillation risk, and a reduction in catecholamine-induced (beta-1) cardiac necrosis and apoptosis (2); thus, intrinsic sympathomimetic activity reduces efficacy (2). The situation with hypertension is complex, as diastolic hypertension in the young/middle-aged arises from a link with obesity (3) and high sympathetic nerve activity plus raised cardiac output (2). In contrast, isolated systolic hypertension arises in the elderly via a decrease in vascular compliance (3).

The 3 main contributor trials in the Bangalore et al. (1) study were the ASCOT (Anglo-Scandinavian Cardiac Outcomes), LIFE (Losartan Intervention for Endpoint Reduction in Hypertension), and INVEST (International Verapamil SR Trandolapril Study) studies in elderly patients with hypertension, which involved moderately beta-1 selective atenolol as the first-line choice. Atenolol does not improve vascular compliance (2), so it does not lower central systolic pressure; indeed first-line atenolol slightly increases central pressure (4), possibly linked to partial beta-2 block-
ade (2) and a fall in HR (1). Thus, a low HR would be linked to a high central pressure.

In contrast, second-line beta-blockade alongside a first-line agent that improves vascular compliance and lowers central pressures in the elderly (e.g., a low-dose diuretic or calcium antagonist [4]), is linked to highly significant falls in CV end points as in the SHEP (Systolic Hypertension in the Elderly Program), ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), and MRC (Medical Research Council)-Elderly (2) studies.

The next 2 main contributor trials (1) were the IPPPSH (International Prospective Primary Prevention Study in Hypertension) and HAPPHY (Heart Attack Primary Prevention in Hypertension) trials involving young/middle-aged hypertensive patients. The first-line beta-blockers were nonselective oxprenolol and partially beta-1 selective atenolol/metoprolol—beta-blockers that lower blood pressure in different ways (5). Metoprolol and atenolol act via a fall in HR and cardiac output; oxprenolol acts via a modest fall in HR and cardiac output plus a modest fall in peripheral resistance via beta-2 intrinsic sympathomimetic activity. Thus, linking a final HR or HR difference with CV events is unhelpful. For atenolol/metoprolol, quoting intra-trial (rather than end-trial) changes in HR (if known) would be useful, enabling HR/CV-event relationships to be studied.

Cigarette smoking is another relevant, vital issue for younger and middle-aged hypertensive patients, as significant benefit with oxprenolol (IPPPSH), propranolol (MRC-1), and metoprolol (MAPHY [Metoprolol Atherosclerosis Prevention in Hypertensives]) occurred only in nonsmokers (2). Nonsmokers (70% of the whole) in MRC-1 experienced a significant 38% reduction in CV events on propranolol, similar to the results of atenolol versus less-tight blood pressure control in overweight middle-aged hypertensive patients with type-2 diabetes in the UKPDS (United Kingdom Prospective Diabetes Study) (6,7), in which all 7 hard end point trends (including myocardial infarction and stroke) favoring the beta-blockers over the angiotensin-converting enzyme inhibitor at 9-year follow-up (7), strengthened over 20-year follow-up, achieving significance in the case of all-cause death (8). Smoking induces epinephrine release (9) and in the presence of beta-1/beta-2 blockade, unopposed alpha stimulation occurs; the resultant increase in blood pressure induces reflex falls in HR (10). In such a scenario, a low HR would be linked to an increase in CV events. Such a worrisome beta-blocker–epinephrine interaction is not observed with high beta-1 selectivity (e.g., bisoprolol) (11).

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REFERENCES


Reply

We thank the several authors who wrote a letter concerning our recent paper (1).

1. Dr. Phillips’s criticism of our observation, being possibly the result of confounding by indication, needs to be considered carefully. Although we do not have definitive evidence to rule this out, we think it is unlikely because in our data, there was poor correlation between heart rate achieved at the end of treatment and the systolic blood pressure difference between the treatment modalities (r = 0.154; p = 0.717). Similarly, there was no correlation between heart rate achieved and diastolic blood pressure difference between treatment modalities (r = −0.255; p = 0.542). This would indicate that the negative chronotropic effect of beta-blockade can, to some extent, be dissociated from its anti hypertensive effect. However, as Dr. Phillips indicates, the only way to rule out confounding by indication would be in looking at the individual patient data, which obviously is no longer possible.

2. We agree with Drs. Aursnes and Osnes as well as with Dr. Cockcroft that most of the findings in all meta-analyses of beta-blocker trials are driven by atenolol. However, atenolol remains the most widely prescribed beta-blocker worldwide, with more than 40 million prescriptions per year in the U.S. alone. No head-to-head comparisons of atenolol with other beta-blockers have been done. Until we have convincing morbidity and mortality data in trials done with beta-blockers other than atenolol, we should not automatically exculpate these agents. Thus, it is high time to sound the death knell for atenolol, as Dr. Cockcroft suggests, but we should continue prescribing beta-blockers (particularly those with a better hemodynamic and metabolic profile) for well-defined cardiovascular indications.

3. We take issue with Dr. Gupta’s statement that our study merely seeks “to convert a small-to-moderate statistical relative risk into an absolute biological risk with important practical impli-