**EDITORIAL COMMENT**

**Beta-Blockers as First-Line Antihypertensive Therapy**

The Crumbling Continues*

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Supposing is good but finding out is better.

—Mark Twain (1)

Ever since Prichard and Gillam reported the antihypertensive effect of propranolol in 1964 (2), beta-blockers (BBs) have been among the most prescribed drugs in the U.S. for the treatment of hypertension (HTN) and are still recommended as first-line agents by national and international guidelines (3,4). In fact, BBs have been promoted to be used on an equal footing with thiazide diuretics and equal or preferentially to renin angiotensin aldosterone system (RAAS) blockers or calcium-channel blockers (CCBs) for initial treatment of uncomplicated HTN (4–7). A closer look at the available evidence, however—including data presented in this issue of the Journal (8)—casts serious doubt regarding the efficacy of BBs compared with other agents for the treatment of HTN (3,4,9).

**Autonomic function and resting heart rate.** Many studies have established an elevated resting heart rate (HR) as a risk factor for cardiovascular (CV) disease and mortality (10–12). The importance of resting HR as a prognostic factor and potential therapeutic target has recently been reviewed in detail (11). In fact, resting HR has been shown to be an independent risk factor for CV morbidity and mortality for patients without known CV disease as well as for patients with acute myocardial infarction (MI), known coronary heart disease (CHD), or HTN (11). Among 4,530 untreated patients with HTN in the Framingham Study, the risk of CV mortality increased by nearly 70% for each 40-beats/min increase in resting HR, and all-cause mortality increased by over 2-fold (13). Similar results have been noted in other cohorts with HTN (14,15). Clearly, chronic imbalance of the autonomic nervous system, characterized by activation of the sympathetic nervous system and/or diminished vagal tone, is a marker of an unhealthy CV system and is associated with increased risk of CV events and mortality (9,11). Conversely, nonpharmacological interventions that lower HR (e.g., exercise and/or reductions in psychological stress) reduce CV risk (10,12,16–19).

**Pharmacologic HR lowering.** In contrast to the clear evidence of HR being an independent predictor of CV and total mortality in patients with and without CV disease (10–12), the benefits of pharmacologic HR slowing are considerably less well-documented (15,20). As Fox et al. (11) recently reviewed, substantial data suggest that HR reduction, even within the physiologic range, is an important mechanism for the benefits of BBs and other HR-lowering drugs after acute MI as well as in patients with left ventricular dysfunction and heart failure (HF). In patients with uncomplicated HTN, however, the opposite might be true (15,20). In fact, Bangalore et al. (15) recently reviewed 9 studies with HR data in HTN, including nearly 65,000 patients, over one-half of whom were treated with BBs. Paradoxically, low HR attained in the BB group was associated with a significantly higher risk for all-cause mortality, CV mortality, MI, stroke, and HF. Theoretically, pharmacologically induced bradycardia and HTN might lead to dysynchrony between outgoing and reflective pulse wave, thereby increasing central aortic pressure and the hemodynamic burden to the target organ, particularly to the brain (15,20–22). Therefore, in contrast to patients with MI and HF, BB-associated HR reduction might actually increase CV risk in patients with HTN.

**Potential problems with BBs.** Compared with other agents used in the treatment of uncomplicated HTN, BBs have a number of potential adverse effects. In fact, after 4 decades of using BBs as primary treatment for HTN, no study has shown reduced morbidity or mortality when used as monotherapy when compared with placebo (3,4,10). In contrast, many meta-analyses have suggested the potential detrimental effects of these agents. In a recent meta-analysis of 12 studies evaluating over 90,000 patients with HTN, BB therapy resulted in a 22% increased risk for new-onset diabetes mellitus, a known powerful risk factor for CV disease (23). Recent studies have focused on the epidemic in obesity (24), and therapy with BBs might be associated with weight gain (25). One of the major long-term risks of long-standing HTN is HF, and prevention of HF seems to be strongly dependent on blood pressure reduction (26). Although BBs might be highly effective for the treatment of...
patients with established HF, in a meta-analysis of 12 studies in over 100,000 patients with HTN, BBs provided no incremental benefit for prevention of HF above and beyond that provided by other blood pressure-lowering therapy (26). Also, compared with other therapies for HTN, first-line therapy with BBs was associated with an increased risk of stroke in elderly patients with uncomplicated HTN, with no significant benefits for the other CV end points (4,20,26). The fact that BBs might be less effective than other agents, not only to reduce peripheral arterial pressure but also having less effect on the potentially more important central aortic pressure, might partly explain the “pseudo-antihypertensive” effect of BBs (4,20,26,27).

Left ventricular hypertrophy (LVH) is a potent predictor of CV morbidity and mortality, and its regression seems to lower CV risk, even independent of arterial pressure (27). BBs—compared with RAAS blockers, CCBs, and diuretics—seem to be less effective at LVH regression and, unlike RAAS blockade, do not reduce collagen content in the myocardium (27–29).

Despite the potential detrimental effects of BBs in HTN, it seems tempting to hypothesize that high resting HR could predict a greater responsiveness to BBs, resulting in a greater reduction in major CV events. Poulter et al. (8) could predict a greater responsiveness to BBs, resulting in a greater reduction in major CV events. Poulter et al. (8) from ASCOT (Anglo-Scandinavian Cardiac Outcome Trial) assessed the impact of baseline HR on the CV event reduction with amiodipine- versus atenolol-based therapy in nearly 13,000 patients with HTN uncomplicated by baseline CHD. Prior studies from ASCOT have demonstrated that amiodipine-based therapy was superior to atenolol-based therapy and have even demonstrated a potentiation of effect between amiodipine and statin therapy (with atorvastatin) in the lipid-lowering arm of this trial (30,31). Unexpectedly, BB therapy did not provide greater benefit in those with higher resting HR, and the benefit of the long-acting CCB over BB was maintained regardless of resting HR.

CV benefits of amiodipine. Although the present study adds to the evidence supporting the relative weak clinical impact of BBs, separating the detrimental effects of BBs versus the CV protection with amiodipine might be difficult. In the early 1990s considerable controversy surfaced regarding the efficacy and safety of CCBs, particularly related to the unfavorable hemodynamic profile and impact on CV events noted with the short-acting CCBs (32). Conversely, data with the long-acting CCBs, especially amiodipine, have been impressive. In HTN, for example, amiodipine seemed to have advantages over lisinopril for CV outcomes, particularly in black patients and women, among over 30,000 patients in the ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial) (33,34). In the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) trial of over 15,000 patients with HTN, amiodipine and valsartan were equivalent for the primary outcome, but amiodipine was significantly better than valsartan for preventing MI with a trend favoring amiodipine noted for stroke (35). In the recent ACCOMPLISH (Avoiding Cardiovascular Events through Combined Therapy in Patients Living with Systemic Hypertension) trial of over 11,000 high-risk patients with HTN, an amiodipine–benazepril combination was superior to a hydrochlorothiazide–benazepril combination in reducing CV events with a relative risk reduction of nearly of 20% (36). In addition, amiodipine has been safe and effective in patients with CHD (32,37), including those without HTN (38), even having efficacy and safety in patients with advanced HF (39). Therefore, long-acting CCBs have considerable efficacy and safety in the prevention and treatment of CV diseases, and this evidence seems to be particularly striking with the now-generic amiodipine preparation.

Conclusions. On the basis of the current information, how should clinicians currently proceed when treating patients with HTN? The seminal question to be asked is: “Are BBs still alive as first-line therapy for HTN?” Certainly, BBs provide benefits for many CV patients (e.g., post-MI, CHD, HF, and tachyarrhythmias) regardless of level of blood pressure. Conversely, for the patient with HTN without other compelling indications, the evidence supporting BB therapy has vanished, although newer vasodilating BBs (e.g., carvedilol and nebivolol) might require further study (3). Thus, in response to Mark Twain (1), we no longer need to suppose—we have found out! On the basis of considerable evidence, including data in the present study (8), one can make 2 conclusions: 1) resting HR seems to be useless as a guide to choice of antihypertensive therapy; and 2) BBs seem to be equally ineffective in reducing CV events in hypertensive patients with tachycardia as in those with bradycardia. Finally, as the evidence supporting BBs as first-line therapy for HTN continues to crumble, one could answer the question posed earlier, “Maybe alive, but barely breathing!”

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