Hypertension, Heart Failure, and Beta-Adrenergic Blocking Drugs*

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Beta-adrenergic receptor blocking drugs have arguably prevented or delayed more deaths in patients with established heart disease that any other class of pharmaceutical agent (1). These drugs fundamentally alter the clinical course of patients with heart failure and a reduced left ventricular ejection fraction, improving left ventricular performance, reversing left ventricular remodeling, and reducing the risk of hospitalization or dying (2). Beta-adrenergic receptor blocking drugs (beta-blockers) were also the first, and still arguably one of the more powerful, interventions to improve survival when prescribed as long-term therapy after acute myocardial infarction (3). The role of beta-blockers to prevent the development of heart failure is less clear. Some agents have been shown to reduce reinfarction, one important contributor to subsequent heart failure. Beta-blockers were included with the optimal therapy prescribed in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial (4), the result testifying to the efficacy of medical therapy for coronary artery disease. These drugs protect against acute myocardial infarction in patients undergoing noncardiac surgery (5), but this indication has been associated with increased stroke risk, especially in patients in whom sepsis or hypotension developed (6). Even the presentation of ischemic heart disease seems to be influenced by beta-blockers, with fewer patients on these drugs experiencing acute myocardial infarction (7).

The American College of Cardiology/American Heart Association guidelines for the treatment of heart failure emphasize control of blood pressure as an important strategy to prevent heart failure. This is an important issue because hypertension precedes heart failure in the majority of patients who develop this devastating condition (8,9). Hypertension is especially significant in patients with heart failure and a preserved left ventricular ejection fraction. Insulin resistance, diabetes, and obesity are also important in the development of heart failure and are closely linked to hypertension (10).

Introduced in the 1960s as drugs to treat angina, beta-blockers were soon realized to be effective and, compared with many other available agents at that time, well tolerated antihypertensive agents. Based on the limited trials data available beta-blockers were included as first-line therapy in national guidelines for the treatment of hypertension (11). Most of the evidence for this recommendation came from trials that compared thiazide-type diuretics and/or beta-blockers to placebo or usual care. Reduced risk of stroke or heart failure was the benefit most commonly reported. The impact on coronary artery disease events was modest, and at the time was attributed to the short duration of the trials. Subsequently the SHEP (Systolic Hypertension in the Elderly Program) trial (12), which evaluated chlorthalidone in elderly hypertensive patients, did show a reduction in major coronary events and a substantial reduction by 49% in the risk of developing heart failure. The ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) (13) study results suggested that most of the benefits of treating hypertension were related to lowering blood pressure with little impact dependant on a specific drug class. All of the comparison therapies were found to be similar to chlorthalidone (again, perhaps significantly, chosen to represent the thiazide diuretic class, and associated with the greatest reduction in blood pressure) in preventing the primary composite coronary heart disease end point. Doxazosin, an alpha-blocker, was shown to be the least effective in preventing heart failure, a secondary end point. Heart failure was also 38% more frequent in the amlopidine group and 15% more frequent in the lisinopril group. Beta-blockers were not included in the randomized drug classes but were included as one potential add-on therapy. In the ANBP2 (Second Australian National Blood Pressure Study) trial (14), in which 6,085 hypertensive patients were followed up for 4.1 years, hydrochlorothiazide was associated with 15% more heart failure than enalapril.

Diabetic hypertensive patients are at especially high risk for developing heart failure and were shown to have 57% less risk of developing heart failure with more aggressive blood pressure control in a UKPDS (UK Prospective Diabetes Study) trial (15). Interestingly, in this trial the more aggressive multiple agent regimens could be based on atenolol or captopril.

The paper by Bangalore et al. (16) in this issue of the Journal used meta-analysis to examine the role of beta-blockers to prevent heart failure in patients being treated for hypertension and to compare them with other classes of antihypertensive drugs. The Bangalore et al. (16) meta-

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analysis found that beta-adrenergic blocking drugs were as effective as any other class of agents in preventing heart failure. Heart failure was not the primary end point in any of the individual trials of antihypertensive therapy examined in this analysis, nor was there a uniform definition for the development of this syndrome. Another analysis has suggested that calcium channel blockers may be inferior as first-line agents to prevent heart failure, but as the investigators point out, this analysis may have been impacted though inclusion of comparison trials that included diuretics with beta-blockers. Based on this meta-analysis, beta-adrenergic blocking drugs are rightly included among the agents used to prevent the development of heart failure. Although it is not possible to predict which complication of hypertension may be inflicted on an individual patient, practitioners should be reassured that they can include beta-blocking drugs as cardioprotective agents supporting their use in patients with pre-existing heart disease.

Both diuretics and beta-blockers are recognized to have important limitations that argue against their routine use as first-line antihypertensive agents (11,17). An adverse effect on glucose metabolism poses a significant disadvantage in a therapy given to protect against the adverse cardiovascular consequences of hypertension. Both diuretics and beta-blockers have been associated with the development of diabetes (11,18). Meta-analysis has shown a 32% increased risk of new-onset diabetes with beta-blockers in trials comparing placebo or nondiuretic therapy. With diuretics, the increased risk of diabetes was 35% compared with placebo or nonbeta-blocker antihypertensive agents (11). It is conceivable that the adverse metabolic consequence of thiazide diuretics may be less than that seen with conventional beta-blockers. The use of chlorthalidone in particular seems not to be associated with any diminution of benefit (13). The results of the ACCOMPLISH (Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension) study do question our complacency regarding this adverse effect of all thiazides (19). Although this study design was criticized for being of limited scientific relevance, the results, reported at the American College of Cardiology annual meeting this year, showed fewer events in the group on the combination of an angiotensin-converting enzyme (ACE) inhibitor with amiodipine compared with the group on an ACE inhibitor and hydrochlorothiazide. These findings indicate the importance of considering drug combinations rather than extrapolating from the results based on choice of first-line therapy. The results also suggest that different drugs within a class may not be equally effective. Beta-blockers should be recognized as having more heterogeneity within a drug class than other agents. Beta-blockers vary in their affinity for beta-1 and -2 receptors; some also block alpha receptors, conferring vasodilator properties even to nonselective agents. Some have intrinsic sympathomimetic activity. These different characteristics have been found to be significant in outcome trials after acute myocardial infarction (3) and heart failure (2). The adverse metabolic effect of nonvasodilating beta-blockers is likely to assume even greater significance in hypertension when the therapy is being prescribed for long periods to prevent the vascular and cardiac consequences of high blood pressure. Two comparison trials with atenolol, a lipophobic beta-1 selective agent, not only showed less stroke prevention but also more new development of diabetes compared with the patients randomized, in one trial, to the angiotensin receptor blocking (ARB) drug losartan (20), and in the other, to the dihydropyridine calcium channel blocking drugamlodipine (21). A subsequent meta-analysis, not confined to atenolol, reported 16% more stroke with beta-blockers and contributed to the recommendation that beta-blockers as a class should no longer be chosen routinely as first-line agents to treat hypertension (22). Whether this adverse effect is common to all beta-blocking drugs, or whether the absence of an adverse impact on glucose metabolism as demonstrated with the vasodilating beta-blocking drug carvedilol in the GEMINI (Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives) study (23) has a mitigating effect on stroke prevention has not been established. The American Association of Clinical Endocrinologists do advise in their guidelines (24) that beta-blockers with vasodilating properties are preferable as second-line or third-line agents. But other factors not related to insulin resistance, such as a differential impact on central aortic pressure, may be of equal importance. A randomized trial in hypertension is needed to determine whether beta-adrenergic blocking drugs with vasodilator properties, especially if combined with an ACE inhibitor or an ARB, would result in improved protection from all the adverse outcomes associated with hypertension, including stroke and heart failure, than can be achieved with traditional beta-blocking drugs. Based on the available data and in the absence of any other new outcomes trial, beta-blockers cannot be recommended as routine first-line therapy to treat hypertension (16,21,25).

The majority of patients with hypertension will require more than one agent to achieve target blood pressure. The impact of beta-blockers when combined with other classes of drugs, especially ACE inhibitors in patients with established cardiac disease, support their use in hypertensive patients who are not at target blood pressure. These patients are especially likely to progress to heart failure. It is conceivable that the combination of beta-blockers with ACE inhibitors or ARBs, shown to be beneficial after acute myocardial infarction or in heart failure, irrespective of an effect on blood pressure, would also be advantageous at an earlier stage of the disease even in the absence of hypertension. Given the importance of insulin resistance in the development of heart failure, it is reassuring that the conventional nonvasodilating beta-blockers, the principal agents evaluated in the meta-analysis by Bangalore et al. (16), were found to be effective in preventing heart failure.
Treatement of patients with hypertension should be based on the outcomes observed in randomized trials or meta-analyses. Ultimately, drug choices in individual patients will be determined by tolerability and response to specific agents, and especially by the need to manage concomitant conditions. Despite the number of inexpensive well-tolerated drugs, only one-half of patients with hypertension are adequately treated. The tendency to demonize one class of drugs, especially a drug class with profound benefits to patients with established cardiac disease, can only contribute to further therapeutic nihilism. Although it is becoming increasingly apparent that differences do exist between different classes of antihypertensive agents, it is also apparent that these differences, although important, are of trivial consequence compared with the adverse impact of inadequate treatment. Calcium–channel blockers were erroneously targeted in the 1990s (26). Thiazide diuretics, lauded after the findings of the ALLHAT study, are now under scrutiny after finding hydrochlorothiazide (given in combination with benazapril) was less effective in preventing adverse outcomes than a combination benazapril/amlodipine preparation. In an era when scientific discourse regarding drug therapy is played out in the lay press, it is hardly surprising that patients do not persist with effective antihypertensive therapy but turn instead to alternative medicines, blissfully unaware that the subsequent development of heart failure could have been prevented.

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