Doxazosin and Congestive Heart Failure
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Congestive heart failure (CHF) is the most devastating cardiac sequella of long-standing hypertension. Recent data from the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) have shown the risk of CHF to be twice as high with doxazosin than with chlorthalidone. Although some questions remain regarding the diagnosis and mortality of CHF in the doxazosin arm and regarding the risk of dying from malignancy in the diuretic arm of ALLHAT, drugs used to treat hypertension should lower the CHF risk. Therefore, until ironclad safety data are provided, doxazosin, and probably all alpha-blockers, should no longer be used as first-line antihypertensive therapy.

On May 24, 2001, the U.S. Food and Drug Administration held a public meeting to discuss a petition requesting the agency to notify the medical community and users of doxazosin of the recent findings of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). The study showed that patients using doxazosin were twice as likely to be hospitalized for congestive heart failure (CHF) and had a higher risk of suffering from certain serious cardiac events than patients using chlorthalidone (1,2). After several hours of deliberation, the Cardiovascular Drugs Advisory Committee decided that, indeed, this information should be made available to physicians in the package insert, but refrained from recommending a change in the labeling of indications for doxazosin or other alpha-blockers. Thus, most likely, alpha-blockers will continue to be used as first-line therapy in patients with essential hypertension, as was recommended by the Joint National Committee four years ago (3), long before the findings of the ALLHAT study were known.

Congestive heart failure is a common outcome of hypertensive heart disease. In the Framingham cohort, more than 90% of patients with CHF had a history of hypertension (4), and long-standing hypertensive cardiovascular disease invariably leads to CHF. The prevention of CHF must, therefore, be considered as one of the major therapeutic goals in the treatment of hypertension. Indeed, most major drug classes (diuretics, angiotensin-converting enzyme [ACE] inhibitors and calcium antagonists) that the Joint National Committee recommended for initial therapy of hypertension have been shown to reduce the risk of CHF when compared with placebo or active therapy. Before publication of the first results of the ALLHAT study in March 2000, however, no such data and no morbidity or mortality data were available for alpha-blockers, despite the fact that this class of drugs has been promoted and used for the treatment of hypertension for more than 20 years.

In the Vascular Heart Failure Trial study, treatment with another alpha-blocker—prazosin, 5 mg twice a day—also showed no benefits in patients with CHF when compared with placebo, whereas cumulative mortality was lowered by 38% with combination therapy of isosorbide dinitrate and hydralazine (5). The data from the ALLHAT study indicate that the risk of CHF with doxazosin was more than 100% (relative risk 2.04; 95% confidence interval 1.79–2.32) higher than the risk in patients who were treated with chlorthalidone (1). Although systolic blood pressure was 2 to 3 mm Hg higher in the doxazosin group than in the diuretic group (diastolic blood pressure was equal), this difference is unlikely to explain the excessive incidence of CHF. The small systolic pressure difference could account, however, for the 25% increased risk of combined cardiovascular events in the doxazosin arm.

Interestingly enough, all-cause mortality in the chlorthalidone arm was very similar to that in the doxazosin arm in CHF patients in the ALLHAT study. This would indicate either that patients on doxazosin had a remarkably benign nonlethal form of CHF or that patients in the diuretic arm died more commonly from causes other than CHF. Congestive heart failure was a secondary end point and, because there was no regular end point committee, it was poorly defined in the ALLHAT study. This raises the question of whether vasodilatory edema, not an uncommon side effect of alpha blockade (6), could have been misdiagnosed as CHF in some patients. Also, before randomization to doxazosin, many patients most likely were receiving diuretics or ACE inhibitor drug classes that are known to be beneficial in the management of CHF. The switch to doxazosin may, therefore, merely have unmasked CHF in patients with left ventricular dysfunction rather than causing CHF per se.

A very recent report (7) seems to shed some light on this puzzle by showing that mortality from CHF was not unexpectedly low in the doxazosin arm and that, surpris-
Cardiovascular causes. Specifically, patients using diuretics died more often from extracardiovascular causes. Specifically, the risk of dying from malignancy was >50% (14% vs. 9%) higher in patients using chlorthalidone than in those using doxazosin (7). Although this difference was not statistically significant, it seems to lend credence to the observation that long-term diuretic therapy has been associated with an increased risk for certain malignancies, such as renal cell carcinoma and colon cancer (8,9).

In contrast, doxazosin has been shown to suppress human prostate cancer cell growth by inducing apoptosis among epithelial cells and could, therefore, lower the risk of prostate cancer (10). As provocative and plausible as this explanation may seem, it must be interpreted with great caution because it is based on the small number of patients with CHF only. However, the ALLHAT study was powered to provide a more definite answer to this question, and malignancy data in the diuretic and the doxazosin arm should have been made available to the medical community at the time the doxazosin arm was stopped. This could throw light on the fascinating hypothesis that antihypertensive drug classes differ not only with regard to prevention of cardiovascular events but also with regard to morbidity and mortality from extracardiovascular causes such as malignancy (11).

In numerous drug company-sponsored symposia and journal supplements, alpha-blockers have been touted as being more beneficial than other antihypertensive drug classes because alpha-blockers not only lowered arterial pressure but also had additional benefits in that they improved insulin resistance and lipid abnormalities. Physicians, therefore, have been under the impression that these drugs were particularly efficacious for the prevention of hypertensive heart disease. Although this may be possible for coronary heart disease (the rate of which was similar in the diuretic and doxazosin arm despite lessened blood pressure control), doxazosin does not seem to prevent the most common cardiac complications of long-standing hypertension, namely CHF. Recent data from the Framingham Heart Study have shown that the prognosis for survival after the onset of hypertensive CHF remains bleak (4). Once CHF was diagnosed, only 24% of men and 31% of women survived five years. These findings suggest that until ironclad safety data in patients with CHF are provided, doxazosin, and probably all alpha-blockers as a class, should no longer be used as initial therapy in the treatment of hypertension and that these drugs should be used with caution, if at all, even as add-on therapy in hypertension or for symptomatic relief of prostatic hyperplasia in patients at risk of CHF.

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REFERENCES