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VIEWPOINT

Outcome Studies—Are All Antihypertensive Drugs Created Equal?

Franz H. Messerli, MD, FACC
New Orleans, Louisiana

Several recent prospective, randomized trials leave us with the perception that there are little if any differences in outcome among various drug classes in patients with essential hypertension. The Captopril Prevention Project (CAPPP), which compared an angiotensin-converting enzyme (ACE) inhibitor with conventional therapy (i.e., agents, diuretic beta-blockers) in more than 10,000 patients, reported similar rates of heart attack, stroke and cardiovascular and all-cause mortality in patients who were treated with either an ACE inhibitor (captopril) or conventional therapy (diuretic agents and beta adrenergic blocking agents) (1). A comparison of the Systolic Hypertension in the Elderly Program (SHEP) (2) with the recently published Systolic Hypertension in Europe study (Syst-Eur) (3) in patients with isolated systolic hypertension again shows a remarkably similar reduction in cardiovascular morbidity and mortality and all-cause mortality with treatment strategy based on a diuretic agent (chlorthalidone) and one based on a calcium antagonist (nitrendipine). This was true in the nondiabetic population, whereas in the diabetic population the calcium antagonist seemed to have an advantage over diuretic therapy (4). Nitrendipine-based therapy had a greater reduction in all-cause and cardiovascular mortality in the diabetic than in the nondiabetic patient with isolated systolic hypertension (4). But even in the diabetic hypertensive population, differences, if any, are far from clear cut. In the Appropriate Blood Pressure Control in Diabetes (ABCD) study (5) there were fewer cardiovascular events in the ACE inhibitor arm than in the calcium antagonist arm, but there was no difference in the renal outcome between the two strategies. After four years of follow up, renal function (as measured by creatinine clearance), microproteinuria and diabetic neuropathy were exactly the same in the two treatment groups. Similarly, in the UK diabetes study (6), it did not seem to matter whether blood pressure was lowered by a beta-blocker (atenolol) or an ACE inhibitor (captopril) in the diabetic hypertensive patient—outcome was similar.

Does this mean that as long as blood pressure is lowered sufficiently, the means by which it is achieved is unimportant? Clearly, high blood pressure is a powerful risk factor, and its reduction is prone to exert benefits that can override small synergistic or antagonistic properties of antihypertensive drugs. However, before we conclude that the drug does not matter as long as the blood pressure is low, we should remember that recent studies also have documented some extracardiovascular effects of antihypertensive drugs that are prone to influence our selection of antihypertensive drugs in the future. The data of Lever et al. (7), suggesting a 30% decrease in malignancy with ACE inhibitors as compared with other antihypertensive drugs, are provocative and require urgent confirmation. Hypertension and malignancy share several risk factors, such as smoking, diabetes, obesity and alcohol consumption. Malignancies, therefore, are common in the hypertensive population (8), and any treatment strategy that could diminish this risk would be extremely important. In contrast, the recent data suggesting that the long-term use of diuretic agents is associated with a low grade risk of renal cell carcinoma (9,10) are perturbing, and they too need to be confirmed. Finally, the drastic reduction of dementia of the Alzheimer type in the Syst-Eur study (11) by a calcium antagonist–based treatment strategy is yet another hint that calcium antagonists are an "appropriate alternative" in the elderly, as suggested by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) (12). Dementia and cognitive impairment are more common in the hypertensive than in the normotensive patient, and any treatment strategy that could prevent these would be welcome. Thus, although all antihypertensive drugs lower blood pressure (by definition), and so far, differences in cardiovascular outcome, if any, between various antihypertensive strategies seem to be small, it could well be that the true merit of various therapeutic strategies will quite unexpectedly stand and fall with the effect of these drugs on extracardiovascular disorders.

Correspondence: Dr. Messerli, Ochsner Clinic, 1514 Jefferson Highway, New Orleans, Louisiana 70121. E-mail: Fmesserli@aol.com.

From the Department of Internal Medicine, Section on Hypertensive Diseases, Ochsner Clinic, New Orleans, Louisiana.

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