Editorials

Initial Medication Selection For Treatment Of High Blood Pressure

In this issue of *JABFP*, Jerome, et al.[1] report on a study in which they utilized paid claims data from an open-panel health maintenance organization (HMO) in the midwestern United States to determine prescribing patterns for antihypertensive therapy of patients with newly diagnosed disease. They found that most patients received monotherapy, with a minority receiving either stepped care or sequential monotherapy. Calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors were used most frequently as initial monotherapy, and treatment did not appear to be customized for comorbid conditions. The authors concluded that costs for treating hypertension could be reduced and care improved if thiazide diuretics, combination potassium-sparing thiazide diuretics, or β-blockers were used more frequently as initial monotherapy.

In choosing calcium channel blockers and ACE inhibitors most often as initial monotherapy for essential hypertension, the physicians in this HMO are consistent with current prescribing practices in the United States, where calcium channel blockers are the most widely prescribed and ACE inhibitors are the second most widely prescribed drugs for hypertension. These prescribing patterns prevail even though expert panels in the United States,[2] Canada,[3] Great Britain,[4] and New Zealand[5] have designated the diuretics (often along with β-blockers) "preferred" therapy for hypertension. The World Health Organization International Society of Hypertension has made similar, but less emphatic, recommendations.[6] The rationale for this recommendation is that diuretics and β-blockers are the only classes of antihypertensive drugs that reduce morbidity and mortality from cardiovascular causes in long-term controlled clinical trials. Therefore, they were recommended as first-choice agents except when contraindicated or poorly tolerated, or there were special indications for other agents in any given patient. This recommendation has aroused much debate and controversy, because the diuretics and β-blockers have adverse biochemical effects, whereas the newer classes of antihypertensive drugs, including the calcium–channel-blocking agents, the ACE inhibitors, and the α-adrenergic-blocking agents, have favorable metabolic profiles and salutary effects on the cardiovascular system that are, at least in part, independent of blood pressure lowering. The newer classes of drugs have not yet been tested in long-term controlled clinical trials with cardiovascular events as end points, and there is no a priori reason to think that they should be less protective than the diuretics and β-blockers. Data from animal studies and short-term studies in humans with established cardiac disease suggest that the ACE inhibitors, in particular, are cardioprotective and vasoprotective and thus may prove superior to the older agents in the prevention of morbid cardiovascular events.

The adverse metabolic effects of the diuretics could increase coronary risk and offset the benefit of blood pressure reduction. These effects include increased serum cholesterol and triglyceride levels, hypokalemia, reduced glucose tolerance, and hyperuricemia. Whether these drug-induced metabolic abnormalities are clinically important is a matter of active debate. Most published clinical trials lack the statistical power to confirm or refute a relation between the adverse metabolic effects of the diuretics and cardiovascular end points. An exception to this rule is the recent case-control trial which showed that thiazide treatment of hypertension was associated with a higher incidence of sudden death than treatment with a combination thiazide–

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potassium-sparing agent.[7] These results have yet to be confirmed in a controlled prospective study.

Only two long-term randomized trials have compared the effects of representatives of all of the major classes of antihypertensive drugs in large numbers of patients with essential hypertension.[8,9] Both of these trials included only patients who had uncomplicated stage 1 and 2 disease. The Treatment of Mild Hypertension Study (TOMHS) was a randomized double-blind placebo controlled clinical trial that compared the effects of five antihypertensive agents from dif-ferent therapeutic classes administered in combination with lifestyle modification to men and women with stage 1 essential hypertension for an average of 4.4 years of follow-up.[8] Outcome measures included blood pressure, quality of life, adverse effects of antihypertensive drugs, blood lipid levels, echocardiographic and electrocardiographic changes, and incidence of cardiovascular events. Blood pressure reductions were sizable in all six groups (five drug treatment groups and a group with lifestyle modification alone) and were significantly greater for participants assigned to drug treatment than for participants receiving lifestyle modification alone. A smaller percentage of participants assigned to the drug-treatment groups died or experienced a major nonfatal cardiovascular event compared with those assigned to the lifestyle modification group. Incidence rates of most resting electrocardiographic abnormalities were lower, and quality of life was reported more improved for those assigned to drug-treatment groups than those in the lifestyle modification group. Differences among the five drug treatments did not consistently favor one group in terms of any outcome measure, but the study lacked the statistical power to discriminate among the relatively small individual drug treatment groups with respect to outcome. Adverse experiences did not differ significantly among drug treatment groups except that the diuretic was associated with a significantly higher incidence of impotence in men (personal communication, Richard Grimm, MD). These results suggest that in selected, well-motivated patients who have uncomplicated stage 1 hypertension, antihypertensive treatment with a drug from any of the five major classes of agents is equally effective in lowering blood pressure rate and maintaining quality of life.

In contrast, the Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents, in a comparison of the effects of six antihypertensive drugs from different classes, each of which was administered as monotherapy to a group of male veterans, found that a sustained-release preparation of the calcium channel blocker diltiazem had a small but statistically significant advantage in achieving blood pressure control over representatives of the other five classes of antihypertensive agents.[9] Lifestyle modification therapy was not used; quality of life and cardiovascular events were not assessed, and only 41 percent of the patients initially randomized completed the 1-year follow-up period of the study.

The ultimate test of antihypertensive therapy is its ability to reduce morbidity and mortality from cardiovascular disease.[10] To settle the question of whether classes of antihypertensive drugs, such as ACE inhibitors and calcium channel blockers, that lack adverse metabolic effects and have demonstrable vasoprotective effects independent of blood-pressure lowering are superior to diuretics, long-term clinical trials are needed. The Antihypertensive and Lipid-Lowering Treatment for Prevention of Heart Attack Trial (ALLHAT) of the National Heart, Lung, and Blood Institute is addressing this issue by testing the main hypothesis that the combined incidence of fatal coronary heart disease and nonfatal myocardial infarction will be lower in hypertensive patients receiving a calcium antagonist, an ACE inhibitor, or an α-adrenergic blocker as first-line therapy than in those in whom a similar degree of blood pressure control is achieved using a thiazide-like diuretic as first-line therapy.[11] This hypothesis is being tested in a population of men and women 60 years of age and older, all with at least one coronary risk factor in addition to hypertension, of whom at least 55 percent are African-American. A sample size of 40,000 patients and a mean follow-up period of 6 years will be needed to reach significant end points. This "large, simple trial" is being carried out by physicians in practice in the office setting, where the participants receive their routine medical care. This design, in addition to the great number of participants in the study, should enhance its generalizability to the high-risk American population as a whole. A study such as this one is critically needed to clarify the very important issue of the differential long-

term benefits of blood pressure reduction with different classes of antihypertensive agents.

Until such information becomes available, it is reasonable to initiate treatment with the agent that is best tolerated and most likely to be effective in lowering blood pressure in a given patient.[12] When monotherapy is unsuccessful, a second agent, usually of a different class, should be added. Prescribing antihypertensive therapy should take into consideration the physiologic, economic, and social characteristics of each patient, as well as any concomitant illnesses, to provide effective blood pressure control as simply and as inexpensively as possible. Expensive, complicated, and inconvenient regimens can promote poor compliance, as do regimens that interfere with quality of life. In this regard, it should be emphasized that, according to NHANES III, blood pressure is being adequately controlled (<140/90 mmHg) in only 21 percent of hypertensive patients in the US.[13] Thus, although a plethora of therapeutic options is available to physicians (including more than 70 drugs in eight therapeutic classes, plus a variety of lifestyle modifications), only a small minority of patients with hypertension are having this condition adequately treated.[10] What proportion of this shortfall is related to lack of access to care, poor prescribing habits by physicians, inability to afford medications, adverse effects or intolerance of prescribed medications, or other factors is unknown and is an important topic for further study.

In the face of these unknowns, the cost of medication should not be the overriding consideration in choosing antihypertensive therapy. Of the $148 billion spent on the care of patients with cardiovascular diseases and stroke in the US in 1993, 50 million of whom have hypertension, only $8 billion was spent on medications.[14] This amount contrasts with $97 billion spent on hospital and nursing home care and $21 billion in lost productivity resulting from disability. The costs of administering inexpensive but poorly tolerated and ineffective antihypertensive therapy are dear and can be measured in terms of human suffering and cardiovascular and stroke-related death and disability, as well as health care dollars.

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