Diuretics and Their Side Effects
Dilemma in the Treatment of Hypertension

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SUMMARY
Diuretics have traditionally been the keystone of antihypertensive therapy. A variety of clinical trials, designed to examine the benefit of blood pressure reduction in decreasing morbidity and mortality from hypertension-related cardiovascular disease, have surprisingly failed to show a decrease in coronary artery disease death rate, although other forms of vascular disease were impressively reduced. These trials have consistently used diuretics as the initial therapeutic choice. Such observations have stimulated a reevaluation of the "stepped-care" approach and a critical appraisal of diuretic effects. This review examines the efficacy of diuretics in reducing blood pressure and attempts to identify individuals most likely to respond to these agents. The side effects of diuretic therapy are reviewed in hemodynamic, cardiac, metabolic, and symptomatic terms, but because some of these aspects of diuretic or antihypertensive therapy are detailed elsewhere in this monograph, the present discussion focuses on cardiac, metabolic, hemodynamic, and symptomatic effects. Finally, alternative therapeutic options and guidelines for therapy are outlined.

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KEY WORDS • diuretics • potassium • lipids • glucose • arrhythmias

Background

UNTIL the late 1950s, the only therapeutic intervention in hypertension directed toward sodium excess was the Kempner "rice diet" or some modification thereof. This diet, which was very low in sodium and protein and high in potassium, was lifesaving in many patients with severe, accelerated, or malignant hypertension, but it was impractical for the majority of hypertensive patients to achieve or maintain. The availability of diuretics, first in the form of organomercurials and then the sulfonamide-derived chlorothiazide in the late 1950s, made it possible to reduce extracellular fluid volume and sodium in hypertensive patients without marked changes in dietary habits and life-style or, indeed, much interruption of their daily routine. With the advent of diuretics, the treatment of hypertension became routine, and the next challenge became the demonstration that blood pressure reduction was beneficial to health.

Trials of Blood Pressure Reduction

A cooperative study based at several Veterans Administration hospitals was organized and conducted to examine this question. Patients were randomly assigned to receive either placebo or a sequential therapeutic approach beginning with a diuretic and then adding antihypertensive agents (reserpine, hydralazine, and guanethidine) until a predetermined level of blood pressure reduction was achieved. Both groups were followed for several years to compare morbidity and mortality of hypertension treated by placebo with the active treatment. This study demonstrated a significant reduction in both morbidity and fatal events among severe and moderate hypertensive patients receiving active drug therapy compared with the placebo-treated group. However, when the causes for morbidity and mortality were compared between the groups, no difference in coronary artery disease was identifiable. Longitudinal studies at Framingham, Massachusetts, indicated that coronary artery disease has multiple antecedents. In addition to hypertension, elevation of cholesterol and glucose and cigarette smoking, as well as increases in uric acid and left ventricular hypertrophy, were shown to increase the risk of cardiovascular death in an additive or synergistic fashion. More recently, this long-term study has suggested that diuretic treatment of hypertension may itself be associated with sudden death in hypertensive patients.

In the United States, Europe, and Australia, studies were designed and conducted to examine the benefit of intervention upon one or more of these cardiovascular disease risk factors to determine whether their associated cardiovascular disease morbidity and mortality.
could be modified. One of the largest such trials, the Multiple Risk Factor Intervention Trial (MRFIT), compared a special intervention program attacking one or more of three major risk factors to less-structured community health care resources. The subjects were selected because of the presence of one or more risk factors: elevated blood pressure, cholesterol, or cigarette smoking habit. Qualifying men were randomly assigned to each group at multiple participating sites. The special intervention group received behavior modification designed to decrease cigarette smoking, dietary counseling to reduce consumption of saturated fats and, thus, lower their blood cholesterol levels, and a stepped-care antihypertensive regimen modeled on the VA Cooperative Study algorithm. Individuals in the comparison group were referred to their usual care resources and were followed in parallel for outcome comparisons. Significant reductions in all three risk factor levels were accomplished in the special intervention group compared with those receiving usual care. However, a reduction in death rate from coronary artery disease was not discernible among the special intervention group when compared to usual care. These observations were confirmed by an Australian trial that also failed to demonstrate a decrease in myocardial infarction during diuretic-treated hypertensive patients compared to those receiving placebo. Another large trial, the Hypertension Detection and Follow-up Program (HDFP), which also used a diuretic-first, stepped-care approach, appeared to have been associated with a decrease in myocardial infarction. However, when the high risk individuals in that study were examined, rates similar to that of the MRFIT study were reported. The failure to observe a decrease in heart attack rate in several trials has focused attention on the impact of antihypertensive agents on cardiovascular disease risk.

Diuretics constitute the most frequently prescribed single class of drugs in the United States. The popularity of diuretic therapy for hypertension in this country has both a scientific and practical basis. The first large-scale trial of the benefit of antihypertensive therapy, the VA Cooperative Study, began treatment with these agents and demonstrated an overall reduction in morbidity and mortality in comparison with placebo. It is important to recognize that the population participating in that study was not representative of the general American hypertensive population. The VA patients were almost exclusively men; the majority were over age 40 and included a substantial proportion of black individuals. These demographic characteristics often favor sodium sensitivity and, hence, diuretic responsiveness of blood pressure. In contrast, studies have shown that β-blockers are equal or greater in efficacy to diuretics among European hypertensive patients, an observation not observed among VA patients. The practical advantage of diuretic therapy resides in its cheap financial cost in comparison with other antihypertensive agents. However, diuretics may have other costs that are currently receiving considerable attention and scrutiny.

General Effects of Diuretics

Diuretics reduce blood pressure primarily by reducing extracellular fluid volume, although they may have secondary effects of reducing pressor responsiveness to vasoconstrictor agents and reducing sodium and water content of vascular smooth muscle. When used to excess or in individuals susceptible to volume depletion, such as the elderly or those with impaired sympathetic reflexes, or in conjunction with sodium restriction, diuretics can cause orthostatic hypotension or even cardiovascular collapse. The reduction in renal blood flow secondary to volume depletion can produce oliguria and azotemia. Other consequences of volume depletion may include lethargy and mental confusion.

Metabolic Effects of Diuretics

Diuretics regularly induce a variety of metabolic side effects. Hypokalemia is a consistent, dose-dependent consequence of diuretic therapy that is directly related to volume-induced stimulation of the renin-aldosterone system and the level of sodium intake. Diuretic-induced hypokalemia has been associated with a variety of undesirable consequences. Digitalis toxicity is more frequent in the presence of hypokalemia. Gastrointestinal disorders, including constipation and paralytic ileus, are more apt to be observed in hypokalemic subjects. Diuretic-induced magnesium depletion also occurs in parallel with potassium loss and exacerbates potassium loss in cardiac muscle. This can modify the action potential of cardiac myocytes and influence the threshold for arrhythmias. Hypokalemia suppresses pancreatic insulin release and, thus, predisposes to hyperglycemia or worsening of existing diabetes mellitus. Diuretic-induced hyperglycemia does not appear to be a transient phenomenon since it persists with treatment for a year or more. Hyperuricemia occurs secondary to a reduction in glomerular filtration rate and inhibition of uric acid secretion because of competition from organic acid-diuretic at the renal tubule. Volume depletion also enhances proximal tubular uric acid reabsorption. Thiazides and loop diuretics may produce hyponatremia, particularly in the presence of dietary sodium restriction, because of their actions to decrease free water clearance. Enhanced proximal tubular calcium reabsorption may lead to hypercalcemia. Diuretics can reduce lithium clearance, thus increasing serum lithium concentration and increasing the likelihood of lithium toxicity. The MRFIT, HDFP, and VA Cooperative Studies have demonstrated adverse effects on serum lipids that persist for the duration of therapy up to 6 years. These effects included increases in total cholesterol, triglycerides, and low-density lipoproteins. Some have argued that these changes are transitory since they return to baseline levels with continued therapy. However, parallel placebo control groups have demonstrated progressive declines in lipid levels with long-term surveillance, and in other studies, withdrawal of diuretic therapy after several years was
associated with a significant fall in serum lipids.\textsuperscript{23-25} Other studies suggest that significant changes in lipids may only be seen in men.\textsuperscript{22}

**Potassium and Arrhythmias**

The most worrisome effects of diuretic therapy have revolved around hypokalemia and its relationship to cardiac arrhythmias and sudden death. This interrelationship is a complex one and may also involve changes in magnesium content of plasma or cells. It has been recognized that potassium can reverse digitalis-induced arrhythmias.\textsuperscript{16} In one study of this problem among hypokalemic patients, arrhythmias were observed in 50%, and 25% were receiving digitalis.\textsuperscript{26} This is not surprising in view of the fact that extracellular potassium concentration is the primary determinant of the cardiac action potential.\textsuperscript{16} In the Oslo Study, diuretic treatment lowered blood pressure 17/10 mm Hg compared with placebo, yet there was no difference in the mortality rate between the two groups.\textsuperscript{15} Among Australian hypertensive patients, the mortality rate among those treated with thiazide, presumably from fatal myocardial infarction and sudden death, was twice that of any other treatment group (placebo, dietary sodium restriction, and propranolol).\textsuperscript{17} The large Medical Research Council trial reported an increased frequency of ventricular ectopy among hypertensive patients receiving thiazides when compared with placebo-treated patients.\textsuperscript{28} They also observed an inverse relationship between ventricular ectopy and serum potassium concentration and a direct relationship with age, inferring that older hypertensive patients were more susceptible to thiazide-associated cardiac arrhythmias.\textsuperscript{28}

**Diuretic treatment increases catecholamines.**\textsuperscript{29} Some studies have suggested a relationship between arrhythmias and such increases. Certainly pathological states associated with increased catecholamine release, such as some forms of essential or accelerated hypertension, acute myocardial infarction, asthmatic attacks, and alcohol or narcotic withdrawal symptoms, have demonstrated increased susceptibility to cardiac arrhythmias and sudden death in the presence of hypokalemia and diuretic therapy. Indeed, catecholamines themselves, acting by the $\beta_2$-adrenergic receptor, are capable of rapidly lowering serum potassium.\textsuperscript{30, 31} Presumably the cardiac protective effects of nonselective $\beta_1$- and $\beta_2$-blockade are due, at least in part, to their ability to preserve potassium levels.

Recent studies have demonstrated ventricular ectopy in 33% of asymptomatic hypertensive patients that was reversed by increasing the serum potassium concentration.\textsuperscript{32} Other investigators have shown an increase in cardiac arrhythmias in hypokalemic patients during exercise\textsuperscript{33} or in the presence of known coronary artery disease.\textsuperscript{34} Curry et al.\textsuperscript{35} have reported an association between "torsade de pointes," a hypokalemia-related ventricular tachycardia, and quinidine. It must, however, be emphasized that not all investigators have confirmed an increased incidence of arrhythmias with diuretic therapy.\textsuperscript{36-38} Studies in animals have also been conflicting. One study demonstrated an increase in malignant arrhythmias after myocardial infarction in diuretic-treated dogs given a low potassium diet compared with dogs not receiving diuretic treatment.\textsuperscript{39} Another study did not observe increased myocardial irritability in response to electrical pacing in diuretic-treated dogs that were not subjected to coronary artery ligation.\textsuperscript{40}

In the presence of an acute myocardial infarction, cardiac arrhythmias and sudden death appear to be more frequent in hypokalemic, diuretic-treated patients.\textsuperscript{41} Solomon and Cole\textsuperscript{42} demonstrated a dose-response relationship between serum potassium concentration and ventricular tachycardia among patients with myocardial infarction. Only 20% of patients with potassium levels above 3.5 mEq/L demonstrated such arrhythmias in comparison with 40% of those with levels 3.1 to 3.5 mEq/L and 67% of those with levels below 3.1 mEq/L.\textsuperscript{42} This observation was confirmed by Nordrehaug\textsuperscript{43} who reported that 17% of patients with acute myocardial infarction having serum potassium levels greater than 3.5 mEq/L demonstrated ventricular tachycardia or ventricular fibrillation as compared with 29% of those with potassium levels below 3.5 mEq/L. An explanation for this frighteningly high rate of ventricular arrhythmias during myocardial infarction in thiazide-treated patients may be derived from other recent studies. Struthers et al.\textsuperscript{44} observed that thiazide treatment was associated with a greater fall in serum potassium after epinephrine administration than had been observed in untreated subjects.\textsuperscript{33} Further evidence linking diuretics and arrhythmias is provided by a European study demonstrating a direct relationship between serum potassium levels and all cardiac arrhythmias observed after acute myocardial infarction.\textsuperscript{45}

Acute myocardial infarction does not provide the only setting in which increased risks of cardiac arrhythmias and sudden death have been reported to be associated with diuretic treatment. The MRFIT study identified a 3.5-fold increase in risk for coronary artery disease death for men with baseline electrocardiographic abnormalities receiving diuretic therapy when compared with those without electrocardiographic abnormalities.\textsuperscript{8} This was also observed in the HDFP study.\textsuperscript{11} Other investigators have reported an increased likelihood of an abnormal electrocardiogram among hypertensive blacks (when compared with whites) and among Japanese.\textsuperscript{46} While the explanation for this observation is not clear, it may represent an increased frequency of electrocardiographic manifestations of left ventricular hypertrophy in blacks and Japanese. Messerli and colleagues\textsuperscript{47} identified left ventricular hypertrophy as a risk factor for sudden death. They noted a marked increase in ventricular arrhythmias and a six-fold increase in sudden death among subjects with left ventricular hypertrophy.\textsuperscript{47} Recent observations from the Framingham Study confirm the risk of left ventricular hypertrophy.\textsuperscript{8} A recent study has demonstrated the risk of arrhythmias associated with diuretic-induced hypokalemia in hypertensive patients with left ventric-
cular hypertrophy but without evidence of coronary artery disease. Diuretic treatment could affect this risk in another way. Tarazi and Drayer have reported that not all agents producing blood pressure reduction in hypertensive subjects are associated with regression of left ventricular hypertrophy when present. Diuretics have been reported to be associated with no change, or progression, of cardiac enlargement rather than regression. In addition, diuretic-induced sympathetic nervous system stimulation in the presence of decreased potassium levels, cardiac hypertrophy, or coronary artery disease could increase myocardial irritability and, thus, provoke arrhythmias and sudden death. Recent observations from the Framingham Study appear to link diuretic treatment directly to sudden death in humans. A

Symptomatic Side Effects

Side effects of diuretics have also been identified as a significant problem in recent large-scale trials. In the HDFP, among 5485 patients receiving stepped-care treatment, drug discontinuation because of side effects occurred in 33%. Diuretics were frequently discontinued because of side effects. With chlorthalidone, the rate was 20.6% and with spironolactone, 16.9%. Specific side effects observed in more than 1% of study participants included gastrointestinal distress, weakness, dizziness, lethargy, skin rash, sexual dysfunction and impotence, and muscle cramps. The Medical Research Council of Great Britain studying 7229 patients reported similar side effects, including impotence at a frequency of 19.6 per 1000 patient-years in diuretic-treated men. Other idiosyncratic reactions include ototoxicity with loop diuretics. This appears to be more common with ethacrynic acid than with furosemide, which in turn appears to cause hearing impairment more frequently than bumetanide. Many diuretics can provoke nausea, vomiting, hemolytic anemia in subjects with glucose-6-phosphate dehydrogenase deficiency, decreased platelet count, pancreatitis, and photosensitivity.

All of these concerns about the adverse effects of diuretic therapy have forced a reevaluation of the traditional, diuretic-first, stepped-care treatment of hypertension. Indeed, the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure in its 1984 Report, for the first time, proposed the use of β-blocking drugs as an alternative to diuretics as the first step in the treatment of elevated blood pressure. Further, the Committee recommended a trial of dietary sodium reduction and weight loss (for those overweight) with mild blood pressure elevation (diastolic 90–95 mm Hg) as well as those with high-normal pressure (85–89 mm Hg). β-Adrenergic blocking drugs, however, may not be ideal alternatives to diuretics for the treatment of mild hypertension since they also induce some of the adverse effects on glucose and lipids seen with diuretics. In addition, they may exacerbate pulmonary disease, provoke asthma, provoke congestive heart failure, or worsen peripheral vascular disease. They also may not be effective in cigarette smokers or in hypertensive blacks. The use of other agents such as angiotensin converting enzyme inhibitors, α-blockers, or calcium channel blockers may provide an effective alternative to initial therapy of mild hypertension without many of the adverse effects of diuretics and β-blocking drugs, although their beneficial effect in reducing cardiovascular morbidity and mortality awaits confirmation.

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