Continued importance of diuretics and β-adrenergic blockers in the management of hypertension

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Thiazide diuretics were introduced in 1957 and became widely accepted as an effective, inexpensive, and generally well-tolerated antihypertensive treatment [1]. β-Blockers became available in the 1960s and were initially used in the therapy of angina pectoris, but soon found widespread application in treating high blood pressure [2]. Numerous large randomized clinical trials have subsequently demonstrated the effectiveness of these compounds in reducing morbidity and mortality in the hypertensive patient. This article reviews the actions of diuretics and β-blockers in blood pressure regulation; surveys early clinical trial evidence that firmly established their position in the modern antihypertensive armamentarium; and presents data from recent trials and guidelines that reaffirm the principal roles to be played by these medications in the prevention of cardiovascular and renal disease in the hypertension population, now numbering nearly 60 million in the United States.

Physiology and pharmacology

Diuretics

Available diuretic agents fall into four classes. Thiazide-type diuretics (including hydrochlorothiazide, chlorthalidone, methyclothiazide, and metolazone) interfere with renal sodium reabsorption in the early distal tubule (Fig. 1) [3]. These compounds are best used as antihypertensive...
agents in patients who have normal or near normal serum creatinine values (1–2 mg/dL), with the exception of metolazone, which retains its diuretic properties despite the presence of renal impairment. Indoline derivatives (including indapamide) may also exert some diuretic action through inhibition of calcium influx into vascular smooth muscle cells. Loop diuretics (including furosemide, bumetanide, torsemide, and ethacrynic acid) are potent, rapidly acting compounds that exert their effects proximally and interrupt sodium reabsorption in the loop of Henle. These agents are effective in patients with renal impairment. Potassium-sparing diuretics (including amiloride, triamterene, spironolactone, and eplerenone) act in the distal tubule, preventing in part the exchange of sodium for potassium that occurs in this section of the tubule. Amiloride and triamterene directly inhibit potassium secretion and are effective in maintaining potassium balance, but both compounds are weak diuretics alone; they are frequently used with hydrochlorothiazide in combined preparations. Spironolactone and eplerenone inhibit aldosterone by competitive or direct blockade of the aldosterone receptor, respectively; both medications exhibit significant potassium-conserving and antihypertensive properties.

The antihypertensive mechanism of diuretics comprises several phases. Initially, plasma volume decreases, with a decrease in cardiac output and systemic blood pressure [4]. Later, plasma volume returns toward normal, but blood pressure remains low with reduced peripheral vascular resistance (Fig. 2). This may be related to direct vasorelaxation mediated by effects on ion flux across arterial smooth muscle cells [5]. In contrast to higher doses previously used (50–200 mg hydrochlorothiazide), the use of as little as 12.5 mg results in significant blood pressure lowering in many patients. In the Systolic Hypertension in the Elderly Program (SHEP), low-dose chlortha-
Lidone (12.5 mg) lowered blood pressure to goal levels in nearly half of the study patients [6]. In patients who are responsive to diuretics, blood pressure is reduced in almost two-thirds of patients with 12.5 mg hydrochlorothiazide; an additional 15% respond to 25 mg. Up to 90% may respond to 50 mg daily; above this dose level side effects may be troublesome in certain patients. Compared with placebo, diuretics lower blood pressure by almost 10 to 15/5 to 10 mm Hg, showing a preferential effect on systolic blood pressure, an important consideration in caring for older patients who have isolated systolic hypertension [6]. Overall, in a randomized, nonselected population, diuretics reduce blood pressure to goal levels in about 50% to 60% of patients, a percentage as high as or higher than other antihypertensive medications. Black and elderly patients are more responsive to diuretics than younger or white individuals.

Fig. 2. Physiologic effects of diuretics. Initially plasma volume (a) and cardiac output (b) are decreased. Plasma volume gradually returns toward normal and cardiac output returns to normal after several weeks. The ultimate result of diuretic therapy is reduction of arterial resistance and blood pressure. A continuing increase in the activity of the renin-angiotensin system, however, is noted. This does not, in most cases, negate the blood pressure response, but can be counteracted in nonresponsive patients by the addition of small doses of an angiotensin converting enzyme inhibitor, a β-blocker, or an angiotensin II receptor blocker. (From Moser M. Clinical management of hypertension. 6th edition. Caddo, OK: Professional Communications; 2002; with permission.)
Low-dose diuretics are also highly effective in lowering blood pressure when used with other agents, such as β-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and calcium channel blockers. Using such combinations may result in normotensive levels in up to 80% of patients, whereas any type of monotherapy in the general hypertensive population may only be effective in 40% to 50% of patients. The mechanism for this beneficial effect of combination therapy may relate to the fact that diuretics may stimulate the renin-angiotensin-aldosterone system because of the decrease in plasma volume that persists. Opposing the activation of this system through use of β-blockers, ACE inhibitors, and angiotensin receptor blockers augments blood pressure reduction [7].

β-Blockers

β-Adrenergic receptor blockers, or β-blockers, inhibit the effects of β-adrenergic stimulation in various organs and body systems. β-Adrenergic stimulation leads to renin release; vasodilation; bronchodilation; increased heart rate and cardiac output; and an increase in insulin secretion, glycogenolysis, and gluconeogenesis in liver and peripheral muscle [8]. Blocking these effects tends to lower blood pressure, primarily by decreasing renin release and reducing cardiac output. β-Receptor selectivity is an important characteristic of β-blocking agents. Nonselective β-blockers (having peripheral and bronchial and cardiac effects) lower blood pressure by decreasing heart rate, cardiac output, myocardial oxygen demand, cardiac contractility, renin release, and the production of angiotensin II and aldosterone but may induce vasoconstriction and bronchoconstriction. Nonselective agents should be avoided or used with care in those patients with asthma or peripheral arterial obstructive disease. β1 selective agents, which have more of an effect on cardiac than peripheral β receptors, may be used in these patients but dosages should be kept in a range where selectivity is maintained. Nonselective agents may be difficult to use in insulin-dependent diabetic patients because of a theoretical concern that peripheral manifestations of hypoglycemia as part of an insulin reaction are masked and compensatory mechanisms that raise blood glucose levels are blunted. β1 selective blocking agents include acebutolol, atenolol, betaxolol, bisoprolol, and metoprolol. Propranolol, the first β-blocker to be extensively used, is nonselective, as are pindolol and nadolol.

In addition to selectivity, β-blockers can be characterized by lipid solubility, and whether or not they possess intrinsic sympathomimetic activity (ISA). Lipid-soluble agents, such as propranolol and metoprolol, cross the blood-brain barrier. Their use may result in central nervous system side effects; they are activated more rapidly in the liver. Non–lipid-soluble agents, such as atenolol and nadolol, may have fewer central nervous system side effects, and are excreted more slowly by the kidney. Pindolol and
acebutolol manifest ISA, a β₂ agonist property that permits blood pressure lowering without significantly diminishing heart rate and cardiac output. This is a potentially useful characteristic in patients with borderline bradycardia, but the evidence that these agents are as effective in treating hypertension as the β-blockers without ISA is limited. Two agents, carvedilol and labetalol, have both β and α blocking (vasodilatory) capabilities.

β-Blockers are particularly useful in hypertension for the treatment of young, white patients in whom the first physiologic manifestation of an elevated blood pressure may be an increase in heart rate and cardiac output. These agents are indicated in patients with resting tachycardias, angina, and post–myocardial infarction. A reduction of more than 20% to 30% in mortality and sudden death is noted in post–myocardial infarction patients when a β-blocker is given. In addition, these agents are useful in various arrhythmias and congestive heart failure once euvolemia and vasodilation have been achieved with diuretics, an ACE inhibitor, or an angiotensin receptor blocker. Recent clinical trial evidence indicates that carvedilol, bisoprolol, and metoprolol are effective as add-on therapy in congestive heart failure.

Small doses of β-blocker–diuretic combination antihypertensive agents have been found to be as or more effective in reducing blood pressure than other antihypertensive agents in moderate dosages.

**Early clinical trial evidence**

Most hypertension trials published before 1995 evaluated the use of diuretics and β-blockers. In some cases, centrally acting agents or vasodilators were added to achieve blood pressure goals. A meta-analysis of 17 placebo-controlled studies showed that patients treated with a diuretic or a diuretic and β-blocker–based treatment program achieved a 52% lower incidence of congestive heart failure, 38% decrease in stroke morbidity and mortality, 35% lower occurrence of ventricular hypertrophy, 21% less cardiovascular disease (CVD) mortality, and a 16% decrease in coronary events compared with placebo (Fig. 3) [9]. The natural progression to more severe levels of hypertension was dramatically reduced [9]. A similar analysis confirmed the favorable impact of a diuretic or β-blocker–based treatment program on stroke in 18 trials, with a lesser impact on coronary events [10].

Early trials included the Veterans Administration Study, which demonstrated a marked reduction in strokes using diuretics and other agents in moderately severe and severe hypertensive patients, with a trend toward improved coronary event outcomes [11]. The Hypertension Detection and Follow-up Program (HDFP), which was a diuretic-based trial, reported a 45% reduction in stroke mortality and a 20% reduction in coronary heart disease (CHD) mortality in the more intensively treated
group compared with a less aggressively treated group of patients [12]. The SHEP study compared diuretics (and β-blockers, if necessary) with a placebo group and reported a 54% reduction in heart failure, 30% fewer myocardial infarctions, 37% reduction in stroke, and a 25% lower rate of transient ischemic neurologic attacks in the treated compared with the placebo group [6]. Although β-blockers have been shown to reduce events in post–myocardial infarction patients, their role in preventing CHD events in hypertensive patients has not been as consistent as that of diuretics, although they have been protective against stroke when used as initial therapy in high blood pressure [6,13,14]. One trial reported that β-blockers were more protective against coronary events than diuretics in hypertensive patients [15], but the results of this study have been questioned. Most investigations have reported that diuretics are more effective, especially in the elderly.

The First and Second Joint National Committees (JNC) on Detection, Evaluation and Treatment of High Blood Pressure in 1977 and 1980 [16,17] recommended diuretics as initial therapy as part of a stepped-care regimen. Beginning with the Third JNC in 1984, national guidelines indicated that diuretics and β-blockers were preferred agents for the initiation of antihypertensive treatment in most patients [18–20]. In the elderly the JNC VI recommended diuretics or diuretics in combination with β-blockers as preferred therapy, based on reduction of morbidity and mortality data from clinical trials where these medications were used [21]. JNC VII has recently recommended diuretics as initial therapy for most patients with β-blockers as a possible alternative treatment or for use in special situations (angina, post–myocardial infarction, congestive heart failure, and so forth)

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**Fig. 3. Results of therapy. Effect of antihypertensive drug treatment on cardiovascular events (decrease in events, treated with compared controls). Combined results from 17 randomized, placebo-controlled treatment trials (48,000) subjects diuretic or β-blocker based.**
These agents have stood the test of time and the results of comparative trials over the past 30 years have justified these recommendations (Table 1).

The question of tolerability and possible metabolic changes with diuretics and β-blockers

Diuretics

In general, diuretics are well tolerated. Two large double-blinded randomized controlled series reported that only 3% of diuretic-treated subjects withdrew because of side effects [23,24]. Yet important questions regarding treatment with these medications were raised by the observation that, in large clinical trials, antihypertensive therapy had resulted in major reductions in direct pressure-related complications (stroke, heart failure, renal dysfunction, and ventricular hypertrophy) but less impressive benefits for coronary artery disease end points (angina and fatal and nonfatal myocardial infarction). According to one viewpoint, atherosclerotic coronary artery disease is a complex, multifactorial, longitudinal process, the outcome of which may not be altered easily by a limited course of treatment aimed at only a single risk factor, hypertension. An alternate perspective held that the metabolic side effects of thiazide diuretics (electrolyte, lipid, and glucose changes) may negate favorable effects of blood pressure reduction. These criticisms have been addressed in some detail [9,25]. It is possible that the short duration of the diuretic-based treatment trials compared with the longer duration of epidemiologic follow-up accounted for the so-called short fall in benefit with CHD events. For example, a 12/4 to 5 mm Hg decrease in blood pressure should result in a decrease of about 20% to 25% in CHD events over a 10-year or more period of time. In the 3- to 5-year clinical trials, a blood pressure decrease of this degree only resulted in a 16% decrease. Did this represent a shortfall or just a shorter duration of follow-up [26]? Some data suggest that a longer-term reduction in blood pressure reduced CHD events to a greater degree than in the shorter-term trials. In addition, several recent thiazide diuretic-based trials, especially in the elderly, have reported that CHD events are reduced to levels predicted by epidemiologic studies, and in a large comparative trial [27] the use of these medications reduced CHD events to the same degree as an ACE inhibitor or a calcium channel blocker despite some differences in lipids and blood glucose levels among the drugs. It is of interest to explore some of the metabolic abnormalities arguments as they relate to diuretics.

Electrolytes

Hypokalemia as a result of thiazide diuretics is dose related. Up to one third of patients experience a decrease in serum potassium in the range of 0.5 to 0.8 mEq/L on high doses of hydrochlorothiazide (50–100 mg daily). Less
Table 1
Evolution of the recommendations of the Joint National Committees on Detection, Evaluation and Treatment of High Blood Pressure

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<tr>
<td>Step 1</td>
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</tr>
<tr>
<td>Diuretics</td>
<td>Diuretics</td>
<td>Less than full dose of diuretic β-blocker</td>
<td>Diuretic, β-blocker, calcium antagonist, or ACE inhibitor</td>
<td>Alternative therapy: ACE inhibitor, CCB, α-β-blocker, or α1-blocker</td>
<td>Diuretic, β-blocker</td>
<td>Thiazide diuretics for most: may consider ACE-I, ARB, β-blocker, or combination</td>
</tr>
<tr>
<td>Add methyl dopa, reserpine or propranolol</td>
<td>Adrenergic inhibiting agents - clonidine, methyl-dopa, β-blocking drugs, α1-blocker, rauwolfa</td>
<td>Add small dose of adrenergic inhibiting agent or thiazide-type diuretic</td>
<td>Add second drug of different class; increase dose of first drug or substitute a drug of a different class</td>
<td>Increase dose or substitute another drug, or add a second agent from a different class</td>
<td>Low-dose combination may be appropriate initial therapy</td>
<td>Low-dose combinations in stage II patients</td>
</tr>
</tbody>
</table>

Specific Indications for ARB, ACE1, α-β-blocker, β-blocker, CCB and diuretic

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; JNC, Joint National Committees.
hypokalemia is observed at a dose of 25 mg hydrochlorothiazide (serum potassium a decrease of 0.3–0.4 mEq/L), and even less is noted at 12.5 mg/d of hydrochlorothiazide. Potassium-sparing diuretics can be recommended in patients who are particularly sensitive to hypokalemia, especially elderly individuals, those receiving digitalis preparations, or diabetic patients whose insulin use may be influenced by hypokalemia. A logical approach to thiazide-induced hypokalemia indicates the use of combination agents, such as spironolactone-thiazide or ACE inhibitor or ARB-thiazide. In each case the potassium-elevating tendency of the former component serves to offset any hypokalemia induced by the latter, but are the changes in potassium levels of clinical significance?

Initial reports suggested that hypokalemia induced by thiazide diuretics could lead to increased ventricular ectopy, including ventricular tachycardia and sudden death [28]. In addition, in what was likely a statistical aberration, subjects with abnormal electrocardiograms in the special-care higher-dose diuretic group in the Multiple Risk Factor Intervention Trial were reported to experience a higher CHD mortality compared with usual-care patients who received smaller doses of the diuretics [29]. These results have been questioned, based on a careful analysis of the Multiple Risk Factor Intervention Trial data [30]. Nonrandomized prospective case-control studies also raised the possibility of increased sudden death in diuretic-treated patients. Treatment groups were not adequately matched in these studies [31,32]. In carefully controlled 24- and 48-hour Holter monitoring studies using high doses (100 mg) of hydrochlorothiazide, however, no significant increase in simple or complex ventricular ectopy was noted, despite some degree of hypokalemia (Table 2) [33]. Ectopy was not significant before or after exercise in patients with or without left ventricular hypertrophy [6,24,33]. There had also been some question about the ability of diuretics to reduce left ventricular hypertrophy. Data have established that the lowering of blood pressure with a thiazide diuretic results in regression of left ventricular hypertrophy, itself a risk factor for ventricular ectopy [34].

With regard to the low serum potassium levels noted in diuretic-treated patients who experience a cardiac arrest, this can be explained as a consequence of endogenously released or exogenously administered epinephrine at the time of the cardiac event. This tends to drive potassium into cells, thereby lowering its serum concentration. Finally, more recent large trials using diuretics compared with placebo and diuretics compared with ACE inhibitors or calcium channel blockers showed no greater incidence of sudden cardiac death in the diuretic-treated groups [6,27]. In any case, concerns regarding treatment-related hypokalemia have decreased given the lower doses of diuretic therapy that are presently being used.

**Lipid changes**

Within the first year of treatment, thiazide diuretics may increase total and low-density lipoprotein cholesterol by about 5% to 7%, without alteration in
high-density lipoprotein cholesterol concentration. Two small trials suggested that diuretics elevate lipids significantly [35,36], but these trials were not controlled or randomized. Large long-term clinical trials using diuretics, however, report no change or even a decrease in total cholesterol in the thiazide-treated groups [37]. Studies that showed no effect on lipids include the Medical Research Council Study [13], the Medical Research Council Study in the Elderly [14], the Metoprolol Atherosclerosis Prevention in Hypertension Study [15], and the Heart Attack Primary Prevention in Hypertension Study [38]. Other investigations have actually demonstrated improved lipid status in diuretic treatment study arms. For example, subjects in the HDFP experienced an overall decrease in total cholesterol (232–223 mg/dL) in the active diuretic treatment (special care) group [39], as did diuretic-treated patients in several other large prospective trials. These studies include the Multiple Risk factor Intervention Trial [29], the European Working Party on High Blood Pressure in the Elderly Study [40], the Treatment of Mild Hypertension Study [24], the Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [27], and the Verapamil in Hypertension Atherosclerosis Study [41]. In the latter 2-year study changes in lipids were similar in the lipid-neutral calcium channel blocker and diuretic arms of the trial. It should be noted, however, that a significant number of ALLHAT subjects were taking statin agents by the end of the trial as part of the study protocol. Despite a slightly higher average cholesterol concentration in the diuretic compared with the lisinopril or amlodipine groups at the conclusion of ALLHAT, coronary disease rates were similar among study arms [27]. In SHEP and HDFP, cardiovascular morbidity and mortality were reduced by the use of diuretics irrespective of whether participants had high or low baseline serum cholesterol values [6,39].

Table 2
Ventricular Ectopy in patients with or without left ventricular hypertrophy before and after hydrochlorothiazide (50 to 100 mg/d for 4 w)

<table>
<thead>
<tr>
<th></th>
<th>LVH (N = 28)</th>
<th>No LVH (N = 16)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Diuretic</td>
</tr>
<tr>
<td>LVPWT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK (mEq/L)</td>
<td>4.06</td>
<td>3.39</td>
</tr>
<tr>
<td>PVC/h</td>
<td>16.6</td>
<td>10.1</td>
</tr>
<tr>
<td>Total couplets</td>
<td>123</td>
<td>15</td>
</tr>
<tr>
<td>Total VT episodes</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

No increase in ectopy following high-dose diuretic therapy in subjects with or without LVH.

Abbreviations: LVH, left ventricular hypertrophy; LVPWT, left ventricular posterior wall thickness; PK, plasma potassium; PVC, premature ventricular contractions; VT, ventricular tachycardia.

On the basis of these observations, it can be concluded that the long-term effects of thiazide diuretics on lipid levels are minimal and probably are of limited clinical significance [42,43]. Patients can be treated safely with thiazide diuretics whatever their lipid status, particularly in light of the availability of statin lipid modifying drugs.

**Glucose and insulin metabolism**

Thiazide diuretics may exert unfavorable influences on insulin sensitivity and glucose utilization, but evidence of adverse clinical effects in large clinical trials is lacking [44]. This is an important issue given the cardiovascular risks inherent in insulin resistance and abnormal glucose tolerance, particularly in light of the rising prevalence of obesity and type 2 diabetes in the United States. In multiple trials involving diuretics, fasting glucose changes are minimal, and when data are pooled, diabetes is increased by only 0.6% above placebo [6,13,38–40,45]. Given the older population who usually has been studied in the clinical trials and who, in all probability, had a degree of increased insulin resistance, for several or many years prior to entering a trial a higher rate of overt diabetes would have been anticipated over the trial period if diuretics were indeed causative factors in diabetes. Although hypertensive patients tend to develop diabetes more frequently than normotensive patients, those treated with diuretics do not require antidiabetic therapy any more often than those receiving other blood pressure–lowering agents (Fig. 4) [46].

Fig. 4. Risk of hyperglycemia with use of antihypertensive drugs. Risk for development of hyperglycemia requiring treatment with antidiabetic drugs in users of antihypertensive drugs relative to nonusers. Note increased risk overall in hypertensive subjects compared with nonhypertensives, but no difference between drugs. (From Gurwitz JH, Bohn RL, Glynn RJ, Monane M, Mogun H, Avorn J. Antihypertensive drug therapy and the initiation of treatment for diabetes mellitus. Ann Intern Med 1993;118:273–8; with permission.)
The ALLHAT study confirmed a small rise in serum glucose and an absolute increase of 3.5% in new-onset diabetes in the diuretic compared with the lisinopril group (11.6% compared with 8.1%), but this finding did not translate into a greater frequency of adverse cardiovascular outcomes in the thiazide diuretic group [27]. In diabetic subjects in ALLHAT, patients receiving diuretics achieved the same CHD outcomes as with the ACE inhibitor or calcium channel blocker and had fewer strokes and episodes of heart failure compared with lisinopril. Heart failure was less in both diabetic and nondiabetic groups in the thiazide-treated patients compared with the amlodipine group [27]. In the Controlled Onset Verapamil Investigation of Cardiovascular End Points Trial, diabetic subjects fared equally well in terms of cardiovascular end points whether they were assigned to verapamil, a diuretic, or a β-blocker [47].

In most trials diabetic patients treated with diuretics achieved fewer cardiovascular events than nondiabetics, illustrating the safety and efficacy of diuretics in these patients [48]. Fig. 5 depicts data with diabetic and nondiabetic subjects from the SHEP trial [6]. The need to lower blood pressure aggressively using effective agents in type 2 diabetics was underscored in the United Kingdom Prospective Diabetes Study Group trial [49], in which tighter versus less strict blood pressure control was linked to better cardiovascular outcomes. A difference of $-10/-5$ mm Hg between the two groups resulted in a dramatic decrease in both microvascular and macrovascular events. There was no difference in outcome between an ACE inhibitor and a diuretic and β-blocker–based treatment group [49]. A summary of the possible metabolic changes resulting from the use of diuretics is noted in Table 3 and reviewed in detail in other publications [50].

![Fig. 5. Reduction in morbidity and mortality in diabetic and nondiabetic subjects in the SHEP study.](image-url)

The SHEP study: low-dose diuretic as initial therapy; β-blocker added if necessary. CABG, coronary artery bypass surgery; MI, myocardial infarction; SCD, sudden cardiac death; SHEP, Systolic Hypertension in the Elderly Program Cooperative Research Group. Open bars represent the diabetic therapy group (283 subjects) and placebo group (300 subjects). Filled bars represent the nondiabetic therapy group (2080 subjects) and placebo group (2069 subjects).
Angiotensin receptor blockers have been shown to slow or reverse the progression of nephropathy in type 2 diabetic patients and prevent the occurrence of end-stage renal disease. They are clearly indicated in these patients [51–53]. Yet because many diabetic patients are sodium sensitive and volume expanded, a thiazide diuretic is usually a necessary part of multidrug therapy if blood pressure goals (130/80 mm Hg) are to be achieved [22,54]. Indeed, almost every trial in the past 30 or more years has been a multidrug trial and a thiazide diuretic has most often been part of the regimen.

Several trials have demonstrated prevention of new-onset type 2 diabetes with pharmacologic inhibitors of the renin-angiotensin-aldosterone system. These include captopril in the Captopril Prevention Project, ramipril in the Heart Outcomes Prevention Evaluation study, and losartan in the Losartan Intervention for Endpoint reduction in hypertension study [55–57]. A significant proportion of patients in these studies also required diuretic therapy to attain blood pressure goals; in patients who are obese or who have a family history of diabetes, it may be logical to commence antihypertensive therapy with a combination diuretic and ACE inhibitor or diuretic and angiotensin receptor blocker.

**β-Blockers**

Although fatigue is sometimes noted as a β-blocker side effect, it is not clear whether it is related to reduced cardiac output or central nervous system effects. Using modest doses of non–lipid soluble preparations may be

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### Table 3
Potential metabolic changes with diuretic use

<table>
<thead>
<tr>
<th>Metabolic change</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Hypokalemia</td>
<td>Less marked with lower dosages; avoid if possible, especially in diabetics and patients receiving digitalis</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Short term: an increase of 5% to 7% in total cholesterol and low-density lipoproteins (may be less with smaller doses); no effect on high-density lipoproteins. Long term: little effect; cardiovascular events reduced to the same degree in subjects with hyperlipidemia or normal cholesterol levels</td>
</tr>
<tr>
<td>Increased insulin resistance</td>
<td>Insulin resistance increased, but only slight increase in blood glucose levels in long-term trials in diuretic-treated compared with placebo subjects. Overall cardiovascular mortality reduced to same or greater degree in diabetics than in nondiabetics</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>Gout in less than 3% of patients; if diuretic essential to management, allopurinol can be given</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>May be advantage in treatment of osteoporosis and prevention of fractures</td>
</tr>
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</table>

helpful. It should be noted, however, that in randomized studies of \(\beta\)-blockers, diuretics, and ACE inhibitors, selective \(\beta\)-blockers demonstrated similar quality of life measures, and in the Treatment of Mild Hypertension Study, \(\beta\)-blockers and diuretics were associated with improved quality of life compared with other agents [24].

The long-term use of \(\beta\)-blockers may result in elevated triglyceride levels and slightly reduced high-density lipoprotein cholesterol levels [58], effects that are less prominent with agents that are selective or that possess ISA. Nonetheless, \(\beta\)-blockers have demonstrated highly significant benefits in reducing morbidity and mortality post–myocardial infarction, and in a 9-year study showed significant cardiovascular benefits in a type 2 diabetic population [49].

A major trial in the elderly [14] that reported less benefit on CHD events with a \(\beta\)-blocker compared with a diuretic was unblinded. Results are difficult to assess based on the large number of patients who were lost to follow-up or discontinued therapy. Nevertheless, as noted, these agents are generally less effective in lowering blood pressure in the elderly than diuretics and, as recommended by the JNC VI, may best be used in combination for effective therapy. In JNC VII, they are specifically indicated in patients post–myocardial infarction, with angina, and so forth.

Recent trials and an update on recommendations

Recent studies have reaffirmed the role of diuretics as initial therapy for most high blood pressure patients [22]. The benefit of \(\beta\)-blockers is also not in dispute as an add-on agent or in combination with a diuretic as initial therapy. For other patients, including those with resistant hypertension, diabetes, or renal impairment (where goals are now lower than previously set [130/80 mm Hg]), diuretics and in many cases \(\beta\)-blockers may still be used as part of a multidrug regimen [22,54,59,60]. Frequently in these situations the use of a diuretic with an ACE inhibitor or an ARB and in some cases a calcium channel blocker is indicated. In many recent and older controlled prospective trials, the importance of diuretics as part of a treatment program has been validated. In several of these trials \(\beta\)-blockers were also used. The following points are noted: (1) In diabetic hypertensive patients, a regimen of \(\beta\)-blockers and diuretics and the achievement of tight blood pressure control produced favorable cardiovascular outcomes over an 8.5-year period (Table 4) [49]; (2) In the Controlled Onset Verapamil Investigation of Cardiovascular End Points Trial, the use of a calcium channel blocker did not prove to be superior to either \(\beta\)-blocker or thiazide diuretic in preventing adverse cardiovascular events [47]; (3) In the Perindopril Protection Against Recurrent Stroke Study investigation, the ACE inhibitor perindopril required the addition of the diuretic indapamide before significant benefit could be demonstrated in reducing stroke and
transient ischemic neurologic attacks in hypertensive patients who had suffered a stroke [61]; (4) The Multicentre Isradipine Diuretic Atherosclerosis Study found fewer cardiovascular events in a diuretic group compared with a short-acting dihydropyrimidine calcium channel blocker [62]; (5) In the Verapamil in Hypertension and Atherosclerosis Study, there was no difference in cardiovascular event outcome between long-acting verapamil and diuretic therapy [41]; (6) In the International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment there was no overall difference in cardiovascular events with long-acting nifedipine compared with a diuretic and potassium-sparing combination. Although the numbers were small, the diuretic group experienced fewer fatal myocardial infarction and congestive heart failure events [63]; (7) In the NORDIC Diltiazem trial there was no overall difference in primary end points between a diltiazem and a β-blocker–diuretic combination. There were fewer strokes, however, in the diltiazem group but a trend toward higher rates of MI, cardiovascular deaths, and congestive heart failure in the calcium channel blocker group [64]; (8) The Swedish Trial in Old Patients with Hypertension-2 also failed to demonstrate a difference in outcomes among older hypertension patients treated with diuretics and β-blockers, calcium channel blockers, or ACE inhibitors [65].

None of these trials have demonstrated a long-term mortality-morbidity benefit of the newer agents (ie, ACE inhibitors or calcium channel blocker) when compared with a diuretic or a diuretic and β-blocker combination.

The Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

Some details of the most recent trial, the ALLHAT [27], which was published in late 2002, are of interest. Thirty-three thousand hypertensive

| Table 4 |

Comparative study of ACE inhibitor and β-blocker–based treatment program in UKPDS

- Number of patients in study (non–insulin dependent diabetics): 1148
- Tight blood pressure control; achieved blood pressure of 144/82 mm Hg compared with group with blood pressures of 154/87 mm Hg
- % Reduction in events
  - Strokes
  - Heart failure
  - Deaths related to diabetes
  - Microvascular disease
  - Myocardial infarction and sudden death (not significant)
- No difference in outcome between different treatment groups; difference in achieved blood pressure accounted for difference in outcome.

patients were studied over a 5-year period. It was designed to assess differences in cardiovascular outcomes among patients treated with a diuretic (low-moderate dose of chlorthalidone); a calcium channel blocker (amlodipine); or an ACE inhibitor (lisinopril). An earlier β-adrenergic blocker arm of the study (doxazosin) had been discontinued when it became clear to investigators that there was a significant excess in congestive heart failure events in the doxazosin group compared with the diuretic group.

To reach goal blood pressure in ALLHAT, β-blockers, reserpine, clonidine, or hydralazine could be added as second- or third-line agents. The study participants averaged 67 years of age and represented a high-risk group for cardiovascular outcomes. Thirty-five percent were black and 36% were diabetic. At the end of 5 years there were no differences in the primary outcome of coronary events or CHD deaths among the three drugs. There were, however, fewer overall cardiovascular events in the diuretic group. For example, compared with lisinopril-treated patients, the diuretic cohort had fewer strokes and heart failure events, particularly in black patients. Compared with amlodipine-treated patients, the diuretic group had a reduced occurrence of severe heart failure events leading to death or hospitalization.

Some of the differences may be explained by overall blood pressure differences among the groups. There was a 4 mm Hg lower average systolic blood pressure in blacks who were treated with diuretics compared with lisinopril and a 3 mm Hg lower systolic blood pressure in patients over 65 years of age. The ALLHAT study has been criticized because of protocol limitations but on balance the data are consistent with other trials. Previous clinical and investigator experience indicate that hypertensive patients respond as well or better to diuretic agents compared with other compounds. In addition, combination therapies that contain a diuretic have been shown to be more effective than those that do not include a diuretic.

The equivalent primary outcome results and the more favorable secondary end point results for the diuretic-treated group in ALLHAT tend to counter arguments that metabolic effects of diuretic drugs detract from their potential to reduce cardiovascular events compared with other agents [66]. Because more than half of the ALLHAT study participants did not reach goal blood pressure on monotherapy, multidrug treatment was required; the study findings suggest that at least one of the drugs should be a diuretic.

Based on ALLHAT and the previous trials, the JNC VII affirmed that diuretics be considered as first-step therapy in most patients, acknowledging that many if not most patients require a multidrug program [22]. The committee recognized compelling or specific reasons for using other agents (β-blockers, ACE inhibitors, angiotensin receptor blockers, or calcium channel blockers). These indications include heart failure, diabetes, diabetic nephropathy, and so forth or in some instances possibly to prevent diabetes.
in individuals at risk. Most patients who are given these medications also require a diuretic in some form to achieve goal blood pressures. Perhaps more important than the question of how one begins therapy is the question of how one ends it. For most hypertension patients that ending consists of a multidrug program.

The Australian National Blood Pressure-2 trial

The recently reported Australian National Blood Pressure study noted a marginally significant benefit in reducing CVD events from ACE inhibitor–based therapy compared with a diuretic-based regimen [67]. Benefit was noted only in men. Less than two thirds of patients remained on the original study drug and the demographics of this trial were different from those of ALLHAT. The results of this study do not negate previous data but indicate that ACE inhibitor–based therapy is also highly effective in reducing the complications of hypertension.

Summary

The use of thiazide diuretics as one of the preferred antihypertensive medications has stood the test of time. Since the introduction of orally effective agents in 1957 to 1958, these drugs have continued to prove their usefulness. Numerous clinical trials have confirmed that these medications are as or more effective in reducing blood pressure and cardiovascular events than any of the other effective antihypertensive agents. Although some metabolic changes may occur with higher dosages of these medications, they seem to be of limited clinical significance. In addition to being well tolerated and effective, thiazide-type diuretics are less expensive than other agents. This should be considered in view of the fact that quality of care is not compromised when the less expensive medication is used.

β-Blockers should also be considered as a major drug class in the management of hypertensive patients. There are few studies directly comparing these drugs with other agents. Although some data suggest that they are less effective in reducing CHD events in the elderly, there are numerous situations where β-blockers are clearly indicated. Combination therapy with a β-blocker and diuretic has been shown to be highly effective in reducing cardiovascular events in both diabetic and nondiabetic patients.

References


