Thiazide diuretics were the first tolerated efficient antihypertensive drugs that significantly reduced cardiovascular morbidity and mortality in placebo-controlled clinical studies. Although these drugs today still are considered a fundamental therapeutic tool for the treatment of hypertensive patients, the following considerations should be taken into account. Although there are some indications that chlorthalidone can offer additional advantages as compared with other compounds, a recent meta-analysis of placebo-controlled trials suggested that the beneficial effects of thiazide diuretics could be a class effect. Thiazide diuretics must be used at appropriate and/or optimal doses to achieve the optimal antihypertensive effect with the smallest occurrence of side effects, including alterations in glucose and lipid profiles and hypokalemia. Moreover, because thiazide diuretics can increase the incidence of new-onset diabetes, especially when combined with β blockers, caution is advised in using these drugs above all in patients who are at high risk for developing diabetes, in whom thiazide diuretics should be used at the lowest active dose and possibly in combination with drugs that block the renin-angiotensin system. Finally, the current debate on whether thiazide diuretics are the first-choice drug for most patients with uncomplicated hypertension, as stated in the Seventh Joint National Committee Report, or are included in the major classes of antihypertensive agents that are suitable for initiation and maintenance of therapy, as reported in the European Society of Hypertension–European Society of Cardiology Guidelines, derives from different interpretations of controlled clinical trial data on drug class comparison and of cost-benefit analyses. However, considering that the benefit of antihypertensive drugs seems to be due principally to BP lowering per se without definitive evidence of the superiority of a particular drug class and that there is no cost-benefit analysis showing the superiority of thiazide diuretics, it is believed that these drugs should not be considered as the only first-choice drug but included among first-choice drugs.

Do All Thiazide Diuretics Give the Same Benefit?

This debate first was raised by data from the Multiple Risk Factor Intervention Trial (3), which aimed to examine special intervention and usual care groups. The data indicated that coronary heart disease (CHD) and total mortality trends were less favorable at clinics where special intervention clinicians favored hydrochlorothiazide over chlorthalidone. This led to a protocol change with the recommendation that all patients switch from hydrochlorothiazide to chlorthalidone at a maximum dose from 100 to 50 mg/d, which subsequently led to a more favorable trend in CHD and total mortality (3). Although these results suggested a beneficial effect of chlorthalidone as compared with hydrochlorothiazide, such conclusions are not robust, especially considering that they are based on a post hoc subgroup analysis. Furthermore, the data are based on a group identifier (clinic) rather than individual patient treatments, and the beneficial effect of the change in treatment could be due to reduction in the chlorthalidone dose (4).

The debate has been reinforced further by the data from two large, controlled, clinical studies on drug class comparison. Whereas in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (5) chlorthalidone as compared with lisinopril-based treatment showed no inferiority for primary outcomes (CHD mortality and nonfatal myocardial infarction) and a superiority for stroke and heart failure (HF) prevention, the Second Australian National Blood Pressure trial (ANBP2) (6) indicated a marginal superiority of enalapril versus hydrochlorothiazide-based treatment on primary end points (all CV [first and recurrent] plus all-cause mortality) with no substantial difference for stroke and HF. Although these conflicting results could be dependent on the specific thiazide diuretic used, there are other likely explanations, such as samples studied, trial design, and type of statistical analysis (4). Finally, a recent meta-analysis of placebo-
controlled trials that used chlorthalidone or other thiazide-like diuretics indicated that major health outcomes did not differ between two treatments, a finding that suggests that the beneficial effects of thiazide diuretics could be a class effect (7).

Choice of Optimal Dose

The relevance of dosage choice of thiazide diuretics can be evaluated considering both the effect of different diuretic therapy doses on CV mortality and morbidity and the dose-response curve in terms of antihypertensive efficacy and metabolic effects. With regard to the first issue, a meta-analysis of clinical studies indicated that low-dose (12.5 to 25 mg/d chlorthalidone or hydrochlorothiazide) and high-dose (50 mg/d or more of both drugs) diuretic therapy lowered BP to a similar degree and exerted a similar benefit in reducing stroke, congestive HF, CV, and total mortality, but only low-dose diuretic therapy significantly reduced CHD incidence (8). The concept of a high dose of diuretic therapy should be replaced by that of optimal dose, which derives from studies that evaluated the dose-response curve of thiazide diuretics, as recently reviewed (9).

Data obtained with chlorthalidone so far indicate that the plateau of the dose-response antihypertensive curve is reached with a daily dose of 25 mg and that increasing the dosage does not increase the BP-lowering effect but further increases the occurrence of negative metabolic effects, principally hypokalemia (10,11). Data obtained with hydrochlorothiazide, the most widely used thiazide diuretic in clinical practice, are less certain and suggest that the plateau of the dose-response BP-lowering curve is reached with the dose of 50 mg/d, whereas negative metabolic effects, principally hypokalemia, occur in a dose-dependent manner with a dose up to 100 mg/d (9,12). Therefore it seems rational to recommend that diuretic treatment with chlorthalidone should start with 6.25 mg in the elderly and 12.5 mg in younger patients, with a maximum dose of 25 mg/d, whereas the starting doses of hydrochlorothiazide should be 12.5 mg in the elderly and 25 mg in younger patients, with a maximum dose of 50 mg/d (9). Moreover the decision to increase the dosage of these drugs to achieve BP control should be weighed against the occurrence of negative metabolic effects.

Negative Metabolic Effects of Thiazide Diuretics

Metabolic effects that can have a negative impact on CV risk profile include alterations in lipids, hypokalemia, impairment of glucose metabolism, and, therefore, the occurrence of type 2 diabetes (13). Although changes in lipid profile, characterized by an increase in total and LDL cholesterol and decrease in HDL cholesterol, have been reported to be modest and transient (13), data from ALLHAT (5) indicate that the increase in total cholesterol is detectable up to 4 yr of follow-up.

Hypokalemia, which as already stated is a dose-dependent phenomenon, can worsen the patient’s prognosis because it can increase the risk for sudden death (14) and CV events among diuretic-treated hypertensive patients (15) and could abolish the benefit of treatment in elderly patients with isolated systolic hypertension (16). Furthermore, hypokalemia can impair glucose metabolism by reducing insulin secretion and insulin sensitivity (13).

Data from controlled clinical trials, recently reviewed (17), indicate that the incidence of new-onset diabetes (NOD) is lower in patients who are treated with drugs that block the renin-angiotensin system (RAS), such as ACE inhibitors and angiotensin receptor blockers, as compared with those who are treated with conventional therapy, i.e., thiazide diuretics alone and above all combined with β blockers.

These findings prompted the debate on whether this difference in the incidence of NOD is due to the beneficial effects of RAS-blocking drugs or, conversely, to the negative action of conventional therapy on glucose metabolism. This second hypothesis seems to be a rational explanation for the following considerations. Incidence of NOD also is reduced in patients who receive calcium antagonists, drugs that are believed to be neutral on glucose metabolism, when compared with conventional therapy (17). A longitudinal observational study showed that given similar fasting blood glucose values, low-dose thiazide diuretic treatment further increased the incidence of NOD (18). In the International Verapamil SR-Trandolapril Study (INVEST) (19), the addition of hydrochlorothiazide dose-dependently increased the risk for NOD not only in patients who received atenolol but also in those who were treated with verapamil. Similarly, in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) Trial (20), the greater incidence of NOD in the amlodipine arm can be explained tentatively by the greater occurrence of hypokalemia induced by the association of hydrochlorothiazide. Finally, the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE) Study (21) showed that in 1 yr of follow-up of previously untreated hypertensive patients, treatment with hydrochlorothiazide frequently associated with atenolol impaired glucose metabolism, whereas treatment with candesartan frequently associated with felodipine was neutral. Considering that NOD has a bad prognostic significance because it increases the incidence of CV events in hypertensive diuretic users even when BP is well controlled (22) and gives the same CV risk as pre-existing diabetes in treated hypertensive patients (18), caution is advised in using thiazide diuretics, especially when combined with β blockers, above all in patients who are at high risk for developing diabetes, such as those with genetic (familial or ethnic) predisposition, obesity, fasting glucose intolerance, and/or the metabolic syndrome. Particularly in these patients, thiazide diuretics should be used at the lowest active dose with close monitoring of metabolic parameters and possibly in combination with RAS-blocking drugs.

Are Thiazide Diuretics the First-Choice Drug or One of the First-Choice Drugs?

The debate on whether thiazide diuretics are the first-choice drug, as recommended by the Seventh Joint National Committee (JNC-7) Report (23), or are among first-choice drugs, as recommended by European Society of Hypertension-European Society of Cardiology (ESH-ESC) Guidelines (24), is principally...
based on different interpretations of controlled clinical trials and secondly on drug cost considerations.

The JNC-7 Report (23) recommendation arose from the two-fold recognition that thiazide-type diuretics have been the basis of antihypertensive therapy in most outcome trials and that in these trials, including the recently published ALLHAT (5,25), diuretics have been virtually unsurpassed in preventing the CV complications of hypertension. Moreover, diuretics can be useful in achieving BP control as well as enhancing the antihypertensive efficacy of multidrug regimens, and they are more affordable than other antihypertensive agents. These recommendations need to be evaluated according to these lines of reasoning.

The strengths and limitations of ALLHAT already have been commented on (26) and can be summarized as follows. The main strength of this study is that with regard to primary outcomes (coronary mortality and nonfatal myocardial infarction), chlorthalidone-based treatment was equally as effective as treatment that was based on amloidipine or lisinopril or doxazosin, and with regard to some secondary end points such as prevention of stroke, it was superior when compared with doxazosin and lisinopril. It was also more effective in prevention of morbidity—but not mortality—from congestive HF when compared with the other three treatments (5,25). However, the difference with regard to stroke could be due to a difference in systolic BP (26). In contrast, the difference with regard to congestive HF might be explained by poor accuracy and/or difficulty in diagnosis; alternatively, withdrawal of previous diuretic therapy may have unmasked congestive HF symptoms in patients with left ventricular dysfunction (26). Therefore, ALLHAT confirmed and strengthened the clinical relevance of thiazide diuretics in the treatment of hypertension but did not prove the superiority of these drugs. This conclusion is in agreement with an expanded analysis of the ALLHAT data presented at the American Society of Hypertension Meeting 2004 (27), which suggests the following interpretations:

- The superiority of chlorthalidone versus lisinopril was detectable in black but not in white patients. Therefore, it would be reasonable to state that whereas diuretics remain the preferred first-line drugs for black patients, ACE inhibitors and diuretics could be regarded as coequal recommendations for initiating therapy in white patients.
- The primary coronary end point was not different for amloidipine compared with the other two drugs, and the other major end points of stroke and all-cause mortality tended slightly in its favor. Therefore, for many patients, the excellent antihypertensive efficacy and tolerability of calcium antagonists continue to make them a popular and appropriate choice.

The nonsuperiority of a particular drug class, beyond BP reduction, is also supported by the following considerations:

- Placebo-controlled clinical studies have shown that the benefit of antihypertensive therapy in preventing CV events with diuretics alone or combined with a β blocker (1) is similar to that achieved with ACE inhibitors and calcium antagonists (2). Such a finding suggests that this benefit is due to BP lowering per se (1,2).
- Meta-analyses of controlled clinical studies, including those on drug class comparison, indicate that reduction in CV morbidity and mortality rates depends BP reduction and that larger reductions in BP produce larger reductions in risk for major CV events (2,28,29).

These conclusions are supported further by data from the VALUE Trial (30), which indicate that early (within 6 mo) control of systolic BP (<140 mmHg) can significantly reduce the incidence of CV events in high-risk hypertensive patients.

The overall data given above do not point to a greater benefit of a particular drug class, beyond reduction in BP values, which is actually the more likely explanation of the benefit of antihypertensive therapy. In this setting, thiazide-like diuretics can be viewed as efficient but not as superior to other antihypertensive drugs. Therefore, their preferential choice should be based principally on drug cost and, in particular, whether they are really less expensive.

Certainly thiazide-like diuretics are less expensive than newer types of antihypertensive agents and therefore are favored in terms of cost minimization (4), but cost is not the sole consideration, and further cost–benefit analyses, announced by the ALLHAT authors although not performed so far (4), are awaited. We believe that their analysis also should take into account the adverse metabolic effects of thiazide diuretics, consisting of an increase in cholesterol levels, blood glucose, NOD, and hypokalemia (4,5). Although these metabolic effects did not translate into a greater frequency of CV events in the relatively short-term follow-up of ALLHAT (5), they could have a major impact on cost–benefit analyses because in the long term, they can reduce the benefit of treatment and increase the cost owing to the need for further pharmacologic therapy that is designed to treat the metabolic abnormalities (26).

The last point to be taken into account is that choice of antihypertensive drugs should be based on additional considerations, as follows. First, efficacy in reducing BP and tolerability, the latter also including metabolic effects, must be evaluated in individual patients. Second, as shown in Table 1, the presence of associated clinical conditions with compelling indications (23), subclinical target organ damage (24), and other associated (but not causally related to hypertension) clinical conditions can indicate the choice of a particular antihypertensive drug class not necessarily including thiazide diuretics. Finally, a combination of two or more drugs, not always including diuretics, is needed in the majority of hypertensive patients to achieve goal BP (24). Above all, these last considerations could indicate that the debate on the first-choice drug class probably has been overemphasized (24).

**Conclusion**

The answer to the question of whether thiazide diuretics are the first-choice drug for treatment of hypertension is two-fold: No, if the diuretic is the only first-choice drug; yes, if the diuretic is one of the first-choice drugs.
Table 1. Indications for antihypertensive drug classes choice

<table>
<thead>
<tr>
<th>Compelling indications</th>
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<tbody>
<tr>
<td>heart failure, after myocardial infarctions, high coronary risk, diabetes, chronic kidney disease, recurrent stroke prevention</td>
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<th>Subclinical target organ damage</th>
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<td>left ventricular hypertrophy, carotid atherosclerosis, microalbuminuria</td>
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<table>
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<tr>
<th>Associated, not causally related, clinical conditions</th>
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<tr>
<td>headache, Raynaud’s phenomenon, irritable bowel, gout, prostatic hypertrophy, palpitations, depression and panic, tremor, renal stones, osteoporosis</td>
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</table>

*aDrug classes other than thiazide diuretics.

References


