THIAZIDE DIURETICS BECAME AVAILABLE IN THE LATE 1950S AND WERE the first effective oral antihypertensive agents with an acceptable side-effect profile.\(^1\,^2\) A half-century later, thiazides remain important medications for the treatment of hypertension. These agents reduce blood pressure when administered as monotherapy, enhance the efficacy of other antihypertensive agents, and reduce hypertension-related morbidity and mortality. This review focuses on thiazides, the diuretics most often indicated for long-term therapy for hypertension; loop diuretics and potassium-sparing agents are briefly considered.

**CHEMISTRY AND MECHANISM OF ACTION**

Diuretic therapy for hypertension originated in 1937 with the discovery that sulfonamides caused acidemia and mild diuresis by inhibiting carbonic anhydrase in the proximal tubule.\(^3\,^4\) Chlorothiazide, a benzothiadiazine derivative, was isolated during a search for more potent inhibitors of carbonic anhydrase; chlorothiazide was found to be a more effective diuretic and also to unexpectedly increase the excretion of chloride, rather than bicarbonate.\(^6\) This effect on excretion eventually led to identification of the upstream portion of the distal convoluted tubule as the major site of action of the thiazides, where they interfere with sodium reabsorption by inhibiting the electroneutral sodium–chloride symporter (Fig. 1).\(^7\) Activity against carbonic anhydrase, although maintained by some thiazides, is considered irrelevant to their mechanism of action, since sodium that is rejected proximally is reabsorbed downstream in the renal tubule in the thick ascending limb. Despite structural variation among the different congeners, the term thiazide diuretic includes all diuretics believed to have a primary action in the distal tubule.

**PHARMACOKINETICS**

The pharmacokinetic activities of thiazides are not uniform. All are absorbed orally and have volumes of distribution equal to or greater than body weight (Table 1).\(^8\,^9\) Thiazides are extensively bound to plasma proteins, which helps limit their filtration by the glomeruli, in effect trapping the diuretic in the vascular space and allowing for its delivery to secretory sites of the renal proximal tubular cells. Organic anion transporters may also assist by concentrating thiazides in the tubular lumen.\(^11\)

The onset of action occurs after approximately 2 to 3 hours for most thiazides, with little natriuretic effect beyond 6 hours.\(^12\) Their metabolism, bioavailability, and plasma half-lives are variable. The latter two pharmacokinetic features are the most clinically relevant, as they determine the dose and frequency of administra-
intake enhances absorption. Some thiazides undergo extensive metabolism, whereas others are excreted nearly intact in urine. A 50% reduction in hydrochlorothiazide absorption is observed in patients with heart failure. Relatively little else is known about the influence of disease on the pharmacokinetics of thiazides. Most thiazides have a half-life of approximately 8 to 12 hours, just permitting effective once-daily dosing. Among thiazides, chlorthalidone is uniquely long-acting, with an elimination half-life of 50 to 60 hours, owing to its large volume of distribution. Nearly 99% of chlorthalidone is bound to erythrocyte carbonic anhydrase, and the drug has a stronger inhibitory effect than other thiazides against several catalytically active mammalian isoforms. The substantial partitioning of chlorthalidone into erythrocytes creates a tissue reservoir that allows the constant seeping of chlorthalidone back into plasma, through which it exerts its therapeutic effect. This depot effect of chlorthalidone may be advantageous in patients who occasionally miss doses, and the agent appears to retain measurable efficacy when given less frequently than once daily.

### PHARMACODYNAMICS

#### Hemodynamic Effects

The hemodynamic effects of thiazides can be separated into short-term and long-term phases (Table 2). Initial decreases in blood pressure are attributed to the reductions in extracellular fluid and plasma volumes, leading to depressed cardiac preload and output. Dexam administration during this short-term phase will restore plasma volume and blood pressure to pretreatment levels. Counterregulatory activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system induces a transient rise in peripheral vascular resistance, although this is not usually sufficient to negate the blood-pressure reduction. Combining a thiazide with an angiotensin-converting–enzyme (ACE) inhibitor or an angiotensin II–receptor blocker (ARB) can oppose this transient rise in resistance and increase the antihypertensive response.

The long-term antihypertensive response to thiazides cannot be reliably predicted by the degree of initial reduction in plasma volume, which eventually returns to near-normal levels. Volume expansion due to the use of dextran at this stage no longer restores the blood pressure to pretreat-
A more likely explanation for the persistent antihypertensive effects of most thiazides is an overall reduction in systemic resistance, although the exact mechanisms are unclear. Evidence suggests that chlorthalidone may not lower systemic resistance, even after 8 to 12 months of therapy, indicating that other mechanisms may be responsible. It is not yet clear whether thiazides have direct vasodilatory properties or induce a reverse autoregulation phenomenon; they have also been proposed to cause structural membrane changes or altered ion gradients. A simpler possibility is that a low level of prolonged diuresis produced by long-term thiazide administration may maintain a nominal state of volume contraction, thereby promoting a downward shift in vascular resistance.

Thiazides have substantial residual effects after discontinuation. Rapid volume expansion, weight gain, and decreased renin levels occur after stopping thiazides, but blood pressure rises slowly and does not immediately reach pretreatment levels. With adherence to lifestyle modifications (e.g., weight loss, reduction in sodium and alcohol intake), nearly 70% of patients may not require antihypertensive medications for up to 1 year after long-term thiazide-based therapy is withdrawn.

### Table 1. Pharmacokinetic Characteristics of the Thiazide Diuretics Approved for Use in the United States.

<table>
<thead>
<tr>
<th>Diuretic†</th>
<th>Relative Carbonic Anhydrase Inhibition‡</th>
<th>Oral Bioavailability</th>
<th>Volume of Distribution</th>
<th>Protein Binding</th>
<th>Route of Elimination</th>
<th>Elimination Half-Life hr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thiazide-type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>++</td>
<td>15–30</td>
<td>1</td>
<td>70</td>
<td>100% Renal</td>
<td>1.5–2.5</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>+</td>
<td>60–70</td>
<td>2.5</td>
<td>40</td>
<td>95% Renal</td>
<td>9–10</td>
</tr>
<tr>
<td>Methylochlothiazide</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hepatically metabolized</td>
<td>—</td>
</tr>
<tr>
<td>Polythiazide</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>25% Renal</td>
<td>26</td>
</tr>
<tr>
<td>Bendroflumethiazide</td>
<td>0</td>
<td>90</td>
<td>1.0–1.5</td>
<td>94</td>
<td>30% Renal</td>
<td>9</td>
</tr>
<tr>
<td><strong>Thiazide-like</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>+++</td>
<td>65</td>
<td>3–13</td>
<td>99</td>
<td>65% Renal</td>
<td>50–60</td>
</tr>
<tr>
<td>Metolazone</td>
<td>+</td>
<td>65</td>
<td>113 (total)§</td>
<td>95</td>
<td>80% Renal</td>
<td>8–14</td>
</tr>
<tr>
<td>Indapamide</td>
<td>++</td>
<td>93</td>
<td>25 (total)§</td>
<td>75</td>
<td>Hepatically metabolized</td>
<td>14</td>
</tr>
</tbody>
</table>

* All the diuretics listed are available in generic form in the United States as monotherapy, except polythiazide (not currently available) and bendroflumethiazide (available only in combination with nadolol). Dashes indicate an absence of data.
† The terms thiazide-type and thiazide-like are used to group thiazides on the basis of the presence of a benzothiadiazine molecular structure. Thiazide-like diuretics lack the benzothiadiazine structure but have a mechanism of action similar to that of thiazide-type diuretics, which have the benzothiadiazine structure.
‡ Plus signs indicate inhibition, with greater numbers of plus signs reflecting increased inhibition (lower inhibition constants); the zero indicates an inhibition constant of 0.
§ The volumes of distribution of metolazone and indapamide are given for the total volume, in liters; data on liters per kilogram were not available.

**Tolerance to Diuretics**

The use of diuretics elicits both short- and long-term adaptations intended to protect intravascular volume. Short-term tolerance may result from a period of post-dose antinatriuresis triggered by the initial reduction in extracellular fluid volume, corresponding to a decline in the drug level in plasma and tubular fluid to below the diuretic threshold. Activation of the renin–angiotensin–aldosterone system and the sympathetic nervous system, as well as suppression of the secretion of atrial natriuretic peptide and renal prostaglandin, also contribute to short-term tolerance. Post-dose sodium retention is significantly influenced by dietary sodium intake. Sodium restriction promotes an overall negative sodium balance and enhances the therapeutic response to thiazides, whereas persistently high dietary sodium offsets this effect.

Long-term diuretic adaptation, or the braking effect, refers to a gradual return of the sodium–chloride balance to an electroneutral level. Persistent volume removal appears to trigger long-term activation of the renin–angiotensin–aldosterone system, increasing circulating angiotensin II levels, which in turn promotes increased proximal sodium reabsorption and limits the overall delivery of sodium to the distal site. Other volume-inde-
Dependent mechanisms may be involved, including the up-regulation of sodium transporters downstream from the primary site of diuretic action and structural hypertrophy of distal nephron segments. 29-31

Tolerance to diuretics can be overcome by administering higher doses or combinations of diuretics. For example, synergistic diuresis occurs when a thiazide is added to loop-diuretic monotherapy in patients with edema. 32 Occult volume expansion can be present in patients with resistant hypertension, despite existing diuretic therapy; increasing the dose of diuretics may improve the blood pressure. 33 High doses and combinations of diuretics must be used carefully to avoid renal injury and marked electrolyte disturbances.

**Table 2. Hemodynamic and Physiological Effects after Initiation and Cessation of Diuretic Therapy.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Short-Term Phase (first 2–4 wk)</th>
<th>Long-Term Phase (mo)</th>
<th>Post-Therapy Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output</td>
<td>Decrease</td>
<td>Increase (return to pretreatment level)</td>
<td>No change</td>
</tr>
<tr>
<td>Plasma volume</td>
<td>Decrease</td>
<td>Increase (near-return to pretreatment level)</td>
<td>Increase (possibly exceeding pretreatment level)</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>Increase</td>
<td>Increase</td>
<td>Decrease (return to pretreatment level)</td>
</tr>
<tr>
<td>Peripheral resistance</td>
<td>Transient increase</td>
<td>Gradual decrease</td>
<td>Increase (gradual return to pretreatment level)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Gradual increase</td>
</tr>
</tbody>
</table>

Many physicians consider thiazides the diuretics of choice for long-term therapy. On average, after adjustment for reductions seen with the use of placebo, thiazides induce a reduction in the systolic and diastolic blood pressures of 10 to 15 mm Hg and 5 to 10 mm Hg, respectively. Hypertension responding preferentially to thiazides is considered to be low-renin or salt-sensitive hypertension. The elderly, blacks, and patients with characteristics associated with high cardiac output (e.g., obesity) tend to have this type of hypertension. Thiazides also correct the hypertension and electrolyte abnormalities associated with pseudohypoaldosteronism type 2 (Gordon’s syndrome), a rare mendelian form of hypertension in which the sodium–chloride symporter is excessively active. Thiazides potentiate other antihypertensive agents when they are used in combination, often producing an additive decrease in blood pressure. The addition of a thiazide minimizes racial differences usually observed in response to monotherapy with inhibitors of the renin–angiotensin–aldosterone system, and the use of such an inhibitor can lessen the degree of the hypokalemia and the metabolic perturbations that may be evoked by thiazides.

The dosing of thiazides has evolved in parallel to our progressive understanding of their mechanism of action and dose–response relationships. Earlier use of high doses was based on the belief that efficacy was directly linked to the amount of renal sodium excretion and reduction in plasma volume; the larger the dose, the greater the assumed reduction in blood pressure. However, thiazides are now used in substantially smaller doses, and the term low-dose thiazide has become synonymous with hydrochlorothiazide at a dose of 12.5 to 25 mg per day (or the equivalent dose of another thiazide). Approximately 50% of patients will respond initially to these low doses. In the Systolic Hypertension in the Elderly Program (SHEP), 34 chlorthalidone given at a dose of 12.5 mg per day controlled blood pressure, for several years, in more than 50% of patients. Increasing the dose of hydrochlorothiazide from 12.5 to 25 mg per day may result in a response in an additional 20% (approximately) of patients; at 50 mg per day, 80 to 90% of patients should have measurable decreases in blood pressure. 35 Increased electrolyte losses at the higher doses of diuretics may preclude their routine use.

For many hypertensive patients, several agents will be needed to achieve desired blood-pressure targets. Combination regimens that include a thiazide can achieve therapeutic synergy while min-
imizing adverse effects. The lack of appropriate diuretic use is often identified as the primary drug-related cause of resistance to treatment.

**DIURETICS IN RENAL IMPAIRMENT**

Thiazides are typically considered ineffective when the glomerular filtration rate decreases below 30 to 40 ml per minute per 1.73 m² of body-surface area, although direct evidence is lacking. Small studies have shown that thiazides can elicit an antihypertensive response in patients with chronic kidney disease; however, their use in patients with severe renal impairment remains impractical, for two reasons: first, the reduced glomerular filtration rate limits the overall filtered sodium load reaching the distal tubule; and second, reabsorption in the distal tubule is only modestly effective as compared with that in the large-capacity, thick ascending limb. These features underscore the rationale for substituting so-called high-ceiling diuretics that act more proximally, in the loop of Henle, in hypertensive patients with renal impairment.

Metolazone, a quinazoline derivative, is an exception among thiazides because it retains its efficacy in patients who have renal insufficiency or other diuretic-resistance states. Its effect is limited by slow, erratic absorption; the more predictable bioavailability of other thiazides makes them better suited as long-term therapy of hypertension. Metolazone should be reserved for use in combination with loop diuretics in patients with volume overload whose fluid and electrolyte balance are being closely monitored. It is administered daily for a short period (3 to 5 days), with administration reduced to thrice weekly after this period or after euvolemia is achieved.

**LOOP DIURETICS**

Diuretics that act in the loop of Henle can lower blood pressure but are less effective in the long term than thiazides. Most loop diuretics have a short duration of action (approximately 6 hours), resulting in an initial diuresis that is followed closely by a period of antinatriuresis lasting up to 18 hours per day when the drug is administered once daily. A net neutral sodium balance, or even a positive balance, can occur with the use of loop diuretics. These agents are most appropriate for the treatment of hypertension that is complicated by a reduced glomerular filtration rate (<30 to 40 ml per minute per 1.73 m² of body-surface area) or by volume overload (e.g., in congestive heart failure or the nephrotic syndrome); in patients with such complications, loop diuretics provide consistent natriuresis and diuresis. Furosemide should be administered twice daily, whereas torsemide is a longer-acting alternative that may be administered once daily.

**POTASSIUM-SPARING AGENTS AND MINERALOCORTICOID-RECEPTOR ANTAGONISTS**

Potassium-sparing agents induce only minimal natriuresis and are relatively ineffective in lowering blood pressure (Fig. 1). Their primary value is their ability to reduce the loss of potassium when they are used with thiazides. They also avert the urinary loss of magnesium, which is important, since restoration of magnesium balance is necessary for optimal correction of diuretic-induced hypokalemia. Triamterene is commonly administered with hydrochlorothiazide, although other fixed-dose combinations of thiazides and potassium-sparing agents are available. Amiloride, an epithelial sodium-channel blocker, is reportedly more effective than spironolactone as therapy in blacks who have resistance to treatment.

The phenomenon of aldosterone escape, whereby aldosterone activity is incompletely suppressed in hypertensive patients who are receiving inhibitors of the renin–angiotensin–aldosterone system, can lead to increased salt and water retention. Agents that block the effect of aldosterone are useful for treating this retention. Spironolactone, a nonselective mineralocorticoid-receptor antagonist, is well absorbed and has a long half-life (approximately 20 hours), attributable to its active metabolites. Spironolactone not only corrects thiazide-induced potassium and magnesium losses, but also, in low doses (12.5 to 50 mg per day), provides additive hypotensive effects in patients who have resistance to treatment. Spironolactone remains effective when renal function is impaired, but patients must be monitored carefully for the development of hyperkalemia. Eplerenone, a newer agent that is more selective for aldosterone than for androgen and progesterone receptors, is associated with less gynecomastia and breast tenderness than is found with spironolactone. However, direct comparisons of the efficacies of eplerenone and spironolactone in patients with treatment-resistant hypertension are lacking.
The efficacy of thiazides in reducing the risk of major cardiovascular events was first established in 1967, in the landmark Veterans Affairs Cooperative Study. In the ensuing years, thiazide regimens have proved highly effective in the prevention of stroke, coronary heart disease, and heart failure (see the Supplementary Appendix, available with the full text of this article at NEJM.org).

Combined meta-analyses and systematic reviews report that, as compared with placebo, thiazide-based therapy reduces relative rates of heart failure (by 41 to 49%), stroke (by 29 to 38%), coronary heart disease (by 14 to 21%), and death from any cause (by 10 to 11%). These and other analyses also show that the benefit from thiazides is broadly similar to that from other antihypertensive drugs, with results consistent across age and sex strata.

The largest randomized, blinded study performed to date, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), compared initial treatment consisting of chlorthalidone, at a dose of 12.5 mg per day, with treatment consisting of amlodipine, lisinopril, or doxazosin. The 42,418 high-risk study participants were 55 years of age or older, and 35% were black. The doxazosin treatment was stopped prematurely owing to a significantly greater incidence of heart failure events than with chlorthalidone. At the end of the study, no significant differences were found between the chlorthalidone group and any other treatment group in the rate of the composite primary end point of fatal coronary heart disease or nonfatal myocardial infarction; however, chlorthalidone was superior with respect to several predefined secondary end points, including heart failure (vs. amlodipine and lisinopril) and stroke (vs. lisinopril). The explanation for these findings may be related to the improved blood-pressure control maintained throughout the study in the patients receiving chlorthalidone as compared with those receiving another treatment. Analyses of data stratified on the basis of race and metabolic status consistently indicate that chlorthalidone, used as initial therapy, was not surpassed by any of the three comparison drugs with regard to antihypertensive efficacy or event-rate reduction.

Although chlorthalidone and hydrochlorothiazide have been commonly used in the United States, other thiazides, such as bendroflumethiazide and indapamide, have also been studied. Recently, the use of a sustained-release indapamide-based regimen as initial therapy led to relative reductions of 39%, 64%, and 21% in the rates of fatal stroke, heart failure, and death, respectively, in patients older than 80 years of age.

The concept of a class effect among thiazides has been promulgated in the absence of comparative studies. In the United States, this debate largely centers on whether to use hydrochlorothiazide or chlorthalidone. Chlorthalidone is frequently suggested for use, since the rate of cardiovascular events has been reduced in every study in which it was used, including at the low doses in the SHEP study and ALLHAT, whereas the effects of other thiazide regimens have been less consistent. Trials in which hydrochlorothiazide was associated with favorable reductions in the rate of cardiovascular events have typically used higher doses (between 25 and 50 mg per day) than currently advocated. These dose-based differences are underappreciated, and the perception that thiazides are interchangeable is reinforced by the abundance of fixed-dose combinations containing low-dose hydrochlorothiazide. Two trials of low-dose hydrochlorothiazide in combination with other medications showed less effectiveness as compared with the nontiazide regimen.

Hydrochlorothiazide and chlorthalidone are often incorrectly described as equipotent. However, early trials comparing the two drugs often involved the administration of hydrochlorothiazide twice daily to achieve reductions in blood pressure similar to those effected by chlorthalidone. When evaluated on the basis of the dose required to achieve equivalent reductions in the systolic blood pressure, 24-hour ambulatory blood-pressure monitoring confirmed that chlorthalidone is approximately twice as potent as hydrochlorothiazide. These findings may be attributable to the ability, with chlorthalidone therapy, to maintain efficacy throughout the night and reduce the gradual rise in blood pressure that may occur during the interval between daily doses.

Whether hydrochlorothiazide and chlorthalidone are interchangeable in reducing the risk of cardiovascular events is questionable. An analysis in the Multiple Risk Factor Intervention Trial...
Several antihypertensive agents, including diuretics, as initial therapy. The United States who are eligible for thiazide therapy actually receive it.

Future.

National Committee is anticipated in the near future.

diabetes mellitus.

elderly and blacks.

hypothesized for ACE inhibitors and ARBs but not for thiazides.

promotion of diuretics and the heavy marketing of new medications.

Safet y and Adverse Effects of Thiazides

Much of the criticism against thiazides is directed toward their adverse-effect profile, but low doses are usually well tolerated and have been shown to improve quality-of-life measures. Most complications of thiazide therapy are related to the dose and duration of use (Fig. 2).

Thiazides can reduce the excretion of calcium and uric acid and thereby increase their plasma levels, and the drugs increase potassium and magnesium excretion, potentially leading to hypokalemia and hypomagnesemia. On average, measured plasma potassium levels decrease by about 0.3 to 0.4 mmol per liter with typical dosing of thiazide monotherapy, but coadministration of an ACE inhibitor or an ARB can reduce the incidence of clinically relevant hypokalemia. In ALLHAT, the average potassium level among patients receiving chlorthalidone decreased from 4.3 mmol per liter to 4.1 mmol per liter over a 4-year period. The plasma potassium level should be measured at baseline, before the initiation of thiazide monotherapy; a potassium-sparing agent may be considered if the baseline level is less than 3.8 mmol per liter.

Maintaining potassium homeostasis is essential, since epidemiologic evidence implicates hypokalemia in the pathogenesis of thiazide-induced dysglycemia. The importance of potassium balance is also emphasized by findings from the SHEP study, in which the rate of coronary events among patients with potassium levels below 3.5 mmol per liter was reduced to a lesser degree than among patients with higher potassium levels. Hypokalemia can be managed with the use of a potassium-sparing agent or supplemental potassium chloride. Potassium-sparing agents are preferred because they correct the underlying cause. Dietary salt restriction can also minimize thiazide-induced potassium losses.

New-onset diabetes has been reported in patients receiving thiazides; however, newly diagnosed diabetes occurs over time in many hypertensive patients, regardless of which class of antihypertensive agent is used. Data suggest that receipt of thiazides, as compared with other antihypertensive agents, over several years may lead to an excess of 3 to 4% of new cases of diabetes.

In ALLHAT, the rates of fatal and nonfatal myocardial infarction were similar among patients re-

**Optimal Role of Diuretics — Initial or Add-on Therapy?**

Despite a long, well-established record of efficacy, the role of thiazides in hypertension therapy continues to provoke debate. Based on the benefits observed in studies in which thiazides were used as initial therapy in a stepped-care approach, with agents added sequentially, guidelines for hypertension therapy in the United States have advocated thiazides as initial treatment since 1977, when the first Joint National Committee report was issued. In contrast, British guidelines recommend diuretics more selectively, such as for use in the elderly and blacks. European guidelines endorse several antihypertensive agents, including diuretics, as initial therapy. An update from the Joint National Committee is anticipated in the near future.

Slightly more than one third of the patients in the United States who are eligible for thiazide therapy actually receive it. The reasons for this low rate of use may include the absence of corporate promotion of diuretics and the heavy marketing of newer medications. Pleiotropic effects in addition to the blood-pressure–lowering effect have been hypothesized for ACE inhibitors and ARBs but not for thiazides. In addition, there is discussion about the importance of adverse electrolyte and metabolic changes in association with thiazides and whether these changes abrogate the overall blood-pressure–lowering benefits of the drugs.

Cumulative evidence from trials suggests that the magnitude of blood-pressure lowering is the most important determinant in reducing the cardiovascular risks associated with hypertension. As diuretics are eventually required in many hypertensive patients to achieve blood-pressure goals, debate about their role as initial or add-on therapy may be predominantly academic.
receiving chlorthalidone, despite the fact that newly diagnosed diabetes was more frequent in the chlorthalidone group (seen in 11.6% of patients) than in the amlodipine group (9.8%) or the lisinopril group (8.1%). To date, no analyses of ALLHAT data have indicated that the development of diabetes obviates the benefit of the thiazide.\textsuperscript{53-57} Similar findings have been reported in a large meta-analysis and in long-term follow-up data of the SHEP cohort.\textsuperscript{81-83} Despite these reassurances, newly diagnosed diabetes in patients receiving thiazides remains a potential concern, since the period of monitoring for long-term diabetes-related adverse effects on cardiovascular outcomes may have been too short.

Few clinically relevant drug interactions occur with the use of thiazides; most notably, nonsteroidal antiinflammatory drugs diminish the therapeutic effect of thiazides by causing sodium retention. Thiazides can increase serum lipid levels, primarily total cholesterol and low-density lipoprotein cholesterol levels, by approximately 5 to 7% in the first year of therapy.\textsuperscript{84} A summary of common clinical problems encountered with thiazides, and potential solutions, are detailed in Table 3.

\textbf{Figure 2. Potential Complications of Diuretics and Their Associated Mechanisms.}\n
RAAS denotes the renin–angiotensin–aldosterone system.
Diuretics are a heterogeneous class of antihypertensive medications that have long demonstrated effectiveness in reducing blood pressure and the risk of cardiovascular events. With proper attention to appropriate selection, dosing, and monitoring, diuretic-based regimens can greatly improve the ability to achieve blood-pressure goals. Few pharmacologic discoveries have advanced the treatment of any disease in such a profound and enduring manner.

Dr. Ernst reports receiving advisory fees and consulting fees from Takeda Pharmaceuticals; and Dr. Moser, advisory fees from Takeda Pharmaceuticals and GlaxoSmithKline and lecture fees from Kaiser and the Consortium for Southeastern Hypertension Control. No other potential conflict of interest relevant to this article was reported.

| Table 3. Common Clinical Problems Encountered with Thiazides, and Possible Solutions. * |
|----------------------------------|---------------------------------------------------------------|
| Clinical Problem                  | Possible Solution                                             |
| Attack of acute gouty arthritis   | Obtain uric acid level, and discontinue thiazide if level is elevated. Recheck level after resolution of the attack, and assess the need for prophylaxis. Use another antihypertensive agent if uricosuric prophylaxis is not tolerated or indicated. |
| Hypokalemia (serum potassium ≤3.5 mmol/liter) | Correct hypomagnesemia if present. Add potassium-sparing agent or supplemental potassium chloride. Advise salt restriction. If blood pressure is not controlled, consider adding a RAAS inhibitor. † |
| Increase in serum creatinine from baseline level | Assess hydration status and discontinue any concurrent and unnecessary nephrotoxic drugs (e.g., NSAIDs). Recognize that a slight elevation in creatinine may be the result of improved blood-pressure control in patients with microvascular disease, in whom renal function is dependent on blood pressure for adequate perfusion. |
| No apparent response to hydrochlorothiazide at a dose of 25 mg/day | Assess lifestyle and advise salt restriction if needed. Consider increase in diuretic dose, switch to longer-acting thiazide such as chlorthalidone, or addition of RAAS inhibitor. † |
| Report of dizziness on standing | Check for orthostasis. Reduce diuretic dose if necessary. Assess hydration status, and insure diuretic is administered in the morning. Instruct the patient to stand up slowly. |
| Discovery of asymptomatic hyponatremia | Assess concurrent medications (e.g., SSRIs) and determine risks and benefits of continuing thiazide. Evaluate patient for excessive water intake. |
| Thiazide therapy recommended for patient with documented history of allergy to a sulfa antibiotic | Sulfa antibiotic allergy is not a contraindication to receiving a thiazide. The risk for cross-sensitivity appears to be more dependent on an underlying propensity for atopy than on any specific cross-reactivity among the classes. If true allergy to thiazide is documented, ethacrynic acid (a non–sulfa-containing loop diuretic) can be used. |
| Report of muscle cramps | Check serum potassium level and normalize if low. Consider another diuretic if electrolyte levels are normal. |
| Impaired fasting glucose level or diabetes at baseline | Institute appropriate management of cardiovascular risk factors. Thiazide use is not precluded. |
| Development of diabetes during thiazide therapy | Institute appropriate management of diabetes and related cardiovascular risk factors. The average excess increase in glucose attributed to thiazide use is approximately 3–5 mg/dl (0.2–0.3 mmol/liter). Thiazides will probably be necessary for achieving blood-pressure targets. The addition of a RAAS inhibitor † should be considered, especially if blood pressure is not controlled. |
| Nocturia or incontinence | Avoid thiazide dosing in the afternoon or evening. Limit evening fluid intake. Consider discontinuing thiazide if symptoms are intolerable. |
| Baseline GFR <30–40 ml/min/1.73 m² of body-surface area | Substitute furosemide or torsemide. A practical formula for determining the dose of furosemide, in milligrams to be given twice daily, is as follows: (patient age + blood urea nitrogen level) ÷ 2. Torsemide can be given once daily. |
| Development of sun sensitivity | Encourage sunscreen use. |

* GFR denotes glomerular filtration rate, NSAID nonsteroidal antiinflammatory drug, and SSRI selective serotonin-reuptake inhibitor. † Examples of renin–angiotensin–aldosterone system (RAAS) inhibitors are angiotensin-converting–enzyme inhibitors and angiotensin II–receptor blockers.
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