The Evidence-Based Use of Thiazide Diuretics in Hypertension and Nephrolithiasis

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Thiazide-type diuretics are commonly used in the treatment of hypertension and nephrolithiasis. Evidence from randomized clinical trials needs to be considered in decisions about agent choice and dose. In nephrolithiasis, one of the major limitations of the literature is a paucity of data on the dose-response effect of hydrochlorothiazide (HCTZ) on urinary calcium excretion. The best available evidence for prevention of stone recurrence suggests the use of indapamide at 2.5 mg/d, chlorthalidone at 25 to 50 mg daily, or HCTZ 25 mg twice a day or 50 mg daily. In hypertension, chlorthalidone (12.5 to 30 mg daily) may be the best choice when a diuretic is used for initial therapy, with indapamide (1.5 mg daily) being a valuable alternative for older patients. When adding a thiazide to other drug classes, indapamide (2.5 mg daily) has demonstrated value in hypertensive patients who have had a stroke, and HCTZ (12.5 to 25 mg daily) has a safe track record in several patient groups. Although chlorthalidone has not been tested as add-on therapy, the authors believe it is a safe option in such cases.

Ernst stated “the practitioner who bases decisions on evidence from randomized trials expecting to see similar benefits in practice should use the doses of antihypertensive drugs that were used in trials” (1). Although this statement seems intuitively obvious, it is commonly violated in the prescribing practices of thiazide diuretics when used for the treatment of hypertension or nephrolithiasis. Not only with respect to the dose used, but also with respect to the individual thiazide diuretic used. For example, despite the more compelling data in hypertension involving chlorthalidone use (1,2), hydrochlorothiazide (HCTZ) remains the most commonly prescribed antihypertensive medication in the United States (1). In the treatment of nephrolithiasis, it has been shown that thiazide and thiazide-like diuretics, especially HCTZ, are commonly not used in an evidence-based fashion (3). In this manuscript, we will review the use of thiazide and thiazide-like diuretics in randomized controlled trials for the treatment of hypertension and nephrolithiasis. We will place special emphasis on the specific thiazide used, dosage used, and in the case of hypertension whether the thiazide was used in combination with a potassium-sparing diuretic.

History
The modern era of diuretic therapy began in 1957 when Novello and Sprague synthesized the thiazide diuretic chlorothiazide. Further modification of the benzothiadiazine core led to the synthesis of HCTZ and subsequently the thiazide-like diuretics: chlorthalidone (phthalimidine), metolazone (quinazolinone), and indapamide (indoline) (Figure 1). Thiazide-like diuretics bind and inhibit the Na-Cl co-transporter in the distal convoluted tubule and connecting tubule but do not contain the benzothiadiazine core. The term thiazide diuretics will be used hereafter to refer to thiazide and thiazide-like diuretics.

Thiazide Diuretics and Nephrolithiasis
In 1959, Lamberg and Kühlebäck found that chlorothiazide (1 g twice daily) and HCTZ (100 mg twice daily) reduced urinary calcium excretion (4). Lichtwitz suggested this property might be exploited to prevent calcium-containing kidney stone recurrence (5), and in 1970 Yendt reported, in uncontrolled studies, reduced kidney stone recurrence rates using HCTZ in doses from 100 mg daily to 100 mg twice daily (6).

Randomized controlled trials (RCTs) are critical in the evaluation of stone therapies because of confounding from the “stone clinic effect” and regression to the mean. Referral of patients to a stone clinic is often followed by a reduction in stone-formation rate (stone clinic effect) independent of drug treatment (7). This likely is the result of changes in dietary habits, especially increased fluid intake. In addition, patients often seek medical attention for stone disease after a period of increased disease activity and this may subsequently be followed by a period of reduced disease activity regression to the mean (8).

At least ten RCTs have examined the effects of several different thiazide diuretics on preventing calcium-containing kidney stone recurrence (Table 1) (9–18). Seven of the ten RCTs reported a reduction in recurrence rate in treated patients (9–12,14–16). Two trials that showed no difference in outcome were limited by their short follow-up duration of <2 years (17,18). A consistent finding in these trials is that stone-forma-
tion rate between treated and control groups did not begin to diverge until after at least 1 year of therapy. Stones too small to be detected by imaging studies may be passed in the first few months and obscure beneficial effects of treatment (10).

All but one of the RCTs with thiazide diuretics were conducted between 1981 and 1993 and used HCTZ, bendroflumethiazide, chlorthalidone, trichlormethiazide, or indapamide. Trichlormethiazide is no longer available. Importantly, in the four trials that utilized HCTZ, it was prescribed in high dose (50 to 100 mg daily) (12,16–18). The lowest dose used was 50 mg daily. The following currently available thiazide diuretics, at the doses indicated, were shown to reduce risk for recurrence of calcium-containing kidney stones: indapamide at 2.5 mg/d, chlorthalidone at 25 to 50 mg/d, or HCTZ 25 mg twice daily or 50 mg/daily.

A recent report showed that thiazide diuretics are often not used in an evidence-based fashion in the treatment of calcium-containing kidney stone recurrence (3). One hundred and seven patients with a filled prescription for thiazide diuretics that underwent a 24-hour urine stone risk factor analysis and had medical record documentation that the thiazide was prescribed for calcium-containing kidney stone recurrence were analyzed. Patients on thiazides for <6 months or who had side effects on uptitration of drug were excluded (n = 8). Of the 107 patients that met these criteria, 102 were treated with HCTZ, 4 with indapamide, and 1 with chlorthalidone. Only 35% of HCTZ-treated patients received ≥50 mg/d; a dose previously shown to reduce stone recurrence in RCTs. Fifty-two percent were prescribed 25 mg daily and 13% 12.5 mg daily; these doses were not studied in RCTs. No RCT that we are aware of has used low-dose HCTZ (12.5 to 25 mg daily) to examine reduction in calcium-containing kidney stone recurrence. Whether this dose would be effective is unknown.

Interestingly, in only 2 of 10 RCTs was hypercalciuria an inclusion criterion (9,14). Despite this fact, 7 of 8 trials of adequate duration showed a reduction of kidney stone-formation rate with thiazide diuretics. There are at least two potential explanations for why thiazide diuretics may reduce stone recurrence in those without hypercalciuria. The first is that even as urinary calcium excretion increases within the “normal” range, the risk of stone formation increases. This was shown by Curhan et al. in an analysis of the Nurses Health Studies (NHS) I and II and the Health Professions Follow-Up Study (HPFS) (19). An increase in relative risk for kidney stone formation was seen with urinary calcium excretion >100 mg/d in NHS I, >150 mg/d in NHS II, and >125 mg/d in HPFS.

The hypocalciuric action of thiazides is the most likely mechanism whereby this drug class reduces calcium-containing kidney stone recurrence. One small trial involving six healthy subjects without hypercalciuria attempted to establish a dose-response relationship between HCTZ and urinary calcium excretion (20). Each subject was maintained for 1 week on increas-

### Table 1. RCTs of thiazide diuretics in stone prevention

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Treatment</th>
<th>Selection/Percent Hypercalciuria</th>
<th>Follow-Up (years)</th>
<th>n Treated/n Placebo</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brocks, 1981 (17)</td>
<td>Bendroflumethiazide 2.5 mg TID</td>
<td>None</td>
<td>1.6</td>
<td>33/29</td>
<td>NS</td>
</tr>
<tr>
<td>Scholz, 1982 (18)</td>
<td>HCTZ 25 mg BID</td>
<td>None</td>
<td>1</td>
<td>25/26</td>
<td>NS</td>
</tr>
<tr>
<td>Lærum, 1984 (12)</td>
<td>HCTZ 25 mg BID</td>
<td>None/20%</td>
<td>3</td>
<td>25/25</td>
<td>0.39</td>
</tr>
<tr>
<td>Wilson, 1984 (16)</td>
<td>HCTZ 100 mg daily</td>
<td>None</td>
<td>2.8</td>
<td>23/21</td>
<td>0.48</td>
</tr>
<tr>
<td>Robertson, 1985 (15)</td>
<td>Bendroflumethiazide 2.5 mg TID</td>
<td>None</td>
<td>3 to 5</td>
<td>13/9</td>
<td>0.38</td>
</tr>
<tr>
<td>Mortensen, 1986 (13)</td>
<td>Bendroflumethiazide 2.5 mg + KCl</td>
<td>None</td>
<td>2</td>
<td>12/10</td>
<td>NS</td>
</tr>
<tr>
<td>Ettinger, 1988 (10)</td>
<td>Chlorthalidone 25/50 mg</td>
<td>None/13% to 15.8%</td>
<td>3</td>
<td>19/23/31 25 mg/50 mg/placebo</td>
<td>0.23</td>
</tr>
<tr>
<td>Ohkawa, 1992 (14)</td>
<td>Trichlormethiazide 4 mg</td>
<td>Hypercalciuria</td>
<td>2.1 to 2.2</td>
<td>82/93</td>
<td>0.42</td>
</tr>
<tr>
<td>Borghi, 1993 (9)</td>
<td>Indapamide 2.5 mg daily</td>
<td>Hypercalciuria</td>
<td>3</td>
<td>43/14</td>
<td>0.21</td>
</tr>
<tr>
<td>Fernandez-Rodriguez, 2006 (11)</td>
<td>HCTZ 50 mg daily</td>
<td>None/52%</td>
<td>3</td>
<td>50/50</td>
<td>0.56</td>
</tr>
</tbody>
</table>

TID, 3 times a day; BID, twice a day; KCl, potassium chloride; RR, relative risk.
ing doses of HCTZ daily (12.5, 25, and 50 mg). HCTZ at 12.5 mg/d did not show a statistically significant reduction in urinary calcium, whereas 25 mg/d showed some response and HCTZ at 50 mg/d showed the most significant reduction in urinary calcium. To our knowledge, similar studies have not been performed in stone formers with or without hypercalciuria.

The second potential explanation for why thiazide diuretics reduce stone recurrence is that they have favorable effects on other urinary constituents (magnesium and oxalate) that may reduce stone risk. They increase magnesium excretion, which may reduce stone formation (6). However, some have reported that this effect persists for only days to weeks (21,22). In addition, prolonged thiazide use (>1 year) may reduce urinary oxalate excretion (23,24). The authors of these studies speculated that with long-term thiazide administration intestinal calcium absorption declines. The resultant increase in intestinal luminal calcium would then bind oxalate and reduce its absorption.

Not all effects of thiazides on urinary chemistries are beneficial. In one short-term study of 13 patients administered high-dose thiazides for 1 week, urinary citrate excretion was substantially reduced although calcium oxalate relative supersaturation fell (25). Urinary citrate excretion returned to baseline and calcium oxalate relative supersaturation declined further with potassium chloride and potassium citrate supplementation, although the effects with potassium citrate were more pronounced than potassium chloride.

Given the fact that most patients enrolled in RCTs were not hypercalciuric, that thiazide diuretics may have effects on other urinary risk factors that play a role in stone recurrence, and that a dose-response effect for HCTZ was shown within the range of doses commonly used to treat calcium-containing kidney stone recurrence, the most prudent approach would be to use those drugs that were shown to be beneficial in RCTs in adequate doses. This would require the use of indapamide at 2.5 mg/d, chlorthalidone at 25 to 50 mg/d, or HCTZ at 25 mg twice daily or 50 mg/daily.

**Thiazide Diuretics and Hypertension**

Thiazide diuretics have been used as part of treatment strategies in large-scale hypertension clinical trials since the 1960s and are unequivocally effective in improving outcomes in hypertensive patients. An extensive network meta-analysis established that no other antihypertensive class results in greater outcomes achieved by different thiazides in clinical trials? and (3) Are there differences in choice and dosing according to whether thiazides are used as primary or add-on therapy?

**Thiazide Choice in Hypertension**

**BP-Lowering Effects.** Current evidence indicates that the effects of different thiazides on office BP are relatively similar, although very few head-to-head comparisons are available, so most inferences are based on comparisons across studies (reviewed in detail in several publications (1,59–62)). However, recent observations indicate that individual agents may have differing effects on overall BP control measured by ambulatory BP. Ernst et al. compared the effects of 8 weeks of treatment with chlorthalidone at 12.5 mg (force-titrated to 25 mg) or HCTZ at 25 mg (force-titrated to 50 mg) administered in the morning on 24-hour BP control (63). Although the office (morning trough) and daytime BP were similar with both drugs, the longer-acting chlorthalidone resulted in greater BP reduction during the night (−13.5/−7.2 versus −6.4/−4.6 mmHg, P = 0.009 for systolic BP, and P = 0.29 for diastolic BP), and thereby better overall 24-hour systolic BP reduction (−12.4/−7.1 versus −7.4/−5.1 mmHg, P = 0.05 for systolic BP and P = 0.29 for diastolic BP). The study was initially planned as a crossover study but was ultimately analyzed as a parallel group trial because of a significant drug-order-time interaction through which chlorthalidone was better than HCTZ only when used during the first study block. If used after exposure to HCTZ, the differences were NS despite the 4-week washout period (63). The reason and relevance of this finding is uncertain, but it does raise the possibility that there are other confounders that one needs to consider, such as different effects according to baseline BP, volume status, or previous effects of other diuretics. This caveat notwithstanding, the finding of possible superiority of chlorthalidone over HCTZ cautions us about possible differences in BP effects observed with different agents; in this case, likely related to chlorthalidone’s longer half-life (50 to 60 hours versus 9 to 10 hours for HCTZ) (64). In further support of this possibility are the results of an older study comparing the effects of chlorthalidone at 50 mg once daily with HCTZ 50 mg twice daily on office BP (65). Twice-daily dosing was used to account for HCTZ’s shorter duration of action. BP fell by 18/15 mmHg with chlorthalidone and 22/16 mmHg with HCTZ at the 4-week mark (P = NS). Therefore, it appears that HCTZ requires twice-daily dosing to achieve results that are comparable to chlorthalidone.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>n</th>
<th>Primary (P)/Add-On (A)</th>
<th>Control</th>
<th>Agent/Dose (mg)</th>
<th>Diuretic Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA Cooperative Study (29)</td>
<td>1970</td>
<td>380</td>
<td>P</td>
<td>Placebo</td>
<td>HCTZ 50 BID in combination with reserpine</td>
<td>Better</td>
<td>70% less deaths and major CV events</td>
</tr>
<tr>
<td>Hypertension Detection and Follow-Up Study (HDFP) (33)</td>
<td>1979</td>
<td>10,940</td>
<td>P</td>
<td>Placebo</td>
<td>Chlorthal 25 to 100 daily</td>
<td>Better</td>
<td>17% to 20% less all-cause deaths</td>
</tr>
<tr>
<td>Australian Therapeutic Trial in Mild Hypertension (31)</td>
<td>1980</td>
<td>3427</td>
<td>P</td>
<td>Placebo</td>
<td>Chlorothiazide 500 daily BID</td>
<td>Better</td>
<td>30% less all-cause deaths, 58% less CV deaths</td>
</tr>
<tr>
<td>The Oslo Study (30)</td>
<td>1980</td>
<td>785</td>
<td>P</td>
<td>Placebo</td>
<td>HCTZ 50 daily</td>
<td>Better</td>
<td>Effect restricted to decreased strokes. All CV events decreased (54%) only in patients with baseline DBP ≥ 100 mmHg</td>
</tr>
<tr>
<td>European Working Party on High Blood Pressure in the Elderly (34)</td>
<td>1985</td>
<td>840</td>
<td>P</td>
<td>Placebo</td>
<td>HCTZ/Triamterene 25/50 to 50/100 daily</td>
<td>Better</td>
<td>27% lower CV mortality, no difference in all-cause deaths</td>
</tr>
<tr>
<td>Heart Attack Primary Prevention in Hypertension Trial (HAPPHY) (40)</td>
<td>1987</td>
<td>7569</td>
<td>P</td>
<td>Active (metoprolol)</td>
<td>HCTZ 50 daily or Bendro 5 daily</td>
<td>Same</td>
<td>No differences in any outcomes. Only trend was toward more fatal strokes in the diuretic group (OR = 3.37 [0.96 to 9.53])</td>
</tr>
<tr>
<td>Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) (39)</td>
<td>1988</td>
<td>3234</td>
<td>P</td>
<td>Active (metoprolol)</td>
<td>HCTZ 50 daily or Bendro 5 daily</td>
<td>Worse</td>
<td>48% less all-cause deaths and 58% less CV deaths in the metoprolol group</td>
</tr>
<tr>
<td>Multiple Risk Factor Intervention Trial (MRFIT) (36)</td>
<td>1990</td>
<td>8012</td>
<td>P</td>
<td>Placebo</td>
<td>HCTZ 50 to 100 or chlorthal 50 to 100 daily</td>
<td>Better</td>
<td>Less CV deaths at some points during follow-up, especially if baseline DBP &gt;100 mmHg. No effect during randomized trial phase. Chlor better than HCTZ</td>
</tr>
<tr>
<td>Swedish Trial of Old Patients with Hypertension (STOP) (37)</td>
<td>1991</td>
<td>1627</td>
<td>P</td>
<td>Placebo</td>
<td>Co-amilozide 2.5/25 daily</td>
<td>Better</td>
<td>40% less CV events, 43% lower all-cause mortality</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>n</td>
<td>Primary (P)/Add-On (A)</td>
<td>Control</td>
<td>Agent/Dose (mg)</td>
<td>Diuretic Outcome</td>
<td>Comments</td>
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<tr>
<td>Systolic Hypertension in the Elderly Program (SHEP) (32)</td>
<td>1991</td>
<td>4736</td>
<td>P</td>
<td>Placebo</td>
<td>Chlorthal 12.5 to 25 daily</td>
<td>Better</td>
<td>36% decrease in stroke (primary endpoint). 20% lower CV mortality and 32% less CV events</td>
</tr>
<tr>
<td>Medical Research Council Working Party (35)</td>
<td>1992</td>
<td>4396</td>
<td>P</td>
<td>Placebo</td>
<td>Co-amilozide 25/2.5 to 50/5 daily</td>
<td>Better</td>
<td>Diuretics decreased CV events by 35% compared with placebo. β-blockers had no significant effect</td>
</tr>
<tr>
<td>Treatment of Mild Hypertension Study (TOMHS) (43)</td>
<td>1993</td>
<td>902</td>
<td>P</td>
<td>Active (placebo, acebutolol, doxazosin, amlodipine, enalapril)</td>
<td>Chlorthal 15 to 30 daily</td>
<td>Same</td>
<td>Active treatment modestly better than placebo. No difference among the five drug classes</td>
</tr>
<tr>
<td>Shangai Trial of Nifedipine in the Elderly (STONE) (54)</td>
<td>1996</td>
<td>1632</td>
<td>A</td>
<td>Placebo</td>
<td>HCTZ 25 daily</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Systolic Hypertension in Europe (Syst-Eur) (52)</td>
<td>1997</td>
<td>4695</td>
<td>A</td>
<td>Placebo</td>
<td>HCTZ 12.5 to 25 daily</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Verapamil in Hypertension and Atherosclerosis Study (46)</td>
<td>1998</td>
<td>498</td>
<td>P</td>
<td>Active (verapamil)</td>
<td>Chlorthal 25 daily</td>
<td>Same/Worse</td>
<td>Trend toward more CV events in chlor group, who also had greater progression of carotid atherosclerosis</td>
</tr>
<tr>
<td>Captopril Primary Prevention Project (CAPPP) (42)</td>
<td>1999</td>
<td>10,985</td>
<td>P</td>
<td>Active (captopril)</td>
<td>HCTZ 25 daily or Bendro 2.5 daily</td>
<td>Same</td>
<td></td>
</tr>
<tr>
<td>Swedish Trial of Old Patients with Hypertension 2 (STOP 2) (41)</td>
<td>1999</td>
<td>6614</td>
<td>P</td>
<td>Active (enalapril or lisinopril, felodipine or isradipine)</td>
<td>Co-amilozide 2.5/25 daily</td>
<td>Same</td>
<td></td>
</tr>
<tr>
<td>International Nifedipine GITS Study (INSIGHT) (44)</td>
<td>2000</td>
<td>6321</td>
<td>P</td>
<td>Active (nifedipine GITS)</td>
<td>Co-amilozide 25/2.5 daily to 50/5 daily</td>
<td>Same</td>
<td></td>
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<tr>
<td>Chinese Trial on Isolated Systolic Hypertension in the Elderly (Syst-China) (53)</td>
<td>2000</td>
<td>1253</td>
<td>A</td>
<td>Placebo</td>
<td>HCTZ 1.5 to 25 daily or BID</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>n</td>
<td>Primary (P)/Add-On (A)</td>
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</tr>
<tr>
<td>Losartan Intervention for Endpoint Reduction in Hypertension (LIFE)</td>
<td>2002</td>
<td>9193</td>
<td>A</td>
<td>NA</td>
<td>HCTZ 12.5 to 25 daily</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Anti-Hypertensive and Lipid-Lowering to Prevent Heart Attack Trial (ALLHAT)</td>
<td>2002</td>
<td>33,357</td>
<td>P</td>
<td>Active (lisinopril, amlodipine)</td>
<td>Chlorthal 12.5 to 25 daily</td>
<td>Same</td>
<td></td>
</tr>
<tr>
<td>Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE)</td>
<td>2003</td>
<td>16,602</td>
<td>P, A</td>
<td>Active (verapamil COER)</td>
<td>HCTZ 12.5 daily</td>
<td>Same</td>
<td></td>
</tr>
<tr>
<td>Second Australian National Blood Pressure Study (ANBP2)</td>
<td>2003</td>
<td>6083</td>
<td>P</td>
<td>Active (enalapril)</td>
<td>HCTZ recommended, no dose specified</td>
<td>Worse</td>
<td>11% less CV events or deaths with enalapril</td>
</tr>
<tr>
<td>Valsartan Antihypertensive Long Term Use Evaluation (VALUE)</td>
<td>2004</td>
<td>15,245</td>
<td>A</td>
<td>NA</td>
<td>HCTZ 12.5 to 25 daily</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)</td>
<td>2005</td>
<td>19,257</td>
<td>A</td>
<td>NA</td>
<td>Bendro 1.25 to 2.5 daily</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH)</td>
<td>2008</td>
<td>11,506</td>
<td>P</td>
<td>Active</td>
<td>HCTZ 12.5 to 25 daily as fixed combination with benazepril</td>
<td>Worse</td>
<td>20% less CV events in the benazepril/amlodipine group</td>
</tr>
<tr>
<td>Hypertension in the Very Elderly Trial (HyVET)</td>
<td>2008</td>
<td>3845</td>
<td>P</td>
<td>Placebo</td>
<td>Indapamide 1.5 daily</td>
<td>Better</td>
<td>39% less stroke deaths, 21% lower total mortality, 64% less heart failure</td>
</tr>
</tbody>
</table>

Bendro, bendroflumethiazide; Chlorthal, chlorthalidone; CV, cardiovascular; DBP, diastolic blood pressure; GITS, gastrointestinal treatment system; COER, controlled-onset extended release; NA, not applicable (diuretic add-on studies). Table includes large RCTs that analyzed hypertension endpoints. Search strategy (MEDLINE): thiazide diuretics AND hypertension AND randomized clinical trial (reviews excluded). We excluded studies that focused on specific subpopulations such as patients with previous strokes or established coronary disease.
Similar observations were made with indapamide, another longer-acting thiazide (half-life 14 to 18 hours). Radveski et al. compared HCTZ at 12.5 mg daily with indapamide at 2.5 mg daily in black South African hypertensive patients (66). Overall control after 3 months was better with indapamide (24-hour BP average 130/82 mmHg) than with HCTZ (24-hour BP average 139/88 mmHg), although this difference did not reach statistical significance (final daytime diastolic BP was the only variable reaching significance, 87 mmHg on indapamide versus 93 mmHg on HCTZ, P < 0.05). Akin to chlorthalidone, these results with indapamide suggest that there are subtle differences in BP control among different agents that are only detected with 24-hour BP monitoring.

Thiazides are often used as add-on therapy to other classes of antihypertensive drugs. In a recent meta-analysis, Chen et al. reported that 53 trials evaluated the effects of thiazide diuretics as second-line (add-on) agents in hypertension (61). In these studies, with follow-up typically between 4 and 12 weeks, HCTZ was the most commonly used agent (49 studies). Overall, these agents were effective in reducing BP at the standard recommended dose (average 6/3 mmHg), although a dose-dependent effect was noted. For example, at doses of one half of the recommended starting dose (e.g., HCTZ 6.25 mg daily), the average BP reduction was 4/2 mmHg, whereas the average reduction at twice the starting dose was 8/4 mmHg and 14/6 mmHg at doses ≥3 times the recommended starting dose (61). These results have implications for the routine clinical use of thiazides diuretics, although dose escalation must be mindful of the fact that high doses of diuretics (50 mg/d for HCTZ or chlorthalidone) are associated with loss of the coronary benefit provided by diuretic therapy (67).

In summary, there appear to be small differences in antihypertensive efficacy among agents, suggesting that longer-acting thiazides (chlorthalidone, indapamide) provide better 24-hour BP control than HCTZ. The relevance of these differences to clinical outcomes other than BP control is uncertain.

**Metabolic Side Effects.** Hypokalemia, hyperglycemia, hyperlipidemia, hyperuricemia, and hypomagnesemia are all metabolic derangements induced by thiazide diuretics. These factors have potential implications to cardiovascular risk, either by way of arrhythmogenesis (hypokalemia, hypomagnesemia) or atherosclerotic risk (diabetes, hyperlipidemia, hyperuricemia). All of these side effects are dose dependent. Therefore, limiting the dose administered to that necessary to achieve maximal BP reduction and improved cardiovascular outcomes is potentially relevant (67). A meta-analysis of the effect of different thiazide agents on hypokalemia did not observe any differences between HCTZ and chlorthalidone, despite previous concerns about excessive potassium losses with the latter (68). In a study comparing indapamide at 2.5 mg daily with HCTZ at 50 mg daily, the decline in serum potassium was 0.46 mEq/L with indapamide and 0.9 mEq/L with HCTZ (69). Twelve of 19 (63%) HCTZ patients had potassium levels <3.5 mEq/L, whereas only 2 of 23 (9%) had such levels in the indapamide group (P < 0.001). Indapamide also resulted in less hyperuricemia than HCTZ in this study (69), and a subanalysis of the Systolic Hypertension in the Elderly Program study demonstrated that patients experiencing an increase in serum uric acid >1 mg/dl during treatment with chlorthalidone (49% of subjects) resulted in loss of the coronary heart disease benefit associated with treatment (hazard ratio 0.95 [95% confidence interval [CI]: 0.67 to 1.39] and 0.56 [95% CI: 0.37 to 0.85] for patients with and without increased uric acid levels, respectively) (70). The risk of new-onset diabetes mellitus is increased with thiazides, but there does not appear to be a difference among agents, at least on the basis of the incidence of new-onset diabetes in different trials using HCTZ, chlorthalidone, or bendroflumethiazide (50,71). Likewise, effects of different agents on serum lipids also appear to be similar (72–74). In addition, effects of low-dose thiazides on the lipid profile are very small (increased LDL cholesterol by <4 mg/dl) and likely irrelevant (73). Overall, it appears that there are no significant differences among thiazides from the standpoint of metabolic derangements, although indapamide may be associated with less hypokalemia and hyperuricemia than HCTZ.

**Clinical Outcomes—Thiazides as Initial Therapy.** Among studies where thiazides were used as primary therapy, a summary analysis of the differences between chlorthalidone and nonchlorthalidone regimens was not significant (75). However, this brief meta-analysis did not include an interesting set of observations from the Multiple Risk Factor Intervention Trial (MRFIT). In this trial, 8012 hypertensive subjects were initially assigned to a diuretic, either HCTZ (nine study sites) or chlorthalidone (six study sites), both at doses of 50 to 100 mg daily (36). A few years into the trial, the MRFIT Policy Advisory Board recommended that all subjects be switched to chlorthalidone (at a dose to 50 mg daily), because interim analyses indicated more favorable outcomes in sites using chlorthalidone. Indeed, HCTZ use was associated with a 44% excess risk of coronary death in interim analyses, whereas chlorthalidone was associated with a 55% reduction in risk (62). Follow-up of this cohort demonstrated that a change from HCTZ to chlorthalidone was associated with reversal of the adverse profile experienced earlier in the trial. In addition, chlorthalidone has been uniformly effective as primary therapy in clinical trials (2,32,33,36,43,46), whereas HCTZ has performed below other therapies in some studies (39,47). Lastly, HCTZ was often used in combination with a potassium-sparing diuretic, thus raising concerns about the extrapolation of its favorable effects to its use alone. Therefore, it is possible that chlorthalidone is a better choice than HCTZ in hypertension.

No other two thiazides have been compared for clinical outcomes. Indapamide was used successfully in the Hypertension in the Very Elderly Trial study in patients aged 80 years or older at the relatively low dose of 1.5 mg daily (38). Finally, bendroflumethiazide was used as an alternative to HCTZ in several studies (39,40,42). In one of these studies (39), the diuretic group had a significant increase in cardiovascular mortality compared with the β-blocker (metoprolol) group.

In summary, chlorthalidone (12.5 to 50 mg, mostly 12.5 to 30 mg), HCTZ (25 to 100 mg, mostly 25 to 50 mg), and indapamide (1.5 mg, only tested as primary therapy in patients aged 80 or older) have all been used successfully as primary therapy. However, as discussed, it is possible that chlorthalidone is
superior to HCTZ. Furthermore, given its better overall BP effects, we believe chlorthalidone should be the preferred thiazide in clinical practice.

**Clinical Outcomes—Thiazides as Add-On Therapy.** HCTZ has been the most used add-on thiazide, typically at the dose of 12.5 to 50 mg daily. It has been used in various populations, including uncomplicated hypertension, high-risk hypertension (55,58), hypertension with left ventricular hypertrophy (51), and in patients with hypertension and coronary artery disease (49). Until recently, there was no evidence that exposure to it during a clinical trial was associated with worse outcomes. However, the ACCOMPLISH study has raised concerns about the use of HCTZ as combination therapy (48). In this study, the fixed combination benazepril/amlopidine resulted in a 20% reduction ($P = 0.001$) in a composite of cardiovascular events compared with the combination benazepril/HCTZ in high-risk hypertensives (48). It is uncertain if these results reflect lower efficacy of thiazides in general or HCTZ specifically, and it is not clear that HCTZ should be abandoned based on these results. Indapamide (2 to 2.5 mg daily) was used successfully in patients with a previous stroke as initial therapy (76) and as add-on treatment (56). On the other hand, bendroflumethiazide (2.5 to 5 mg daily) has not performed favorably when used as add-on therapy (50). Finally, there are no studies using chlorthalidone as add-on therapy. However, because additional therapy was needed for most patients receiving chlorthalidone as initial therapy in clinical trials, it is likely that it would perform equally well when tested as add-on therapy.

**Conclusions**

In nephrolithiasis, RCTs are critical in evaluating the efficacy of therapies to reduce the recurrence rate of calcium-containing kidney stones because of confounding from the stone clinic effect and regression to the mean. Most of these studies were conducted between 1981 and 1993 when thiazides were more commonly used in higher doses. In the current era, thiazide diuretics are commonly used at lower doses because of concerns about side effects. There are few data in the literature regarding the dose-response effect on urinary calcium excretion and no data regarding efficacy of low-dose thiazides to reduce stone recurrence. Therefore, the most conservative therapeutic approach would be to use those thiazides that were shown to be beneficial in RCTs in adequate doses. Of those currently available in the United States, this would include indapamide at 2.5 mg/d, chlorthalidone at 25 to 50 mg daily, or HCTZ at 25 mg twice daily or 50 mg daily. Future studies examining the role of low-dose thiazides on calcium-containing kidney stone recurrence would be of interest.

In hypertension, chlorthalidone (12.5 to 30 mg daily) may be the best option for initial therapy, with indapamide (1.5 mg daily) being a valuable alternative for older patients. When adding a thiazide to other drug classes, indapamide (2.5 mg daily) has clear value in hypertensive patients who have had a stroke, and HCTZ (12.5 to 25 mg daily) has a safe track record in several groups. Although chlorthalidone has not been tested as add-on therapy, we believe it is a safe option in such cases.

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**Disclosures**

None.

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