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 cotransporter 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 Kuhlbäck 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-

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Figure 1. Chemical structure of thiazide and thiazide-like diuretics.

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, bendroflumethazide, 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

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

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 protection than low-dose thiazides (26). Not surprisingly, thiazides are recommended as the initial choice for the treatment of most hypertensive patients by all major current guidelines (27,28).

In several studies, thiazides were tested against placebo (29–38) or active control groups (2,39–47) as primary treatment choices. In other studies, they were tested as initial therapy but were administered in fixed combinations with other nondiuretic agents (29,48). Lastly, they have been used as first or second add-on agents in other representative large trials (49–58). Table 2 provides a summary of major outcome studies using thiazides in hypertensive patients. HCTZ has been the agent

most commonly used (19 studies), although chlorthalidone (6 studies), indapamide (1 study), bendroflumethiazide (4 studies), and chlorothiazide (1 study) have also been tested. In some studies, more than one option of thiazide diuretic was available for use at the discretion of the investigators (39,40,42,47,57). In others, the thiazide (always HCTZ) was administered along with a potassium-sparing diuretic, either amiloride (37,41,44) or triamterene (34).

In the discussion that follows, we will analyze three separate questions related to the use of thiazides in hypertension: (1) Are there differences in the blood pressure (BP)-lowering effects among different thiazides? (2) Are there differences in clinical 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 2. Thiazide diuretic use in large-scale hypertension trials

Study	Year	n	Primary (P)/ Add-On (A)	Control	Agent/Dose (mg)	Diuretic Outcome	Comments
VA Cooperative Study (29)	1970	380	P	Placebo	HCTZ 50 BID in combination with reserpine	Better	70% less deaths and major CV events
Hypertension Detection and Follow-Up Study (HDFP) (33)	1979	10,940	P	Placebo	Chlorthal 25 to 100 daily	Better	17% to 20% less all-cause deaths
Australian Therapeutic Trial in Mild Hypertension (31)	1980	3427	P	Placebo	Chlorothiazide 500 daily BID	Better	30% less all-cause deaths, 58% less CV deaths
The Oslo Study (30)	1980	785	P	Placebo	HCTZ 50 daily	Better	Effect restricted to decreased strokes. All CV events decreased (54%) only in patients with baseline DBP ≥ 100 mmHg
European Working Party on High Blood Pressure in the Elderly (34)	1985	840	P	Placebo	HCTZ/Triamterene 25/50 to 50/100 daily	Better	27% lower CV mortality, no difference in all-cause deaths
Heart Attack Primary Prevention in Hypertension Trial (HAPPHY) (40)	1987	7569	P	Active (metoprolol)	HCTZ 50 daily or Bendro 5 daily	Same	No differences in any outcomes. Only trend was toward more fatal strokes in the diuretic group (OR = 3.37 [0.96 to 9.53])
Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) (39)	1988	3234	P	Active (metoprolol)	HCTZ 50 daily or Bendro 5 daily	Worse	48% less all-cause deaths and 58% less CV deaths in the metoprolol group
Multiple Risk Factor Intervention Trial (MRFIT) (36)	1990	8012	P	Placebo	HCTZ 50 to 100 or chlorthal 50 to 100 daily	Better	Less CV deaths at some points during follow-up, especially if baseline DBP >100 mmHg. No effect during randomized trial phase. Chlor better than HCTZ
Swedish Trial of Old Patients with Hypertension (STOP) (37)	1991	1627	P	Placebo	Co-amilozide 2.5/25 daily	Better	40% less CV events, 43% lower all-cause mortality

Table 2. (Continued)

Study	Year	n	Primary (P)/ Add-On (A)	Control	Agent/Dose (mg)	Diuretic Outcome	Comments
Systolic Hypertension in the Elderly Program (SHEP) (32)	1991	4736	P	Placebo	Chlorthal 12.5 to 25 daily	Better	36% decrease in stroke (primary endpoint). 20% lower CV mortality and 32% less CV events
Medical Research Council Working Party (35)	1992	4396	P	Placebo	Co-amilozide 25/ 2.5 to 50/5 daily	Better	Diuretics decreased CV events by 35% compared with placebo. β-blockers had no significant effect
Treatment of Mild Hypertension Study (TOMHS) (43)	1993	902	P	Active (placebo, acebutolol, doxazosin, amlodipine, enalapril)	Chlorthal 15 to 30 daily	Same	Active treatment modestly better than placebo. No difference among the five drug classes
Shangai Trial of Nifedipine in the Elderly (STONE) (54)	1996	1632	A	Placebo	HCTZ 25 daily	NA	
Systolic Hypertension in Europe (Syst-Eur) (52)	1997	4695	A	Placebo	HCTZ 12.5 to 25 daily	NA	
Verapamil in Hypertension and Atherosclerosis Study (46)	1998	498	P	Active (verapamil)	Chlorthal 25 daily	Same/ Worse	Trend toward more CV events in Chlor group, who also had greater progression of carotid atherosclerosis
Captopril Primary Prevention Project (CAPPP) (42)	1999	10,985	P	Active (captopril)	HCTZ 25 daily or Bendro 2.5 daily	Same	
Swedish Trial of Old Patients with Hypertension 2 (STOP 2) (41)	1999	6614	P	Active (enalapril or lisinopril, felodipine or isradipine)	Co-amilozide 2.5/ 25 daily	Same	
International Nifedipine GITS Study (INSIGHT) (44)	2000	6321	P	Active (nifedipine GITS)	Co-amilozide 25/ 2.5 daily to 50/5 daily	Same	
Chinese Trial on Isolated Systolic Hypertension in the Elderly (Syst-China) (53)	2000	1253	A	Placebo	HCTZ 1.5 to 25 daily or BID	NA	

Table 2. (Continued)

Study	Year	n	Primary (P)/ Add-On (A)	Control	Agent/Dose (mg)	Diuretic Outcome	Comments
Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) (51)	2002	9193	A	NA	HCTZ 12.5 to 25 daily	NA	
Anti-Hypertensive and Lipid-Lowering to Prevent Heart Attack Trial (ALLHAT) (2)	2002	33,357	P	Active (lisinopril, amlodipine)	Chlorthal 12.5 to 25 daily	Same	
Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE) (58)	2003	16,602	P, A	Active (verapamil COER)	HCTZ 12.5 daily	Same	
Second Australian National Blood Pressure Study (ANBP2) (47)	2003	6083	P	Active (enalapril)	HCTZ recommended, no dose specified	Worse	11% less CV events or deaths with enalapril
Valsartan Antihypertensive Long Term Use Evaluation (VALUE) (55)	2004	15,245	A	NA	HCTZ 12.5 to 25 daily	NA	
Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) (50)	2005	19,257	A	NA	Bendro 1.25 to 2.5 daily	NA	
Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) (48)	2008	11,506	P	Active	HCTZ 12.5 to 25 daily as fixed combination with benazepril	Worse	20% less CV events in the benazepril/amlodipine group
Hypertension in the Very Elderly Trial (HyVET) (38)	2008	3845	P	Placebo	Indapamide 1.5 daily	Better	39% less stroke deaths, 21% lower total mortality, 64% less heart failure

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/amlodipine 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 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.

Disclosures
None.

References

1. Ernst ME, Carter BL, Basile JN: All thiazide-like diuretics are not chlorthalidone: Putting the ACCOMPLISH study into perspective. *J Clin Hypertens (Greenwich)* 11: 5–10, 2009
2. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker *versus* diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 288: 2981–2997, 2002
3. Vigen R, Weideman RA, Reilly RF: Thiazide diuretics in the treatment of nephrolithiasis: Are we using them in an evidence-based fashion? *Int Urol Nephrol* 2010, in press
4. Lamberg BA, Kuhlback B: Effect of chlorothiazide and hydrochlorothiazide on the excretion of calcium in urine. *Scand J Clin Lab Invest* 11: 351–357, 1959
5. Lichwitz A, Parlier R, De Seze S, Hioco D, Miravet L: L'effect hypocalciurique des sulfamides diuretiques. *Sem Hop Paris* 37: 2350–2352, 1959
6. Yendt ER, Guay GF, Garcia DA: The use of thiazides in the prevention of renal calculi. *CMAJ* 102: 614–620, 1970
7. Hosking DH, Erickson SB, Van den Berg CJ, Wilson DM, Smith LH: The stone clinic effect in patients with idiopathic calcium urolithiasis. *J Urol* 130: 1115–1118, 1983
8. Spector R, Park GD: Regression to the mean: A potential source of error in clinical pharmacological studies. *Drug Intell Clin Pharm* 19: 916–919, 1985
9. Borghi L, Meschi T, Guerra A, Novarini A: Randomized prospective study of a nonthiazide diuretic, indapamide, in preventing calcium stone recurrences. *J Cardiovasc Pharmacol* 22[Suppl 6]: S78–S86, 1993
10. Ettinger B, Citron JT, Livermore B, Dolman LI: Chlorthalidone reduces calcium oxalate calculous recurrence but magnesium hydroxide does not. *J Urol* 139: 679–684, 1988
11. Fernandez-Rodriguez A, Arrabal-Martin M, Garcia-Ruiz MJ, Arrabal-Polo MA, Pichardo-Pichardo S, Zuluaga-Gomez A: Papel de las tiazidas en la profilaxis de la litiasis calcica recidivante. *Actas Urol Esp* 30: 305–309, 2006
12. Laerum E, Larsen S: Thiazide prophylaxis of urolithiasis. A double-blind study in general practice. *Acta Med Scand* 215: 383–389, 1984
13. Mortensen JT, Schultz A, Ostergaard AH: Thiazides in the prophylactic treatment of recurrent idiopathic kidney stones. *Int Urol Nephrol* 18: 265–269, 1986
14. Ohkawa M, Tokunaga S, Nakashima T, Orito M, Hisazumi H: Thiazide treatment for calcium urolithiasis in patients with idiopathic hypercalciuria. *Br J Urol* 69: 571–576, 1992
15. Robertson WG, Williams RE, Hargreaves, TB: A multicenter trial to evaluate three treatments for recurrent idiopathic calcium stone disease—A preliminary report. In: *Urolithiasis and Related Clinical Research*, edited by Schwille

PO, Smith LH, Robertson WG, Vahlensieck W, New York, Plenum Press, 1965, pp 545–548

16. Wilson DR, Strauss AL, Manuel MA: Comparison of medical treatment for the prevention of recurrent calcium nephrolithiasis. *Urol Res* 12: 39–40, 1984

17. Brocks P, Dahl C, Wolf H, Transbol I: Do thiazides prevent recurrent idiopathic renal calcium stones? *Lancet* 2: 124–125, 1981

18. Scholz D, Schwille PO, Sigel A: Double-blind study with thiazide in recurrent calcium lithiasis. *J Urol* 128: 903–907, 1982

19. Curhan GC, Willett WC, Speizer FE, Stampfer MJ: Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. *Kidney Int* 59: 2290–2298, 2001

20. Martins MC, Meyers AM, Whalley NA, Margolius LP, Buys ME: Indapamide (Natrilix): the agent of choice in the treatment of recurrent renal calculi associated with idiopathic hypercalciuria. *Br J Urol* 78: 176–180, 1996

21. Jorgensen FS, Transbol I: The effect of bendroflumethiazide on the renal handling of calcium, magnesium and phosphate in normocalcaemic renal stone formers and in hyperparathyroidism. *Acta Med Scand* 194: 327–334, 1973

22. Pak CY: Hydrochlorothiazide therapy in nephrolithiasis. Effect on the urinary activity product and formation product of brushite. *Clin Pharmacol Ther* 14: 209–217, 1973

23. Pena JC, Monforte MF, Briceno A: The role of oxalate and calcium oxalate activity and formation product ratio in patients with renal stones before and during treatment. *J Urol*, 138: 1137–1140, 1987

24. Yendt ER, Cohanim M: Prevention of calcium stones with thiazides. *Kidney Int* 13: 397–409, 1978

25. Nicar MJ, Peterson R, Pak CY: Use of potassium citrate as potassium supplement during thiazide therapy of calcium nephrolithiasis. *J Urol* 131: 430–433, 1984

26. Psaty BM, Lumley T, Furberg CD, Schellenbaum G, Pahor M, Alderman MH, Weiss NS: Health outcomes associated with various antihypertensive therapies used as first-line agents: A network meta-analysis. *JAMA* 289: 2534–2544, 2003

27. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT, Jr, Roccella EJ: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. *JAMA* 289: 2560–2572, 2003

28. Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, Cifkova R, Clement D, Coca A, Dominiczak A, Erdine S, Fagard R, Farsang C, Grassi G, Haller H, Heagerty A, Kjeldsen SE, Kiowski W, Mallion JM, Manolis A, Narkiewicz K, Nilsson P, Olsen MH, Rahn KH, Redon J, Rodicio J, Ruilope L, Schmieder RE, Struijker-Boudier HA, van Zwieten PA, Viigimaa M, Zanchetti, A: Reappraisal of European guidelines on hypertension management: A European Society of Hypertension Task Force document. *J Hypertens* 2009 [Epub ahead of print]

29. Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *JAMA* 213: 1143–1152, 1970

30. Helgeland A: Treatment of mild hypertension: A five year controlled drug trial. The Oslo study. *Am J Med* 69: 725–732, 1980

31. The Australian therapeutic trial in mild hypertension. Report by the Management Committee. *Lancet* 1: 1261–1267, 1980

32. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA* 265: 3255–3264, 1991

33. Five-year findings of the hypertension detection and follow-up program. I. Reduction in mortality of persons with high blood pressure, including mild hypertension. Hypertension Detection and Follow-Up Program Cooperative Group. *JAMA* 242: 2562–2571, 1979

34. Amery A, Birkenhager W, Brixko P, Bulpitt C, Clement D, Deruyttere M, De Schaepdryver A, Dollery C, Fagard R, Forette F, *et al.*: Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. *Lancet* 1: 1349–1354, 1985

35. Medical Research Council trial of treatment of hypertension in older adults: Principal results. MRC Working Party. *BMJ* 304: 405–412, 1992

36. Mortality after 10 1/2 years for hypertensive participants in the Multiple Risk Factor Intervention Trial. *Circulation* 82: 1616–1628, 1990

37. Dahlof B, Lindholm LH, Hansson L, Schersten B, Ekbom T, Wester PO: Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet* 338: 1281–1285, 1991

38. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt CJ: Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*, 358: 1887–1898, 2008

39. Wikstrand J, Warnold I, Olsson G, Tuomilehto J, Elmfeldt D, Berglund G: Primary prevention with metoprolol in patients with hypertension. Mortality results from the MAPHY study. *JAMA* 259: 1976–1982, 1988

40. Wilhelmsen L, Berglund G, Elmfeldt D, Fitzsimons T, Holzgreve H, Hosie J, Hornkvist PE, Pennert K, Tuomilehto J, Wedel H: Beta-blockers *versus* diuretics in hypertensive men: Main results from the HAPPHY trial. *J Hypertens* 5: 561–572, 1987

41. Hansson L, Lindholm LH, Ekbom T, Dahlof B, Lanke J, Schersten B, Wester PO, Hedner T, de Faire U: Randomised trial of old and new antihypertensive drugs in elderly patients: Cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 354: 1751–1756, 1999

42. Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, Luomanmaki K, Dahlof B, de Faire U, Morlin C, Karlberg BE, Wester PO, Bjorck JE: Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: The Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 353: 611–616, 1999

43. Neaton JD, Grimm RH, Jr, Prineas RJ, Stamler J, Grandits GA, Elmer PJ, Cutler JA, Flack JM, Schoenberger JA, McDonald R, *et al.*: Treatment of Mild Hypertension Study. Final results. Treatment of Mild Hypertension Study Research Group. *JAMA* 270: 713–724, 1993

44. Brown MJ, Palmer CR, Castaigne A, de Leeuw PW, Mancia G, Rosenthal T, Ruilope LM: Morbidity and mortality in patients randomised to double-blind treatment with a

long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet* 356: 366–372, 2000

45. Hansson L, Hedner T, Lund-Johansen P, Kjeldsen SE, Lindholm LH, Syvertsen JO, Lanke J, de Faire U, Dahlof B, Karlberg BE: Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. *Lancet* 356: 359–365, 2000

46. Zanchetti A, Rosei EA, Dal Palu C, Leonetti G, Magnani B, Pessina A: The Verapamil in Hypertension and Atherosclerosis Study (VHAS): Results of long-term randomized treatment with either verapamil or chlorthalidone on carotid intima-media thickness. *J Hypertens* 16: 1667–1676, 1998

47. Wing LM, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GL, Johnston CI, McNeil JJ, Macdonald GJ, Marley JE, Morgan TO, West MJ: A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med* 348: 583–592, 2003

48. Jamerson K, Weber MA, Bakris GL, Dahlof B, Pitt B, Shi V, Hester A, Gupte J, Gatlin M, Velazquez EJ: Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 359: 2417–2428, 2008

49. Pepine CJ, Handberg EM, Cooper-DeHoff RM, Marks RG, Kowey P, Messerli FH, Mancia G, Cangiano JL, Garcia-Barreto D, Keltai M, Erdine S, Bristol HA, Kolb HR, Bakris GL, Cohen JD, Parmley WW: A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): A randomized controlled trial. *JAMA* 290: 2805–2816, 2003

50. Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J: Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required *versus* atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): A multicentre randomised controlled trial. *Lancet* 366: 895–906, 2005

51. Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H: Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): A randomised trial against atenolol. *Lancet* 359: 995–1003, 2002

52. Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, Bulpitt CJ, de Leeuw PW, Dollery CT, Fletcher AE, Forette F, Leonetti G, Nachev C, O'Brien ET, Rosenfeld J, Rodicio JL, Tuomilehto J, Zanchetti A: Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet* 350: 757–764, 1997

53. Wang JG, Staessen JA, Gong L, Liu L: Chinese trial on isolated systolic hypertension in the elderly. Systolic Hypertension in China (Syst-China) Collaborative Group. *Arch Intern Med* 160: 211–220, 2000

54. Gong L, Zhang W, Zhu Y, Zhu J, Kong D, Page V, Ghadirian P, LeLorier J, Hamet P: Shanghai trial of nifedipine in the elderly (STONE). *J Hypertens* 14: 1237–1245, 1996

55. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A: Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: The VALUE randomised trial. *Lancet* 363: 2022–2031, 2004

56. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 358: 1033–1041, 2001

57. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 351: 1755–1762, 1998

58. Black HR, Elliott WJ, Grandits G, Grambsch P, Lucente T, White WB, Neaton JD, Grimm RH Jr, Hansson L, Lacourciere Y, Muller J, Sleight P, Weber MA, Williams G, Wittes J, Zanchetti A, Anders RJ: Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. *JAMA* 289: 2073–2082, 2003

59. Neff KM, Nawarskas JJ: Hydrochlorothiazide *versus* chlorthalidone in the management of hypertension. *Cardiol Rev* 18: 51–56, 2010

60. Carter BL, Ernst ME, Cohen JD: Hydrochlorothiazide *versus* chlorthalidone: Evidence supporting their interchangeability. *Hypertension* 43: 4–9, 2004

61. Chen JM, Heran BS, Wright, JM: Blood pressure lowering efficacy of diuretics as second-line therapy for primary hypertension. *Cochrane Database Syst Rev* CD007187, 2009

62. Elliott WJ, Grimm, RH Jr: Using diuretics in practice—One opinion. *J Clin Hypertens (Greenwich)* 10: 856–862, 2008

63. Ernst ME, Carter BL, Goerdt CJ, Steffensmeier JJ, Phillips BB, Zimmerman MB, Bergus GR: Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. *Hypertension* 47: 352–358, 2006

64. Ernst ME, Moser M: Use of diuretics in patients with hypertension. *N Engl J Med* 361: 2153–2164, 2009

65. Finnerty FA Jr: A double-blind study of chlorthalidone and hydrochlorothiazide in an outpatient population of moderate hypertensives. *Angiology* 27: 738–744, 1976

66. Radevski IV, Valtchanova ZP, Candy GP, Wald AM, Ngcezula T, Sareli P: Comparison of indapamide and low-dose hydrochlorothiazide monotherapy in black patients with mild to moderate hypertension. *S Afr Med J* 92: 532–536, 2002

67. Psaty BM, Smith NL, Siscovick DS, Koepsell TD, Weiss NS, Heckbert SR, Lemaitre RN, Wagner EH, Furberg CD: Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. *JAMA* 277: 739–745, 1997

68. Ernst ME, Carter BL, Zheng S, Grimm, RH Jr: Meta-analysis of dose-response characteristics of hydrochlorothiazide and chlorthalidone: Effects on systolic blood pressure and potassium. *Am J Hypertens* 23: 440–446, 2010

69. Plante GE, Robillard C: Indapamide in the treatment of essential arterial hypertension: Results of a controlled study. *Curr Med Res Opin* 8[Suppl 3]: 59–66, 1983

70. Franse LV, Pahor M, Di Bari M, Shorr RI, Wan JY, Somes GW, Applegate WB: Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP). *J Hypertens* 18: 1149–1154, 2000

71. Verdecchia P, Angeli F, Reboldi G, Gattobigio R: Is the development of diabetes with antihypertensive therapy a problem?—Pro. *J Clin Hypertens (Greenwich)* 8: 120–126, 2006

72. Greenberg A: Diuretic complications. *Am J Med Sci* 319: 10–24, 2000

73. Weir MR, Moser M: Diuretics and beta-blockers: is there a risk for dyslipidemia? *Am Heart J* 139: 174–183, 2000

74. Spence JD, Huff M, Barnett PA: Effects of indapamide *versus* hydrochlorothiazide on plasma lipids and lipoproteins in hypertensive patients: A direct comparison. *Can J Clin Pharmacol* 7: 32–37, 2000

75. Psaty BM, Lumley T, Furberg CD: Meta-analysis of health outcomes of chlorthalidone-based *versus* nonchlorthalidone-based low-dose diuretic therapies. *JAMA* 292: 43–44, 2004

76. Post-stroke antihypertensive treatment study. A preliminary result. PATS Collaborating Group. *Chin Med J (Engl)* 108: 710–717, 1995