Using Diuretics in Practice—One Opinion

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Many authors have decried the lack of appropriate use of diuretics in the treatment of hypertension, despite their proven benefits and evidence that these agents are as (or even more) effective in preventing one or more forms of major cardiovascular disease in most hypertensive patients than other available agents. This commentary summarizes data suggesting that an appropriate diuretic should be a part of the hypertension regimen for most patients. If the estimated glomerular filtration rate (using the simplified Modification of Diet in Renal Disease equation) is <40 mL/min/1.73 m^2, most authorities suggest that a loop diuretic (eg, furosemide twice daily at a dose that is half the sum of the blood urea nitrogen level (in mg/dL) + patient age (in years) twice daily) be used, based on fluid balance and lowering blood pressure. Otherwise, the preferred diuretic is chlorthalidone at 12.5 mg/d to start (a dosage not approved by the US Food and Drug Administration), rather than hydrochlorothiazide. Most of the hypertension treatment trials performed in the United States that reported beneficial results used chlorthalidone as the diuretic. Most American physicians instead have used hydrochlorothiazide, but it is neither as potent in

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lowering blood pressure nor as evidence-based in preventing cardiovascular disease as chlorthalidone is. Most doctors abandoned chlorthalidone in the 1980s because the dosages considered moderate then (50–200 mg/d) are by today's standards actually high and caused hypokalemia (potassium <3.5 mEq/L) in a number of patients. More recent clinical trial data using dosages of 12.5–25 mg/d have shown that hypokalemia is rarely a problem, particularly when this medication is used with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). While all drugs, and indeed, all diuretics, have the potential for side effects and drug-drug interactions, blood pressure control and prevention of cardiovascular events would likely be improved if more physicians were aware of the strong evidence base for chlorthalidone.

Diuretics have a long and distinguished history in the treatment of hypertension. Although some recent treatment guidelines from international or foreign sources are not as specific,[1–3] the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) recommends, in the absence of a compelling indication, a low-dose thiazide-like (eg, chlorthalidone or indapamide) or thiazide-type diuretic for initial treatment of most stage 1 hypertension and a combination of such a diuretic and another antihypertensive drug for stage 2 hypertension.[4] This recommendation was based on outcomes data from several landmark clinical trials, particularly the Antihypertensive and Lipid-Lowering to Prevent Heart Attack Trial (ALLHAT).[5,6] In ALLHAT, as in many other trials, diuretics were particularly beneficial in black and older hypertensive persons.[5,6] After the existing data are combined, a diuretic-based regimen was significantly better than

ACE inhibitor–based treatment in preventing stroke (by 14%; 95% confidence interval [CI], 2%–27%; $P<.03$) or heart failure (by 16%; 95% CI, 5%–29%; $P<.004$).[7] Similarly, a diuretic-based program was significantly better than a calcium channel blocker–based regimen in preventing heart failure (by 41%; 95% CI, 27%–56%; $P<.0001$).[7] There were no significant differences between initial treatment with a diuretic or either comparator for the end points of all-cause mortality, cardiovascular death, coronary heart disease, or first major adverse cardiovascular event.

The "compelling indications" for specific medications listed by JNC 7, as well as many of those established by research studies since then, also involve diuretics. Heart failure can seldom be successfully treated without a diuretic. Although the American Diabetes Association recommends either an ACE inhibitor or an ARB as the first-step antihypertensive drug in diabetics,[8] a diuretic was typically used with such an agent in the Captopril Cooperative Study Group's regimen,[9] the Irbesartan Diabetic Nephropathy Trial,[10] and the Reduction of Endpoints in Non–Insulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan trial.[11] In patients with nondiabetic chronic kidney disease, an ACE inhibitor reduced the time to doubling of serum creatinine level or end-stage renal disease,[12] but a diuretic was typically given with the ACE inhibitor. In all of these trials, thiazide diuretics were typically and appropriately replaced by loop diuretics when renal function declined. Of importance, the ALLHAT comparisons of chlorthalidone compared to lisinopril or amlodipine in patients with initial serum creatinine levels ≤2.0 mg/dL showed no significant differences in the composite end point of end-stage renal disease or a 50% decline in renal function[13] nor in cardiovascular outcomes across all initial stages of chronic kidney disease.[14]

A diuretic (chlorthalidone 12.5–25 mg/d) was used as initial therapy in the Systolic Hypertension in the Elderly Program (SHEP),[15] which was the first study to show a significant reduction in stroke among older persons with isolated systolic hypertension; a diuretic was the third drug used in both the Systolic Hypertension in Europe and Systolic Hypertension in China studies.[16,17] Many authorities will not make a diagnosis of resistant hypertension unless an appropriate diuretic has been prescribed for the patient.[18] Perhaps most indicative of the importance of a diuretic as part of the regimen was the Perindopril Protection Against Recurrent Stroke Study (PROGRESS).[19] In PROGRESS, a secondary stroke prevention study, 6105 participants with a prior
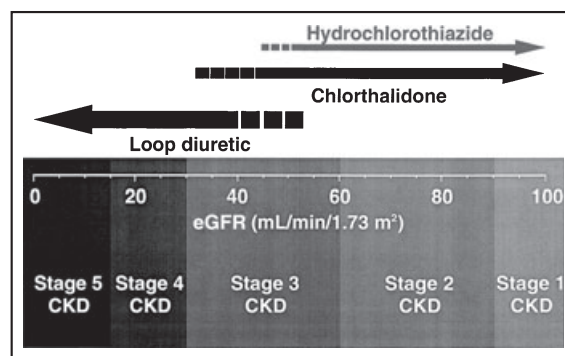

Figure 1. Selection of a diuretic based on the patient's estimated glomerular filtration rate (eGFR). Note that low-dose hydrochlorothiazide is typically less effective when the eGFR is less than about 45 mL/min/1.73 m² (using the simplified Modification of Diet in Renal Disease equation),[21] whereas low-dose chlorthalidone begins to lose its antihypertensive efficacy at a somewhat lower threshold. In general, a loop diuretic is recommended for patients with an eGFR<35 mL/min/1.73 m². The stages of chronic kidney disease (CKD) are based on the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guidelines.[22]

history of a neurologic event in the preceding 5 years were randomized to either placebo ± placebo or an ACE inhibitor (perindopril) ± a diuretic (indapamide). The latter group had significant reductions in blood pressure (by 9/5 mm Hg), recurrent stroke (by 28%), and cardiovascular events (by 26%; $P<.001$ in each case). The major benefits, however, were seen in those who received *both* the ACE inhibitor and the diuretic (12/5 mm Hg, 43%, and 40%, respectively, compared with placebo ± placebo), whereas those who received only the ACE inhibitor had nonsignificant improvements in outcomes (5/3 mm Hg, 5%, and 4%, respectively) compared with individuals given placebo.

WHICH DIURETIC?
The only diuretic suitable for patients with a verified allergy to "sulfa drugs" is ethacrynic acid, which became available again in 2003 after not being available for several years. It is usually used in dosages of 25 to 50 mg twice daily.[20]

In the absence of the rare true sulfa allergy, the choice of a diuretic primarily depends on the patient's renal function (Figure 1). If the estimated glomerular filtration rate is lower than about 40 mL/min/1.73 m², a loop diuretic such as furosemide (twice daily), bumetanide (twice daily), or torsemide (which is more expensive but sometimes can be given just once daily) is generally more effective than a low-dose thiazide for diuresis and lowering blood pressure.[23] Most physicians forget
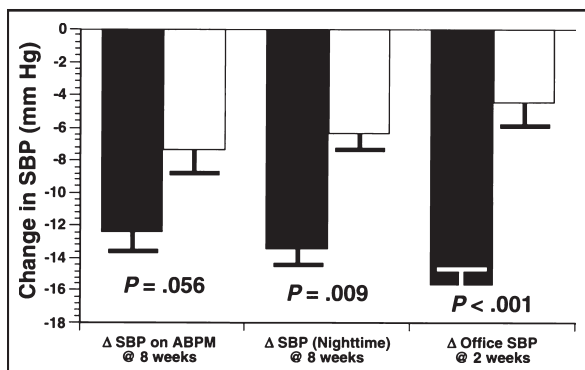
Figure 2. Summary of the results of the randomized, head-to-head comparison of low-dose chlorthalidone (12.5 mg/d initially, force-titrated to 25 mg/d, black bars) vs hydrochlorothiazide (25 mg/d initially, force-titrated to 50 mg/d, open bars) in 30 hypertensive patients. The primary end point (change in 24-hour systolic blood pressure [SBP] from baseline at 8 weeks by ambulatory blood pressure monitoring [ABPM]) barely missed statistical significance, but the change in average nighttime SBP and the change in office SBP at 2 weeks both were significantly greater with chlorthalidone than with twice the daily dose of hydrochlorothiazide. Data are from Ernst et al, 2006.[30]

that the trade name for furosemide is derived from the fact that its diuretic effect "lasts 6 hours." Furosemide is therefore relatively ineffective as a once-daily medication, simply because fluid and sodium retention occur during the remaining 18 hours of the day, especially if a major salt load occurs during the evening meal and furosemide is taken in the morning. Of course, there is more to blood pressure control than fluid balance, but in patients with chronic kidney disease, they are often related. The appropriate daily dose of furosemide is typically the sum of the patient's age in years plus the blood urea nitrogen concentration (in mg/dL) (eg, 40 years + 80 mg/dL = 120 mg/d).[24]

If the estimated glomerular filtration rate is $\geq$40 mL/min/1.73 m^2, the most common choice in clinical practice in the United States is hydrochlorothiazide, which ranked fifth in total prescriptions (with 45,124,000) dispensed by retail pharmacists in 2006, after hydrocodone/acetaminophen, atorvastatin, lisinopril, and amoxicillin).[25] Hydrochlorothiazide has been commonly paired in fixed-dose combination products with most β-blockers, several centrally acting drugs, most ACE inhibitors, and every currently marketed ARB. With the exception of the latter, these products are generally inexpensive, generically available, and sometimes available in a full range of doses.

The National Heart, Lung, and Blood Institute, however, has used chlorthalidone in their large clinical trials. Since about 1980, these trials have

started with about half of a 25-mg pill daily (a dose not approved by the US Food and Drug Administration). Today, 50 mg/d of chlorthalidone is seldom required. The major advantage of hydrochlorothiazide over chlorthalidone is that the former has been combined with approximately 21 different antihypertensive drugs, whereas only 3 fixed-dose combination products are available with chlorthalidone. Ironically, they are the 3 "step 2" treatments available for participants in ALLHAT (atenolol, clonidine, or reserpine), which may not be completely coincidental. A strong evidence-based case can be made for the use of chlorthalidone instead of hydrochlorothiazide.

CHLORTHALIDONE IS MORE EFFECTIVE FOR LOWERING BLOOD PRESSURE COMPARED WITH HYDROCHLOROTHIAZIDE

Thirty years ago, when doses of diuretics were much higher than today, 4 independent, head-to-head clinical trials were performed that compared the blood pressure–lowering effects of chlorthalidone and hydrochlorothiazide.[26–29] Despite differences in study design (crossover[26] vs parallel-group[27]), duration of treatment (4[27]–12[29] weeks), adjuvant potassium-sparing diuretic with hydrochlorothiazide,[28,29] and baseline blood pressures (152[27]–181[26]/100[28]–110[26] mm Hg), patients receiving chlorthalidone 50 mg/d had numerically superior blood pressure reductions (weighted average, −21.4/−12.6 mm Hg) compared with either hydrochlorothiazide 50 mg/d (−10.6/−5.0 mm Hg) or hydrochlorothiazide 100 mg/d (−20.4/−16.5 mm Hg).

More recently, Ernst and colleagues[30] compared hydrochlorothiazide (initially 25 mg/d, force-titrated to 50 mg/d) with chlorthalidone (initially 12.5 mg/d, force-titrated to 25 mg/d) in 30 hypertensive patients. Although originally designed as a crossover study, there was a large carryover effect in the group originally assigned to chlorthalidone (even after a 4-week washout period), so the data were analyzed as a parallel-group study. The primary end point was change in 24-hour mean blood pressure based on ambulatory blood pressure monitoring at 8 weeks compared with baseline. Nighttime mean blood pressure and office systolic blood pressure levels at 2-week intervals were secondary end points. The results are shown in Figure 2. It should not be surprising that the nocturnal fall in blood pressure was greater with chlorthalidone, given its much longer serum elimination half-life ($\sim$70 vs $\sim$8 hours) and duration of action.[31] These data suggest that,

Table. Summary of Results of Outcomes-Based Clinical Trials Involving Chlorthalidone or Hydrochlorothiazide

CHLORTHALIDONE	HYDROCHLOROTHIAZIDE
Hypertension Detection and Follow-Up Program[33] (HDFP, better than "referred care")	Veterans Affairs Cooperative Study Group on Antihypertensive Agents[34] (better than placebo, with help)
Multiple Risk Factor Intervention Trial[35] (MRFIT, better than hydrochlorothiazide)	Multiple Risk Factor Intervention Trial[35] (MRFIT, inferior to, and replaced by, chlorthalidone)
Systolic Hypertension in the Elderly Program[15] (SHEP, better than placebo)	Heart Attack Primary Prevention in Hypertension[36] (better than 2 β-blockers)
Treatment of Mild Hypertension Study[37] (TOMHS, no outcomes data available)	Metoprolol Atherosclerosis Prevention in Hypertensives[38] (MAPPHY, inferior to metoprolol)
Verapamil Hypertension Atherosclerosis Study[39] (VHAS, similar to verapamil)	Medical Research Council Trial in the Elderly[40] (MRC-E, better than placebo and atenolol)
Antihypertensive and Lipid-Lowering to Prevent Heart Attack Trial[5,6] (ALLHAT, better than doxazosin, lisinopril, and amlodipine for heart failure)	Multicenter Isradipine Diuretic Atherosclerosis Study[41] (MIDAS, similar to isradipine)
	International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment[42] (INSIGHT, similar to nifedipine)
	Post-stroke Antihypertensive Treatment Study[43] (PATS, better than placebo)
	Controlled Onset Verapamil Investigation of Cardiovascular Endpoints[44] (CONVINCE, similar to verapamil in subgroup analysis)
	Second Australian National Blood Pressure trial[45] (ANBP-2, similar to enalapril, but worse in men)

even at half the daily dose, chlorthalidone provides quicker and more sustained blood pressure reduction than hydrochlorothiazide, especially at the low doses recommended today.

Supporting evidence in favor of chlorthalidone's better blood pressure–lowering efficacy comes from an unblinded consecutive series of 19 hypertensive patients taking hydrochlorothiazide who were switched to the same dose of open-label chlorthalidone.[32] When reassessed after about a month, these patients experienced a 12-mm Hg reduction in systolic blood pressure ($P<.03$) on average and no difficulties with hypokalemia. This was most likely due to the low doses used and the fact that all were taking either an ACE inhibitor or an ARB.

CHLORTHALIDONE HAS MORE EXTENSIVE AND BETTER OUTCOMES DATA THAN HYDROCHLOROTHIAZIDE

Both chlorthalidone and hydrochlorothiazide have been used in outcomes-based clinical trials (Table), but their performance records are different. Evidence suggests that patients treated with chlorthalidone have better outcomes than those treated with a hydrochlorothiazide-based regimen.

A network meta-analysis of outcomes studies in hypertension provided an indirect comparison of the risk for several cardiovascular end points with chlorthalidone compared with other types of thiazide-like diuretics and concluded that there were no significant differences between the two.[46] However, this analysis did not include the only study in which 8012 hypertensive men in the Multiple Risk Factor Intervention Trial (MRFIT) were given either chlorthalidone or hydrochlorothiazide, based on the choice of the principal investigator at each study site. Although the assignment of the diuretic in this study was not randomized, the outcomes were compared at each site with the control group (randomized to usual care [UC] in each community). During the first half of 1980, the steering committee of MRFIT recommended that all special intervention (SI) participants should be switched from hydrochlorothiazide to chlorthalidone (at ≤50 mg/d). This decision was based on several lines of evidence comparing both coronary heart disease and all-cause mortality experience across the 22 participating clinics, all of which pointed to less benefit in patients taking hydrochlorothiazide compared with chlorthalidone. These data have not yet been published in full form.[35,47,48] When the clinics were divided into tertiles regarding the relative use of the 2 diuretics (before switching), there was a significant decrease in both end points in the SI and the UC groups (as well as the cohort as a whole) as the use of hydrochlorothiazide decreased. This was

seen only in hypertensive men (G. E. Bartsch, written communication, June 1986). Further analyses were performed and reported after completion of the trial.[35] The major findings were that in the 9 clinics that predominantly prescribed hydrochlorothiazide, the SI group had a 44% *excess* risk of death from coronary heart disease compared with their randomized UC groups, whereas the 6 clinics that predominantly prescribed chlorthalidone had a 58% *reduction* in risk compared with their UC controls.[35,47] In addition, all-cause mortality in the SI groups in the clinics that prescribed hydrochlorothiazide was *increased* (by 16%), compared to a 41% *decrease* in all-cause mortality in the 6 clinics that prescribed mostly chlorthalidone. During the 5 years of follow-up *after* the switch from hydrochlorothiazide to chlorthalidone, coronary heart disease mortality in the 9 clinics decreased by 28%, compared with their UC groups (*P*=.04 for comparison of percentage differences in coronary heart disease mortality rates for the 2 time periods). After the switch was accomplished, a similar 26% reduction was also seen in all-cause mortality (compared with the UC controls, *P*=.06).[35] It has been difficult to understand why a difference in mortality in MRFIT between the SI and UC groups was not seen during the initial years of funded follow-up but appeared much later. The switch in diuretic may have played a role, because after 1980 almost all SI participants received chlorthalidone. However, most UC participants received hydrochlorothiazide from their community-based physicians because these physicians were not aware of the protocol change or the reasons behind it.

ADVERSE EFFECTS OF DIURETICS
Many of the adverse effects of diuretics are dose-dependent (eg, possible hypotension, volume depletion, polyuria, hypokalemia, hypomagnesemia, and hyponatremia). Hypercalcemia may be dose-related with thiazide-like diuretics, but hypocalcemia is more common with loop diuretics. Erectile dysfunction may be more common with diuretics than with other commonly-used antihypertensive drugs, but the inhibitors of phosphodiesterase-5 are usually quite effective in alleviating this possible adverse effect. Metabolic effects of diuretics (including increased insulin resistance and other components of the metabolic syndrome) are relatively widely recognized, but their long-term consequences (if any) are still quite controversial. Although increased cardiovascular risk has been noted after 5 to 28 years of follow-up among individuals in whom diabetes developed during follow-up,[49–53] 2 important clinical trials with chlorthalidone (SHEP and ALLHAT) reported no excess cardiovascular risk despite these metabolic changes.[6,54,55] Of greatest concern to many is the increased risk of incident diabetes, which was higher with initial diuretic therapy compared with an ACE inhibitor or an ARB in a recent network meta-analysis of antihypertensive drugs.[56] In a sensitivity analysis, the risk of incident diabetes with chlorthalidone (compared with placebo) was 1.25 (95% CI, 1.00–1.55; *P*=.055), whereas it was 1.48 (95% CI, 1.16–1.90; *P*=.002) with non-chlorthalidone thiazide-type diuretics.[56] Although this difference was not statistically significant (in an indirect comparison), it may be one more reason to favor chlorthalidone over hydrochlorothiazide. Similarly, the increase in serum cholesterol and uric acid concentrations typically seen with thiazide diuretics has been greatly reduced by using lower doses and has not been linked to increased cardiovascular risk in follow-up of randomized clinical trials. Most such studies last only 5 or so years, however, and longer follow-up may be needed to discern such an effect.[52]

CONTRAINDICATIONS, WARNINGS, AND DRUG INTERACTIONS WITH DIURETICS
Thiazide-like and thiazide-type diuretics are contraindicated in patients with anuria and those with absolute contraindications to sulfa drugs[20] and are typically not very effective at low doses if the estimated glomerular filtration rate is <40 mL/min/1.73 m^2. Similarly, loop diuretics are contraindicated in patients with anuria, hepatic coma, and severe electrolyte derangements. Potassium-sparing diuretics (including triamterene, amiloride, and spironolactone) are contraindicated in patients with hyperkalemia or those with stage 4 or 5 chronic kidney disease. In addition, hyperkalemia (and death related to it) with these drugs is a concern when they are given with salt substitutes, ACE inhibitors, ARBs, high-potassium foods, and nonsteroidal anti-inflammatory drugs.

All diuretics have the possibility of interacting with digoxin, lithium, and nonsteroidal anti-inflammatory drugs. Alcohol and central nervous system depressants increase the risk of orthostatic hypotension with coadministered diuretics. Corticosteroids, corticotropin, and amphotericin B increase the risk of hypokalemia when administered with diuretics. On the positive side, diuretics increase the blood pressure–lowering efficacy of essentially every other class of antihypertensive drug. Thiazide-type and thiazide-like diuretics can potentiate the nondepolarizing muscle relaxants, antagonize norepinephrine, and interfere with parathyroid blood testing.

Eplerenone has significant interactions with drugs that are metabolized by the CYP3A4 system (eg, the azole antifungal agents). However, placebo-controlled studies have shown that all of these adverse effects are uncommon and are generally outweighed by the benefits of diuretics, which can reduce pharyngeal edema in patients with obstructive sleep apnea.[57]

CONCLUSIONS

This brief review has attempted to remind the reader that diuretics are extremely useful antihypertensive drugs, particularly for individuals with chronic kidney disease (in whom loop diuretics are often more useful),[22] diabetes (because of their lower blood pressure target),[8] and those at high risk for heart failure.[2] Generally, furosemide, given twice daily for the total daily dose that is the sum of the patient's age plus blood urea nitrogen concentration, or chlorthalidone (starting at 12.5 mg/d, a dose not approved by the US Food and Drug Administration) can be recommended. Although available in fewer fixed-dose combinations, chlorthalidone has better blood pressure–lowering efficacy than the much more commonly prescribed hydrochlorothiazide, more and better results in long-term outcomes-based clinical trials, a longer duration of action, and perhaps a lower risk of new-onset diabetes. Perhaps if physicians were not allowed to use the abbreviation "HCTZ," they would be more likely to avoid hydrochlorothiazide and would write "chlorthalidone" instead, since it has 5 fewer letters.

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