

DANIELLE COONEY, PharmDLouis Stokes Cleveland VA Medical Center,
Cleveland, OH**SHERRY MILFRED-LaFOREST, PharmD**Louis Stokes Cleveland VA Medical Center,
Cleveland, OH**MAHBOOB RAHMAN, MD, MS**Louis Stokes Cleveland VA Medical Center;
University Hospitals Case Medical Center, Case
Western Reserve University, Cleveland, OH

Diuretics for hypertension: Hydrochlorothiazide or chlorthalidone?

ABSTRACT

Thiazide diuretics are the cornerstone of treatment of hypertension in most patients. Hydrochlorothiazide is the most commonly used thiazide diuretic in the United States, but interest in chlorthalidone is increasing. The authors summarize the literature comparing these two agents.

KEY POINTS

Chlorthalidone has a longer duration of action and a longer half-life than hydrochlorothiazide.

Chlorthalidone may be more potent than hydrochlorothiazide in lowering blood pressure, but it also may be associated with more metabolic adverse effects, such as hypokalemia.

No study has conclusively shown either drug to be better in preventing adverse clinical outcomes.

These differences should be considered when making choices about thiazide diuretic therapy for hypertension.

THE THIAZIDE DIURETIC hydrochlorothiazide and the thiazidelike diuretic chlorthalidone are two old drugs that are still useful. Although similar, they differ in important ways still not fully appreciated more than a half century after they were introduced.

Most hypertension guidelines recommend thiazide diuretics as one of the classes of agents that can be used either as initial antihypertensive drug therapy or as part of combination therapy.¹⁻³

In the United States, hydrochlorothiazide is used more often than chlorthalidone, but many clinical trials of antihypertensive therapy have used chlorthalidone.^{4,5} In recent years, particularly after the publication of the Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), interest in chlorthalidone has been increasing, and new data are now available comparing these two diuretics.⁶ While current US guidelines do not recommend one over the other, British guidelines prefer chlorthalidone.⁷

This review summarizes the data comparing the two drugs' pharmacology, antihypertensive effect, and impact on clinical outcomes to help guide clinicians in choosing antihypertensive drug therapy.

■ PHARMACOLOGY AND MECHANISM OF ACTION

Many of the differences in effectiveness and adverse effects of hydrochlorothiazide and chlorthalidone are thought to be due to their different pharmacodynamic and pharmacokinetic effects.

Pharmacodynamic effects

Hydrochlorothiazide and chlorthalidone differ significantly in chemical structure (**Figure 1**),

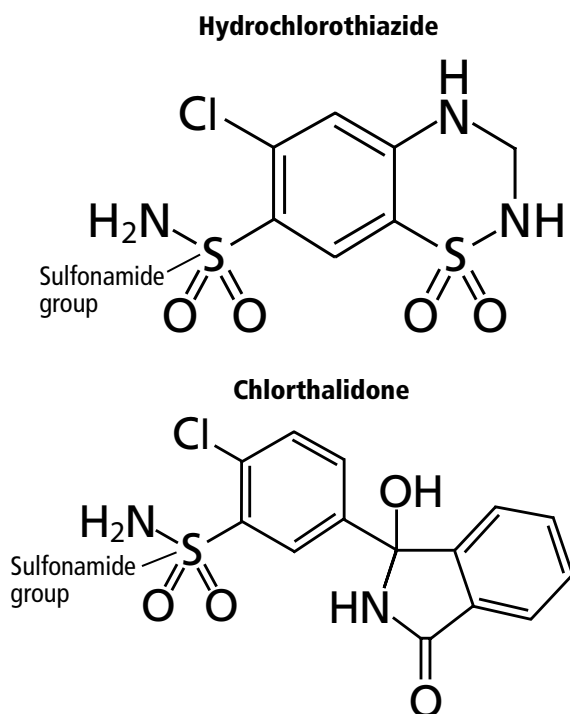


FIGURE 1. Although the chemical structures of hydrochlorothiazide (top) and chlorthalidone (bottom) differ, they both contain a sulfonamide group that inhibits carbonic anhydrase activity. This action may be associated with lower vascular contractility.

A pleiotropic effect of chlorthalidone: inhibition of platelet function

but both contain a sulfonamide group that inhibits carbonic anhydrase activity, which may be associated with lower vascular contractility. Both drugs are concentrated in the kidney and secreted into the tubular lumen⁸; therefore, their therapeutic diuretic effects are often achieved with relatively low plasma concentrations.

Both drugs inhibit the sodium-chloride cotransporter in the luminal membrane of the distal convoluted tubule of the ascending loop of Henle, leading to a modest natriuresis and diuresis. The exact mechanism by which they lower blood pressure is not known: while the initial response is from diuresis and volume changes, long-term reduction in blood pressure is through uncertain mechanisms. In addition, chlorthalidone may have beneficial effects on endothelial function and oxidative stress.^{9,10}

Both drugs also increase secretion of potassium and hydrogen ions and promote increased reabsorption of calcium through increased expression of a sodium-calcium exchange channel.⁸ Chlorthalidone may cause more

inhibition of carbonic anhydrase than hydrochlorothiazide, which can lead to lower intracellular pH and cell volume. This effect may in part explain a pleiotropic effect of chlorthalidone, ie, inhibition of platelet function, which in turn may contribute to this drug's beneficial effect on cardiovascular outcomes.⁹

Pharmacokinetic differences

Hydrochlorothiazide and chlorthalidone have important differences in their pharmacokinetic properties (Table 1).¹¹

Hydrochlorothiazide has its onset of action in about 2 hours, and it reaches its peak in 4 to 6 hours. Though its duration of action is short—up to 12 hours—its pharmacodynamic response can be much longer than predicted by its kinetics, allowing once-daily dosing.⁸

Chlorthalidone has a longer duration of action than hydrochlorothiazide. This may be because it has a very high volume of distribution, since it is taken up into red blood cells and is bound to carbonic anhydrase.¹² This may result in a “drug reservoir” that keeps drug levels higher for a longer time.¹³ Its long duration of action makes it a favorable choice for patients who have difficulty adhering to medication instructions. In addition, a missed dose is unlikely to have a “rebound” effect like that seen with some other antihypertensive agents. However, both chlorthalidone and hydrochlorothiazide are effective if taken once daily.

BLOOD PRESSURE-LOWERING

Both hydrochlorothiazide and chlorthalidone are effective antihypertensive agents. Table 2 summarizes findings from studies that evaluated their blood pressure-lowering effect at various doses.^{14–33} However, relatively few studies have directly compared these two agents' effects on blood pressure.

Ernst et al,³⁴ in a small study (but probably the best one to address this issue), compared chlorthalidone 12.5 mg/day (force-titrated to 25 mg/day) and hydrochlorothiazide 25 mg/day (force-titrated to 50 mg/day) in untreated hypertensive patients. After 8 weeks, ambulatory blood pressure monitoring indicated a greater reduction from baseline in systolic blood pressure with chlorthalidone 25 mg/day than with hydrochlorothiazide 50 mg/day (24-hour mean -12.4 vs -7.4 mm Hg, $P = .05$). Interestingly,

the change in nighttime blood pressure was greater in the chlorthalidone group (−13.5 mm Hg) than in the hydrochlorothiazide group (−6.4 mm Hg; $P = .009$). These data suggest that at the doses studied, chlorthalidone is more effective than hydrochlorothiazide in lowering systolic blood pressure.

Bakris et al,³⁵ using a different study design, compared the single-pill combination of azilsartan medoxomil and chlorthalidone vs coadministration of azilsartan medoxomil and hydrochlorothiazide in participants with stage 2 primary hypertension ($\geq 160/100$ mm Hg). Systolic blood pressure, as measured in the clinic, declined more with the chlorthalidone combination (−35.1 mm Hg) than with the hydrochlorothiazide combination (−29.5 mm Hg, mean difference −5.6 mm Hg, $P < .001$).

Meta-analyses also support the conclusion that chlorthalidone is more potent than hydrochlorothiazide in lowering blood pressure.^{35,36} Several studies have shown that chlorthalidone at the same dose is 1.5 to 2 times as potent as hydrochlorothiazide.^{33,36,37} Therefore, for clinical purposes, it is reasonable to consider chlorthalidone 12.5 mg daily as similar to 25 mg of hydrochlorothiazide daily.

ADVERSE EFFECTS

Electrolyte disturbances are a common adverse effect of thiazide diuretics.

Hypokalemia. All thiazide diuretics cause potassium wasting. The frequency of hypokalemia depends on the dose, frequency of administration, diet, and other pharmacologic agents used.

Two large clinical trials, the Systolic Hypertension in the Elderly Program and ALLHAT, found that chlorthalidone caused hypokalemia requiring therapy in about 6% to 8% of patients.^{38,39} Chlorthalidone therapy was associated with a lowering of serum potassium levels of 0.2 to 0.5 mmol/L.³⁶ In ALLHAT, chlorthalidone was associated with a reduction in potassium levels of approximately 0.2 mmol/L after 4 years.³⁸

All diuretics require monitoring of electrolytes, especially during the first 2 weeks of therapy. Once a steady state is reached, patients are not usually at risk of hypokalemia

TABLE 1

Pharmacokinetics and pharmacodynamics of hydrochlorothiazide and chlorthalidone

	Hydrochlorothiazide	Chlorthalidone
Onset	2 hours	2.6 hours
Peak effect	4–6 hours	1.5–6 hours
Absorption	Well absorbed ^a	65%
Duration	6–12 hours	48–72 hours
Protein binding	40%–68%	75%
Metabolism	Not metabolized	Hepatic
Elimination half-life	10–12 hours ^b	40–89 hours
Excretion pathway	Urine (as unchanged drug)	Urine ^c

^a When taken with food, time to maximum concentration increases from 1.6 hours to 2.9 hours. Absorption is reduced in patients with chronic heart failure.

^b Large variation due to biphasic elimination; may be much longer with renal impairment.

^c Data not available on the percentage of dose as unchanged drug and metabolites, concentration of the drug in body fluids, degree of uptake by a particular organ or in the fetus, or passage across the blood-brain barrier.

Information from US National Library of Medicine. DailyMed. dailymed.nlm.nih.gov. Accessed May 31, 2015.

unless the dose is increased, extrarenal losses of potassium increase, or dietary potassium is reduced.

Other electrolyte changes. Thiazide and thiazide-like diuretics can cause other metabolic and endocrine abnormalities such as hypochloremic alkalosis, hyponatremia, and hypercalcemia.^{40,41} They can also cause photosensitivity and can precipitate gout.⁴²

Observational studies have suggested that metabolic adverse effects such as hypokalemia and hyperuricemia are more common with chlorthalidone than with hydrochlorothiazide.⁴³ It is prudent to monitor laboratory values periodically in patients on diuretic therapy.

DRUG INTERACTIONS

The drug interaction profiles of hydrochlorothiazide and chlorthalidone are also similar. The most common interactions are pharmacodynamic interactions resulting from potassium depletion caused by the diuretics.

TABLE 2

Effect of different diuretic doses on systolic blood pressure

Diuretic and dose	Study	Mean difference in SBP vs placebo (mm Hg)
Hydrochlorothiazide 12.5 mg	Pool et al, 1997 ¹⁴	−4.40
	Pool et al, 2007 ¹⁵	−5.20
	Horie et al, 2007 ¹⁶	−7.80
	Chrysant, 1994 ¹⁷	−7.00
	Lacourcière and Arnott, 1994 ¹⁸	−10.2
	Villamil et al, 2007 ¹⁹	−6.40
	McGill and Reilly, 2001 ²⁰	−5.30
	Weir et al, 1992 ²¹	−9.60
	Goldberg et al, 1989 ²²	−7.10
	Papademetriou et al, 2006 ²³	−7.10
	Chrysant and Chrysant, 2004 ²⁴	−4.80
	Kocher et al, 1999 ²⁵	−6.60
Hydrochlorothiazide 25 mg	Villamil et al, 2007 ¹⁹	−6.80
	McGill and Reilly, 2001 ²⁰	−15.10
	Benz et al, 1998 ²⁶	−10.81
	Jounela et al, 1994 ²⁷	−9.90
	Scholze et al, 1993 ²⁸	−9.90
	Goldberg et al, 1989 ²²	−10.30
	Canter et al, 1994 ²⁹	−7.00
Chlorthalidone 25 mg	Vardan et al, 1987 ³⁰	−12.40
	Materson et al, 1978 ³¹	−15.40
	Morledge et al, 1986 ³²	−15.70
Chlorthalidone 50 mg	Morledge et al, 1986 ³²	−16.70
	Materson et al, 1978 ³¹	−14.50

Information from Peterzan MA, Hardy R, Chaturvedi N, Hughes AD. Meta-analysis of dose-response relationships for hydrochlorothiazide, chlorthalidone, and bendroflumethiazide on blood pressure, serum potassium, and urate. *Hypertension* 2012; 59:1104–1109.

Hydrochlorothiazide 25 mg is roughly equivalent to chlorthalidone 12.5 mg

Antiarrhythmic drugs. Hypokalemia is a risk factor for arrhythmias such as torsades de pointes, and the risk is magnified with concomitant therapy with antiarrhythmic agents that prolong the QT interval independently of serum potassium concentration (eg, sotalol, dronedarone, ibutilide, propafenone). Therefore, combinations of drugs that can cause hypokalemia (eg, diuretics) and antiarrhythmic agents require vigilant monitoring of potassium and appropriate replenishment.⁴⁴

Dofetilide is a class III antiarrhythmic agent and, like other antiarrhythmic drugs, carries a risk of QT prolongation and torsades de pointes, which is magnified by hypokalemia.⁴⁵ In addition, dofetilide undergoes active tubular secretion in the kidney via the cation transport system, which is inhibited by hydrochlorothiazide.⁴⁵ The resulting increase in plasma concentrations of dofetilide may magnify the risk of arrhythmias. Chlorthalidone has not been specifically studied in combination with dofetilide, but thiazide diuretics in general are thought to have a similar effect on tubular secretion and, therefore, should be considered similar to hydrochlorothiazide in this regard.

Digoxin. Similarly, digoxin toxicity may be enhanced in hypokalemia. As with antiarrhythmic agents, serum potassium should be carefully monitored and replenished appropriately when diuretics are used in combination with digoxin.

Lithium is reabsorbed in the proximal tubule along with sodium. Diuretics including hydrochlorothiazide and chlorthalidone that alter sodium reabsorption can also alter lithium absorption.⁴⁶ When sodium reabsorption is decreased, lithium ion reabsorption is increased and may result in lithium toxicity. Although this combination is not contraindicated, monitoring of serum lithium concentrations and clinical signs and symptoms of lithium toxicity is recommended during initiation and dose adjustments of thiazide diuretics.

Nonsteroidal anti-inflammatory drugs can decrease the natriuretic, diuretic, and antihypertensive effects of both hydrochlorothiazide and chlorthalidone.⁴⁷

Renin-angiotensin-aldosterone system antagonists, ie, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and

the renin inhibitor aliskiren, have potentially beneficial interactions with hydrochlorothiazide and chlorthalidone, producing additive decreases in blood pressure when coadministered with these diuretics. These effects may be particularly potent early in concomitant therapy and allow use of lower doses of diuretics, typically 12.5 mg of hydrochlorothiazide in combination therapy.

■ LONG-TERM EFFECTS ON CARDIOVASCULAR EVENTS

The long-term goal in treating hypertension is to lower the risk of cardiovascular disease. Therefore, the clinician needs to consider the effect of antihypertensive drug therapy on long-term clinical outcomes.

Antihypertensive drug therapy based on thiazide diuretics has been shown to lower cardiovascular risk when compared with placebo.⁴⁸ In addition, the effect of chlorthalidone-based antihypertensive therapy was similar to that of other antihypertensive drug classes in preventing most cardiovascular outcomes in ALLHAT.⁴

However, no study has directly compared hydrochlorothiazide and chlorthalidone with the primary outcome of reduction in long-term cardiovascular events. The data to date come from observational studies and meta-analyses. For example, in a retrospective analysis of the Multiple Risk Factor Intervention Trial, cardiovascular events were significantly fewer in those receiving chlorthalidone vs hydrochlorothiazide ($P = .0016$).⁴³

In a systematic review and meta-analysis, chlorthalidone was associated with a 23% lower risk of heart failure and a 21% lower risk of all cardiovascular events.⁴⁹

However, a Canadian observational study of 29,873 patients found no difference in the composite outcome of death or hospitalization for heart failure, stroke, or myocardial infarction between chlorthalidone recipients (3.2 events per 100 person-years) and hydrochlorothiazide recipients (3.4 events per 100 person-years; adjusted hazard ratio 0.93, 95% confidence interval 0.81–1.06).⁵⁰

In summary, it is unclear whether chlorthalidone or hydrochlorothiazide is superior in preventing cardiovascular events.

Monitor potassium closely in patients on a thiazide plus an antiarrhythmic agent

SUMMARY

Thiazide and thiazidelike diuretics play an important role in managing hypertension in most patients. The eighth Joint National Committee guidelines do not recommend either hydrochlorothiazide or chlorthalidone over the other. The target dose recommendations are hydrochlorothiazide 25 to 50 mg or

chlorthalidone 12.5 to 25 mg daily, with lower doses considered for the elderly.

There are important differences between hydrochlorothiazide and chlorthalidone in pharmacology, potency, and frequency of metabolic side effects. Clinicians should consider these factors to tailor the choice of thiazide diuretic therapy in hypertensive patients. ■

REFERENCES

- James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; 311:507–520.
- Dasgupta K, Quinn RR, Zarnke KB, et al; Canadian Hypertension Education Program. The 2014 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. *Can J Cardiol* 2014; 30:485–501.
- Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013; 34:2159–2219.
- ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group; The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; 288:2981–2997.
- 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* 1991; 265:3255–3264.
- Roush GC, Kaur R, Ernst ME. Diuretics: a review and update. *J Cardiovasc Pharmacol Ther* 2014; 19:5–13.
- McCormack T, Krause T, O'Flynn N. Management of hypertension in adults in primary care: NICE guideline. *Br J Gen Pract* 2012; 62:163–164.
- Bhattacharaya M, Alper SL. Pharmacology of volume regulation. In: Golan DE, Tashjian AH Jr, Armstrong EJ, Armstrong AW, editors. *Principles of Pharmacology: The pathophysiologic Basis of Drug Therapy*. 3rd ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012:332–352.
- Woodman R, Brown C, Lockette W. Chlorthalidone decreases platelet aggregation and vascular permeability and promotes angiogenesis. *Hypertension* 2010; 56:463–470.
- Sato K, Dohi Y, Kojima M, Takase H, Suzuki S, Ito S. Antioxidative effects of thiazide diuretics in refractory hypertensive patients. A randomized crossover trial of chlorthalidone and trichlormethiazide. *Arzneimittelforschung* 2010; 60:612–616.
- US National Library of Medicine. DailyMed. dailymed.nlm.nih.gov. Accessed May 14, 2015.
- Collste P, Garle M, Rawlins MD, Sjöqvist F. Interindividual differences in chlorthalidone concentration in plasma and red cells of man after single and multiple doses. *Eur J Clin Pharmacol* 1976; 9:319–325.
- Roush GC, Buddharaju V, Ernst ME, Holford TR. Chlorthalidone: mechanisms of action and effect on cardiovascular events. *Curr Hypertens Rep* 2013; 15:514–521.
- Pool JL, Cushman WC, Saini RK, Nwachuku CE, Battikha JP. Use of the factorial design and quadratic response surface models to evaluate the fosinopril and hydrochlorothiazide combination therapy in hypertension. *Am J Hypertens* 1997; 10:117–123.
- Pool JL, Glazer R, Weinberger M, Alvarado R, Huang J, Graff A. Comparison of valsartan/hydrochlorothiazide combination therapy at doses up to 320/25 mg versus monotherapy: a double-blind, placebo-controlled study followed by long-term combination therapy in hypertensive adults. *Clin Ther* 2007; 29:61–73.
- Horie Y, Higaki J, Takeuchi M. Design, statistical analysis and sample size calculation of dose response study of telmisartan and hydrochlorothiazide. *Contemp Clin Trials* 2007; 28:647–653.
- Chrysant SG. Antihypertensive effectiveness of low-dose lisinopril-hydrochlorothiazide combination. A large multicenter study. Lisinopril-Hydrochlorothiazide Group. *Arch Intern Med* 1994; 154:737–743.
- Lacourcière Y, Arnott W. Placebo-controlled comparison of the effects of nebivolol and low-dose hydrochlorothiazide as monotherapies and in combination on blood pressure and lipid profile in hypertensive patients. *J Hum Hypertens* 1994; 8:283–288.
- Villamil A, Chrysant SG, Calhoun D, et al. Renin inhibition with aliskiren provides additive antihypertensive efficacy when used in combination with hydrochlorothiazide. *J Hypertens* 2007; 25:217–226.
- McGill JB, Reilly PA. Telmisartan plus hydrochlorothiazide versus telmisartan or hydrochlorothiazide monotherapy in patients with mild to moderate hypertension: a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. *Clin Ther* 2001; 23:833–850.
- Weir MR, Weber MA, Punzi HA, Serfer HM, Rosenblatt S, Cady WJ. A dose escalation trial comparing the combination of diltiazem SR and hydrochlorothiazide with the monotherapies in patients with essential hypertension. *J Hum Hypertens* 1992; 6:133–138.
- Goldberg MR, Rockhold FW, Offen WW, Dornseif BE. Dose-effect and concentration-effect relationships of pinacidil and hydrochlorothiazide in hypertension. *Clin Pharmacol Ther* 1989; 46:208–218.
- Papademetriou V, Hainer JW, Sugg J, Munzer D; ATTACH Study Group. Factorial antihypertensive study of an extended-release metoprolol and hydrochlorothiazide combination. *Am J Hypertens* 2006; 19:1217–1225.
- Chrysant SG, Chrysant GS. Antihypertensive efficacy of olmesartan medoxomil alone and in combination with hydrochlorothiazide. *Expert Opin Pharmacother* 2004; 5:657–667.
- Kochar M, Guthrie R, Triscari J, Kassler-Taub K, Reeves RA. Matrix study of irbesartan with hydrochlorothiazide in mild-to-moderate hypertension. *Am J Hypertens* 1999; 12:797–805.
- Benz JR, Black HR, Graff A, Reed A, Fitzsimmons S, Shi Y. Valsartan and hydrochlorothiazide in patients with essential hypertension. A multiple dose, double-blind, placebo controlled trial comparing combination therapy with monotherapy. *J Hum Hypertens* 1998; 12:861–866.
- Jounela AJ, Lilja M, Lumme J, et al. Relation between low dose of hydrochlorothiazide, antihypertensive effect and adverse effects. *Blood Press* 1994; 3:231–235.
- Scholz J, Breitstadt A, Cairns V, et al. Short report: ramipril and hydrochlorothiazide combination therapy in hypertension: a clinical trial of factorial design. East Germany Collaborative Trial Group. *J Hypertens* 1993; 11:217–221.
- Canter D, Frank GJ, Knapp LE, Phelps M, Quade M, Texter M. Quinapril and hydrochlorothiazide combination for control of hypertension: assessment by factorial design. Quinapril Investigator Group. *J Hum Hypertens* 1994; 8:155–162.
- Vardan S, Mehrotra KG, Mookherjee S, Willsey GA, Gens JD, Green DE. Efficacy and reduced metabolic side effects of a 15-mg chlorthalidone formulation in the treatment of mild hypertension. A multicenter study. *JAMA* 1987; 258:484–488.
- Materson BJ, Oster JR, Michael UF, et al. Dose response to chlorthalidone in patients with mild hypertension. Efficacy of a lower dose. *Clin*

- Pharmacol Ther 1978; 24:192–198.
32. **Morledge JH, Ettinger B, Aranda J, et al.** Isolated systolic hypertension in the elderly. A placebo-controlled, dose-response evaluation of chlorthalidone. *J Am Geriatr Soc* 1986; 34:199–206.
 33. **Peterzan MA, Hardy R, Chaturvedi N, Hughes AD.** Meta-analysis of dose-response relationships for hydrochlorothiazide, chlorthalidone, and bendroflumethiazide on blood pressure, serum potassium, and urate. *Hypertension* 2012; 59:1104–1109.
 34. **Ernst ME, Carter BL, Goerdt CJ, et al.** Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. *Hypertension* 2006; 47:352–358.
 35. **Bakris GL, Sica D, White WB, et al.** Antihypertensive efficacy of hydrochlorothiazide vs chlorthalidone combined with azilsartan medoxomil. *Am J Med* 2012; 25:1229.e1–1229.e10.
 36. **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* 2010; 23:440–446.
 37. **Carter BL, Ernst ME, Cohen JD.** Hydrochlorothiazide versus chlorthalidone: evidence supporting their interchangeability. *Hypertension* 2004; 43:4–9.
 38. **Alderman MH, Piller LB, Ford CE, et al; Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group.** Clinical significance of incident hypokalemia and hyperkalemia in treated hypertensive patients in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *Hypertension* 2012; 59:926–933.
 39. **Franssen LV, Pahor M, Di Bari M, Somes GW, Cushman WC, Applegate WB.** Hypokalemia associated with diuretic use and cardiovascular events in the Systolic Hypertension in the Elderly Program. *Hypertension* 2000; 35:1025–1030.
 40. **Egom EE, Chirico D, Clark AL.** A review of thiazide-induced hyponatremia. *Clin Med* 2011; 11:448–451.
 41. **Palmer BF.** Metabolic complications associated with use of diuretics. *Semin Nephrol* 2011; 31:542–552.
 42. **Hueskes BA, Roovers EA, Mantel-Teeuwisse AK, Janssens HJ, van de Lisdonk EH, Janssen M.** Use of diuretics and the risk of gouty arthritis: a systematic review. *Semin Arthritis Rheum* 2012; 41:879–889.
 43. **Dorsch MP, Gillespie BW, Erickson SR, Bleske BE, Weder AB.** Chlorthalidone reduces cardiovascular events compared with hydrochlorothiazide: a retrospective cohort analysis. *Hypertension* 2011; 57:689–694.
 44. **Trinkley KE, Page RL 2nd, Lien H, Yamanouye K, Tisdale JE.** QT interval prolongation and the risk of torsades de pointes: essentials for clinicians. *Curr Med Res Opin* 2013; 29:1719–1726.
 45. **Crist LW, Dixon DL.** Considerations for dofetilide use in the elderly. *Consult Pharm* 2014; 29:270–274.
 46. **Handler J.** Lithium and antihypertensive medication: a potentially dangerous interaction. *J Clin Hypertens (Greenwich)* 2009; 11:738–742.
 47. **Pavlicević I, Kuzmanić M, Rumboldt M, Rumboldt Z.** Interaction between antihypertensives and NSAIDs in primary care: a controlled trial. *Can J Clin Pharmacol* 2008; 15:e372–e382.
 48. **Psaty BM, Smith NL, Siscovick DS, et al.** Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. *JAMA* 1997; 277:739–745.
 49. **Roush GC, Holford TR, Guddati AK.** Chlorthalidone compared with hydrochlorothiazide in reducing cardiovascular events: systematic review and network meta-analyses. *Hypertension* 2012; 59:1110–1117.
 50. **Dhalla IA, Gomes T, Yao Z, et al.** Chlorthalidone versus hydrochlorothiazide for the treatment of hypertension in older adults: a population-based cohort study. *Ann Intern Med* 2013; 158:447–455.

ADDRESS: Mahboob Rahman, MD, MS, University Hospitals Case Medical Center, 11100 Euclid Avenue, Cleveland OH 44016;
e-mail: Mahboob.Rahman@uhhospitals.org