Pediatr Nephrol (2016) 31:2223–2233
DOI 10.1007/s00467-016-3334-4

EDUCATIONAL REVIEW

Diuretics in the treatment of hypertension

Douglas L. Blowey[1]

Received: 8 May 2015 / Revised: 11 January 2016 / Accepted: 12 January 2016 / Published online: 16 March 2016

Abstract Diuretics have long been used for the treatment of hypertension. Thiazide diuretics are the most commonly prescribed diuretics for hypertension, but other classes of diuretics may be useful in alternative circumstances. Although diuretics are no longer considered the preferred agent for treatment of hypertension in adults and children, they remain acceptable first-line options. Diuretics effectively decrease blood pressure in hypertensive patients, and in adults with hypertension reduce the risk of adverse cardiovascular outcomes. Because of varied pharmacokinetic and pharmacodynamic differences, chlorthalidone may be the preferred thiazide diuretic in the treatment of primary hypertension. Other types of diuretics (e.g., loop, potassium sparing) may be useful for the treatment of hypertension related to chronic kidney disease (CKD) and other varied conditions. Common side effects of thiazides are mostly dose-related and involve electrolyte and metabolic abnormalities.

Keywords Hypertension · Children · Thiazide diuretic · Hydrochlorothiazide · Chlorthalidone · Diuretics

While supervising the nephrology fellow's clinic you are presented with an obese 15-year-old Caucasian boy with repeated elevated office blood pressure readings that have persisted despite a 6-month trial of lifestyle modifications. Both parents developed hypertension in their mid-20s and several members of the family developed cardiovascular disease between 40 and 50 years of age. Aside from obesity, his physical examination is unremarkable as are his serum electrolytes, creatinine, urinalysis, and thyroid studies. Hemoglobin A1c is mildly elevated and the fasting lipid profile demonstrates a mild increase in total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The echocardiogram shows mild concentric left ventricular hypertrophy (LVH) with normal function.

In view of the blood pressure elevations that have persisted despite lifestyle modifications, a strong family history of hypertension and cardiovascular disease, and target organ involvement (e.g., LVH), the fellow recommends starting pharmacologic treatment and suggests initiating therapy with a diuretic. A discussion among the fellows in clinic results in the formation of several clinical questions related to diuretic use and hypertension.

Are diuretics recommended as preferred first-line antihypertensive agents in current hypertension guidelines?

In the current adult guidelines for the management of hypertension [1–6], the thiazide class of diuretics is recommended as one of several potential preferred drugs for initial antihypertensive drug therapy (Table 1). This is a change from previous guidelines that recommended the use of thiazide diuretics as the preferential initial therapy, a recommendation that was based on outcome trials available at that time (e.g., ALLHAT) [7, 8], cost, and other considerations. Using the most up-to-date literature on treatment, overall mortality, and cardiovascular, cerebrovascular, and renal outcomes, the member consensus opinion of the majority of the Eighth Joint National Committee (JNC 8) [1] concluded that a thiazide diuretic, angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor antagonist (ARB), or long-acting

✉ Douglas L. Blowey
dblowey@cmh.edu

[1] Pediatrics and Pharmacology, Division of Pediatric Nephrology, Children's Mercy Hospital, University of Missouri, 2401 Gillham Road, Kansas City, MO 64108, USA

Table 1 Summary of the guideline recommendations for the use of diuretics in primary hypertension

Guideline		Recommendation
Adult		
JNC 8 [1]	2014	Recommended selection among four medication classes • Thiazide-type diuretics • ACE inhibitors • Angiotensin receptor antagonist • Calcium channel blockers (long-acting)
ESH/ESC [5]	2013	Recommended selection among five medication classes • Thiazide-type diuretics • ACE inhibitors • Angiotensin receptor antagonist • Calcium channel blockers (long-acting) • Beta-blocker
NICE [6]	2011	>55 years or African American/ Caribbean • Thiazide-type diuretic if calcium channel blocker not suitable for evidence of high risk of heart failure Step #3 • Thiazide-type diuretic
Canadian [3]	2014	Recommended selection among four medication classes • Thiazide-type diuretics • Beta-blocker (<60 years) • ACE inhibitors • Calcium channel blockers (long-acting)
WHO [4]	2003	Thiazide-type diuretic
Management of hypertension in blacks [2]	2010	Thiazide-type diuretics Calcium channel blockers
Pediatric		
Task force 4th Report [15]	2004	No preferred agents, diuretics can be considered
European Society of Hypertension [16]	2009	No preferred agents, diuretics can be considered

ACE, angiotensin converting enzyme

calcium channel blocker are all reasonable options for initial drug therapy in the non-black hypertensive patient. In the black population, a thiazide diuretic or calcium channel blocker is preferred for initial therapy based on studies that demonstrated inferior blood pressure reduction and worse cardiovascular outcomes in black patients receiving monotherapy with ACE inhibitors as compared to those that received a calcium channel blocker or thiazide diuretic [7]. In hypertensive patients with chronic kidney disease (CKD) and proteinuria, including black patients, an ACE inhibitor or ARB is preferred as the initial antihypertensive agent with the addition of a diuretic agent if the blood pressure goal is not achieved [1].

For primary hypertension, a diuretic from the thiazide class is preferred unless there is a compelling indication for an agent from a different diuretic classification. An alternative diuretic may be considered with hypertension that occurs in patients with advanced CKD, acute glomerulonephritis, oliguric acute kidney injury (AKI), hyperaldosteronism, heart failure, ENaC mutations (e.g., Liddle syndrome), and apparent drug resistance. Despite the long-held belief that thiazide diuretics are not effective when the glomerular filtration rate (GFR) is below 30 ml/min/1.73 m^2, there are important differences in potency, duration of action, and off-target effects such that there may be some circumstances where thiazide diuretics can provide some blood pressure-lowering benefit in patients with moderate-to-advanced CKD [9–13]. The mechanism responsible for improved blood pressure control in patients with CKD needs to be further examined but could result from a mild diuresis produced by the more potent and/or longer-acting thiazide agents, or more likely, a result of the off-target effects causing vasodilatation. When thiazides are not used as the initial treatment option in primary hypertension, they are appropriate agents to be added to the antihypertensive regimen when blood pressure goals have not been reached with the initial agent. Due to a different mechanism of action and the potential for counteracting the sodium and water retention induced by many of the other classes of antihypertensive agents, diuretics produce an additive blood pressure-lowering effect [14].

Although the indications for antihypertensive drug treatment in a hypertensive child are relatively clear, the pediatric hypertension guidelines do not endorse a specific agent for initial treatment of children with primary hypertension [15, 16]. Mostly, this is due to a lack of any comparative studies of antihypertensive agents in children. Nonetheless, diuretics are considered an appropriate choice for initial drug therapy in children requiring pharmacologic intervention. Other antihypertensive agents considered appropriate for initial therapy by all pediatric guidelines include ACE inhibitors, ARBs, and calcium channel blockers. The European guidelines [16] also include beta-blockers in the list of acceptable first-line agents. If diuretic therapy is initiated, it is recommended that therapy begin with low doses and that the dosage is titrated slowly.

Have thiazide diuretics been shown to decrease blood pressure in patients with hypertension?

Thiazide diuretics have been widely used to treat high blood pressure for more than 50 years and numerous studies in adults have demonstrated a significant dose-related blood pressure-lowering effect [17]. The evidence for a blood pressure-lowering effect of thiazide diuretics in children is

limited. A systematic review of the dose–response relationship of thiazides in lowering blood pressure in adult patients with hypertension was completed by the Cochrane Collaboration in 2014 [17]. The analysis included 60 trials involving over 11,000 adult subjects who participated in a randomized trial where a thiazide diuretic was compared to placebo. While the vast majority of participants received hydrochlorothiazide, the pooled analysis included, in decreasing frequency of use, indapamide, chlorthalidone, bendrofluazide, metolazone, and cyclopenthiazide. In the pooled data, using the lowest dose that achieved maximal blood pressure reduction for each of the six drugs, the average magnitude in systolic and diastolic blood pressure lowering was (−)9.1 and (−)3.6 mmHg, respectively. While the magnitude of blood pressure lowering among the different thiazide agents using study visit (e.g., office) blood pressure measurements did not favor a specific thiazide diuretic, other studies suggest that there may be pharmacokinetic and/or pharmacodynamic factors that favor specific thiazide agents in the treatment of primary hypertension, namely, chlorthalidone.

Thiazide diuretics are characterized by a flat or shallow dose–response curve, meaning that there is minimal difference between the blood pressure reduction observed at the lowest and highest effective dose. Initial thiazide dosing strategies were mistakenly based on the assumption that the long-term antihypertensive effect of a thiazide diuretic was directly related to the level of sodium excretion (natriuresis) and doses at the upper end of the natriuretic dose–response curve were prescribed (e.g., hydrochlorothiazide 100 mg/day). In 1990, the concept that the maximal blood pressure lowering dose of a thiazide diuretic may not be the same as the maximal natriuretic dose was investigated by Carlsen et al. [18]. The placebo-controlled trial enrolled 257 adult patients with hypertension and compared the blood pressure-lowering effect of four escalating doses of bendrofluazide, the most potent of the thiazide diuretics [19]. At 3 months, there was no significant difference in the magnitude of blood pressure lowering between those subjects that received the lowest dose (i.e., 1.25 mg/day) and the higher dosing regimens (i.e., 2.5, 5, and 10 mg/day). The suggestion that maximal blood pressure reduction occurs at the lower end of the thiazide dosing range was examined on a larger scale by the previously described Cochrane systemic review of thiazide diuretics for primary hypertension [17]. The analysis of hydrochlorothiazide included 40 trials with dosages ranging from 3 to 100 mg/day. Hydrochlorothiazide doses of 6.25, 12.5, 25, and 50–100 mg/day resulted in approximately 40, 60, 80, and 100 % of the maximal diuretic-induced blood pressure reduction (Fig. 1). As most of the blood pressure-lowering benefit was realized with titration to the 25 mg/day dose, this was defined as the lowest dose that causes maximal blood pressure reduction and currently characterizes the upper end of the hydrochlorothiazide dosing range for primary hypertension [1]. In contrast, no dose response was observed for chlorthalidone as maximal blood pressure lowering was observed at the lowest dosage studied (12.5 mg/day). The fact that chlorthalidone is more potent than hydrochlorothiazide [19] is the most likely explanation for the lack of a dose–response relationship that may have been observed if lower doses (e.g., 6.25 mg or lower) were studied.

The other meaningful observation in the trials evaluating the blood pressure-lowering effect of thiazide diuretics is that changes in blood pressure occur slowly, with the greater part of the response being apparent by 4–6 weeks [19, 20]. In some circumstances, the complete blood pressure-lowering effect may not be fully realized until 12 weeks of therapy [20].

While extrapolation of the adult data would support the use of thiazide diuretics in children with hypertension, there are only a few studies available involving a small number of children with hypertension [21–23]. In a cross-over study comparing propranolol and chlorthalidone in 12 children with essential hypertension, treatment with chlorthalidone prescribed as a single dose every 48 h (0.5–1.7 mg/kg/dose) decreased the mean arterial pressure by 15 mmHg [22]. Four children (25 %) required potassium supplementation for hypokalemia. In a study that randomized 94 children with hypertension to placebo or treatment with escalating doses of the beta-blocker bisoprolol fumarate combined with a fixed dose of hydrochlorothiazide (6.25 mg), the combined drug regimen induced significant reductions in systolic and diastolic blood pressure [21]. Although the study protocol did include an independent hydrochlorothiazide arm, there were too few children enrolled for analysis, and it remains unclear if the blood pressure reduction was due to the bisoprolol, the hydrochlorothiazide, or the combination. A similar study randomized 90 children with high blood pressure measurements (e.g., >90th percentile) to observation or treatment with a program that included education on dietary and exercise modification and combined drug therapy consisting of propranolol (20–40 mg per day) and chlorthalidone (6.25–12.5 mg per day) [23]. The treatment group had a mild decrease in both systolic (−3.59 mmHg) and diastolic (−1.73 mmHg) blood pressure. Again, due to the absence of an independent chlorthalidone arm, its contribution to the blood pressure reduction is unclear.

In what conditions are other types of diuretics useful in the treatment of hypertension?

In CKD, acute glomerulonephritis, or oliguric AKI where extracellular fluid (ECF) volume is expanded and there is an impaired natriuretic response, a more efficacious diuretic such as a loop diuretic may be needed to achieve the level of diuresis required to reduce ECF volume and decrease blood pressure. In adults with CKD, acute treatment with a loop diuretic results in a significant increase in natriuresis, reduction in ECF

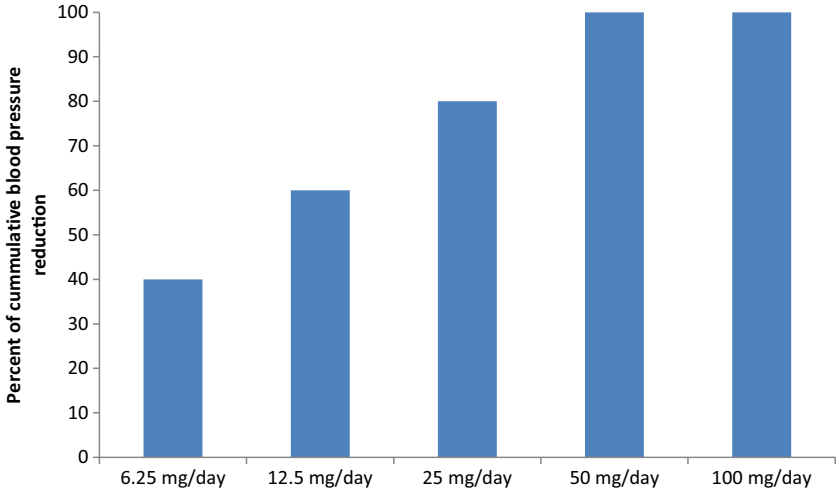

Fig. 1 Percentage of maximal blood pressure reduction based on hydrochlorothiazide dosage (data plotted from [17])

volume, and lowering of blood pressure [24, 25]. Similar to the mechanism of blood pressure lowering with long-term thiazide diuretics, blood pressure lowering with chronic dosing of loop diuretics in CKD involves both volume regulation and direct vascular effects [24]. In children, loop diuretics are often prescribed to treat the hypertension associated with acute glomerulonephritis (e.g., acute post-infectious glomerulonephritis). Despite the intuitive benefits one would expect, there is very little published on the blood pressure-lowering effectiveness of loop diuretics in these settings [26, 27]. While loop diuretics may be useful in lowering blood pressure in those with CKD, acute glomerulonephritis and AKI, there is not enough information on the magnitude and pattern of blood pressure lowering, impact on cardiovascular outcomes, or potential for harm to support the routine use of loop diuretics in patients with primary hypertension [28].

Potassium-sparing diuretics, which include mineralocorticoid receptor antagonists (i.e., spironolactone and eplerenone) and epithelial sodium channel (ENaC) blockers (i.e., amiloride) can be beneficial in hypertension associated with hyperaldosteronism, heart failure, ENaC mutations (e.g., Liddle syndrome), and apparent drug-resistant hypertension. Eplerenone, an agent that in contrast to spironolactone has relative selectivity in binding mineralocorticoid receptors compared to progesterone and androgen receptors, decreases blood pressure in adults with essential hypertension [29]. Low-dose aldosterone blockade is also effective in lowering blood pressure in adults with apparent drug-resistant hypertension [30–32]. The blood pressure-lowering effect of eplerenone was evaluated in a randomized, dose–response study involving 304 children aged 4–16 years of age with hypertension defined as a systolic BP ≥95th percentile [33]. About 30 % were receiving other antihypertensive drugs at study entry. Children were randomized to 6 weeks of eplerenone therapy in a dose-stratified protocol: low-dose (25 mg once daily), medium-dose (25 mg twice daily), and high-dose (25 mg twice daily titrated to 50 mg twice daily). The reduction in systolic blood pressure at the end of 6 weeks ranged from (−)7.66 to (−)7.99 mmHg with no impact of dose on the extent of blood pressure reduction. The diastolic blood pressure reduction ranged from (−)2.7 to (−)3.8 mmHg. At the end of the 6-week treatment phase, subjects were randomized to continued treatment with eplerenone or placebo for an additional 4 weeks. The blood pressure reduction compared to placebo was significant only for the high-dose eplerenone group (50 mg BID) with a modest systolic blood pressure reduction of (−)2.76 mmHg. No significant reduction was observed for diastolic blood pressure. No subject discontinued the study due to hyperkalemia or serious adverse events related to the study drug. While eplerenone may provide a modest reduction in blood pressure in children with hypertension, its place in the treatment algorithm for children with hypertension remains unclear.

How do diuretics lower blood pressure in patients with hypertension?

The modern era of diuretic therapy began in the 1950s with the synthesis of chlorothiazide, followed closely by the development of several similar agents [34]. Thiazide and thiazide-type diuretics are characterized by their chemical structure (Table 2). A thiazide diuretic contains a benzothiadiazene ring plus a sulfonamide moiety. In contrast, thiazide-type diuretics contain the sulfonamide group but lack the benzothiadiazene core. As a class, thiazide diuretics have a common mechanism of action as it relates to natriuresis, but there are pharmacokinetic and pharmacodynamic differences among the thiazide diuretics that may impact the extent and temporal pattern of blood pressure reduction, cardiovascular outcomes, and frequency of adverse events.

Table 2 Classification of thiazide and thiazide-type diuretics

Thiazide drugs
• Chlorothiazide *
• Hydrochlorothiazide *
• Bendroflumethiazide
• Polythiazide
• Methyclothiazide
Thiazide-type drugs
• Chlorthalidone
• Metolazone *
• Indapamide
• Xipamide

*Pediatric dosing present on labeling/drug insert

Thiazide diuretics inhibit sodium reabsorption by blocking the electroneutral sodium-chloride cotransporter (NCCT) located on the apical membrane in the distal convoluted tubule where 5–10 % of the filtered sodium load is reabsorbed [34–36]. The thiazides are rapidly absorbed by the gastrointestinal tract and display a high degree of plasma protein binding, which limits their filtration at the glomerulus. In order for thiazide diuretics to reach the site of action, which is located on the luminal (filtrate) side of the nephron, thiazide diuretics must be actively secreted through the renal organic anion transporter in the proximal tubule. In renal failure, competition for the proximal tubular anion transporter by accumulated organic anions may decrease the amount of thiazide diuretic that reaches the tubular fluid and diminish the natriuretic effect. Additionally, there are marked differences in the volume of distribution and elimination half-life of some thiazides that have clinical significance. Due to binding with erythrocyte carbonic anhydrase and partitioning of the drug within the erythrocyte, chlorthalidone, indapamide, and to some extent metolazone have a much larger volume of distribution and longer elimination half-life as compared to the other diuretics in this class. The prolonged elimination half-life results in an extended duration of action that, in part, may play a role in the improved BP control and cardiovascular outcomes observed with chlorthalidone [37–40].

The mechanism(s) responsible for the blood pressure-lowering effect observed with a thiazide diuretic are incompletely understood and are likely different for blood pressure lowering seen at the onset of treatment and blood pressure lowering observed with chronic therapy [41]. The blood pressure-lowering effect observed at the onset of therapy with a thiazide diuretic is associated with a reduction in ECF volume and diminished cardiac output. This mechanism of blood pressure reduction is supported by the observation that restoration of the plasma volume during this phase with infusions of dextran returns the blood pressure to pretreatment levels [42]. The reduced cardiac output induced by the thiazide-associated volume depletion leads to stimulation of the renin–angiotensin–aldosterone (RAAS) and sympathetic nervous (SNS) systems resulting in gradual sodium and water retention. Within 4–6 weeks, the compensatory salt and water reabsorption returns the ECF volume towards baseline. Interestingly, the antihypertensive effect of thiazides persists despite normalization of the ECF volume due to a decrease in peripheral vascular resistance [43, 44]. The factors responsible for the vasodilatation and enduring blood pressure lowering are not clearly defined and appear to involve both a direct and indirect action on the vascular endothelium and/or musculature (Table 3). The capacity of an individual thiazide diuretic to induce off-target (pleiotropic) effects, including vasodilatation, may be the foundation for the efficacy of blood pressure lowering and the extent of cardiovascular benefit.

Similar to other antihypertensive agents, around one-half of adult patients treated with a thiazide diuretic achieve adequate blood pressure control [5]. Determinants of a favorable response may include a higher baseline blood pressure, female gender, and lower plasma renin activity (e.g., black, elderly, diabetics) but these factors only explain a small percentage of the variability in response [34]. Other factors possibly related to the magnitude of blood pressure response to thiazide diuretics may include genetic variations in the genes associated with NCCT function (e.g., *SLC12A3*, *WNK1*, *WNK 4*) [34, 41, 45–48], the activity of other blood pressure counter-regulatory systems (e.g., RAAS, SNS), compliance, and dietary indiscretion, among others.

Do thiazide diuretics improve the cardiovascular outcome in patients with hypertension?

Hypertension is a strong and independent risk factor for death and cardiovascular events [49]. Lowering blood pressure decreases the risk of these undesired outcomes [50]. Although thiazide diuretics have a dose-related blood pressure-lowering effect [17], the magnitude of blood pressure reduction does not necessarily correlate with the observed reduction in morbidity and mortality [50]. Other factors outside of the extent of blood pressure lowering, such as off-target effects and the rate

Table 3 Proposed mechanisms for the thiazide vasodilatory effect

• Activation of vascular potassium channels
• Opening of large conductance Ca^{2+}-activated K^+ channels (BK_{Ca})
• Ca^{2+} desensitization
• Inhibition of voltage-dependent L-type Ca^{2+} channels
• Endothelial-dependent relaxing factor/nitric oxide release
• Increased release of local vasodilatory factors (e.g., prostaglandins)

and magnitude of metabolic complications (e.g., electrolyte abnormalities, alterations in lipid or glucose metabolism), may play a role in the advantageous as well as unfavorable effects of thiazide drugs.

In the 1970s, a series of randomized controlled trials that enrolled adult patients with hypertension showed that, when compared to placebo, a thiazide diuretic reduced mortality and the rate of cardiovascular events [50]. A recent Cochrane analysis of 19 randomized controlled trials compared outcomes from patients with hypertension treated with a thiazide diuretic as a first-line agent to those patients that received a placebo or no pharmacologic treatment. Compared to the untreated control group, those receiving a first-line thiazide diuretic as treatment for hypertension demonstrated a reduction in mortality [relative risk (RR) 0.89], stroke (RR 0.63), coronary heart disease (RR 0.84), and all-cause cardiovascular events (RR 0.70). Total cardiovascular events were defined as strokes, coronary heart disease, hospitalization or death from congestive heart failure, and other significant vascular death (e.g., ruptured aneurysm). Despite similar reductions in blood pressure, there was a significant difference in the impact on outcome between low-dose thiazide trials and high-dose thiazide trials. High-dose regimens for the most commonly encountered drugs were defined as: hydrochlorothiazide ≥50 mg/day, chlorthalidone ≥50 mg/day, indapamide and bendrofluazide ≥5 mg/day. First-line low-dose thiazide therapy reduced the risk of all outcomes (i.e., mortality, stroke, coronary heart disease, and total cardiovascular events). In contrast, first-line high-dose thiazide therapy reduced the risk of stroke and total cardiovascular events but not the risk of coronary heart disease or mortality despite a similar reduction in blood pressure. One possible explanation for this discrepancy is that high-dose thiazide regimens induce more metabolic complications (e.g., hypokalemia, glucose, and lipid abnormalities, etc.) that mask the beneficial effect of blood pressure lowering.

Subsequent randomized controlled trials compared the blood pressure-lowering effect and cardiovascular outcomes of thiazide diuretics and the newer classes of antihypertensive drugs [50] that include ACE inhibitors, ARBs, and calcium channel blockers. The largest and most influential study was The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack trial (ALLHAT) [7]. In this community-based study, over 33,000 patients who were at least 55 years of age and had at least one other cardiovascular disease risk factor were randomized to receive either the thiazide diuretic chlorthalidone, the calcium channel blocker amlodipine, the ACE inhibitor lisinopril, or the alpha-adrenergic blocker doxazosin. The doxazosin arm was stopped early when the interim analysis found an increased rate of cardiovascular disease and heart failure. At the conclusion of the study, the mean follow-up was 4.9 years and there was no difference between treatments groups in the occurrence of the primary outcome—combined fatal coronary heart disease or nonfatal myocardial infarction. Systolic blood pressure control was slightly better with chlorthalidone, which measured 1–2 mmHg lower than the other groups. When compared to chlorthalidone, amlodipine was associated with an increased risk of heart failure, but the consensus opinion of the JCN8 members concluded that while this should be considered when selecting the drug for initial therapy, calcium channel blockers remain a viable option for first-line therapy [1]. In blacks, when compared to those allocated to lisinopril, chlorthalidone treatment was associated with a significant reduction in systolic blood pressure ((−)4 mmHg) and a reduced risk for stroke and combined cardiovascular disease. For blacks, including those with diabetes, thiazide diuretics along with calcium channel blockers are the preferred first-step antihypertensive agents [1, 2].

Do all thiazide diuretics have the same effect on blood pressure and cardiovascular outcome?

Thiazide diuretics are prescribed with the primary goal of lowering blood pressure and improving health outcomes by decreasing the incidence of death and adverse cardiovascular events. As discussed above, it is clear that thiazide diuretics, as a group, lower blood pressure and improve cardiovascular outcomes. Because hypertension is a complex disease that results from alterations in multiple pathways of blood pressure regulation, it is not surprising that there are a significant number of people with hypertension that do not achieve normal blood pressure values with a thiazide diuretic [5] and that the blood pressure response and outcome may vary among the different thiazide agents [28, 37–39, 50]. The variability in the blood pressure lowering effects and the rate of cardiovascular events among thiazide diuretics may result from pharmacokinetic differences, pharmacodynamic differences, or variations in genes (e.g., single nucleotide polymorphisms) related to treatment effects.

Despite the lack of large randomized trials directly comparing the effectiveness of the different thiazide diuretics, there is mounting evidence that favors chlorthalidone as the preferred agent. The factors that favor chlorthalidone likely emanate from pharmacokinetic (e.g., prolonged half-life) and pharmacodynamic differences (e.g., potency and off-target effects). Thiazide diuretics appear to have parallel dose–response curves as it relates to natriuresis, but different thiazide agents display diversity in potency and duration of action. Potency is the amount of drug, either dose or concentration in the plasma, required to produce an effect. A more potent drug does not imply a superior therapeutic agent but simply reflects the dose required to achieve an effect. Thiazides have similar efficacy, or maximal effect, but different potency. Compared to hydrochlorothiazide, chlorthalidone is 2–3 times more potent and

has a much longer elimination phase (48 vs. 6–12 h, respectively) [19, 34, 36].

Although the Cochrane meta-analysis on the blood pressure lowering effect of thiazide diuretics prescribed as monotherapy in primary hypertension [17] did not find a significant difference in the extent of blood pressure lowering among the thiazide diuretics when using the study-based (e.g., office) blood pressure measurements, there does appear to be a benefit that favors chlorthalidone when the blood pressure profile across an entire day is assessed by 24-h ambulatory blood pressure (ABPM) monitoring. In a trial of 20 adults with hypertension or pre-hypertension [37], office and 24-h ABPM were compared after 8 weeks of active treatment with either chlorthalidone (force titrated to 25 mg/day) or hydrochlorothiazide (force titrated to 50 mg/day). Whereas office blood pressure values were similar, the 24-h ABPM indicated that chlorthalidone produced a greater reduction in systolic blood pressure compared to hydrochlorothiazide (−12.4 ± 1.8 vs. –7.4 ± 1.7 mmHg, $p = 0.05$), an effect that was primarily driven by the lower nighttime blood pressure for chlorthalidone (−13.5 ± 1.9 vs. –6.4 ± 1.7 mmHg, $p = 0.009$). An improved 24-h blood pressure pattern in the chlorthalidone arm was also observed in a study combining the ARB azilsartan with either chlorthalidone or hydrochlorothiazide [51].

In the 1970s, a randomized primary prevention trial (MRFIT) was completed to test the effect of an intervention program aimed at the cessation of smoking and the reduction of elevated cholesterol and blood pressure on the mortality from coronary heart disease [52]. In the special intervention group, elevated blood pressure was treated with chlorthalidone or hydrochlorothiazide based on the prescriber's preference. An ecologic analysis (studies of risk-modifying factors on health or other outcomes based on populations defined either geographically or temporally) of the MRFIT data [53] found a lower rate of LVH, defined by ECG criteria, in centers where chlorthalidone was preferred. Using individual patient analysis, those prescribed chlorthalidone were found to have a lower left ventricular mass compared to those prescribed hydrochlorothiazide. A similar benefit favoring chlorthalidone was observed in a more recent meta-analysis of nine randomized trials that had at least one arm based on either hydrochlorothiazide ($n = 3$) or chlorthalidone ($n = 6$) [40]. In the drug-adjusted analysis, there was a 21 % reduction in the risk of cardiovascular events (i.e., myocardial infarction, diagnosis of coronary heart disease, stroke, or congestive heart failure) with chlorthalidone compared to hydrochlorothiazide—a result that was identical to the previously described retrospective cohort analysis of MRFIT [53]. The office systolic blood pressure adjusted analysis, an analysis comparing the risk reduction with comparable reductions in blood pressure, found a significantly lower risk (18 %) for cardiovascular events in patients receiving chlorthalidone compared to hydrochlorothiazide. In contrast, the risk of cardiovascular events in patients receiving hydrochlorothiazide was significantly higher than the risk in the non-diuretic comparators (RR = 1.19) that included calcium channel blockers, ACE inhibitors, and an alpha-adrenergic blocker.

What are the risks associated with the use of diuretics in patients with hypertension?

Thiazide diuretics have been associated with numerous fluid and electrolyte abnormalities. The most common and clinically relevant adverse effects observed in hypertension trials include hyponatremia, hypokalemia, hypomagnesemia, hyperuricemia, hyperlipidemia, hyperglycemia, new-onset diabetes mellitus, and stimulation of the RAAS [19, 41, 53, 54]. Although the associations are not clear, there is concern that the thiazide-induced metabolic effects could negate the health outcome benefits associated with the treatment-related decrease in blood pressure. Many of the adverse metabolic effects are more common with high-dose thiazide therapy and the use of more potent and longer acting agents [17]. Although potentially biased due to lack of reporting, the network meta-analysis of thiazide diuretics as monotherapy in hypertension found that the number of subjects who dropped out of clinical trials secondary to adverse drug effects was different between low-dose and high-dose thiazide regimens [50]. Compared to the control group, the relative risk of dropping out of the clinical trial as a result of an adverse drug effect was 4.5 (95 % CI, 3.8, 5.2) for high-dose thiazide regimens and 2.4 (95 % CI, 2.1, 2.8) for low-dose thiazide regimens.

Diuretic-induced hyponatremia and hypokalemia are relatively common complications when treating hypertensive patients. While usually mild and asymptomatic, occasionally, severe depletion can lead to significant clinical manifestations [55]. Hyponatremia is much more common in patients treated with thiazide diuretics, occurring in up to one third of patients. In contrast to loop diuretics, thiazide diuretics are more prone to cause hyponatremia because they do not disrupt the formation of the medullary concentration gradient. The combination of increased sodium excretion and unaltered water reabsorption in the presence of antidiuretic hormone promotes the development of hyponatremia. While hyperkalemia may occur with the use of potassium-sparing diuretics, hypokalemia is more commonly encountered. The magnitude of hypokalemia observed with low-dose thiazide therapy is mild, with reductions usually around 0.5 mEq/l, but the magnitude may be greater with high-dose thiazide therapy or therapy with more potent or longer-acting agents (e.g., chlorthalidone). In hepatic impairment, hypokalemia induced by thiazides may precipitate coma and should be avoided. The risk of hypokalemia is decreased when diuretics are used in combination with ACE inhibitors or ARBs. Hypokalemia develops due to increased

potassium excretion, and the factors that promote thiazide-induced potassium secretion include increased delivery of sodium to the distal segments, diuretic-induced volume depletion with stimulation of the RAAS, and secondary hyperaldosteronism. Clinically, thiazide-related hypokalemia may induce arrhythmias particularly in patients at risk including those with LVH, congestive heart failure, myocardial ischemia, and those receiving digoxin or other antiarrhythmic drugs [56]. Thiazide and loop diuretics also inhibit renal magnesium absorption and can cause hypomagnesemia. Diuretic-induced hypomagnesemia may increase the risk of arrhythmias associated with hypokalemia, and the simultaneous repletion of magnesium and potassium reduces the occurrence of arrhythmias more than potassium supplementation alone [57]. Hypomagnesemia increases the sensitivity to digitalis likely due to the inhibitory effect of hypomagnesemia on the Na/K ATPase. While hypomagnesemia may be present in the absence of symptoms, when symptoms are present they are usually confined to the neuromuscular system and include; weakness, muscle fasciculation, tremor, tetany, irritability, and personality change. Because the majority of the electrolyte abnormalities emerge within a few weeks of initiating therapy or upward titration of dosage, an assessment of the serum electrolytes and magnesium should be completed 2–4 weeks after starting diuretic therapy for hypertension or upward dosage adjustment and periodically thereafter (e.g., 6–12 months).

There is concern that thiazides have an adverse effect on glucose metabolism, which could impact the cardiovascular benefits of the thiazide-induced blood pressure lowering. Indeed, a network meta-analysis showed an increased risk of new-onset diabetes in patients receiving thiazide diuretics compared to those receiving ACE inhibitors, ARBs, calcium channel blockers, or placebo [58]. However, many of the studies included higher-dose thiazide regimens that may be associated with an increased risk of glucose abnormalities compared to the lower doses used today. The Diuretics in the Management of Essential Hypertension study (DIME) [59] was a randomized trial of 1130 adult patients allocated to low-dose thiazide (12.5 mg hydrochlorothiazide or equivalent) or treatment without diuretics. At a mean follow-up of 4 years, there was no difference in the number of patients who developed new-onset diabetes in the thiazide group (4.6 %) and the non-thiazide group (4.9 %, $p = 0.80$).

Thiazides slightly increase serum total cholesterol, low-density cholesterol, and triglyceride concentrations [17]. Whether the changes in the lipid profiles are dose related or persist with long-term therapy has not been established. Likewise, the clinical importance of these findings is not known, but the laboratory abnormalities may be improved with a diet low in saturated fat and cholesterol.

Elevated uric acid levels are secondary to decreased urate clearance associated with enhanced proximal tubular reabsorption, competition for sites of tubular secretion, or other efflux pathways. The increase in uric acid rarely provokes gout except in patients with a history of gout.

Finally, although manufacturers state that the use of diuretics is contraindicated in patients who are allergic to any sulfonamide derivative, which includes most diuretics, it appears the association between hypersensitivity to sulfonamide antibiotics and non-antibiotic sulfonamides (e.g., thiazide diuretics) may be related to predisposition to allergic reaction in general, rather than cross-reactivity to sulfa [60]. Thus, a history of sensitivity to sulfonamide antibiotics should not be considered an absolute contraindication to the use of thiazide diuretics.

Revisiting the case

The paper began with the presentation of a 15-year-old Caucasian boy with elevated blood pressure measurements. His history was complicated by obesity, mild LVH, and an increase in the hemoglobin A1c and cholesterol. Based on the subsequent review, it is anticipated that a low-dose thiazide diuretic regimen would result in a lowering of his blood pressure. It is unclear if the blood pressure lowering would improve his long-term cardiovascular outcome compared to other agents (e.g., ACE inhibitors, ARBs, calcium channel blockers). While the risk of adverse metabolic effects can be reduced using low-dose regimens, a thiazide may result in worsening of the dyslipidemia and hyperglycemia and mask any beneficial effect that results from the blood pressure lowering. In this setting, it may be more appropriate to initiate therapy with an ACE inhibitor, ARB, or long-acting calcium channel blocker. However, should his blood pressure not be controlled with the initial agent, the addition of a thiazide diuretic is a reasonable next step.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

Key summary points

1. Thiazide diuretics are effective antihypertensive agents that can be considered as first-line therapy for adults and children with hypertension.
2. Chlorthalidone possesses unique pharmacokinetic and pharmacodynamics properties and should be considered the preferred thiazide diuretic for the treatment of hypertension.
3. Although there is a lack of outcome data in children, in adults with hypertension treatment with a thiazide diuretic decreases the morbidity and mortality associated with hypertension.
4. The long-term blood pressure-lowering effect of thiazide diuretics is mediated by vasodilation.

5. Electrolyte abnormalities are the most common adverse effects associated with the use of thiazide diuretics for hypertension and serial assessment of serum electrolytes and magnesium are warranted with chronic therapy.

Multiple-choice questions (answers are provided following the reference list)

1. In children and adults with hypertension, which of the following antihypertensive agents are considered appropriate for first-line pharmacologic therapy?
   a) ACE inhibitors
   b) ARBs
   c) Calcium channel blockers
   d) Thiazide diuretics
   e) All of the above

2. Which of the following thiazide diuretics is associated with a greater improvement in the 24-h blood pressure profile?
   a) Chlorthalidone
   b) Hydrochlorothiazide
   c) Chlorothiazide
   d) Metolazone

3. Loop diuretics (e.g., furosemide) may be useful when hypertension is associated with which of the following conditions?
   a) Essential hypertension
   b) Chronic kidney disease
   c) ENaC mutations
   d) Anuric patients on chronic hemodialysis

4. A documented allergy to sulfa-based antibiotics is a contraindication to the use of thiazide diuretics?
   a) True
   b) False

5. Which of the following is the proposed mechanism for the blood pressure-lowering effect associated with chronic thiazide therapy?
   a) A decrease in the ECF volume
   b) Decreased cardiac output
   c) A reduction in the RAAS activity
   d) Vasodilation

References

1. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC Jr, Svetkey LP, Taler SJ, Townsend RR, Wright JT Jr, Narva AS, Ortiz E (2014) 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 311:507–520
2. Flack JM, Sica DA, Bakris G, Brown AL, Ferdinand KC, Grimm RH Jr, Hall WD, Jones WE, Kountz DS, Lea JP, Nasser S, Nesbitt SD, Saunders E, Scisney-Matlock M, Jamerson KA, International Society on Hypertension in Blacks (2010) Management of high blood pressure in blacks: an update of the international society on hypertension in blacks consensus statement. Hypertension 56:780–800
3. Houle SK, Padwal R, Poirier L, Tsuyuki RT (2014) The 2014 Canadian hypertension education program (CHEP) guidelines for pharmacists: an update. Can Pharm J 147:203–208
4. Whitworth JA, World Health Organization, International Society of Hypertension Writing Group (2003) 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens 21:1983–1992
5. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Task Force for the Management of Arterial Hypertension of the European Society of Hypertension and the European Society of Cardiology (2014) 2013 ESH/ESC practice guidelines for the management of arterial hypertension. Blood Press 23:3–16
6. National Clinical Guideline Centre (2011) Hypertension: the clinical management of primary hypertension in adults: update of clinical guidelines 18 and 34. National Institute for Health and Clinical Excellence: Guidance, London
7. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (2002) 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 288:2981–2997
8. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute, National High Blood Pressure Education Program Coordinating Committee (2003) Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 42:1206–1252
9. Jones B, Nanra RS (1979) Double-blind trial of antihypertensive effect of chlorothiazide in severe renal failure. Lancet 2:1258–1260
10. Dussol B, Moussi-Frances J, Morange S, Somma-Delpero C, Mundler O, Berland Y (2012) A pilot study comparing furosemide and hydrochlorothiazide in patients with hypertension and stage 4 or 5 chronic kidney disease. J Clin Hypertens 14:32–37
11. Karadsheh F, Weir MR (2012) Thiazide and thiazide-like diuretics: an opportunity to reduce blood pressure in patients with advanced kidney disease. Curr Hypertens Rep 14:416–420
12. Agarwal R, Sinha AD (2012) Thiazide diuretics in advanced chronic kidney disease. J Am Soc Hypertens 6:299–308
13. Taber DJ, Srinivas TM, Pilch NA, Meadows HB, Fleming JN, McGillicuddy JW, Bratton CF, Thomas B, Chavin KD, Baliga PK, Egede LE (2013) Are thiazide diuretics safe and effective antihypertensive therapy in kidney transplant recipients? Am J Nephrol 38:285–291
14. Gradman AH, Basile JN, Carter BL, Bakris GL, American Society of Hypertension Writing Group (2011) Combination therapy in hypertension. J Clin Hypertens 13:146–154

15. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (2004) The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 114(2 Suppl 4th Report):555–576
16. Lurbe E, Cifkova R, Cruickshank JK, Dillon MJ, Ferreira I, Invitti C, Kuznetsova T, Laurent S, Mancia G, Morales-Olivas F, Rascher W, Redon J, Schaefer F, Seeman T, Stergiou G, Wuhl E, Zanchetti A, European Society of Hypertension (2009) Management of high blood pressure in children and adolescents: recommendations of the European Society of Hypertension. J Hypertens 27:1719–1742
17. Musini VM, Nazer M, Bassett K, Wright JM (2014) Blood pressure-lowering efficacy of monotherapy with thiazide diuretics for primary hypertension. Cochrane Database Syst Rev 5, CD003824
18. Carlsen JE, Kober L, Torp-Pedersen C, Johansen P (1990) Relation between dose of bendrofluazide, antihypertensive effect, and adverse biochemical effects. BMJ 300:975–978
19. Peterzan MA, Hardy R, Chaturvedi N, Hughes AD (2012) Meta-analysis of dose–response relationships for hydrochlorothiazide, chlorthalidone, and bendroflumethiazide on blood pressure, serum potassium, and urate. Hypertension 59:1104–1109
20. Reyes AJ (2002) Diuretics in the therapy of hypertension. J Hum Hypertens 16(Suppl 1):S78–S83
21. Sorof JM, Cargo P, Graepel J, Humphrey D, King E, Rolf C, Cunningham RJ (2002) Beta-blocker/thiazide combination for treatment of hypertensive children: a randomized double-blind, placebo-controlled trial. Pediatr Nephrol 17:345–350
22. Bachmann H (1984) Propranolol versus chlorthalidone–a prospective therapeutic trial in children with chronic hypertension. Helv Paediatr Acta 39:55–61
23. Berenson GS, Shear CL, Chiang YK, Webber LS, Voors AW (1990) Combined low-dose medication and primary intervention over a 30-month period for sustained high blood pressure in childhood. J Med Sci 299:79–86
24. Vasavada N, Agarwal R (2003) Role of excess volume in the pathophysiology of hypertension in chronic kidney disease. Kidney Int 64:1772–1779
25. Vasavada N, Saha C, Agarwal R (2003) A double-blind randomized crossover trial of two loop diuretics in chronic kidney disease. Kidney Int 64:632–640
26. Zaffanello M, Cataldi L, Franchini M, Fanos V (2010) Evidence-based treatment limitations prevent any therapeutic recommendation for acute poststreptococcal glomerulonephritis in children. Med Sci Monit 16:RA79–RA84
27. Tanphaichitr P (1977) Oral furosemide versus conventional therapy for acute poststreptococcal glomerulonephritis in children. J Med Assoc Thail 60:213–217
28. Musini VM, Rezapour P, Wright JM, Bassett K, Jauca CD (2012) Blood pressure lowering efficacy of loop diuretics for primary hypertension. Cochrane Database Syst Rev 8, CD003825
29. Weinberger MH, Roniker B, Krause SL, Weiss RJ (2002) Eplerenone, a selective aldosterone blocker, in mild-to-moderate hypertension. Am J Hypertens 15:709–716
30. Calhoun DA (2007) Low-dose aldosterone blockade as a new treatment paradigm for controlling resistant hypertension. J Clin Hypertens 9(1 Suppl 1):19–24
31. Chapman N, Dobson J, Wilson S, Dahlof B, Sever PS, Wedel H, Poulter NR, Anglo-Scandinavian Cardiac Outcomes Trial Investigators (2007) Effect of spironolactone on blood pressure in subjects with resistant hypertension. Hypertension 49:839–845
32. Lane DA, Shah S, Beevers DG (2007) Low-dose spironolactone in the management of resistant hypertension: a surveillance study. J Hypertens 25:891–894
33. Li JS, Flynn JT, Portman R, Davis I, Ogawa M, Shi H, Pressler ML (2010) The efficacy and safety of the novel aldosterone antagonist eplerenone in children with hypertension: a randomized, double-blind, dose–response study. J Pediatr 157:282–287
34. Tamargo J, Segura J, Ruilope LM (2014) Diuretics in the treatment of hypertension. Part 1: thiazide and thiazide-like diuretics. Expert Opin Pharmacother 15:527–547
35. Brater DC (2011) Update in diuretic therapy: clinical pharmacology. Semin Nephrol 31:483–494
36. Tamargo J, Segura J, Ruilope LM (2014) Diuretics in the treatment of hypertension. Part 2: loop diuretics and potassium-sparing agents. Expert Opin Pharmacother 15:605–621
37. Ernst ME, Carter BL, Goerdt CJ, Steffensmeier JJ, Phillips BB, Zimmerman MB, Bergus GR (2006) Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. Hypertension 47:352–358
38. Ernst ME, Neaton JD, Grimm RH Jr, Collins G, Thomas W, Soliman EZ, Prineas RJ, Multiple Risk Factor Intervention Trial Research Group (2011) Long-term effects of chlorthalidone versus hydrochlorothiazide on electrocardiographic left ventricular hypertrophy in the multiple risk factor intervention trial. Hypertension 58:1001–1007
39. Roush GC, Buddharaju V, Ernst ME (2013) Is chlorthalidone better than hydrochlorothiazide in reducing cardiovascular events in hypertensives? Curr Opin Cardiol 28:426–432
40. Roush GC, Holford TR, Guddati AK (2012) Chlorthalidone compared with hydrochlorothiazide in reducing cardiovascular events: systematic review and network meta-analyses. Hypertension 59:1110–1117
41. Duarte JD, Cooper-DeHoff RM (2010) Mechanisms for blood pressure lowering and metabolic effects of thiazide and thiazide-like diuretics. Expert Rev Cardiovasc Ther 8:793–802
42. Wilson IM, Freis ED (1959) Relationship between plasma and extracellular fluid volume depletion and the antihypertensive effect of chlorothiazide. Circulation 20:1028–1036
43. Tarazi RC, Dustan HP, Frohlich ED (1970) Long-term thiazide therapy in essential hypertension. Evidence for persistent alteration in plasma volume and renin activity. Circulation 41:709–717
44. van Brummelen P, Man In't Veld AJ, Schalekamp MA (1980) Hemodynamic changes during long-term thiazide treatment of essential hypertension in responders and nonresponders. Clin Pharmacol Ther 27:328–336
45. Cruz DN, Simon DB, Nelson-Williams C, Farhi A, Finberg K, Burleson L, Gill JR, Lifton RP (2001) Mutations in the Na-Cl cotransporter reduce blood pressure in humans. Hypertension 37:1458–1464
46. Hadchouel J, Delaloy C, Faure S, Achard JM, Jeunemaitre X (2006) Familial Hyperkalemic hypertension. J Am Soc Nephrol 17:208–217
47. Ji W, Foo JN, O'Roak BJ, Zhao H, Larson MG, Simon DB, Newton-Cheh C, State MW, Levy D, Lifton RP (2008) Rare independent mutations in renal salt handling genes contribute to blood pressure variation. Nat Genet 40:592–599
48. Turner ST, Schwartz GL, Chapman AB, Boerwinkle E (2005) WNK1 kinase polymorphism and blood pressure response to a thiazide diuretic. Hypertension 46:758–765
49. Kannel WB, Schwartz MJ, McNamara PM (1969) Blood pressure and risk of coronary heart disease: the Framingham study. Dis Chest 56:43–52
50. Wright JM, Musini VM (2009) First-line drugs for hypertension. Cochrane Database Syst Rev 3, CD001841
51. Cheng JW (2013) Azilsartan/chlorthalidone combination therapy for blood pressure control. Integr Blood Press Control 6:39–48
52. Multiple Risk Factor Intervention Trial Research Group (1982) Multiple risk factor intervention trial. Risk factor changes and mortality results. JAMA 248:1465–1477
53. Dorsch MP, Gillespie BW, Erickson SR, Bleske BE, Weder AB (2011) Chlorthalidone reduces cardiovascular events compared

with hydrochlorothiazide: a retrospective cohort analysis. Hypertension 57:689–694
54. Sarafidis PA, Georgianos PI, Lasaridis AN (2010) Diuretics in clinical practice. Part II: electrolyte and acid–base disorders complicating diuretic therapy. Expert Opin Drug Saf 9:259–273
55. van Blijderveen JC, Straus SM, Rodenburg EM, Zietse R, Stricker BH, Sturkenboom MC, Verhamme KM (2014) Risk of hyponatremia with diuretics: chlorthalidone versus hydrochlorothiazide. Am J Med 127:763–771
56. Siscovick DS, Raghunathan TE, Psaty BM, Koepsell TD, Wicklund KG, Lin X, Cobb L, Rautaharju PM, Copass MK, Wagner EH (1994) Diuretic therapy for hypertension and the risk of primary cardiac arrest. N Engl J Med 330:1852–1857
57. Sjogren A, Edvinsson L, Fallgren B (1989) Magnesium deficiency in coronary artery disease and cardiac arrhythmias. J Intern Med 226:213–222
58. Elliott WJ, Meyer PM (2007) Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. Lancet 369:201–207
59. Ueda S, Morimoto T, Ando S, Takishita S, Kawano Y, Shimamoto K, Ogihara T, Saruta T, Investigators DIME (2014) A randomised controlled trial for the evaluation of risk for type 2 diabetes in hypertensive patients receiving thiazide diuretics: diuretics in the management of essential hypertension (DIME) study. BMJ Open 4, e004576
60. Strom BL, Schinnar R, Apter AJ, Margolis DJ, Lautenbach E, Hennessy S, Bilker WB, Pettitt D (2003) Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. N Engl J Med 349:1628–1635

Answers to questions

1: e
2: a
3: b
4: b
5: d