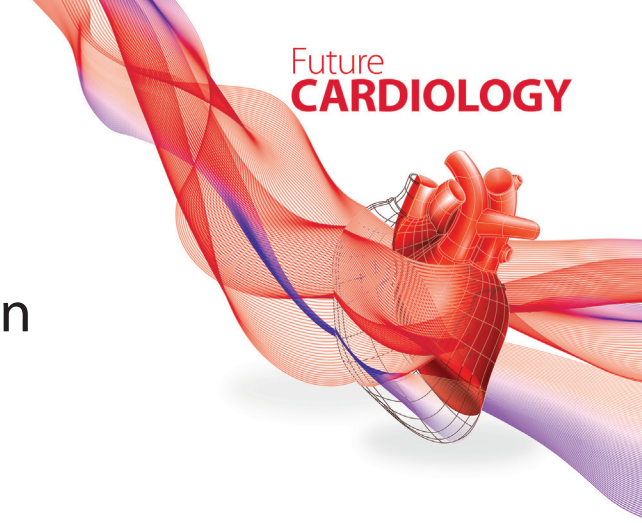
REVIEW

For reprint orders, please contact: reprints@futuremedicine.com

Future CARDIOLOGY



Evidence-based diuretics: focus on chlorthalidone and indapamide

James J DiNicolantonio*[1], Jaikrit Bhutani[2], Carl J Lavie[3,4] & James H O'Keefe[1]

ABSTRACT Thiazide and thiazide-like diuretics are cornerstone treatments for hypertension. However, unlike chlorthalidone (CTD) and indapamide (IDP), hydrochlorothiazide (HCTZ) lacks evidence for reducing morbidity and mortality as monotherapy compared with placebo or control. Despite this fact, HCTZ is prescribed much more frequently than CTD or IDP. We believe that all hypertension guidelines should follow the National Institute for Health and Excellence (NICE) and make IDP and CTD first choice 'thiazide-like diuretics.' This article will focus on the available evidence pertaining to HCTZ versus CTD and IDP. We will review the pharmacological differences between these three diuretics, as well as the clinical trial data and important side effects.

KEYWORDS
• chlorthalidone
• hydrochlorothiazide
• hypertension
• indapamide • thiazide

Hypertension (HTN) is a common problem encountered at the primary care level, and can lead to numerous complications if not managed appropriately and adequately [1]. Thiazide and thiazide-like diuretics have a long history of being used as first-line medications in the treatment of HTN [2]. The recent Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure-8 (JNC-8) guidelines have given the clinician multiple options for first-line treatment of HTN, such as diuretics, angiotensin-converting enzyme inhibitors Inhibitors (ACE-I), angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs); however, β-blockers are no longer recommended as a first-line treatment [3].

Hydrochlorothiazide (HCTZ), though widely prescribed, lacks evidence for reducing morbidity and mortality compared with placebo or control [4]. However, a broad amount of data exists for chlorthalidone (CTD) and indapamide (IDP) for reducing morbidity and mortality versus placebo [4]. Despite this fact, both JNC-8 and the Canadian Hypertension Education Programme (CHEP) guidelines have not given preference to either CTD or IDP over HCTZ [5]. However, recommendations from the 2011 NICE HTN guidelines have bridged this unfortunate gap **(Box 1)** [6]. Arguments for these recommendations can be made based on the pharmacological differences between the structures of CTD and IDP, which are strikingly different from that of HCTZ, as they lack the classic thiazide benzothiadiazine dioxide rings [4]. Thus, the phrase 'thiazide-like diuretics' in itself is inappropriate.

History of diuretics

Thiazides and thiazide-like diuretics have been a cornerstone in HTN treatment for more than half a century. In the early 1950s, mercurial poisoning was reported to cause diuresis. Later intramuscular injections of mercury were employed to treat patients with decompensated heart failure (HF) [7]. Novello and Sprague later synthesized chlorothiazide, which proved to be beneficial in the treatment

[1]Mid America Heart Institute at Saint Luke's Hospital, Kansas City, MO, USA
[2]Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India
[3]John Ochsner Heart & Vascular Institute, Ochsner Clinical School, The University of Queensland School of Medicine, New Orleans, LA, USA
[4]Pennington Biomedical Research Center, Baton Rouge, LA, USA
*Author for correspondence: jjdinicol@gmail.com

Future Medicine part of fsg

Box 1. Summary of guideline recommendations in hypertension pertaining to thiazide and 'thiazide-like' diuretics.

JNC-8 recommendation

- In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, CCB, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker

CHEP 2013 recommendation

- Initial therapy should be monotherapy with a thiazide/thiazide-like, a β-blocker (in patients younger than 60 years of age), an angiotensin-converting enzyme inhibitor (in nonblack patients) and a long-acting CCB or an angiotensin receptor blocker

NICE 2011 recommendation

- Step 1 antihypertensive treatment to be done with a CCB to people aged over 55 years and to black people of African or Caribbean family origin of any age. If a CCB is not suitable (edema/intolerance/heart failure), use a thiazide-like diuretic such as chlorthalidone (12.5–25.0 mg once daily) or indapamide (1.5 mg modified-release or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide

CCB: Calcium-channel blocker.

of HTN [8,9]. It was subsequently used as an adjunctive therapy [10], and is now recommended as a monotherapy.

Pharmacologic properties

Thiazide and thiazide-like diuretics reach their site of action after secretion by the organic acid transporter, and inhibit the electroneutral Na^+Cl^- co-transporter (NCCT) located on the apical membrane of the distal convoluted tubules [11]. They compete for the chloride site on the transporter. By inhibiting the amiloride-sensitive epithelial Na^+ channels they cause natriuresis, and thus cause concomitant loss of water. By inhibiting the capacity of the kidney to alter free water clearance, this can predispose to hyponatremia. Also, these agents promote excretion of K^+, H^+ and Mg^{2+} leading to metabolic hypokalemic alkalosis. Thiazide diuretics are also known to cause hyperuricemia and hypercalcemia, the latter caused by a decrease in urinary calcium excretion. This effect is probably caused by the stimulation of Na^+/Ca^{2+} to transport more calcium in the interstitium, reducing the intracellular Ca^{2+} concentration, and finally increasing the gradient of Ca^{2+} reabsorption (via TRPV5 Ca^{2+} selective channels) [12]. This long-term effect on calcium homeostasis increases bone mineral density and significantly decreases age-related bone loss and risk of hip fractures in the elderly [13].

CTD and IDP have a longer half-life and duration of action as compared with HCTZ. Indeed, CTD is twice as potent in reducing 24-h ambulatory blood pressure (BP) compared with HCTZ [14]. Even twice daily dosing of HCTZ, to compensate for its short duration of action, has not been shown to improve BP control [15]. Although IDP is equally potent at lowering BP compared with HCTZ, its doses are almost a-tenth that of HCTZ. This may be due to its ability to block L-type calcium channels [16]. Also CTD and IDP cause direct arterial vasodilatation, which is responsible for their anti-hypertensive effect, whereas HCTZ mainly lowers BP through natriuresis [4,17].

Despite similar reductions in BP, IDP has been shown to preserve renal function to a greater extent compared with HCTZ, and has also been shown to significantly reduce left ventricular (LV) mass index [18–20]. Similarly, CTD significantly reduces LV hypertrophy (LVH) compared with HCTZ [21]. Apart from the additional BP reduction in clinics using CTD as compared with HCTZ (-10.4 vs -8.6 mmHg, $p = 0.001$, for clinic difference in systolic BP and -6.5 vs -5.1 mmHg, $p < 0.001$, for clinic difference in diastolic BP), CTD also was shown to reduce transforming growth factor β1 and β3 [4]. This in turn prevents collagen deposition and thus slows down target organ damage. Lastly, CTD also aids angiogenesis, decreases platelet aggregation and vascular permeability. These functions may be attributed to a decrease in carbonic anhydrase pathways, catecholamine-medicated platelet aggregation and *VEGF-C* gene downregulation caused by CTD [22]. The above features have been summarized in **Table 1**.

Adverse effects

The adverse effects caused by thiazide and thiazide-like diuretics are well known but yet less researched. Predominantly, these include

hyponatremia, hypokalemia, hyperuricemia, hyperlipidemia and new onset diabetes mellitus (DM). Each of these will be discussed separately. Other side effects include modest hypercalcemia, erectile dysfunction and impotence [24]. Beyond this, the effects of these drugs in regards to complications of HTN will also be discussed.

• Hyponatremia

Hyponatremia is a well-recognized complication of thiazide therapy, occurring anywhere from 7–21% in unselected patients [25]. Hyponatremia is reported to increase both the cost of treatment and mortality [26–29]. An estimated 60% higher overall relative risk (RR) of hyponatremia exists in patients on thiazides than those on alternative anti-HTN therapies. Thiazide-induced hyponatremia can manifest within 3 months to 10 years from initiating therapy [30]. Additionally, mild persistent chronic hyponatremia may cause poor attention span, posture and gait disturbances, which can lead to falls and increases in the risk of bone fractures [31,32].

Although no randomized trial has directly compared the frequency of hyponatremia with CTD versus HCTZ, a recent analysis indicated that patients on CTD were more likely to be hospitalized with hyponatremia compared with those on HCTZ (adjusted hazard ratio: 1.68 [CI: 1.24–2.28]) **(Figure 1)** [33]. However, patients prescribed CTD are likely to be at a greater baseline risk for adverse events. Indeed, CTD is generally used in cases of resistant HTN, which may predispose to side effects. Thus, conclusions from this observational analysis should be interpreted with caution. Additionally, the mean dose on CTD (18.3 mg) would be considered more potent than the mean dose of HCTZ (27.3 mg), which confounds the results.

A case report showed that after 5–6 weeks of taking IDP (immediate release 2.5 mg), severe hyponatremia (plasma sodium concentrations of 103–104 mmol/l) occurred; however, only two patients were involved, both of which were elderly women (aged 60 to 62) [34]. Another study was designed to evaluate patient demographics related to IDP-induced hyponatremia. All patients experiencing hyponatremia were female, elderly (mean age of 81.7 years) with a mean weight of 59 kg (129.8 lbs) [35]. Additionally, all electrolyte abnormalities were corrected without life-threatening complications. Thus, it can be concluded that certain patient demographics predispose to an increased risk of diuretic-induced hyponatremia (e.g., female, elderly and low weight). In another study, which evaluated electrolyte abnormalities caused by IDP therapy (2.5 mg IDP daily), only 84 reports of hyponatremia and 87 reports of hypokalemia were recorded over a 16 year time-frame. Thus, hyponatremia/hypokalemia seem to be quite rare in those prescribed indapamide [36]. While it is still important to monitor for hyponatremia, especially in an elderly female with low body weight, particularly during the first few months of therapy and periodically throughout prolonged use, the incidence is not high.

• Hypokalemia

Hypokalemia is a serious complication of thiazide diuretics, which is associated with an increased risk of ventricular arrhythmias and cardiac arrest [37,38]. Thiazide diuretics are well

Table 1. Comparison of pharmacologic properties of hydrochlorothiazide, chlorthalidone and indapamide.

Variable	HCTZ	CTD	IDP	Remarks
Half life (h)	3–10	24–55	6–15	CTD and IDP have half-lives approximately three-times and two-times greater as compared with HCTZ, respectively
Duration of action (h)	12–18	24–72	24–36	CTD and IDP have a duration of action that is approximately twice that as compared with HCTZ
Usual dosage (mg)	12.5–50	12.5–25	1.25–2.5	IDP is used at one-tenth the dose of HCTZ to produce a similar antihypertensive effect
Antihypertensive effect	Weak	Strong	Intermediate	CTD is twice as potent as HCTZ. While IDP and HCTZ have shown similar antihypertensive efficacy in a direct comparison trial. Trials using add-on indapamide SR have shown large reductions in blood pressure
Pleiotropic effects	No	Yes	Yes	CTD and IDP are renoprotective, block carbonic anhydrase isoenzymes, promote angiogenesis, and decrease vascular permeability and platelet aggregation. This has not been shown with HCTZ

†Data taken from [1–2,4,23].
CTD: Chlorthalidone; HCTZ: Hydrochlorothiazide; IDP: Indapamide; SR: Sustained release.

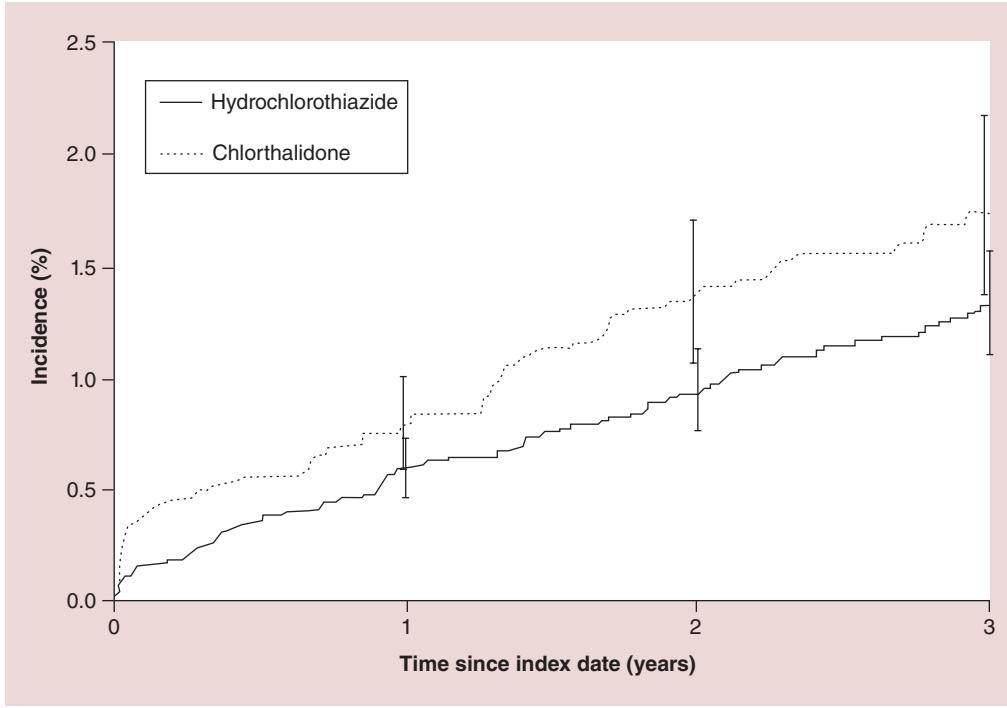


Figure 1. Incidence of hyponatremia: chlorthalidone vs hydrochlorothiazide.
Reproduced with permission from [33].

known to decrease plasma potassium levels, in general, by approximately 0.2–0.4 mmol/l [39]. Importantly, overall mortality has been shown be higher in HTN subjects with hypokalemia (Cox hazard ratio: 1.21 [95% CI: 1.02–1.44]) [40]. A meta-analysis revealed that hypokalemia is highly dose-dependent, with both HCTZ and CTD (r^2 = 0.519 and r^2 = 0.135, respectively; $p < 0.001$ for both drugs separately). This analysis also demonstrated that there were no significant differences in the incidence of hypokalemia when HCTZ was compared with CTD [41]. A study comparing IDP 2.5 mg daily and HCTZ 50 mg daily reported a significantly higher incidence of hypokalemia with HCTZ versus IDP (63 vs 9%, respectively; $p < 0.001$) with an average plasma potassium decline of 0.9 and 0.46 mEq/l and, respectively [42]. Lastly, two randomized double-blind controlled studies confirmed that IDP 1.5 mg sustained release (SR) has a lower risk of hypokalemia compared with IDP 2.5 mg immediate release (IR), where the number of patients with a serum potassium level less than 3.4 mmol/l was reduced by more than 50% with the SR formulation [43].

• Hyperuricemia

Thiazide diuretics compete with uric acid for renal tubular secretion, and have been found to increase serum urate concentrations by 35%, which can precipitate acute gout attacks, especially in patients with a previous history of gout [44]. In a retrospective cohort analysis, CTD was shown to result in significantly higher uric acid level compared with HCTZ ($p < 0.0001$) [45]. Additionally, The Systolic Hypertension in the Elderly Program (SHEP) study demonstrated that patients with coexisting elevated serum uric acid (>1 mg/dl) had lost cardiovascular (CV) benefit of CTD therapy (hazard ratio: 0.95 [95% CI: 0.67–1.39] and 0.56 [95% CI: 0.37–0.85]) for patients with and without serum uric acid >1 mg/dl, respectively) [46]. However, IDP has been shown to cause only modest increases in uric acid levels as compared with HCTZ [47]. While two studies have shown that IDP may increase serum urate concentrations; one of these did not report a statistically significant change, whereas the other reported a significant increase ($p < 0.005$ vs placebo) [48,49].

• Hyperlipidemia & new onset diabetes

Thiazide diuretics notoriously increase DM, total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglycerides. They also decrease the levels of high-density lipoprotein cholesterol (HDL-C); these effects are dose-dependent [50]. Thus, monitoring the lipid

profile may be required during thiazide diuretic therapy. The mechanism of increasing development of DM appears to be linked to insulin resistance and impaired glucose tolerance promoted by these agents, which may further complicate HTN [51]. This risk increases further when a thiazide diuretic is combined with a first-generation β-blocker; however, this does not seem to be the case with concomitant nebivolol and carvedilol [52]. The associated hypokalemia with thiazides is also known to worsen glucose intolerance [53]. These adverse effects of thiazides are known to disappear with long-term therapy [54,55]. In the Multiple Risk Factor Intervention Trial (MRFIT), CTD has been shown to cause less increases in total cholesterol (overall $p < 0.0001$) and LDL-C (overall $p = 0.0009$) as compared with HCTZ [45]. CTD has not been compared specifically for its effects on glucose tolerance with HCTZ; however, in the SHEP trial, CTD increased new onset diabetes as opposed to placebo [56]. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial showed a significantly higher incidence of DM with CTD versus lisinopril in patients with existing metabolic syndrome, and a significantly higher incidence of DM compared with lisinopril and amlodipine in those without metabolic syndrome [57]. IDP may have a more neutral effect on lipids compared with HCTZ. In one study, the increase in total cholesterol with IDP was significantly less versus HCTZ (1.4 vs 6.3% increase from the baseline, respectively, $p < 0.01$), whereas there was no significant difference between HDL-C levels [58]. Natrilix SR versus **E**nalapril **S**tudy in hypertensive Type 2 diabetics with MicrOalbuminuRia (NESTOR) also demonstrated that IDP has a neutral effect on lipids and glucose levels in patients with Type 2 DM (T2DM) [59]. Thus, IDP may be considered a metabolically neutral diuretic, both during short- and long-term administration [60].

• Complications of HTN

A systematic review of randomized controlled trials with two different types of network analyses demonstrated that CTD causes a significant 23% reduction in risk of HF as compared with HCTZ (95% CI: 2–39; $p = 0.032$) [61]. Additionally, CV events were also significantly reduced by 21% with CTD versus HCTZ, (95% CI: 12–28; $p = 0.0001$). This benefit may be due to longer duration of action and pleiotropic effects of CTD as opposed to HCTZ. A retrospective cohort analysis indicated significantly fewer CV events in patients on CTD (adjusted hazard ratio: 0.51 [95% CI: 0.43–0.61]; $p < 0.0001$) and on HCTZ (adjusted hazard ratio: 0.65 [95% CI: 0.55–0.75]; $p < 0.0001$) than patients who took no medication **(Figure 2)**. However, a limitation of these data is that patients who cannot tolerate anti-HTN medication are known to have a higher risk of CV events versus those individuals who can tolerate anti-HTN therapy. Even so, CTD was shown to have fewer CV events as compared with HCTZ ($p < 0.0016$) [45]. In the SHEP trial, low dose CTD-based therapy (12.5 mg) compared with placebo reduced the incidence of total stroke (36% reduction, RR: 0.63; 95% CI: 0.49–0.82), nonfatal myocardial infarction (MI; 27% reduction, RR: 0.73; 95% CI: 0.57–0.94), and overall CV disease (32% reduction, RR: 0.68; 95% CI: 0.58–0.79) [62]. Similarly, in the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) trial, fixed combination of perindopril plus indapamide significantly reduced the risk of total mortality (14%; $p = 0.03$), CV mortality (18%; $p = 0.027$), coronary heart disease (CHD) events (14%; $p = 0.02$) and renal events (worsening nephropathy or new microalbuminuria, 21%; $p < 0.01$) [63]. Additionally, this combination therapy leads to regression of existing albuminuria [64]. Thus, IDP may have inherent reno-protective effects, which has not been shown with HCTZ. Additionally, Perindopril pROtection aGainst Recurrent Stroke Study (PROGRESS) demonstrated that IDP (fixed drug combination with perindopril) also decreased the RR of stroke by 28% (95% CI: 17–38; $p < 0.0001$) [65]. The HYpertension in the Very Elderly Trial (HYVET) trial also demonstrated that the combination of IDP and perindopril reduced the rate of fatal or nonfatal stroke by 30% (95% CI: -1–51; $p = 0.06$), the rate of death from stroke by 39% (95% CI: 1–62; $p = 0.05$), the rate of death from any cause by 21% (95% CI: 4–35; $p = 0.02$), the rate of death from CV causes by 23% (95% CI: -1–40; $p = 0.06$) and the rate of HF by 64% (95% CI: 42–78; $p < 0.001$) [66]. Echoing this benefit, the Post Stroke Antihypertensive Treatment trial (PATS) showed a 29% reduction in fatal and nonfatal stroke ($p = 0.0009$) with IDP IR 2.5 mg monotherapy [67].

Clinical data

• Hydrochlorothiazide

HCTZ is the most widely prescribed diuretic but recently its use as a first choice anti-HTN has been under considerable debate [4,68–69]. When used as a monotherapy, HCTZ is less efficacious at reducing BP [70]. Indeed, only 45% of HTN subjects respond to HCTZ at a dose of 12.5 mg, whereas an additional 20% respond at 25 mg and almost 90% at 50 mg. A randomized controlled trial demonstrated that most anti-HTN agents cause a significant BP reduction compared with low-to-moderate dose HCTZ (12.5 to 25 mg); however, they were not superior to 50 mg HCTZ [69]. Despite this fact, higher doses of thiazide diuretics are associated with a greater risk of hyperuricemia, hyponatremia, hypokalemia and worsening of blood glucose and lipids.

In the Second Australian Blood Pressure Study (ANBP2), the group assigned to an ACE-I had a reduced rate of nonfatal CV events and MI, which was not shown with HCTZ [71], and in the ACCOMPLISH trial (Avoiding Cardiovascular Events in Combination Therapy in Patients Living With Systolic Hypertension), ACE-I/amlodipine decreased the combined end point of CV mortality, stroke and MI by 20% as compared with ACE/HCTZ [72]. In the Oslo Mild Hypertension trial, although HCTZ reduced BP by 17/10 mmHg, patients on HCTZ had a significantly higher CV mortality after a 10-year follow-up versus the untreated group (14 vs 3%, $p < 0.01$) [73]. In summary, the ANBP2, ACCOMPLISH and Oslo Mild Hypertension Trial indicated that HCTZ is inferior to an ACE-I, amlodipine and placebo [4]. This is in stark contrast to CTD, which was found to be superior to an ACE-I, as well as amlodipine and placebo on multiple secondary end points [4]. The Australian Mild Hypertension trial found that chlorothiazide decreased mortality versus placebo, which is also in direct contrast to what occurred in the Oslo trial (where HCTZ increased CV mortality compared with placebo) [73,74].

In Veterans Administration (VA) Cooperative trials, high dose (100 mg/day) of HCTZ was used in patients with diastolic BP between 115 and 120 mmHg. HCTZ caused an impressively large reduction in BP (43/30 mmHg in 1967 trial, and 27/17 mmHg in 1970 trial). In the 1970 VA trial, HCTZ 50 mg twice daily with reserpine was shown to reduce risk of morbidity by 37% over a 5-year period [75,76]. However, this benefit was driven by a reduction in malignant HTN, a complication that is rarely found in current-day practice. Additionally, reserpine is no longer used in clinical practice, making the results of the VA trials completely outdated. Lastly, no benefit was found with the use of HCTZ unless the baseline diastolic BP was ≥105 mmHg, indicating a lack of generalizability to most current-day HTN agents [4].

The European Working Party on High Blood Pressure in the Elderly (EWPHE) trial showed that a combination therapy of 25/50 mg HCTZ and 50/100 mg triamterene caused a 27% reduction in CV mortality when compared with placebo; however all-cause deaths were similar [77]. For every 1000 patients, there were 29 fewer CV events, 14 fewer CV deaths and 11 fewer strokes in the active arm versus placebo. This equated to having to treat 23, 71 and 91 patients for 1 year to prevent one CV event, one CV death and one stroke, respectively. The significant benefit seen in this trial was attributed to approximately 30% of patients having a systolic BP of 160 mmHg or higher at baseline. Thus, while there is some evidence for using the combination HCTZ/triamterene, this would only be generalizable to a stage 2 HTN patient [78].

Comparing HCTZ to other anti-HTN classes such as β-blockers and CCBs, The HAPPHY trial (Heart Attack Primary Prevention in Hypertension) showed that patients assigned to HCTZ (50 mg daily) had a greater risk of fatal strokes (OR: 3.36 [0.96–9.53]) as compared with metoprolol [79]. Additionally, a substudy from The International as a Goal in Hypertension Treatment (INSIGHT) trial reported a 5% rate of renal insufficiency with HCTZ-amiloride compared with only 2% with nifedipine [80]. Moreover, there was a significantly greater decline in estimated glomerular filtration rate in patients on HCTZ/amiloride versus nifedipine therapy [80]. This trial also showed that nifedipine significantly prevented the carotid intima media thickening change, progression and cross-sectional area compared with HCTZ-amiloride ($p = 0.001$, $p = 0.002$ and $p = 0.006$, respectively) [81].

• Chlorthalidone

CTD, the 'long lost diuretic,' is being re-explored, and increased awareness of its broad evidence-base for improving prognosis in HTN is resurfacing. In 1979, the Hypertension Detection and Follow-Up Study (HDFP) showed that utilizing

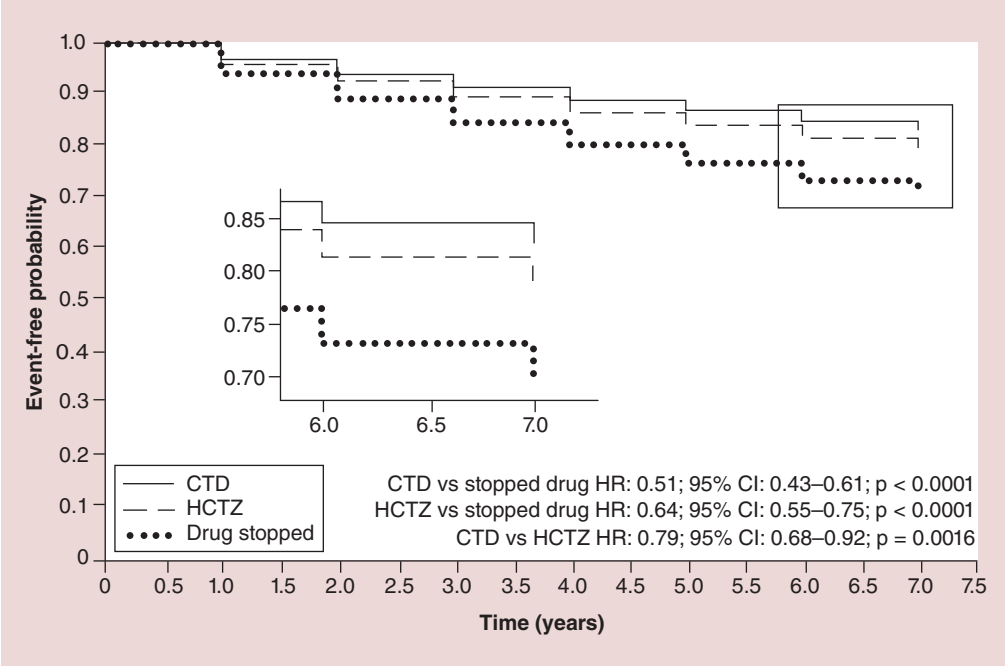


Figure 2. Risk of cardiovascular events: chlorthalidone vs hydrochlorothiazide vs no therapy.
CTD: Chlorthalidone; HCTZ: Hydrochlorothiazide.
Reproduced with permission from [45].

25–100 mg of CTD daily as initial HTN therapy leads to a reduction in all-cause mortality as compared with placebo [82]. In 1990, the MRFIT randomized individuals to HTN therapy with certain clinics utilizing HCTZ whereas other clinics utilized CTD. Compared with HCTZ, CTD was associated with significantly fewer nonfatal CV events, including MIs, compared with HCTZ [8–22,24–84]. Additionally, in the 9 HCTZ clinics that switched to CTD, there was a significant 28% reduction in CHD mortality ($p < 0.04$) [4]. Later in 1992, the Systolic Hypertension in The Elderly Program (SHEP) concluded that 12.5–25 mg CTD daily causes a 36% risk reduction in stroke (primary end point, $p = 0.0003$) versus placebo. Compared with placebo, CTD also resulted in a 27% reduction in the combined end point of clinical nonfatal MI plus CHD death, a 32% reduction in major CV events and a 13% reduction in all-cause mortality [62]. The Treatment of Mild Hypertension Study (TOMHS) labeled CTD equally efficacious as acebutolol, doxazosin, amlodipine and enalapril in regards to regression of LVH, blood lipid levels and other outcome measures [85]. The Verapamil in Hypertension and Atherosclerosis Study (VHAS) showed a significantly greater incidence of a combined end point of fatal and nonfatal, as well as major and minor, CV events in patients randomized to CTD versus verapamil ($p < 0.01$) [86]. The benefit, in regards to a reduction in CV events, was mainly driven by transient ischemic attacks and angina. However, compared with verapamil, CTD was less effective at promoting regression of thicker carotid lesions [86]. Whether this result would be considered clinically relevant is uncertain. In 2002, the ALLHAT trial showed that there was no difference in the primary outcome of combined fatal CHD or nonfatal MI for amlodipine versus CTD; however, there was a higher 6-year rate of HF with amlodipine (10.2 vs 7.7%; RR: 1.38; 95% CI: 1.25–1.52). Compared with CTD, those on lisinopril had a higher 6-year rate of combined CV disease (33.3 vs 30.9%; RR: 1.10; 95% CI: 1.05–1.16); stroke (6.3 vs 5.6%; RR: 1.15; 95% CI: 1.02–1.30) and HF (8.7 vs 7.7%; RR: 1.19; 95% CI: 1.07–1.31) [87].

• Indapamide

IDP SR 1.5 mg is equally efficacious as HCTZ 25 mg or amlodipine 5 mg in reducing BP [20], more efficacious than enalapril 20 mg in reducing LVH [88], and equal to enalapril in reducing microalbuminuria in HTN patients with Type 2 DM [59]. A meta-analysis comparing Indapamide

Table 2. Summary of clinical trials: hydrochlorothiazide, chlorthalidone and indapamide.

Trial name	n	Comparator	Agent/dose	Results/comments	Ref.
HCTZ					
ANBP2	6083	Active (enalapril)	HCTZ	11% reduction in nonfatal CV events and MI with enalapril	[71]
ACCOMPLISH	11506	Active (amlodipine)	HCTZ 12.5 to 25 mg daily as fixed dose combination with benazepril	Benazepril/amlodipine lead to a 20% reduction in CV mortality, stroke and MI vs benazepril/HCTZ	[72]
Oslo Mild Hypertension Trial	785	Placebo	HCTZ 50 mg daily	Five-fold increase in cardiovascular mortality with HCTZ vs placebo (14 vs 3%, respectively; $p < 0.01$)	[73]
Australian Mild Hypertension Trial	3427	Placebo	Chlorthiazide 500 mg twice daily	Chlorothiazide significantly reduced mortality vs placebo	[74]
VA Cooperative Trials (1967 and 1970)		Placebo	High dose HCTZ (100 mg/day)	Massive BP reduction with HCTZ and 37% reduction in mortality over a 5-year period	[75,76]
The European Working Party on High Blood Pressure in the Elderly (EWPHE)	840	Placebo	HCTZ 25/50 mg with Triamterene 50/100 mg daily	Similar outcome on all-cause deaths; however, there was a 27% reduction in CV mortality	[77,78]
HAPPHY	7569	Active (Metoprolol)	HCTZ 50 mg daily	More fatal strokes with HCTZ (OR: 3.36 [95% CI: 0.96–9.53])	[79]
INSIGHT substudy	6321	Active (Nifedipine)	HCTZ-Amiloride	HCTZ-amiloride had a greater rate of renal insufficiency (5 vs 2%) and less benefit on CIMT change, progression and CSA ($p = 0.001$, $p = 0.002$ and $p = 0.006$, respectively) vs nifedipine	[80]
CTD					
HDFP	10940	Placebo	CTD 25–100 mg daily	All cause deaths 17–20% less in the CTD therapy group	[82]
MRFIT	12866	Usual care	HCTZ 50–100 mg or CTD 50–100 mg daily	CTD caused 28% risk reduction in CV mortality when HCTZ clinical were switched to CTD ($p < 0.04$). CTD was associated with significantly less nonfatal CV events, clinical MI and MI determined by annual ECG ($p = 0.0016$, $p = 0.0001$ and $p = 0.0103$, respectively)	[45,83,84]
SHEP	4736	Placebo	CTD 12.5–25 mg daily	36% reduction in stroke (primary end point, $p = 0.0003$), 27% reduction in the combined end point of clinical nonfatal MI plus coronary death and 32% reduction in major CV events with CTD vs placebo	[62]
TOMHS	902	Active (placebo, acebutolol, doxazosin, amlodipine, enalapril)	CTD 15–30 mg daily	CTD and all drugs had similar efficacy and were slightly better than placebo	[85]
Verapamil in Hypertension and Atherosclerosis Study	498	Active (verapamil)	CTD 25 mg daily	More transient ischemic attacks and angina as well as less effect on carotid atherosclerosis with CTD vs verapamil. However, there were less strokes with CTD vs verapamil	[86]

ARB: Angiotensin receptor blocker; BP: Blood pressure; CIMT: Carotid intima media thickness; CSA: Cross-sectional area; CTD: Chlorthalidone; CV: Cardiovascular; HCTZ: Hydrochlorothiazide; IDP: Indapamide; IR: Immediate release; LV: Left ventricular; MI: Myocardial infarction; OR: Odds ratio; PER: Perindopril; RR: Relative risk; SR: Sustained release.

Table 2. Summary of clinical trials: hydrochlorothiazide, chlorthalidone and indapamide (cont.).

Trial name	n	Comparator	Agent/dose	Results/comments	Ref.
CTD (cont.)					
ALLHAT	33357	Active (lisinopril, amlodipine)	CTD 12.5–25 mg daily	Higher 6-year rate of HF with amlodipine (10.2 vs 7.7%; RR: 1.38; 95% CI: 1.25–1.52), higher 6-year rate of combined CVD (33.3 vs 30.9%; RR: 1.10; 95% CI: 1.05–1.16); stroke (6.3 vs 5.6%; RR: 1.15; 95% CI: 1.02–1.30) and HF (8.7 vs 7.7%; RR: 1.19; 95% CI: 1.07–1.31) with lisinopril	[87]
IDP					
ADVANCE	11140	Placebo	PER/IDP 4/1.25 mg daily fixed drug combination	Reduced risk of death by cardiovascular disease lower risk of macro/microvascular events (18% reduction; $p = 0.03$ and 9% reduction; $p = 0.04$; respectively), reduced risk of macro and micro albuminuria (31%, $p = 0.0027$ and 21%; $p < 0.0001$, respectively) and regression of existing albuminuria	[63]
PROGRESS	6105	Placebo	PER/IDP combination	Decreased risk of stroke by 28% with PER/IDP combination (95% CI: 17–38, $p < 0.0001$)	[65]
HYVET	3845	Placebo	IDP SR 1.5 mg as initial therapy, PER/IDP combination	IDP monotherapy lowered mean blood pressure by 15.0/6.1 mmHg. PER/IDP combination caused a 30% reduction in the rate of fatal or nonfatal stroke (95% CI: -1–51; $p = 0.06$), 39% reduction in the rate of death from stroke (95% CI: 1–62; $p = 0.05$), 21% reduction in the rate of death from any cause (95% CI: 4–35; $p = 0.02$), 23% reduction in the rate of death from cardiovascular causes (95% CI: -1–40; $p = 0.06$) and a 64% reduction in the rate of heart failure (95% CI: 42–78; $p < 0.001$)	[66]
PATS	5665	Placebo	IDP 2.5 mg IR daily	Reduction in fatal and nonfatal stroke ($p = 0.0009$) with IDP	[67]
X-CELLENT	1758	Placebo	IDP SR 1.5 mg or candesartan 8 mg or amlodipine 5 mg daily	All of equal antihypertensive efficacy; however, IDP and amlodipine were more effective at decreasing blood pressure variability	[90]
NATIVE	1941	Placebo	IDP SR 1.5 mg daily as add-on therapy with ACE-I, β-blocker, calcium channel antagonist, or ARB	Significant reduction in average blood pressure (166/102 ± 16/9 mmHg to 132/83 ± 9/6 mmHg; $p < 0.0001$)	[91]
REASON	457	Atenolol 50 mg daily	PER/IDP 2/0.625 mg fixed drug combination	PER/IDP combination superior in decreasing pulse wave velocity, central BP and LV mass index	[94–96]
PICXEL	556	Enalapril	PER/IDP 2/0.625 mg fixed drug combination	PER/IDP combination superior in decreasing LV mass index	[95]
LIVE	411	Enalapril 20 mg	IDP SR 1.5 mg daily	IDP SR noninferior to enalapril in effect on LV mass index	[88]
NESTOR	569	Enalapril 10 mg	IDP SR 1.5 mg daily	IDP SR noninferior to enalapril in effect on microalbuminuria	[97]
PREMIER	457	Enalapril	PER/IDP 2/0.625 mg fixed drug combination	PER/IDP combination superior to enalapril in effect on albuminuria	[23]

ARB: Angiotensin receptor blocker; BP: Blood pressure; CIMT: Carotid intima media thickness; CSA: Cross-sectional area; CTD: Chlorthalidone; CV: Cardiovascular; HCTZ: Hydrochlorothiazide; IDP: Indapamide; IR: Immediate release; LV: Left ventricular; MI: Myocardial infarction; OR: Odds ratio; PER: Perindopril; RR: Relative risk; SR: Sustained release.

SR 1.5 mg to other anti-HTN monotherapies demonstrated IDP to be the most effective at lowering systolic BP (-22.2 mmHg); however, diastolic BP was lowered to similar degrees (-11.7 mmHg) by each category of drug [89]. Further the NatriliX SR versus CandEsartan and amLodipine in the reduction of systo**L**ic blood pr**E**ssure in hyperteNsivepatienTs study (X-CELLENT study) showed IDP SR 1.5 mg, candesartan 8 mg and amlodipine 5 mg to be of equal efficacy in lowering BP, whereas IDP and amlodipine significantly decreased BP variability [90]. The NATrilix SR use in combInation antihypertensiVE therapy study (NATIVE study) demonstrated that indapamide SR 1.5 mg when given on top of anti-HTN therapy with either an ACE-I, β-blocker, ARB or a CCB, caused a significant reduction in average BP (166/102 ± 16/9 mmHg to 132/83 ± 9/6 mmHg, $p < 0.0001$) [91]. Another meta-analysis conducted with five placebo-controlled trials using a fixed dose combination of IDP 0.625 mg and perindopril 2 mg demonstrated that this fixed drug combination reduced BP more than placebo (mean difference of 9.0/5.1 mmHg, $p < 0.01$) [92]. A study by Ghiadoni *et al.* concluded that perindopril/IDP 2/0.625 mg combination was superior to atenolol 50 mg in improving endothelium-dependent vasodilation [93]. Similarly the PREterax in Regression of Arterial Stiffness in a ContrOlled Double – BliNd (REASON) trial found a perindopril/IDP combination to be superior to atenolol in altering pulse wave velocity and central BP [94]. Comparing the perindopril/IDP combination versus enalapril and atenolol, the perindopril/IDP in a double blind Controlled study versus Enalapril in Left ventricular hypertrophy (PICXEL) and REASON trials, respectively, showed that the combination of perindopril/IDP was better in reducing LVH index [95,96]. The Left ventricular hypertrophy regression: Indapamide versus enalapril (LIVE) trial compared the effects of IND SR 1.5 mg on LVH with enalapril 20 mg. IDP SR 1.5 mg was significantly more effective than enalapril 20 mg at reducing LV mass index in HTN patients with LVH [88]. Lastly, the Natrilix SR versus EnalaprilStudy in hypertensive Type 2 diabetics with MicrOalbuminuRia (NESTOR) trial showed IDP SR 1.5 mg to be noninferior to enalapril 10 mg [97], and the PREterax in AlbuMInuria REgRession (PREMIER) trial showed the perindopril/IDP combination to be superior to enalapril [23].

• HCTZ vs CTD

The only trial that was able to directly compare the effects of HCTZ versus CTD on CV events was the MRFIT. As mentioned earlier, CTD was associated with significantly less nonfatal CV events, clinical MI and MI determined by annual ECG than with HCTZ ($p < 0.04$, $p = 0.0017$, $p = 0.0001$ and $p=0.0103$, respectively) [45,83–84]. Another comparison can be derived from the ALLHAT trial, which demonstrated CTD to be noninferior or even superior to amlodipine on multiple secondary end points, whereas in ACCOMPLISH HCTZ was inferior to amlodipine [98]. Additionally, CTD was superior to an ACE-I on multiple secondary end points in ALLHAT, whereas HCTZ was inferior to an ACE-I in ANBP2. Thus, taking into consideration the MRFIT, as well as the indirect comparisons from two other clinical trials, it is not unreasonable that CTD could be labeled as being superior to HCTZ for reducing clinical CV end points. Considering differences on the lipid profile, the MRFIT also showed the CTD group to have lower total cholesterol as compared with the HCTZ group ($p < 0.001$ overall; $p < 0.05$ at years 1, 2, 4 and 5) and LDL-C ($p = 0.0009$ overall; $p < 0.05$ at year 2 [83,84,98]. However, CTD therapy led to significantly lower potassium levels as compared with HCTZ therapy, thus predisposing to hypokalemia (3.7 vs 4.0 mEq/l after 7 years,

Box 2. Benefits of indapamide therapy over other thiazide/thiazide-like diuretics.

- Indapamide has a longer half-life and duration of action as compared with hydrochlorothiazide
- Preserves renal function
- Reduces left ventricular mass index
- Infrequent incidence of hyponatremia and hypokalemia (particularly with the SR formulation)
- Minimal increases in serum uric acid and serum cholesterol levels
- Minimal risk of new-onset diabetes (no alteration in fasting blood glucose, A1c, and insulin resistance)
- Decreased risk of stroke, cardiovascular mortality and heart failure
- Improved endothelial and arterial function

p = 0.0003, respectively) [45]. Despite this fact, CTD was superior to HCTZ at reducing CV events.

• HCTZ vs IDP

The relevant trial data for comparison between HCTZ and IDP is minimal. However, a single trial demonstrated an increase in creatinine clearance by 28.5% with IDP, but a 17.4% decrease with HCTZ ($p < 0.01$, for the difference) [18], despite a similar BP control. A similar trend was observed for estimated glomerular filtration rate, which increased significantly from 58 ml/min to 72 ml/min ($p < 0.01$) with IDP, but decreased significantly from 65 ml/min to 53 ml/min ($p < 0.01$) with HCTZ [18]. These findings support the notion that IDP may have reno-protective effects, especially when compared with HCTZ. While not a direct comparison trial, T2DM with mild-to-moderate HTN prescribed IDP (1.5 mg SR) therapy showed no alteration in serum sodium, potassium, chloride, uric acid, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, lipid profiles, fasting blood glucose, insulin, hemoglobin Alc and insulin resistance [99]. Similarly, a recent randomized trial compared effects of IDP versus HCTZ on CV function when added to ACE-I in patients with T2DM and HTN. IDP combination significantly improved mean longitudinal systolic velocity and longitudinal strain by 7 and 14%,

EXECUTIVE SUMMARY

History of diuretics

- Thiazides and thiazide-like diuretics have been a cornerstone in hypertension (HTN) treatment for more than half a century.

Pharmacologic properties

- Thiazide and thiazide-like diuretics reach their site of action after secretion by the organic acid transporter, and inhibit the electroneutral Na^+Cl^- co-transporter) located on the apical membrane of the distal convoluted tubules.

Adverse effects

- The primary side effects of thiazide and thiazide-like diuretics include hyponatremia, hypokalemia, hyperuricemia, hyperlipidemia and new-onset diabetes mellitus.

Complications of HTN

- A systematic review of randomized controlled trials with two different types of network analyses demonstrated that chlorthalidone (CTD) causes a significant 23% reduction in risk of heart failure as compared with hydrochlorothiazide (HCTZ; 95% CI: 2–39; p = 0.032) [100]. Additionally, cardiovascular (CV) events were also significantly reduced by 21% with CTD versus HCTZ (95% CI: 12–28; p = 0.0001).

Hydrochlorothiazide

- HCTZ is the most widely prescribed diuretic but recently its use as a first choice anti-HTN has been under considerable debate.

Chlorthalidone

- CTD, the 'long lost diuretic', is being re-explored, and increased awareness of its broad evidence-base for improving prognosis in HTN is resurfacing.

Indapamide

- Indapamide, used as monotherapy, or in combination therapy seems to prevent target organ damage.

HCTZ vs CTD

- The only trial that was able to directly compare the effects of HCTZ versus CTD on CV events was the Multiple Risk Factor Intervention Trial. In this trial, CTD was associated with significantly less nonfatal CV events, clinical myocardial infarction and myocardial infarction determined by annual ECG than with HCTZ.

HCTZ vs IDP

- Indapamide may provide enhanced renoprotection and cardiovascular protection compared with HCTZ.

respectively (from 5.6 ± 1.8 to 6.0 ± 1.1 cm/s and from 16.2% ± 1.8% to 18.5% ± 1.1%, both $p < 0.05$). Additionally, mean longitudinal early diastolic velocity also increased by 31% with IDP therapy ($p < 0.05$), with no such effects were documented with HCTZ combination and no changes were observed in ejection fraction and radial systolic function [100]. The largely neutral effects that IDP has on the metabolic profile, and the related improved endothelial and arterial function may provide advantages versus other thiazide/thiazide-like diuretics. The above clinical trial data have been summarized in **Table 2** and the advantages of IDP over other thiazide and thiazide-like diuretics in **Box 2**.

Conclusion

Despite the fact that HCTZ is prescribed much more frequently then IDP and CTD in the USA, there is no evidence that HCTZ monotherapy reduces morbidity or mortality. IDP and CTD should be considered the 'thiazide' diuretics of choice.

Future perspective

While the NICE guidelines preferentially recommend IDP and CTD over HCTZ, JNC-8 and CHEP guidelines do not make this distinction. The preferential recommendation of IDP and CTD over HCTZ in national and international HTN guidelines would almost certainly lead to reductions in CV events and mortality. It is now time for all international HTN guidelines to follow the NICE lead, and support the preferential use of IDP and CTD over HCTZ for better treatment of HTN and reduction of adverse events.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:
• of interest

1 Rosamond W, Flegal K, Furie K *et al.* Heart disease and stroke statistics - 2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 117(4), e25–e146 (2008).

2 Roush GC, Kaur R, Ernst ME. Diuretics: a review and update. *J. Cardiovasc. Pharmacol. Ther.* 19(1), 5–13 (2014).

3 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* 311(5), 507–520 (2014).

4 Dinicolantonio JJ. Hydrochlorothiazide: is it a wise choice? *Expert Opin. Pharmacother.* 13(6), 807–814 (2012).

5 Hackam DG, Quinn RR, Ravani P *et al.* The 2013 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. *Can. J. Cardiol.* 29(5), 528–542 (2013).

6 NICE. Hypertension: the clinical management of primary hypertension in adults. CG127/NICE Guideline. National Clinical Guideline Centre. www.guidance.nice.org.uk/cg127

7 Capps J, Wiggins W, Axelrod D *et al.* The effect of mercurial diuretics on the excretion of water. *Circulation* 6(1), 82–89 (1952).

8 Novello FC, Sprague JM. Benzothiadiazine dioxides as novel diuretics. *J. Am. Chem. Soc.* 79(8), 2028–2029 (1957).

9 Freis E, Wanko A, Wilson IM *et al.* Treatment of essential hypertension with chlorothiazide (Diuril). *JAMA* 166(2), 137–140 (1958).

10 Moser M, Macauley AI. Chlorothiazide as an adjunct in the treatment of essential hypertension. *Am. J. Cardiol.* 3(2), 214–219 (1959).

11 Reilly RF, Ellison DH. Mammalian distal tubule: physiology, pathophysiology, and molecular anatomy. *Physiol. Rev.* 80, 277–313 (2000).

12 Hughes AD. How do thiazide and thiazide-like diuretics lower blood pressure? *J. Renin Angiotensin Aldosterone Syst.* 5(4), 155–160 (2004).

13 Aung K, Htay T. Thiazide diuretics and the risk of hip fracture. *Cochrane Database Syst. Rev.* (10), CD005185 (2011).

14 Ernst ME, Carter BL, Goerdt CJ *et al.* Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. *Hypertension* 47, 352–358 (2006).

15 Allen JH, McKenney JM, Stratton MA *et al.* Antihypertensive effect of hydrochlorthiazide administered once or twice daily. *Clin. Pharm.* 1, 239–243 (1982).

16 Mironneau J, Savineau JP, Mironneau C. Compared effects of indapamide, hydrochlorothiazide and chlorthalidone on electrical and mechanical activities in vascular smooth muscle. *Eur. J. Pharmacol.* 75, 109–113 (1981).

17 Cooper-DeHoff JD. Mechanisms for blood pressure lowering and metabolic effects of thiazide and thiazide-like diuretics. *Expert Rev. Cardiovasc. Ther.* 8(6), 793–802 (2010).

18 Madkour H, Gadallah M, Riveline B *et al.* Indapamide is superior to thiazide in the preservation of renal function in patients with renal insufficiency and systemic hypertension. *Am. J. Cardiol.* 77, 23B–25B (1996).

19 Carey PA, Sheridan DJ, de Cordoue A *et al.* Effect of indapamide on left ventricular hypertrophy in hypertension: a meta-analysis. *Am. J. Cardiol.* 77, 17B–19B (1996).

20 Emeriau JP, Knauf H, Pujadas JO *et al.* A comparison of indapamide SR 1.5mg with both amlodipine 5mg and hydrochlorothiazide 25mg in elderly hypertensive patients: a randomized double-blind controlled study. *J. Hypertens.* 19(2), 343–350 (2001).

21 Ernst ME, Neaton JD, Grimm RH Jr *et al.* Long-term effects of chlorthalidone versus hydrochlorothiazide on electrocardiographic

left ventricular hypertrophy in the multiple risk factor intervention trial. *Hypertension* 58(6), 1001–1007 (2011).

22 Woodman R, Brown C, Lockette W. Chlorthalidone decreases platelet aggregation and vascular permeability and promotes angiogenesis. *Hypertension* 56(3), 463–470 (2010).

23 Mogensen CE, Viberti G, Halimi S *et al.* Effect of low-dose perindopril/indapamide on albuminuria in diabetes: preterax in albuminuria regression: PREMIER. *Hypertension* 41(5), 1063–1071 (2003).

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

25 National Collaborating Centre for Chronic Conditions. *Hypertension: Management in Adults in Primary Care: Pharmacological Update.*Royal College of Physicians, London, UK (2006).

26 Boscoe A, Paramore C, Verbalis JG. Cost of illness of hyponatremia in the United States. *Cost Eff. Resour. Alloc.* 4, 10 (2006).

27 Callahan MA, Do HT, Caplan DW *et al.* Economic impact of hyponatremia in hospitalized patients: a retrospective cohort study. *Postgrad. Med.* 121(2), 186–191 (2009).

28 Shea AM, Hammill BG, Curtis LH *et al.* Medical costs of abnormal serum sodium levels. *J. Am. Soc. Nephrol.* 19, 764–770 (2008).

29 Zilberberg MD, Exuzides A, Spalding J *et al.* Epidemiology, clinical and economic outcomes of admission hyponatremia among hospitalized patients. *Curr. Med. Res. Opin.* 24, 1601–1608 (2008).

30 Leung AA, Wright A, Pazo V, Karson A, Bates DW. Risk of thiazide induced hyponatremia in patients with hypertension. *Am. J. Med.* 124(11), 1064–1072 (2011).

31 Decaux G. Is asymptomatic hyponatremia really asymptomatic? *Am. J. Med.* 119(7 Suppl. 1), S79–S82 (2006).

32 GankamKengne F, Andres C, Sattar L *et al.* Mild hyponatremia and risk of fracture in the ambulatory elderly. *QJM* 101(7), 583–588 (2008).

33 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.* 158(6), 447–455 (2013).

34 Chan TY. Indapamide-induced severe hyponatraemia and hypokalaemia. *Ann. Pharmacother.* 29(11), 1124–1128 (1995).

35 Yong TY, Huang JE, Lau SY *et al.* Severe hyponatremia and other electrolyte disturbances associated with indapamide. *Curr. Drug Saf.* 6(3), 134–137 (2011).

36 Chapman MD, Hanrahan R, McEwen J *et al.* Hyponatraemia and hypokalaemia due to indapamide. *Med. J. Aust.* 176(5), 219–221 (2002).

37 Hoes AW, Grobbee DE, Lubsen J. Sudden cardiac death in patients with hypertension: an association with diuretics and beta-blockers? *Drug Saf.* 16(4), 233–241 (1997).

38 Cohen JD, Neaton JD, Prineas RJ *et al.* Diuretics, serum potassium and ventricular arrhythmias in the Multiple Risk Factor Intervention Trial. *Am. J. Cardiol.* 60(7), 548–554 (1987).

39 Cushman WC, Khatri I, Materson BJ *et al.* Treatment of hypertension in the elderly. III. Response of isolated systolic hypertension to various doses of hydrochlorothiazide: results of a Department of Veterans Affairs cooperative study. *Arch. Intern. Med.* 151(10), 1954–1960 (1991).

40 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* 59(5), 926–933 (2012).

41 Ernst ME, Carter BL, Zheng S *et al.* Meta-analysis of dose-response characteristics of hydrochlorothiazide and chlorthalidone: effects on systolic blood pressure and potassium. *Am. J. Hypertens.* 23(4), 440–446 (2010).

42 Plante GE, Robillard C. Indapamide in the treatment of essential arterial hypertension: results of a controlled study. *Curr. Med. Res. Opin.* 8(Suppl. 3), 59–66 (1983).

43 Ambrosioni E, Safar M, Degaute JP *et al.* Low-dose antihypertensive therapy with 1.5 mg sustained-release indapamide: results of randomized doubleblind controlled studies. European study group. *J. Hypertens.* 16(11), 1677–1684 (1998).

44 Sica DA, Schoolwerth A. Renal handing of organic anions and cations and renal excretion of uric acid. In: *The Kidney.* Brenner B, Rector F (Eds). WB Saunders, PA, USA, 637–662 (2004).

45 Dorsch MP, Gillespie BW, Erickson SR *et al.* Chlorthalidone reduces cardiovascular events compared with hydrochlorothiazide: a retrospective cohort analysis. *Hypertension* 57(4), 689–694 (2011).

46 Franse LV, Pahor M, Di Bari M *et al.* Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP). *J. Hypertens.* 18(8), 1149 – 1154 (2000).

47 Myers MG, Asmar R, Leenen FH *et al.* Fixed low-dose combination therapy in hypertension: a dose response study of perindopril and indapamide. *J. Hypertens.* 18(3), 317–325 (2000).

48 Kreeft JH, Langlois S, Ogilvie RI. Comparative trial of indapamide and hydrochlorothiazide in essential hypertension with forearm plethysmography. *J. Cardiovasc. Pharmacol.* 6(4), 622–626 (1984).

49 Elliott WJ, Weber RR, Murphy MB. A double-blind, randomized, placebo-controlled comparison of the metabolic effects of low-dose hydrochlorothiazide and indapamide. *J. Clin. Pharmacol.* 31(8), 751–757 (1991).

50 Savage PJ, Pressel SL, Curb JD *et al.* Influence of long-term, low-dose, diuretic-based, antihypertensive therapy on glucose, lipid, uric acid, and potassium levels in older men and women with isolated systolic hypertension: the Systolic Hypertension in the Elderly Program. *Arch. Intern. Med.* 158(7), 741–751 (1998).

51 Zillich AJ, Garg J, Basu S *et al.* Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. *Hypertension* 48(2), 219–224 (2006).

52 Manrique C, Giles TD, Ferdinand KC *et al.* Realities of newer β-blockers for the management of hypertension. *J. Clin. Hypertens. (Greenwich)* 11(7), 369–375 (2009).

53 Stears AJ, Woods SH, Watts MM *et al.* A double-blind, placebocontrolled, crossover trial comparing the effects of amiloride and hydrochlorothiazide on glucose tolerance in patients with essential hypertension. *Hypertension* 59(5), 934–942 (2012).

54 Mantel-Teeuwisse AK, Kloosterman JM, Maitland-van der Zee AH *et al.* Drug induced lipid changes: a review of the unintended effects of some commonly used drugs on serum lipid levels. *Drug Saf.* 24(6), 443–456 (2001).

55 Lakshman MR, Reda DJ, Materson BJ *et al.* Diuretics and beta-blockers do not have adverse effects at 1 year on plasma lipid and lipoprotein profiles in men with hypertension. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *Arch. Intern. Med.* 159(6), 551–558 (1999).

56 Kostis JB, Wilson AC, Freudenberger RS *et al.* Long-term effect of diuretic-based

therapy on fatal outcomes in subjects with isolated systolic hypertension with and without diabetes. *Am. J. Cardiol.* 95(1), 29–35 (2005).

57 Peer R, Black HR, Davis B *et al.* Metabolic and clinical outcomes in nondiabetic individuals with the metabolic syndrome assigned to chlorthalidone, amlodipine, or lisinopril as initial treatment for hypertension: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Diabetes Care* 31(2), 353–360 (2008).

58 Ames RP. A comparison of blood lipid and blood pressure responses during the treatment of systemic hypertension with indapamide and with thiazides. *Am. J. Cardiol.* 77(6), B12–B16 (1996).

59 Puig JG, Marre M, Kokot F *et al.* Efficacy of indapamide SR compared with enalapril in elderly hypertensive patients with Type 2 diabetes. *Am. J. Hypertens.* 20(1), 90–97 (2007).

60 Weidmann P. Metabolic profile of indapamide sustained-release in patients with hypertension: data from three randomised double-blind studies. *Drug Saf.* 24(15), 1155–1165 (2001).

61 Roush GC, Holford TR, Guddati AK. Chlorthalidone compared with hydrochlorothiazide in reducing cardiovascular events: systematic review and network meta-analyses. *Hypertension* 59(6), 1110–1117 (2012).

- **Chlorthalidone superior to hydrochlorothiazide for reducing cardiovascular events.**

62 SHEP Cooperative Research Group. . 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). *JAMA* 265(24), 3255–3264 (1991).

63 Patel A, Macmahon S, Chalmers J *et al.* Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with Type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 370(9590), 829–840 (2007).

64 de Galan BE, Perkovic V, Ninomiya T *et al.* Lowering blood pressure reduces renal events in Type 2 diabetes. *J. Am. Soc. Nephrol.* 20(4), 883–892 (2009).

65 PROGRESS Collaborative Group. Randomised trial of a peridopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet* 358(9287), 1033–1041 (2001).

66 Beckett NS, Peters R, Fletcher AE *et al.* Treatment of hypertension in patients 80 years of age or older. *N. Engl. J. Med.* 358(18), 1887–1898 (2008).

67 PATS Collaborating Group. Post-stroke antihypertensive treatment study: a preliminary result. *Chin. Med. J. (Engl.)* 108(9), 710–717 (1995).

68 Messerli FH, Bangalore S, Julius S. Risk/benefit assessment of beta- blockers and diuretics precludes their use for first-line therapy in hypertension. *Circulation* 117(20), 2706–2715 (2008).

69 Messerli FH, Makani H, Benjo A *et al.* Antihypertensive efficacy of hydrochlorothiazide as evaluated by ambulatory blood pressure monitoring: a meta-analysis of randomized trials. *J. Am. Coll. Cardiol.* 57(5), 590–600 (2011).

70 Materson BJ, Cushman WC, Goldstein G *et al.* Treatment of hypertension in the elderly. I. Blood pressure and clinical changes. Results of a Department of Veterans Affairs Cooperative study. *Hypertension* 15(4), 348–360 (1990).

71 Wing LM, Reid CM, Ryan P *et al.* A comparison of outcomes with angiotensin-converting enzyme inhibitors and diuretics for hypertension in the elderly. *N. Engl. J. Med.* 348(7), 583–592 (2003).

72 Jamerson K, Weber MA, Bakris GL *et al.* Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N. Engl. J. Med.* 359(23), 2417–2428 (2008).

73 Leren P, Helgeland A. Oslo hypertension study. *Drugs* 31(Suppl. 1), 41–45 (1986).

- **Hydrochlorothiazide increases cardiovascular mortality compared with placebo.**

74 The Management Committee. The Australian therapeutic trial in mild hypertension. Report by the Management Committee. *Lancet* 1(8181), 1261–1267 (1980).

75 Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension: results in patients with diastolic blood pressures averaging 115 through 129 mmHg. *JAMA* 202(11), 1028–1034 (1967).

76 Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mmHg. *JAMA* 213(7), 1143–1152 (1970).

77 Amery A, Birkenhager W, Brixko P *et al.* Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. *Lancet* 1(8442), 1349 –1354 (1985).

78 O'Malley K, Cox JP, O'Brien E. Further learnings from the European Working Party on High Blood Pressure in the Elderly (EWPHE) study: focus on systolic hypertension. *Cardiovasc. Drugs Ther.* 4(Suppl. 6), 1249–1251 (1991).

79 Wilhelmsen L, Berglund G, Elmfeldt D *et al.* Beta-blockers versus diuretics in hypertensive men: main results from the HAPPHY trial. *J. Hypertens.* 5(5), 561–572 (1987).

80 De Leeuw PW, Ruilope LM, Palmer CR *et al.* Clinical significance of renal function in hypertensive patients at high risk: results from the INSIGHT trial. *Arch. Intern. Med.* 164(22), 2459–2464 (2004).

81 Simon A, Gariepy J, Moyse D *et al.* Differential effects of nifedipine and co-amilozide on the porgression of early carotid wall changes. *Circulation* 103(24), 2949–2954 (2001).

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

83 The Multiple Risk Factor Intervention Trial Research Group. Mortality after 10½ years for hypertensive participants in the Multiple Risk Factor Intervention Trial. *Circulation* 82(5), 1616–1628 (1990).

84 The Multiple Risk Factor Intervention Trial Research Group. Mortality rates after 10.5 years for participants in the Multiple Risk Factor Intervention Trial. Findings related to a priority hypotheses of the trial. *JAMA* 263(13), 1795–1801 (1990).

85 Neaton JD, Grimm RH Jr, Prineas RJ *et al.* Treatment of Mild Hypertension Study: final results. Treatment of Mild Hypertension Study Research Group. *JAMA* 270(6), 713–724 (1993).

86 Zanchetti A, Rosei EA, Dal Palu C *et al.* The Verapamil in Hypertension and Atherosclerosis Study (VHAS): results of long-term randomized treatment with either verapamil or chlorthalidone on carotid intima-media thickness. *J. Hypertens.* 16(11), 1667–1676 (1998).

87 ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker versus diuretic: Antihypertensive and Lipid-Lowering

Treatment to Prevent Heart Attack Trail (ALLHAT). *JAMA* 288(23), 2981–2997 (2002).

88 Gosse P, Sheridan DJ, Zannad F *et al.* Regression of left ventricular hypertrophy in hypertensive patients treated with indapamide SR 1.5 mg versus enalapril 20 mg: the LIVE study. *J. Hypertens.* 18(10), 1465–1475 (2000).

89 Baguet JP, Robitail S, Boyer L *et al.* A meta-analytical approach to the efficacy of antihypertensive drugs in reducing blood pressure. *Am. J. Cardiovasc. Drugs* 5(2), 131–140 (2005).

90 London G, Schmieder R, Calvo C *et al.* Indapamide SR versus candesartan and amlodipine in hypertension: the X-CELLENT Study. *Am. J. Hypertens.* 19(1), 113–121 (2006).

91 Akram J, Sheikh UE, Mahmood M *et al.* Antihypertensive efficacy of indapamide SR in hypertensive patients uncontrolled with a background therapy: the NATIVE study. *Curr. Med. Res. Opin.* 23(12), 2929–2936 (2007).

92 Kang S, Wu YF, An N *et al.* A systematic review and meta-analysis of the efficacy and safety of a fixed, low-dose perindopril-indapamide combination as first-line treatment of hypertension. *Clin. Ther.* 26(2), 257–270 (2004).

93 Ghiadoni L, Magagna A, Kardasz I *et al.* Fixed dose combination of perindopril and indapamide improves peripheral vascular function in essential hypertensive patients. *Am. J. Hypertens.* 22(5), 506–512 (2009).

94 Asmar RG, London GB, O'Rourke ME *et al.* Improvement in blood pressure, arterial stiffness and wave reflections with a very-low-dose perindopril/indapamide combination in hypertensive patient: a comparison with atenolol. *Hypertension* 38(4), 922–926 (2001).

95 Dahlof B, Gosse P, Gueret P *et al.* Perindopril/indapamide combination more effective than enalapril in reducing blood pressure and left ventricular mass: the PICXEL study. *J. Hypertens.* 23(11), 2063–2070 (2005).

96 de Luca N, Mallion JM, O'Rourke MF *et al.* Regression of left ventricular mass in hypertensive patients treated with perindopril/indapamide as a first-line combination: the REASON echocardiography study. *Am. J. Hypertens.* 17(8), 660–667 (2004).

97 Marre M, Puig JG, Kokot F *et al.* Equivalence of indapamide SR and enalapril on microalbuminuria reduction in hypertensive patients with Type 2 diabetes: the NESTOR Study. *J. Hypertens.* 22(8), 1613–1622 (2004).

98 Carter BL, Ernst ME, Cohen JD. Hydrochlorothiazide versus chlorthalidone: evidence supporting theirinterchangeability. *Hypertension* 43(1), 4–9 (2004).

99 Kuo SW, Pei-Dee, , Hung YJ *et al.* Effect of indapamide SR in the treatment of hypertensive patients with Type 2 diabetes. *Am. J. Hypertens.* 16(8), 623–628 (2008).

100 Vinereanu D, Dulgheru R, Magda S *et al.* The effect of Indapamide versus Hydrochlorothiazide on ventricular and arterial function in patients with hypertension and diabetes: results of a randomized trial. *Am. Heart J.* 168(4), 446–456 (2014).