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CKJ REVIEW

Thiazide diuretics are back in CKD: the case of chlorthalidone

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ABSTRACT

Sodium and volume excess is the fundamental risk factor underlying hypertension in chronic kidney disease (CKD) patients, who represent the prototypical population characterized by salt-sensitive hypertension. Low salt diets and diuretics constitute the centrepiece for blood pressure control in CKD. In patients with CKD stage 4, loop diuretics are generally preferred to thiazides. Furthermore, thiazide diuretics have long been held as being of limited efficacy in this population. In this review, by systematically appraising published randomized trials of thiazides in CKD, we show that this class of drugs may be useful even among people with advanced CKD. Thiazides cause a negative sodium balance and reduce body fluids by 1–2 l within the first 2–4 weeks and these effects go along with improvement in hypertension control. The recent CLICK trial has documented the antihypertensive efficacy of chlorthalidone, a long-acting thiazide-like diuretic, in stage 4 CKD patients with poorly controlled hypertension. Overall, chlorthalidone use could be considered in patients with treatment-resistant hypertension when spironolactone cannot be administered or must be withdrawn due to side effects. Hyponatremia, hypokalaemia, volume depletion and acute kidney injury are side effects that demand a vigilant attitude by physicians prescribing these drugs. Well-powered randomized trials assessing hard outcomes are still necessary to more confidently recommend the use of these drugs in advanced CKD.

LAY SUMMARY

Low salt diets and diuretic use constitute the cornerstones of blood pressure control in chronic kidney disease (CKD) patients due to their salt-sensitive hypertension. In patients with more advanced CKD, loop diuretics are generally preferred to thiazides because the latter have long been held as being of limited efficacy in this population. In this review, by systematically appraising published randomized trials of thiazides in CKD, we show that this class of drugs, in particular chlorthalidone, a long-acting thiazide-like diuretic, may be useful even among people with advanced CKD for improving hypertension control. Hyponatremia, hypokalaemia, volume depletion and acute kidney injury are side effects that demand a vigilant attitude by physicians prescribing these drugs. Well-powered randomized trials assessing hard outcomes are still necessary to more confidently recommend the use of these drugs in advanced CKD.

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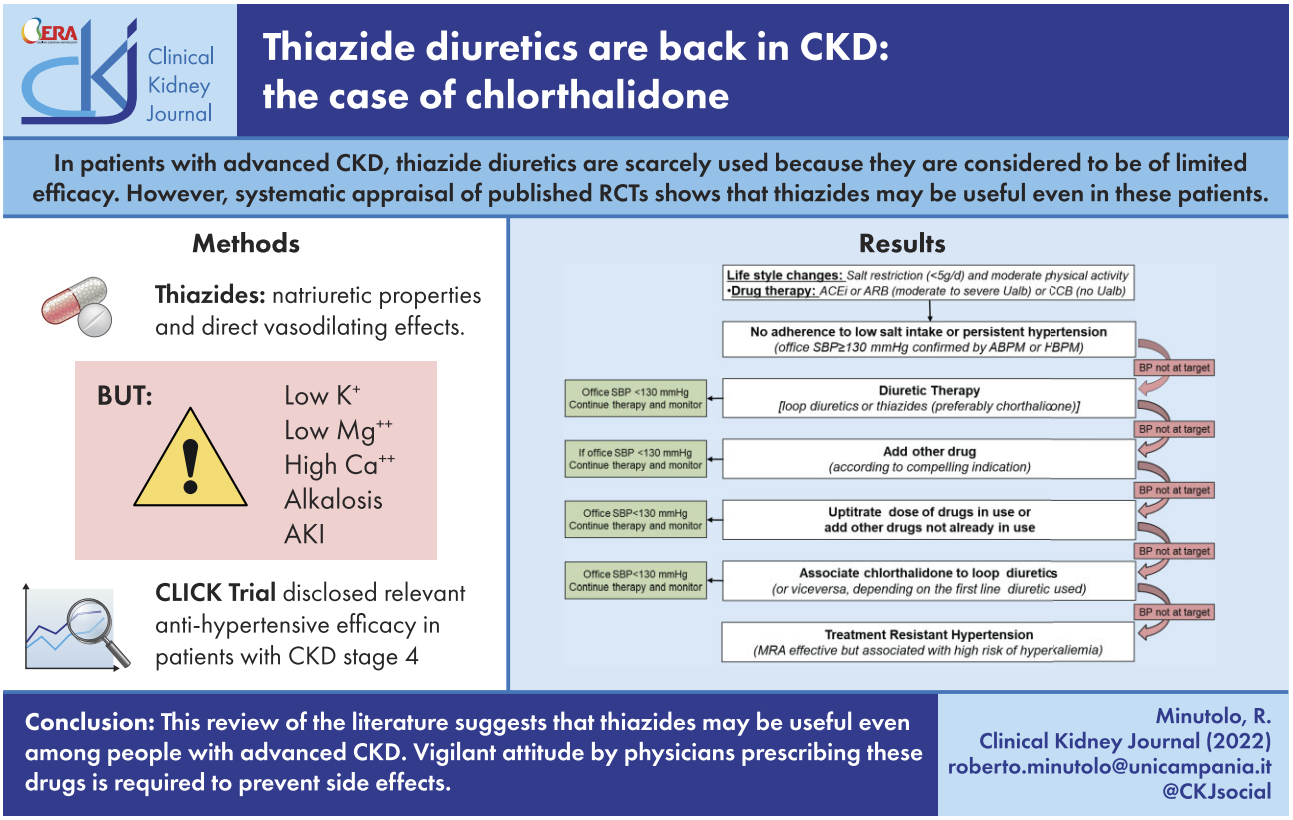
GRAPHICAL ABSTRACT



Keywords: blood pressure, chlorthalidone, CKD, diuretics, thiazides

INTRODUCTION

In patients with chronic kidney disease (CKD), lower glomerular filtration rate (GFR) results in impaired ability to excrete dietary sodium chloride, leading to the onset of positive sodium balance and hypertension. Therefore, maintaining the balance between intake and urinary excretion of sodium is a major treatment challenge in these patients. The low adherence of patients to salt prescription is a notorious unmet clinical need in CKD patients [1]. Loop diuretics can correct volume and sodium overload in CKD. However, loop diuretics may fail to correct sodium and volume overload in CKD patients due to high salt intake, the competing effect of uraemic anions for the tubular transporters that transfer these drugs from the peritubular circulation to the tubular lumen and, at least in some patients, the coexistence of low serum albumin that impairs their delivery to the kidney [2]. Furthermore, most nephrologists are reluctant to prescribe loop diuretics in appropriate doses because of the risk of excessive volume depletion and dependent risk of renal function worsening.

Recent trials have renewed interest in thiazides, and chlorthalidone in particular, for the control volume overload and hypertension at all CKD stages, including the advanced stages of this condition. In this review we will touch upon mechanisms underlying the peculiar salt sensitivity of hypertension in CKD patients. We will briefly summarize the blood pressure (BP) response to low salt diets in the same patients to focus on thiazides, from their pharmacological properties, efficacy and side effects, to randomized controlled trials (RCTs) that tested these drugs in patients with CKD. In particular, we will expand on the Chlorthalidone in Chronic Kidney Disease (CLICK) trial in CKD patients with advanced renal insufficiency (stage 4 CKD) [3].

Salt-sensitivity of hypertension in CKD

The pathogenesis of hypertension in CKD is multifactorial in nature. Sodium retention, imbalance of vasoconstrictors [renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system, endothelin-1] that prevail over vasodilators (nitric oxide, vasodilatory prostaglandins) and vascular stiffness all contribute to raising BP in this condition. Among these factors, salt retention is unquestionably dominant [4]. Due to reduced proximal sodium reabsorption, distal sodium delivery is augmented in CKD, which triggers a 4- to 5-fold increase in distal sodium reabsorption [5]. In CKD patients, the extracellular volume (ECV) expansion correlates with the degree of kidney dysfunction. Indeed, since the early CKD stages, in the absence of peripheral oedema, ECV increases by ~5–10% of body weight [4]. Due to the sodium escape phenomenon, expansion of the ECV preserves the external balance of sodium by triggering natriuretic mechanisms that eliminate most of the volume excess. In this pathophysiological setting, hypertension represents the 'trade-off' to ECV preservation. This renocentric view has been questioned by Titze [6], who remarked that body sodium content in humans and animals is not constant, that sodium may accumulate

without a commensurate water retention and that extrarenal mechanisms play a relevant role in sodium metabolism. Others emphasized that studies of salt and water balance are traditionally short-term studies investigating responses to extremes in salt intake, while ultra-long-term sodium balance studies show that steady-state sodium balance in humans is characterized by storage and release of sodium from the body [7]. In experimental animals, researchers demonstrated that sodium is stored in skeletal muscle and skin and immune cells control sodium metabolism via the lymphatics [8]. Failure of disposing sodium excess in the dermis and in muscles results in skin sodium accumulation and arterial hypertension, a phenomenon confirmed in sodium magnetic resonance imaging studies in CKD patients [9].

Beyond mechanisms, from a clinical point of view the key issue is that hypertension in CKD is resistant to treatment—i.e. uncontrolled despite three antihypertensive drugs, including a diuretic—in about one-fourth of these patients [10]. Of note, patients with CKD and resistant hypertension constitute a definite subgroup characterized by higher ECV expansion and a higher risk of cardiovascular and renal events [10, 11]. Among the BP components of hypertension in CKD, the most important one is nocturnal hypertension, defined as night-time BP above the goal of 120/70 mmHg or as non-dipping status. The combined prevalence of these fundamental alterations of the circadian BP profile is as high as 60% and represents a stronger predictor of poor cardiorenal outcomes [12]. Night-time BP levels are 9% higher in patients with resistant hypertension as compared with patients with other hypertension categories, while daytime BP differs by only 4% [10]. Recent secondary analyses from an RCT on salt intake and BP control in patients with CKD showed a correlation between 24-hour urinary sodium (Na) excretion and night-time BP, while no relationship with daytime or office BP was disclosed [13, 14].

Low salt diets and BP control in CKD patients

Interventions aimed at limiting sodium intake and the attendant ECV expansion improve hypertension control CKD. We studied the renal response to 7 days of salt restriction from 13 to 3 g/day in 21 subjects (7 patients with CKD due to biopsy-proven primary chronic glomerulonephritis and normal inulin-measured GFR, 7 patients with CKD and mean GFR of ~40 ml/min and 7 healthy controls) [15]. In all groups, a neutral external sodium balance during the low salt period was reached on days 4–5, with a cumulative sodium loss of ~150 mmol, i.e. ~1 l of ECV. It should be noted that while in normal subjects BP remained unchanged, the ECV reduction allowed a decrement in mean arterial pressure of 10 mmHg in the two groups with CKD. The finding of salt sensitivity of BP in patients with glomerulonephritis and normal GFR can be ascribed to the presence of volume expansion, as suggested by the significantly higher levels versus normal subjects of plasma atrial natriuretic peptide at baseline in this group as in patients with low GFR. Observations in this study have been confirmed in a recent meta-analysis of 11 RCTs including 738 patients with CKD stage 1–4 [16]. In this meta-analysis, an average reduction of dietary sodium from 179 to 104 mmol/day [i.e. from 10 to 6 g sodium chloride (NaCl)/day] was associated with a decrease in systolic/diastolic office BP of 5/2 mmHg and a 6/3 mmHg ambulatory BP (ABP) reduction and a concomitant 0.39 g/24 hour decrease in proteinuria. Of note, diuretics have antihypertensive and antiproteinuric effects similar or even superior to those of low salt diets [17–20].

Hypertension management in adult CKD patients recommended by the major guidelines in the last 5 years [21–27] is reported in Table 1. Contemporary Kidney Disease: Improving Global Outcomes (KDIGO) CKD Guidelines [27] indicate salt restriction as a mainstay of antihypertensive treatment, while the use of diuretic agents is sparsely and vaguely discussed, and not formally framed, among the key recommendations for treatment. These guidelines recommend lower systolic BP <120 mmHg 'if tolerated'. However, even the less ambitious and better justified systolic BP target of <130 mmHg [28] is difficult to achieve in clinical practice [29–34]. Inadequate BP control in CKD patients is not limited to office measurements but extends to 24-hour ABP monitoring. The International Database of Ambulatory BP in Renal Patients (I-DARE), collecting 24-hour BP levels in patients with CKD, most with stage 3 and 4, from Europe, the USA and Japan, demonstrated elevated 24-hour BP levels in 55% of patients [35]. A proposed practical algorithm for hypertension management in CKD is reported in Fig. 1.

Thiazides: from mechanism of action to efficacy and side effects

Mechanism of action

Thiazides act by inhibiting the sodium–chloride cotransporter (NCC) mainly located in the distal convoluted tubule of the nephron, which is responsible for ~7% of total sodium reabsorption [36]. The main mechanism of the BP-lowering effect of these drugs is enhanced natriuresis, which in turn reduces ECV, cardiac preload and output. Accordingly, the antihypertensive effect of chronic thiazide use is abolished by a very high salt intake (20 g/day of NaCl for 2 weeks) [37]. The lack of BP improvement after 4 weeks of administration of either hydrochlorothiazide or metolazone to anuric dialysis patients supports the crucial role of ECV reduction as the key mechanism for the antihypertensive effect of thiazides [38].

The long-term antihypertensive response to thiazides seems unrelated to the initial reduction of plasma volume. Indeed, dextran administration was effective in restoring plasma volume at values similar to those measured before starting hydrochlorothiazide, while BP levels (168/93 mmHg on average) remained lower than those recorded before diuretic treatment (191/111 mmHg on average) [37, 39]. Interestingly, patients with Gitelman's syndrome who lack a functional NCC have been shown to respond with a decrease in BP and arterial dilatation, suggesting a secondary site or mechanism of action of thiazides [40, 41]. A combination of several factors rather than a single mechanism is likely responsible for the hypotensive effect of thiazides, including a reduction in vascular reactivity, hyperpolarization of the vascular smooth muscle cell (mediated by large-conductance calcium-activated potassium channels), inhibition of voltage-dependent L-type calcium channels and enhanced nitric oxide release [42, 43]. It is likely therefore that the antihypertensive efficacy of thiazides may be initially induced by their natriuretic properties and complemented in the long-term by direct vasodilating effects.

Difference in pharmacological properties and efficacy

The absorption of thiazides occurs rapidly in the gastrointestinal tract and is influenced by food intake, which increases absorption, and renal disease or heart failure, which have an opposite effect. Thiazides are extensively bound to plasma proteins, which limit their glomerular filtration, and are excreted

Table 1: Hypertension management in adult CKD patients recommended by the major guidelines in the last 5 years.

Guideline reference	Office BP goal (mmHg)	Therapy (in addition to physical exercise, body weight control, reduction of alcohol intake)
2017 US Task Force on high BP management [21]	<130/80	NaCl intake: encourage salt reduction RAASi first. Diuretics as additive therapy. Chlorthalidone preferred on the basis of prolonged half-life and proven trial reduction of CVD; loop diuretics preferred in moderate–severe CKD
2018 ESC/ESH [22]	Age <65 y: SBP <140 to 130 if tolerated Age ≥65 y: SBP 139 to 130 if tolerated	NaCl intake: <5.0 g/day RAASi combined with CCB or diuretics as initial therapy. Loop diuretics when eGFR is <30 ml/min/1.73 m^2 because thiazide/thiazide-like diuretics are less effective/ineffective when eGFR is reduced to this level
Canada's 2018 [23]	Non-DM CKD: <140/90 DM CKD: <130/80	NaCl intake: 5.0 g/day RAASi first. Thiazide/thiazide-like diuretics are recommended as additive antihypertensive therapy. For patients with volume overload, loop diuretics are an alternative
2019 ACC/AHA [24]	<130/80	NaCl intake: 3.0 g/day and/or decrease of at least 0.5 g/day RAASi first. No specific indication on diuretics
NICE 2019–2021 [25]	Non-albuminuric: SBP 139 to 120 Albuminuric: SBP 129 to 120	NaCl intake: encourage salt reduction RAASi first in albuminuric patients. As second-line or in non-albuminuric patients, if a CCB is not tolerated (e.g. oedema), offer a thiazide-like diuretic to treat hypertension
2020 ISH [26]	<130/80 <140/80 in elderly patients	NaCl intake: encourage salt reduction RAASi first. CCB and diuretics are second-line therapy (loop-diuretics if eGFR <30 ml/min/1.73 m^2)
KDIGO 2021 [27]	SBP <120 mmHg, when tolerated, using standardized office BP measurement	NaCl intake: <5.0 g/day RAASi first. There are insufficient data on the role of diuretics as first-line therapy. Thiazide diuretics lose efficacy in diuresis and BP lowering as GFR worsens, but chlorthalidone, metolazone and indapamide appear effective at GFRs <30 ml/min/1.73 m^2. Loop diuretics are often effective at lower GFRs

ESC/ESH, European Society of Cardiology/Hypertension; CCB, calcium channel blocker; DM, diabetes mellitus; ACC/AHA, American College of Cardiology/American Heart Association; NICE, National Institute for Health and Care Excellence; ISH, International Society of Hypertension.

in the urine by proximal tubular secretion [44]. The onset of diuresis appears within 1–3 hours and lasts for 6–18 hours with thiazide-type agents and longer with thiazide-like diuretics (Table 2). Most thiazides have a half-life of ∼8–12 hours, thus allowing effective once-daily administration. Chlorthalidone has the longest half-life because >90% of the drug is bound to erythrocyte carbonic anhydrase, thus reaching a 10-fold greater concentration in red blood cells than in plasma [45]. Therefore erythrocytes act as a reservoir that allows a constant flow back of the chlorthalidone to the plasma with persistence of diuretic efficacy when the drug is administered less frequently than once a day or a dose of the drug is missed [44–46]. The same phenomenon has also been described for indapamide and metolazone, though to a lesser extent.

As reported in Fig.2, the estimated antihypertensive effect of thiazide diuretics reported by the Cochrane meta-analysis (60 trials with 11 282 participants) ranges from −6 to −12 mmHg for systolic BP (SBP) and from −3 to −6 mmHg for diastolic BP (DBP), without a formal comparison among thiazides [47]. The most frequently used drug of this class of diuretics is hydrochlorothiazide, which is prescribed 19 times more frequently than chlorthalidone [48]. Nevertheless, comparative data between these drugs show a greater efficacy of chlorthalidone versus hydrochlorothiazide on BP reduction. In a randomized, single-blinded, crossover study in untreated hypertensive patients, the decrease in office SBP was faster and more pronounced after 2 weeks of chlorthalidone (12.5 mg/day) as compared with hydrochlorothiazide (25 mg/day) [49]. Up-titration of both drugs from week 4 to week 8 did not modify office SBP, while it produced a larger reduction in 24-hour SBP mainly due to a greater night-time SBP decline (−13.5 ± 1.9 mmHg for chlorthalidone versus −6.4 ± 1.7 mmHg for hydrochlorothiazide; $P = .009$) [49]. A similar finding was reported by Pareek *et al.* [50] in a 12-week, double-blind RCT in 54 patients with stage 1 essential hypertension, where chlorthalidone significantly reduced systolic and diastolic ABP during daytime (−12.1/−8.7 mmHg) and nighttime (−10.2/−6.8 mmHg) while no significant ABP reduction was seen with hydrochlorothiazide.

A meta-analysis of 26 RCTs (including 4683 participants) compared the effects of hydrochlorothiazide, chlorthalidone and bendroflumethiazide on BP, serum potassium and urate [51]. Meta-regression of the effect of thiazides on SBP reduction showed a greater potency for bendroflumethiazide, followed by chlorthalidone and hydrochlorothiazide. The estimated dose of each drug predicting an SBP reduction of 10 mmHg was 1.4, 8.6 and 26.4 mg, respectively. Accordingly, standard doses of chlorthalidone (12.5–50 mg/day) are expected to produce a greater antihypertensive effect than standard doses of hydrochlorothiazide (12.5–25 mg/day). A network meta-analysis of 37 studies with 57 834 individuals confirmed the superiority of chlorthalidone over hydrochlorothiazide for BP control by

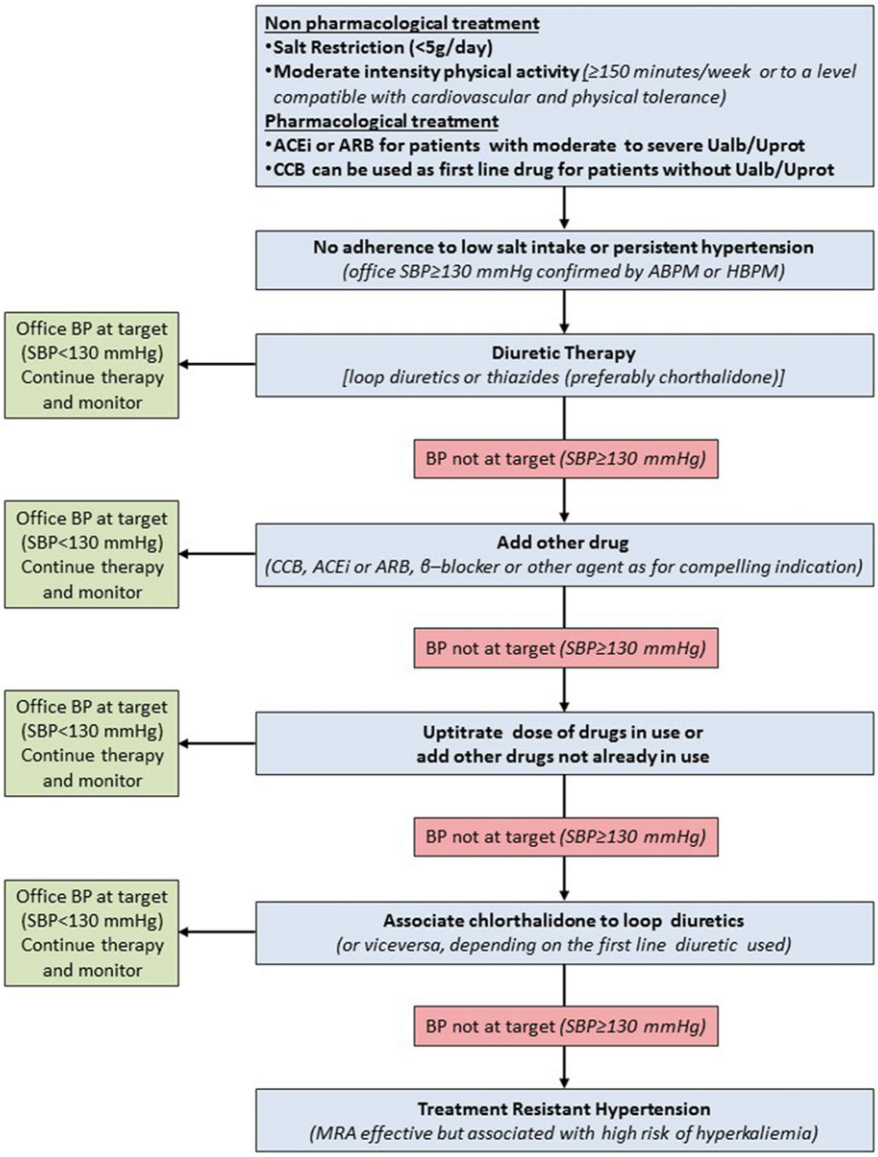


Figure 1: Algorithm for treatment of hypertension in non-dialysis CKD patients. ACEi, angiotensin-converting enzyme inhibitor; ARB angiotensin II receptor blocker; Ualb/Uprot, albuminuria/proteinuria; ABPM, ambulatory blood pressure monitoring; HBPM, home blood pressure monitoring; CCB, calcium channel blocker; MRA, mineralocorticoid receptor antagonist.

showing a greater reduction of SBP [weighted mean difference 4.74 mmHg [95% confidence interval (CI) −7.20 to −2.28] but not DBP [−0.59 mmHg (95% CI −2.02 to 0.84)] [52]. Since thiazides are frequently used in fixed-dose combinations, particularly with RAAS inhibitors (RAASis), it is of obvious importance to establish which thiazide diuretic optimizes BP control when given in association with these drugs. In this regard, a meta-analysis showed that the combination of an angiotensin II receptor blocker with chlorthalidone is more effective than the combination of the same drugs with hydrochlorothiazide in reducing SBP [−6.3 mmHg (95% CI −7.3 to −5.3)] and DBP [−3.6 mmHg (95% CI −4.2 to −3.0)] [53]. The superiority of chlorthalidone over hydrochlorothiazide extends well beyond hypertension control. Indeed, another network meta-analysis of nine trials including 78 350 hypertensive patients documented that this drug is also more effective for the prevention of congestive heart failure (HF) and cardiovascular events [54]; the relative risk of chlorthalidone versus hydrochlorothiazide was 0.77 (95% CI 0.61–0.98; $P = .032$) for HF and 0.79 (95% CI 0.72–0.88; $P < .0001$) for cardiovascular events. Furthermore, an additional meta-analysis of 19 studies including 112 113 hypertensive patients showed that thiazide-like diuretics (indapamide, chlorthalidone and metolazone) reduce cardiovascular risk [odds ratio (OR) 0.78 (95% CI 0.68–0.90)] more effectively than thiazide-type diuretics (chlorothiazide, hydrochlorothiazide, methyclothiazide, trichlormethiazide, polythiazide, bendroflumethiazide) [OR 0.92 (95% CI 0.79–1.07)] [55].

The use of thiazide diuretics has also been proposed in combination with loop diuretics in patients with HF in order to overcome diuretic resistance induced by increased sodium avidity in distal tubules accompanied with chronic loop diuretic use [56]. The most commonly used agent is metolazone, which

Table 2: Pharmacological properties of thiazide-type and thiazide-like diuretics.

Diuretics	Bioavailability (%)	Onset (hours)	Peak (hours)	Protein binding (%)	Half-life (hours)	Duration of action (hours)	Route of excretion (%)	Daily dose (mg)
Thiazide-type								
Hydrochlorothiazide	70	2	4–6	58	6–14	6–12	Renal (95)	12.5–25
Hydroflumethiazide	50				17	12–18	Renal (40–80)	12.5–25
Polythiazide	100				25		Renal (25)	2–4
Bendroflumethiazide	95	2	3–6	96	3–4	8–16	Renal (30)	1.25–5
Thiazide-like								
Xipamide	95	1	1–2	98	5–8	12–20	Renal (30)	5–40
Chlorthalidone	65	2.5	2–6	98	47	40–60	Renal (65)	12.5–50
Metolazone	65	1	2–4	96	8–14	24–48	Renal (80)	2.5–10
Indapamide	95	1–4		79	18	24	Renal (60)	1.25–2.5

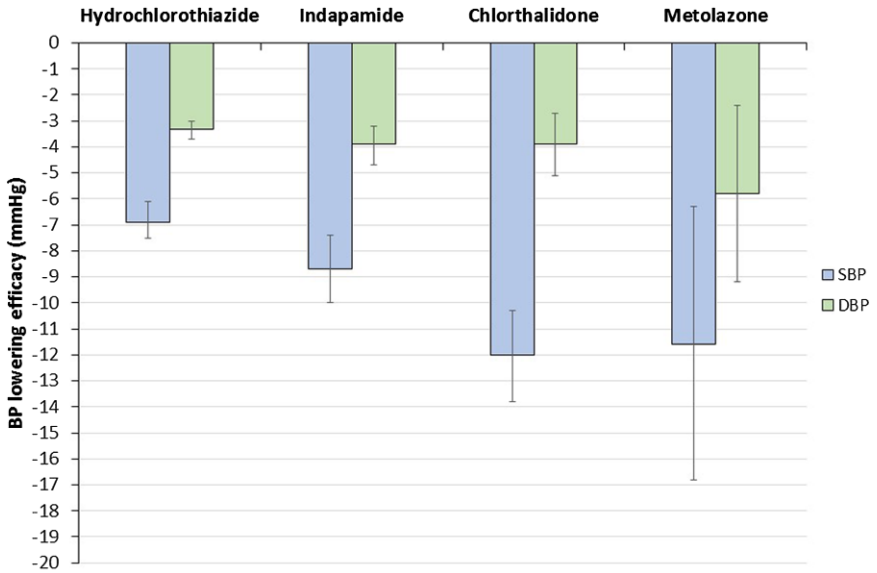


Figure 2: Decline of office SBP and DBP after treatment with thiazide diuretic in randomized clinical trials in patients with essential hypertension [47]. Data are mean and 95% CI.

has been suggested to be superior to other thiazide molecules in CKD patients [56], even though some small studies report a short-term efficacy in urinary sodium excretion when combining furosemide and hydrochlorothiazide [57, 58]. It is important to note, however, that the algorithm proposed by most recent guidelines for combining thiazides and loop diuretics in the management of HF patients is entirely based on expert opinion mainly because of a poor level of evidence (no placebo-controlled trials are available) [59, 60]. In a propensity score–matched analysis in patients with hospitalized HF, the addition of metolazone to loop diuretics was found to increase the risk for electrolyte disturbance (mainly hypokalaemia and hyponatremia) and worsening of renal function. Of note, metolazone use remained associated with increased adjusted risk of death [hazard ratio 1.20 (95% CI 1.04–1.39), $P = .01$], possibly due to the worse clinical conditions requiring the addition of metolazone, which cannot be completely corrected by multivariate and propensity adjustment [61].

Side effects

Hypovolemia, hypokalaemia, hypomagnesemia, hyponatremia, hypercalcemia and hyperchloremic alkalosis are all well-known side effects of thiazides. A significant dose-dependent decline of serum potassium has been consistently reported with all thiazides [−0.25 mEq/l (95% CI −0.28 to −0.22)] [47]. Other metabolic adverse effects of chronic thiazide use are hyperglycaemia and hyperuricemia. Hyperglycaemia may depend on hypokalaemia because low-plasma potassium impairs insulin secretion [62]. Decreased glucose uptake into skeletal muscle, inhibition of Ca^{2+}-dependent release of insulin and hypovolemia-induced activation of the RAAS and sympathetic system may contribute to this side effect [43]. It has been estimated that chronic use of thiazides may lead to an excess of 3–4% of new cases of diabetes compared with other antihypertensive drugs [62].

Thiazides decrease urate clearance and increase serum urate levels by up to 35% in a dose-dependent manner. The mechanism underlying this phenomenon is increased urate

reabsorption in the proximal tubule dependent on the diuretic-induced volume contraction and impaired tubular secretion of uric acid, because thiazides and uric acid compete for the same tubular transporter [63, 64].

Adverse effects of thiazides are more common when these drugs are administered in high doses, in monotherapy and when longer-acting thiazide-like diuretics are used. In fact, indapamide induces changes in serum potassium and uric acid compared with chlorthalidone and metolazone. The risk of hypokalaemia is minimized by using low doses of thiazides and dietary salt restriction, or when these drugs are co-administered with a potassium-sparing diuretic or a RAASi. Furthermore, RAASis can limit the hyperglycaemic effect of thiazides by reducing insulin resistance. In patients predisposed to hyperuricemia, association with losartan may be preferred due its uricosuric property.

RCT with thiazide diuretics in CKD patients

In the last 25 years, six RCTs (including 383 patients overall) investigated the efficacy of thiazide diuretics in CKD [3, 65–69]. The first two trials in the mid-1990s assessed the acute natriuretic effect of combining a loop diuretic with a thiazide diuretic without reporting data on BP changes. In the same years, Fliser *et al.* [65], in a single-blind randomized crossover study in 10 CKD patients with inulin-measured GFR <25 ml/min/1.73 m^2, showed that the natriuretic action of torsemide was markedly increased by a thiazide diuretic (butizid). In a subsequent study in 19 CKD patients with a wide range of renal function (creatinine clearance 4–75 ml/min), furosemide 80 mg or the same drug at a lower dose (40 mg/day) plus hydrochlorothiazide at 25 mg/day [66] induced a significantly higher natriuresis as compared with the two drugs administered in isolation at higher doses, with the effect being more pronounced in patients with more preserved renal function [66].

Dussol *et al.* [67] performed a small randomized trial with a crossover design in seven patients with advanced CKD (GFR assessed by diethylenetriamine pentaacetate clearance of 25 ± 11 ml/min) comparing furosemide (60 mg/day) and hydrochlorothiazide (25 mg/day). Each treatment period lasted 1 month and there was a 1-month washout between the two treatments. At the end of the crossover phase, the combination therapy was administered for an additional month. In this small trial, hydrochlorothiazide, but not furosemide, significantly increased fractional sodium excretion, and the combination of the two drugs did not induce significantly higher natriuretic or antihypertensive effects. In contrast, the same authors tested the same protocol in a larger study (23 patients with stage 4–5 CKD) applying a longer washout period (3 months) [68]. In the trial the hydrochlorothiazide–furosemide combination prompted a larger natriuretic and hypotensive effect as compared with the same drugs administered in isolation. Also, 7 of 23 patients (30%) did not tolerate the combined regimen due to hypotension [68].

Until the CLICK study (see below), the largest trial testing chlorthalidone in CKD patients was a randomized, open-label, blinded endpoint trial that evaluated the effect on left ventricular mass (LVM; primary endpoint) of this drug (daily dose of 25 mg/day) compared with spironolactone (daily dose of 25 mg/day) in 154 patients with non-diabetic stage 2–3 CKD who were on the maximal tolerated dose of RAASi [69]. After 40 weeks of treatment, the reduction of LVM with chlorthalidone (−4 ± 12 g) did not differ from that observed with spironolactone (−9 ± 11 g); the same held true in a sensitivity analysis comparing patients receiving full-dose treatment (chlorthalidone, n = 52/77; spironolactone, n = 50/77). Chlorthalidone was effective in reducing office and 24-hour ABP, with the latter from 128/80 mmHg to 121/75 mmHg. The mean change in serum potassium with chlorthalidone was −0.3 ± 0.4 mEq/l at week 40. Overall, chlorthalidone was poorly tolerated in 30% of patients. The dose of this drug had to be either reduced (n = 4) or permanently discontinued (n = 19) due to side effects (n = 11), estimated GFR (eGFR) decline >30% (n = 10), symptomatic hypotension (n = 1) or hyponatremia (n = 1). Therefore this trial indicates close monitoring of adverse events in patients with mild to moderate CKD.

Chlorthalidone in stage 4 CKD patients

In a recent trial by Agarwal *et al.* [3], stage 4 (eGFR 15–30 ml/min/1.73 m^2) CKD patients revealed in full the relevant antihypertensive potential of this drug in CKD. In this trial, 160 patients with uncontrolled hypertension (confirmed by 24-hour ABP monitoring) were randomized to receive chlorthalidone (12.5 mg/day up-titrated to 50 mg/day, if needed) or placebo for 12 weeks. At baseline, the mean eGFR was 23.2 ml/min/1.73 m^2 (SD 4.2) and the mean number of antihypertensive medications prescribed was 3.4 (SD 1.4), with 60% of the study population receiving loop diuretics. At baseline, the mean 24-hour SBP was 143 mmHg (SD 8) in the chlorthalidone group and 140 mmHg (SD 8) in the placebo group, respectively. The adjusted change in 24-hour SBP from baseline to 12 weeks was −11 mmHg (95% CI −14 to −8 mmHg) in the chlorthalidone group, while no change (−0.5 mmHg) occurred in the placebo group. The BP-lowering effect of chlorthalidone was paralleled by favourable changes in albuminuria. Indeed, the urinary albumin:creatinine ratio change across the trial was 50% more in the chlorthalidone group than in the placebo group. Similarly, the decline of N-terminal pro-brain natriuretic peptide level at week 12 was 21% higher in the chlorthalidone than in the placebo group. Changes in plasma renin and aldosterone levels in the chlorthalidone group were consistent with changes in body fluid volume and, together with BP and albuminuria, in large part reverted by 2 weeks after treatment discontinuation. A synergistic effect for natriuresis exists between chlorthalidone and furosemide in patients with refractory HF [56] and such a synergism may also hold true in stage 4 CKD patients.

Hypokalaemia, reversible increases in serum creatinine level, hyperglycaemia, dizziness and hyperuricemia occurred more frequently in the chlorthalidone group than in the placebo group. However, serious adverse events requiring hospitalization were similar between groups (8 events in the chlorthalidone group versus 11 events in the placebo group). Furthermore, in a post-trial observational follow-up extended up to 3 years, 29 patients in the placebo group and 20 in the chlorthalidone group had an eGFR decrease to <10 ml/min/1.73 m^2, started dialysis or died, possibly suggesting a favourable impact of chlorthalidone on major clinical events.

As previously alluded to, erythrocytes serve as a reservoir for chlorthalidone and the half-life of this drug is 45–60 hours with an effect on BP extended up to 72 hours [70]. The lasting effects on BP and fluid volume in Agarwal's trial confirm the long duration of action of chlorthalidone [3]. Chlorthalidone is mostly eliminated as an unmodified molecule by renal excretion and therefore the longer half-life of this drug in patients with kidney insufficiency may contribute to its lasting hypotensive action in CKD patients [45]. As in previous BP-lowering trials, changes in eGFR were most likely due to reduced BP. Indeed, these changes were fully reversible after drug discontinuation and were not

considered to be of clinical relevance. Accordingly, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, the risk for kidney failure in patients randomized to chlorthalidone did not differ from that in patients randomized to amlodipine or lisinopril [71].

Like the parallel eGFR reduction, the lowering effect on albuminuria rapidly reverted after chlorthalidone discontinuation. Such an observation suggests that, as for other drugs, this is a haemodynamic effect triggered by reduced BP and possibly a potentiation of the effect of RAASis [72]. Since albuminuria is a surrogate of cardiorenal risk [73], chlorthalidone may provide cardiovascular and renal protection in CKD patients. In this respect, evidence that thiazide-type diuretics may reduce cardiovascular risk in patients without CKD exists [54, 55]. Thus chlorthalidone—a drug patented in 1957 that came into medical use in 1960—may represent an important addition to the armamentarium available to nephrologists to counter the high cardiorenal risk of patients with CKD. However, caution is needed when using this drug in CKD patients on loop diuretics, because the risk of a reduction in eGFR is augmented in these patients. Chlorthalidone in CKD patients should be introduced gradually starting with 12.5 mg every other day [74]. Dose escalation should be applied with a vigilant attitude, i.e. by measuring BP frequently and advising patients on how to deal with possible side effects. In highly responsive patients, diuretic treatment optimization may also demand a down-titration of loop diuretics. Finally, we should not forget that the ground-breaking trial by Agarwal *et al.* was based on a relatively small number of patients and did not look at hard endpoints [3]. Therefore, despite the favourable results for BP control with chlorthalidone in patients with advanced CKD, phase 3 trials based on cardiovascular and renal endpoints are still needed to prove that this result translates effectively and safely in the prevention of cardiorenal events.

Given the high number of antihypertensive drugs that CLICK patients were taking at baseline [3.4 (SD 1.4)], the vast majority of these were de facto patients with treatment-resistant hypertension. Spironolactone is recommended as a fundamental drug in resistant hypertension. However effective, this drug imposes a doubling in the risk of hyperkalaemia as compared to angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [75]. The use of patiromer mitigates the risk of hyperkalaemia by spironolactone in stage 3–4 CKD patients with resistant hypertension [76]. However, approximately one in three patients on spironolactone and patiromer still experience hyperkalaemia (serum potassium $\geq$5.5 mEq/l) [76]. In general, spironolactone remains underutilized in resistant hypertension, particularly in CKD patients with this condition. Findings in the CLICK study suggest that chlorthalidone may be a good alternative in the treatment of resistant hypertension in stage 4 CKD patients experiencing adverse effects to spironolactone.

Closing remarks

Hypervolemia is the main causative factor for hypertension in CKD patients and diuretics are central to improve BP control in CKD. Among stage 4 CKD patients, loop diuretics are recommended over thiazides. Thiazide diuretics have long been considered ineffective in this population. This review of the literature suggests that thiazides may be useful even among people with advanced CKD. These drugs cause a negative sodium balance and reduce body fluids by 1–2 l and these effects go hand in hand with improvement in hypertension control. The CLICK trial highlighted the great potential of chlorthalidone for the treatment of stage 4 CKD patients with poorly controlled hypertension and suggests that this drug may be a good alternative to spironolactone in treatment-resistant hypertension with and without CKD. Hyponatremia, hypokalaemia, volume depletion and acute kidney injury are side effects that demand a vigilant attitude from physicians prescribing these drugs. Larger trials in advanced CKD focusing on antihypertensive and anti-albuminuric effects of chlorthalidone, and possibly also on hard outcomes, are still necessary to more confidently recommend the use of these drugs in these frail patients at high risk of iatrogenic adverse events.

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CONFLICT OF INTEREST STATEMENT

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