Literature analysis suggests chlortalidone as first-line antihypertensive agent outperforms hydrochlorothiazide

Chlortalidone: outdated or reborn?

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Summary

Most current guidelines on hypertension regard thiazide and thiazide-like diuretics as equivalent for the first-line treatment of essential hypertension. However, hydrochlorothiazide has been favoured over the thiazide-like chlortalidone in clinical practice for unclear reasons. Although definite scientific evidence is lacking, an objective analysis of the literature indicates that chlortalidone is superior to hydrochlorothiazide regarding blood pressure control and major health outcomes. Haemodynamic, as well as nonhaemodynamic pleomorphic effects could account for these differences. Moreover, the safety profiles of the two molecules seem comparable. Initial concerns about adverse effects, the relative lack of single-pill combination and economical interests have presumably prevented the widespread use of chlortalidone over the years. Based on the available evidence, we think that chlortalidone and thiazide diuretics should not be regarded as equivalent and encourage clinicians to consider chlortalidone as a potential first-line antihypertensive agent.

Key words: hypertension; diuretic; thiazide-like; chlortalidone; hydrochlorothiazide

Introduction

Thiazide and thiazide-like diuretics are old drugs that are nowadays currently used in the daily management of hypertension. Chlortalidone belongs to the thiazide-like group and possesses distinct properties from the more commonly used thiazides such as hydrochlorothiazide. Despite several years of clinical experience and many clinical trials involving both drugs, it is still debated if one molecule is superior to the other. In recent years, interest in chlortalidone has been increasing as new clinical data have been published [1, 2]. Most current guidelines on hypertension, however, still consider thiazide and thiazide-like diuretics as equivalent [3–5]. In this article, we will summarise the available scientific literature on the clinical use of chlortalidone to help the physician in best treating hypertensive patients.

Pharmacology

Chemical structure

Chlortalidone is considered a thiazide-like diuretic as it shares with chlorothiazide a functional sulphonamide group that interacts with carbonic anhydrase, but does not belong to the benzothiadiazine chemical class [6].

Pharmacodynamics

Thiazides and thiazide-like diuretics act via inhibition of the Na^+/Cl^- co-transporter (NCC) in the distal convoluted renal tubule, which accounts for approximately 7% of total sodium reabsorption. In parallel to the decreased sodium reabsorption, there is an increased urinary output resulting in a diminished effective circulating volume. This volume loss results in decreased preload, cardiac output and blood pressure. During the acute phase, volume expansion is able to restore blood pressure to pretreatment levels. After a few months of treatment, however, volume expansion can no longer increase blood pressure to baseline levels. Cardiovascular physiology suggests that a lowering in total peripheral resistances could contribute to the persistent hypotensive effect of thiazide and thiazide-like diuretics. These molecules have indeed shown a vasodilatory effect in various experimental settings [7]. A direct action on the endothelium was suggested by a study showing that methyclothiazide inhibits the contractile response induced by noradrenaline in aortic rings from spontaneously hypertensive rats. This effect was attenuated after mechanical removal of the endothelium [8]. Evidence is conflicting, as other studies have showed that thiazide-like diuretics inhibited angiotensin II- and noradrenaline-induced vasoconstriction of rat aortic rings in the presence and the absence of the endothelium [9], favouring an endothelium-independent mechanism. On a molecular level, the large conductance Ca^{2+}-activated K^+ channel located in the vascular wall seems to play a pivotal role, as hydrochlorothiazide vasodilatation was reduced in the presence of an inhibitor of this channel both *in vitro* and *in vivo* [10, 11]. Finally, there is evidence that the long-term vasodilatory effect is mediated systemically rather than locally by a vascular action. A long-standing hypothesis states that vessels initially constrict to maintain blood pressure in the face of thiazide-induced volume loss and decreased cardiac output. Over time, vasoconstriction is inhibited by a systemic regulatory mechanism to increase cardiac output to baseline levels [12]. Thus, according to this hypo-

thesis, direct inhibition of the NCC and the resulting sodium-induced fluid loss would be responsible for both the acute volume-mediated phenomenon and the later vasodilatation-mediated blood pressure response. In agreement with this, some studies showed that thiazide-induced blood pressure lowering was mediated by total sodium balance, as the addition of an extra 20 g of dietary salt daily returned blood pressure to pre-treatment level [13].

Pharmacokinetics

Chlortalidone serum concentrations peak 2 to 6 hours after a single oral dose, and the mean half-life is approximately 42 hours with a high interindividual variability (29–55 hours) [14]. After absorption, chlortalidone rapidly concentrates in erythrocytes, where a subsequent slow release could explain the notably long half-life [15]. The optimal dose and its equivalence with hydrochlorothiazide remain a subject of debate. Low doses of chlortalidone (12.5–25 mg) seems to offer the most favourable potency-to-side-effect ratio, representing 50 to 75% of the typical hydrochlorothiazide dose [6]. Thus, these diuretics should not be regarded as equipotent [16]. The chlortalidone dose-serum concentration curve flattens at high doses: the serum concentration after a 100-mg dose is only doubled compared with 25 mg, potentially explaining the rather low clinically optimal dose range [6].

Clinical data

Overview

Thiazide diuretics are the cornerstone of treatment of hypertension for most patients. Hydrochlorothiazide is the 10th most commonly prescribed drug in the United States and is used 20 times more frequently than chlortalidone [17]. These prescribing practices are surprising, as many important clinical trials of antihypertensive treatments have used chlortalidone-based rather than hydrochlorothiazide-based regimens [1, 18]. Although most international guidelines do not recommend one diuretic over the other [3–5], British guidelines favour chlortalidone [19]. Similarly, specific guidelines regarding management of resistant hypertension and hypertension in black patients prefer chlortalidone to thiazide diuretics [20, 21].

In this section, we evaluate the scientific evidence supporting the use of chlortalidone over other diuretics in clinical practice. The clinical trials discussed are summarised in table 1.

Blood pressure control

One cannot expect significant clinical outcomes to be achieved with an antihypertensive agent if it does not achieve adequate blood pressure control. Thus, before considering meaningful practical use, the efficiency of chlortalidone as a blood pressure lowering agent has to be assessed. Chlortalidone is an effective antihypertensive agent, as demonstrated by several studies [31, 32]. However, relatively few studies have directly compared blood pressure control with chlortalidone versus another diuretic.

In 2006, Ernst et al. specifically addressed this question and conducted a small randomised, single-blind, 8-week active treatment, crossover study comparing chlortalidone with hydrochlorothiazide in untreated hypertensive patients [25]. Thirty patients were randomised to receive either chlortalidone 12.5 mg/day (titrated to 25 mg/day) or hydrochlorothiazide 25 mg/day (titrated to 50 mg/day). After 8 weeks, ambulatory blood pressure monitoring (ABPM) showed a significantly greater reduction compared with baseline in 24-hour mean systolic blood pressure (SBP) and night-time mean SBP (but not daytime mean SBP) in the chlortalidone group versus the hydrochlorothiazide group. This effect was not statistically significant for office blood pressure measurements. This well-designed study was the first to directly compare the effects of chlortalidone with hydrochlorothiazide on ABPM endpoints and allowed several interesting conclusions to be drawn. First, the superior performance of ABPM over office measurement on blood pressure monitoring is highlighted. Second, the improved dipping status under chlortalidone could be linked to the extended half-life of the molecule, which offers a rationale for the potential impact on clinical outcomes, as night-time readings correlate more closely than office measurements with cardiovascular events [33]. Lastly, the direct comparison of these two diuretics with the use of ABPM endpoints confirms that chlortalidone is approximately twice as potent as hydrochlorothiazide at usual doses.

Bakris et al. observed similar findings in 2012 in their randomised double-blind study comparing coadministration of azilsartan with either chlortalidone or hydrochlorothiazide in patients with stage 2 primary hypertension [34]. Both diuretics were titrated from 12.5 to 25 mg to achieve target blood pressure, for 8 weeks. The chlortalidone group showed a greater reduction in office SBP as well as in 24-hour mean SBP after 4 and 8 weeks of treatment. Moreover, fewer patients in the chlortalidone group needed dose up-titration to achieve target blood pressure. Nocturnal dipping, however, was not different between groups, with the exception of early

Table 1: Clinical data.

Reference	Design	N	Population	Follow-up	Primary endpoint	Groups	Result of interest
SHEP 1991 [18]	RCT	4736	Isolated systolic HT (>60 yo)	4.5 years	Total stroke incidence	CTD vs placebo	Relative risk of stroke of 0.64 for CTD vs placebo (p = 0.0003)
MRFIT 1990 [22]	Cohort study Retrospective analysis	8012	High-risk HT (35–57 yo)	10.5 years	All cause mortality	SI group* vs UC group*	Improvement of CHD mortality rate from +44% to –28% for SI group* vs UC group* in H-clinics** before and after diuretic protocol change respectively*** (p = 0.04)
MRFIT 2011 [23]	Cohort study Retrospective analysis	6441	High-risk HT (35–57 yo)	6 years	CVE	CTD vs HCTZ	Relative risk of CVE of 0.79 for CTD vs HCTZ (p = 0.0016)
MRFIT 2012 [24]	Cohort study Retrospective analysis	8012	High-risk HT (35–57 yo)	7 years	Left ventricular hypertrophy	C-clinics** vs H-clinics**	Differences in left ventricular mass between SI* and UC groups* were larger for C-clinics** vs H-clinics** (p = 0.002)
ALLHAT 2002 [1]	RCT	33357	High-risk HT (>55 yo)	4.9 years	Fatal or nonfatal coronary events	CTD vs amlodipine vs lisinopril	Relative risk of heart failure of 1.38 for amlodipine vs CTD (p <0.001) Relative risk of CVE of 1.10 for lisinopril vs CTD (p <0.001)
Ernst et al. 2006 [25]	RCT	30	HT and pre-HT (18–79 yo)	8 weeks	ABPM	CTD vs HCTZ	CTD showed a greater systolic BP reduction compared to HCTZ (p = 0.054)
Psaty et al. 2004 [26]	Meta-analysis (5 studies)	15086	NA	NA	CVE	CTD vs non-CTD diuretics	No difference in major health outcomes
Ernst et al. 2010 [27]	Meta-analysis (108 studies)	10443	NA	NA	Systolic BP and serum potassium	CTD vs HCTZ	CTD showed a greater systolic BP reduction compared with HCTZ (p <0.05)
Roush et al. 2012 [28]	Meta-analysis (9 studies)	78350	NA	NA	CVE	CTD vs HCTZ	Relative risk of CVE of 0.79 for CTD vs HCTZ (p <0.0001)
Dhalla et al. 2013 [29]	Cohort study Retrospective analysis	29873	Newly treated patients (>66 yo)	255 days (CTD); 398 (HCTZ)	Composite of death and CVE	CTD vs HCTZ	No difference in major health outcomes
Pareek et al. 2016 [30]	RCT	54	Stage I HT (18–65 yo)	12 weeks	ABPM	CTD vs HCT vs HCT-XR	CTD showed a greater systolic BP reduction compared with HCTZ (p = 0.013)

ABPM = ambulatory blood pressure monitoring; BP = blood pressure; CTD = chlortalidone; HCTZ = hydrochlorothiazide; HT = hypertension; yo = years old; NA = not applicable; XR = extended release; RCT = randomised controlled trial; CVE = cardiovascular events.
* SI = special intervention; UC = usual care (see text).
** C-clinics and H-clinics: Clinics predominantly using chlortalidone and hydrochlorothiazide, respectively (see text).
*** See text.

morning trough SBP which differed in favour of chlortalidone.

Finally, Ernst et al. conducted a meta-analysis in 2010, pooling data from 108 clinical trials that compared either chlortalidone or hydrochlorothiazide to other treatments as antihypertensive monotherapy [27]. The authors showed that chlortalidone offers a greater reduction of SBP than hydrochlorothiazide over the 12.5 to 25 mg dose range. However, the authors themselves noted that this equivalence analysis is limited by highly heterogeneous data gathered from studies spanning a 60-year period.

Mortality, and cardiovascular and other clinical outcomes

Although blood pressure control is a prerequisite for any antihypertensive regimen, modifying tangible clinical outcomes is the long-term goal of any well-conducted treatment. It is well established that diuretics lower the global cardiovascular risk compared with placebo [35]. However, to date no prospective study has directly compared the effects of chlortalidone with another diuretic on a clinical primary endpoint. Hence, most evidence come from retrospective analysis of large cohorts or network meta-analysis.

In 1991, the Systolic Hypertension Elderly Program (SHEP) trial was the first clinical study to show that blood pressure control in patients with isolated systolic hypertension reduced the incidence of cardiovascular events [18]. This multicentre, randomised, double-blind, placebo-controlled trial enrolled 4736 patients aged 60 years or more for an average follow-up of 4.5 years. Step 1 treatment consisted of chlortalidone 12.5 mg/day uptitrated to 25 mg/day. Atenolol was added as step 2 therapy to achieve the blood pressure goal, if needed. Compared with placebo, chlortalidone reduced total stroke incidence (primary endpoint) and global cardiovascular events (secondary endpoint) by 37 and 32%, respectively. However, all-cause mortality and cardiovascular mortality were not different between groups. Recently, Kos-

tis et al. conducted an extended 22-year follow-up analysis of the original SHEP cohort [36]. Results showed that initial chlortalidone-based therapy for 4.5 years was associated with higher survival rates and a gain in life expectancy compared with placebo. Since all participants were advised to take active therapy after the initial randomised phase, these findings illustrate a potential "legacy effect" of early chlortalidone treatment. Alternatively, confounding variables could explain these findings, as conditions were not standardised during the 22-year extended follow-up.

The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) enrolled more than 30 000 hypertensive patients from 1994 to 2002 [1]. Participants were randomly assigned to receive chlortalidone (12.5–25 mg/day), lisinopril or amlodipine. After a mean follow-up of 4.9 years, no difference between treatments was found in the rate of myocardial infarction (primary outcome) or mortality. However, chlortalidone was proved to be superior in preventing secondary outcomes. Indeed, the heart failure rate increased by 38% with amlodipine and lisinopril showed 10% higher rates of combined cardiovascular events. In a subsequent study published in 2012, the same cohort was observed for a total follow-up of 8 to 13 years under uncontrolled conditions [2]. Results were virtually identical: chlortalidone reduced the heart failure rate compared with amlodipine and stroke mortality compared with lisinopril. Like the original analysis, the extended follow-up data showed an interaction between treatment and race, as black patients had a higher risk of cardiovascular disease than non-black patients on lisinopril compared with chlortalidone. These findings are in agreement with the known poorer blood pressure response to angiotensin converting-enzyme (ACE) inhibitors in black patients [37].

A third important source of clinical data involving chlortalidone treatment on a large population is the Multiple Risk Factor Intervention Trial (MRFIT), which was a large primary prevention trial that began in 1973 [38]. In this study, 12 866 patients were randomly assigned to two groups: a special intervention (SI) programme providing standard pharmacological treatment associated with lifestyle modification counselling, and a usual care (UC) group received treatment of their risk factors by their usual source of care within the community. Initial therapy in the SI group was either chlortalidone or hydrochlorothiazide, with the choice left to the local clinical staff in a nonrandomised manner. After 5 years, the nine clinics that predominantly used hydrochlorothiazide had a mortality rate 44% higher in the SI group than in the UC group. The safety committee then changed the treatment protocol to exclusive use of chlortalidone. The same nine clinics subsequently had a 28% lower risk of mortality in the SI group than in the UC group [22]. A possible explanation was that hydrochlorothiazide induced a mortality excess compared with chlortalidone. Alternatively, the authors could have just witnessed a delayed favourable effect of their intervention on cardiovascular events. However, one must bear in mind that these data come from a retrospective analysis of a study that used diuretics in a nonrandomised fashion and was not designed to provide direct comparison between chlortalidone and hydrochlorothiazide. Given these intriguing findings, several retrospective analyses of the MRFIT cohort were published thereafter. Dorsch et al. confirmed in 2011 in a *post-hoc* analysis that chlortalidone significantly reduced cardiovascular events as compared with hydrochlorothiazide [23]. The same year, Ernst et al. showed that the incidence of left ventricular hypertrophy (LVH) was significantly lower for patients receiving chlortalidone than with hydrochlorothiazide [24]. As LVH is strongly influenced by blood pressure and is an established risk factor for coronary heart disease, the authors concluded that greater blood pressure reduction under chlortalidone had led to more favourable cardiovascular outcomes in these patients during the MRFIT trial [39]. Because they are retrospective *post-hoc* analyses of the original MRFIT cohort, these two studies suffer from the same limitations as the initial 1990 report [22].

In 2013, Dhalla et al. published an observational cohort study aiming to compare the effectiveness and safety of chlortalidone and hydrochlorothiazide in older adults [29]. They found no difference in major health outcomes. However, a composite primary outcome comprising death and hospitalisation for cardiovascular events, and a median follow-up of only 255 days in the chlortalidone group, could have biased the results toward finding no difference between treatments.

Because of the importance of the problem and the lack of a direct prospective comparison between chlortalidone and other antihypertensive treatments, two network meta-analyses have been conducted. This type of analysis pools several randomised controlled trials in which one arm includes either one of the two drugs of interest and the other represents a shared reference arm. It is considered a statistically more robust analysis than observational cohort studies [40]. One of these studies conducted by Roush et al. in 2012 included nine randomised controlled trials comparing effects of either chlortalidone or hydrochlorothiazide on cardiovascular endpoints with other treatments [28]. In a first drug-adjusted analysis, the risk for cardiovascular events was reduced by 21% in the chlortalidone arm compared with hydrochlorothiazide. In a second blood pressure-ad-

justed analysis, both diuretics reduced cardiovascular risk but chlortalidone offered a greater reduction of that risk for any given blood pressure reduction. This suggested that the superiority of chlortalidone might be driven by pleomorphic, nonhaemodynamic effects. Psaty et al. conducted another network meta-analysis in 2004 without finding any differences in major health outcomes [26]. This study, however, excluded three large trials (ALLHAT, ACCOMPLISH and ANBP2), all favouring chlortalidone in network analysis [17]. Moreover, this study compared chlortalidone with any non-chlortalidone diuretic, preventing indirect comparison with a specific molecule.

Hypokalaemia

Hypokalaemia is probably the main safety concern related to diuretic therapy as it is associated with ventricular arrhythmia [41]. Both hydrochlorothiazide and chlortalidone induce hypokalaemia in a dose-related fashion [31, 42], but whether this increases arrhythmogenic risk is unclear. In 1994, Siscovick et al. conducted a case-control study showing that high-dose (100 mg) diuretics (hydrochlorothiazide or chlortalidone) were associated with an increased risk of cardiac arrest compared with low-dose therapy (25 mg) [43]. In addition, the risk of cardiac arrest was decreased in patients taking a diuretic combined with a potassium-sparing agent, suggesting that resolution of hypokalaemia could account for the decreased cardiac risk. A randomised controlled trial conducted by Siegel et al. in 1992 comparing various diuretic combinations (including hydrochlorothiazide and chlortalidone monotherapy) showed that severe hypokalaemia (<3.0 mmol/l) was associated with an increased risk of ventricular arrhythmia [44]. However, they found no association between diuretic use and arrhythmic events, and whereas chlortalidone was associated with a higher proportion of cases of moderate hypokalaemia (<3.5 mmol/l) compared with hydrochlorothiazide, it was not associated with an increased risk of arrhythmia. Finally, several other previously cited studies analysed hypokalaemia incidence as a secondary outcome. In the 2006 study of Ernst et al., chlortalidone (12.5–25 mg) did not seem to increase the risk of hypokalaemia compared with hydrochlorothiazide (25–50 mg) [25]. In the trial reported by Bakris et al., despite the fact that hydrochlorothiazide and chlortalidone were prescribed at the same dose, hypokalaemia was infrequent (<2%) in patients taking chlortalidone and the rate of adverse events resulting in drug discontinuation was not different between groups [34]. In the 2010 meta-analysis by Ernst et al., although chlortalidone induced a slightly greater potassium loss than hydrochlorothiazide over the 12.5 to 25 mg dose range, the global incidence of hypokalaemia could be viewed as identical according to an equivalence analysis [27]. Finally, in Dhalla et al., a 2013 observational study, the authors found an increased incidence of hypokalaemia with chlortalidone [29]. However, patients treated with chlortalidone were prescribed higher doses than those of hydrochlorothiazide and were less likely to be treated simultaneously with renin-angiotensin inhibitors.

Discussion

Despite similarities, thiazides and thiazide-like diuretics are not alike. Specific molecular, cellular, organic and systemic characteristics can account for clinically relevant differences. Enough evidence to allow definite conclusion is lacking, but chlortalidone seems to offer a slightly better clinical performance than other diuretics, namely hydrochlorothiazide. Here we have reviewed several hypotheses potentially accounting for these differences and explored possible reasons for underutilisation of chlortalidone.

Blood pressure control is an essential element of cardiovascular risk factor reduction, and chlortalidone seems to perform better than thiazide diuretics. In particular, hydrochlorothiazide, because of its shorter half-life, leaves night-time blood pressure inadequately controlled compared with chlortalidone. As nocturnal dipping status is strongly correlated with cardiovascular outcomes, this could account for clinically relevant differences not apparent on office blood pressure monitoring [30].

Meaningful clinical impact may also stem from nonhaemodynamic pleomorphic effects not shared by traditional thiazide diuretics. Thiazides and thiazide-like diuretics were initially developed as an effort to produce more potent carbonic anhydrase inhibitors. Although these two types of diuretic bind nearly equally to the NCC in the distal renal tubule, they differ in their ability to inhibit carbonic anhydrase. Inhibition of carbonic anhydrase pathways decreases catecholamine-mediated platelet aggregation and vascular contractility [45]. Thus, chlortalidone has been shown to reduce platelet aggregation and vascular permeability, as well as promote angiogenesis *in vitro* [46]. Differences in these pleiotropic effects could potentially explain the contrasting ability of different diuretics to reduce cardiovascular morbidity despite comparable reductions in blood pressure.

The potential adverse metabolic effects of thiazides and thiazide-like diuretics include elevations in plasma glucose and cholesterol [47]. In the 2011 retrospective analysis of the MRFIT cohort, patients under chlortalidone had lower low-density lipoprotein and glucose levels

compared with the hydrochlorothiazide group [23]. The reason for this improved metabolic profile is unknown, but authors postulated that it could contribute to the ability of chlortalidone to improve cardiovascular outcome.

In recent years, chlortalidone use seems to have significantly increased, but it still accounts for a very small proportion of total prescriptions for thiazide-type diuretics [48]. Clinicians seem to prefer hydrochlorothiazide as monotherapy, whereas chlortalidone is more commonly added to an existing regimen [48]. Although the latter indication is in agreement with existent guidelines on resistant hypertension, reasons for underutilisation of chlortalidone as a first-line agent are not entirely clear [21]. Initial concerns related to hypokalaemia may have contributed, possibly influenced by the historical use of higher doses (50–100 mg/day) than usually prescribed nowadays and the absence of coadministration with an ACE inhibitor or angiotensin II receptor blocker [22]. The relative lack of single-pill combinations containing chlortalidone might also play a role. So far, the only two combinations available are atenolol/chlortalidone and the newer azilsartan/chlortalidone, which recently proved to be effective and safe [34]. In Switzerland, these two single-pill combinations are marketed under the trade names Tenoretic® and Edarbyclor®, respectively. Finally, economic reasons could account for the relative lack of pharmaceutical involvement in this rather old molecule, although we were not able to find reliable marketing data to support this hypothesis. As an example, chlortalidone monotherapy is not available in Switzerland anymore. From a broader perspective, it has to be noted that, despite most current guidelines, general practitioners seem reluctant to prescribe diuretics as a first-line monotherapy, probably owing to subjective concerns about insufficient blood pressure lowering and potential side effects [49].

It must be remembered that chlortalidone is not the only thiazide-like diuretic available: indapamide and metolazone offer interesting properties as well. Indapamide provided the highest systolic blood pressure reduction in a 2005 meta-analysis comparing several commonly used antihypertensive agents [50]. Moreover, this molecule has been shown to favourably affect important cardiovascular endpoints such as LVH and albuminuria [51, 52]. Two important studies, PROGRESS and HYVET, showed highly favourable clinical outcomes with the perindopril-indapamide combination [53, 54]. Metolazone, on the other hand, has been extensively used as an additional agent to overcome loop-diuretic resistance in acute decompensated heart failure achieving a "sequential nephron blockade" [55]. This molecule, however, has a slow and erratic pattern of absorption which explains the unpredictable diuretic response when it is used in a multidrug regimen [56]. Metolazone is also thought to retain its efficiency in chronic kidney diseases such as renal failure and nephrotic syndrome [57]. Globally, it must be remembered that prospective head-to-head comparisons between hydrochlorothiazide and different thiazide-like diuretics are lacking.

Conclusion

Chlortalidone is not a new molecule. Although thiazide-related, chlortalidone possesses distinct chemical, physiological and clinical properties. Its potency has been attested in several of the largest clinical trials ever conducted on cardiovascular risk reduction in hypertensive patients. Although strong evidence favouring one molecule over another is lacking, chlortalidone as a first-line antihypertensive agent seems to outperform hydrochlorothiazide in respect of major health outcomes. There were initial safety concerns about a higher risk of hypokalaemia, but appropriate dosing and association with a potassium-sparing agent proved to be safe in clinical practice. Despite an increase in chlortalidone use in recent years, hydrochlorothiazide remains the most prescribed diuretic. Given the strong need for low-cost, evidence-based strategies in the management of hypertension, clinicians should strongly consider chlortalidone as part of their first-line therapeutic arsenal.

In Switzerland, chlortalidone as monotherapy is not available anymore, and thiazide-like diuretics are mainly represented by indapamide and metolazone, which also have distinct interesting properties. The single-pill combination azilsartan/chlortalidone is, however, marketed and should be regarded as a potential first-line treatment in the appropriate clinical context.

Practitioners must bear in mind that comorbidities must be fully taken into account when selecting an antihypertensive regimen, as diuretics might not represent an optimal first choice in the presence of compelling evidence for another specific class of medication.

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