EXPERT OPINION

Diuretics in the treatment of hypertension. Part 1: thiazide and thiazide-like diuretics

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Introduction: Thiazides and thiazide-like diuretics inhibit the electroneutral Na^+–Cl^- cotransporter located on the apical membrane of the early segment of the distal convoluted tubule. They have been widely prescribed over 60 years in the treatment of hypertension and various edematous states.
Areas covered: Thiazide diuretics reduce blood pressure (BP), although the mechanisms by which they chronically lower BP remain unknown. These drugs present a flat dose–response curve that explains why when prescribed at high doses their use was associated with a wide range of adverse effects, particularly electrolyte changes and metabolic abnormalities that can be minimized at the low doses actually prescribed. This article reviews the clinical pharmacology of thiazide diuretics to provide an insight into the mechanisms involved in their antihypertensive and adverse effects, the determinants of drug response and the possible differences in their pharmacodynamic and pharmacokinetic properties in an attempt to improve their clinical use in the treatment of arterial hypertension.
Expert opinion: At low doses, thiazide diuretics remain as an effective and safe therapeutic alternative in the treatment of hypertension. Additionally, their ability to increase the efficacy of nearly all other classes of antihypertensives makes them a highly versatile therapeutic intervention in the treatment of hypertension.

Keywords: arterial hypertension, chlorthalidone, diuretics, hydrochlorothiazide, indapamide, thiazide-like diuretics, thiazides

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1. Introduction

Diuretics are drugs that increase the renal excretion of Na^+ and water (natriuresis) due to a direct action at different tubular sites of the nephron where solute reabsorption occurs [1-3]. The main effect is to reduce the reabsorption of Na^+, with increased water loss occurring as a secondary consequence. Their ability to alter long-term sodium balance induces important hemodynamic changes that result in a reduction in peripheral vascular resistances (PVR) and sustained reduction in blood pressure (BP).

Thiazide diuretics were launched in 1957, and according to their chemical structure, they have been classified in two groups, thiazides and thiazide-like diuretics. For more than five decades, thiazide and thiazide-like diuretics have been a mainstay in the treatment of hypertension, alone or in combination with other antihypertensive drugs as they provide additive BP-lowering effects. Low-renin patient groups (e.g., blacks, elderly, and diabetics) and those with metabolic syndrome are commonly more responsive to these drugs. Additionally, thiazides and thiazide-like diuretics are also widely used in volume-overload conditions such as heart failure (HF) and chronic kidney disease (CKD). But even when thiazides and thiazide-like diuretics present a common mechanism of action, there are some differences in their off-target effects and in the incidence of adverse effects, and important differences

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Article highlights.

- Thiazide diuretics have been widely prescribed for > 60 years in the treatment of hypertension and various edematous states.
- They inhibit Na^+ reabsorption by blocking the Na^+–Cl^- cotransporter located on the apical membrane of the early segment of the distal convoluted tubule. Thiazide diuretics lower blood pressure by complex mechanisms that involve direct renal and endothelial and vascular effects and indirect regulatory mechanisms via a chronic response to the acute decrease in cardiac output leading to a reduction in peripheral vascular resistances.
- Thiazide diuretics present important differences in potency and pharmacokinetic properties that can influence their antihypertensive effect and the incidence of adverse effects.
- At high doses, they produce a high incidence of electrolyte changes and metabolic abnormalities. However, these drugs present a flat dose–response curve, so that at low doses, it is possible to achieve an optimal antihypertensive effect and minimize the incidence of adverse effects.
- Thiazide diuretics should be considered among the first-choice drugs in the treatment of arterial hypertension because they have been demonstrated to reduce cardiovascular morbidity and mortality in hypertensive patients and their ability to increase the efficacy of nearly all other classes of antihypertensive agents makes them a highly versatile therapeutic intervention.

This box summarizes key points contained in the article.

in their pharmacokinetic characteristics. These drugs present a flat dose–response curve, so that at high doses there is a significant increase in the incidence of dose-dependent electrolyte (hypokalemia, hypomagnesemia, hyponatremia) and metabolic disturbances (glucose intolerance and new-onset diabetes, hyperuricemia and lipid abnormalities) without a concomitant increase in their antihypertensive effectiveness. As expected, most of these disturbances can be minimized when using the low doses actually prescribed. Thus, it is of interest to review the clinical pharmacology of thiazide diuretics, including the mechanisms by which thiazide diuretics lower BP and cause adverse effects, the determinants of the antihypertensive responses and the differences in their pharmacodynamic and pharmacokinetic properties, in order to improve their use in the daily clinical practice.

2. History

The era of modern diuretic therapy began in 1957 with the synthesis of chlorothiazide. Shortly thereafter, modifications in the benzothiadiazine core led to the synthesis of other thiazides (bendroflumethiazide, cyclothiazide, hydrochlorothiazide [HCTZ], polythiazide) and thiazide-like diuretics (chlorthalidone [CTD], metolazone, indapamide, xipamide), a structurally diverse group of sulfonamide derivatives that do not contain the benzothiadiazine ring (**Figure 1**). The term "thiazide diuretics" will be used in the text to refer to all these compounds. Thiazide diuretics rapidly assumed a leadership position among antihypertensive drugs available at that time. Interestingly, in the first 10 – 20 years, thiazide diuretics were used at unnecessarily high doses (e.g., HCTZ > 100 mg/day, CTD 25 – 100 mg/day) in the treatment of hypertension [4]. In fact, in the *Multiple Risk Factor Intervention Trial* (*MRFIT*) both HCTZ and CTD were administered at doses of 50 or 100 mg/day [5]. The use of high doses was based on the hypothesis that the antihypertensive effect was directly linked to the amount of renal Na^+ excretion and the degree of reduction in plasma volume [2]. At these high doses, however, the use of thiazides was associated with a wide range of adverse effects, particularly hydroelectrolyte disturbances and metabolic disorders. However, in the 1980s and 1990s, several studies confirmed that thiazide diuretics presented a flat dose–response curve, so that near-maximal Na^+ excretion was achieved at relatively low doses of HCTZ (12.5 – 25 mg/day) and further increases in drug dose slightly increased Na^+ excretion but dose-dependently increased hydroelectrolytic and metabolic disorders [6-9]. These low doses of HCTZ were combined in multiple fixed-drug combinations with other antihypertensive drugs in an attempt to exert an additive decrease in BP derived from their different mechanisms of action and to counteract the increase in Na^+ and water retention that these antihypertensives produce. CTD was initially commonly prescribed, but the evidence from clinical trials was largely neglected for two main reasons: concerns about the risk of hypokalemia, an adverse effect frequently observed when CTD was prescribed at high doses (50 – 100 mg/day), and the lack of fixed-dose combinations [10]. However, even when the antihypertensive effect of CTD is similar in patients treated with 25, 50 and 75 mg/day, the risk of hypokalemia does not increase in those treated with the lower dose [11].

3. Mechanism of action

Thiazide-like diuretics inhibit Na^+ reabsorption by blocking the electroneutral Na^+–Cl^- cotransporter (NCCT) located on the apical membrane of the early segment of the distal convoluted tubule (DCT), where ~ 5 – 10% of the filtered Na^+ is normally absorbed probably by competing for the Cl^--binding site [12]. The human NCCT is a transmembrane protein 1002 – 1030 amino acids with a hydrophobic core of 12 - transmembrane domains and intracellular N and C terminus domains encoded by the *SLC12A3* gene located in 16q13 [13]. To reach their renal site of action, thiazide diuretics must be actively secreted via a renal organic anion transporter (rOAT1) in the proximal tubule. In the DCT, the NCCT moves both Na^+ and Cl^- into the cell. Sodium enters the cell down its concentration gradient using the free energy produced by the Na^+/K^+-ATPase located on the basolateral

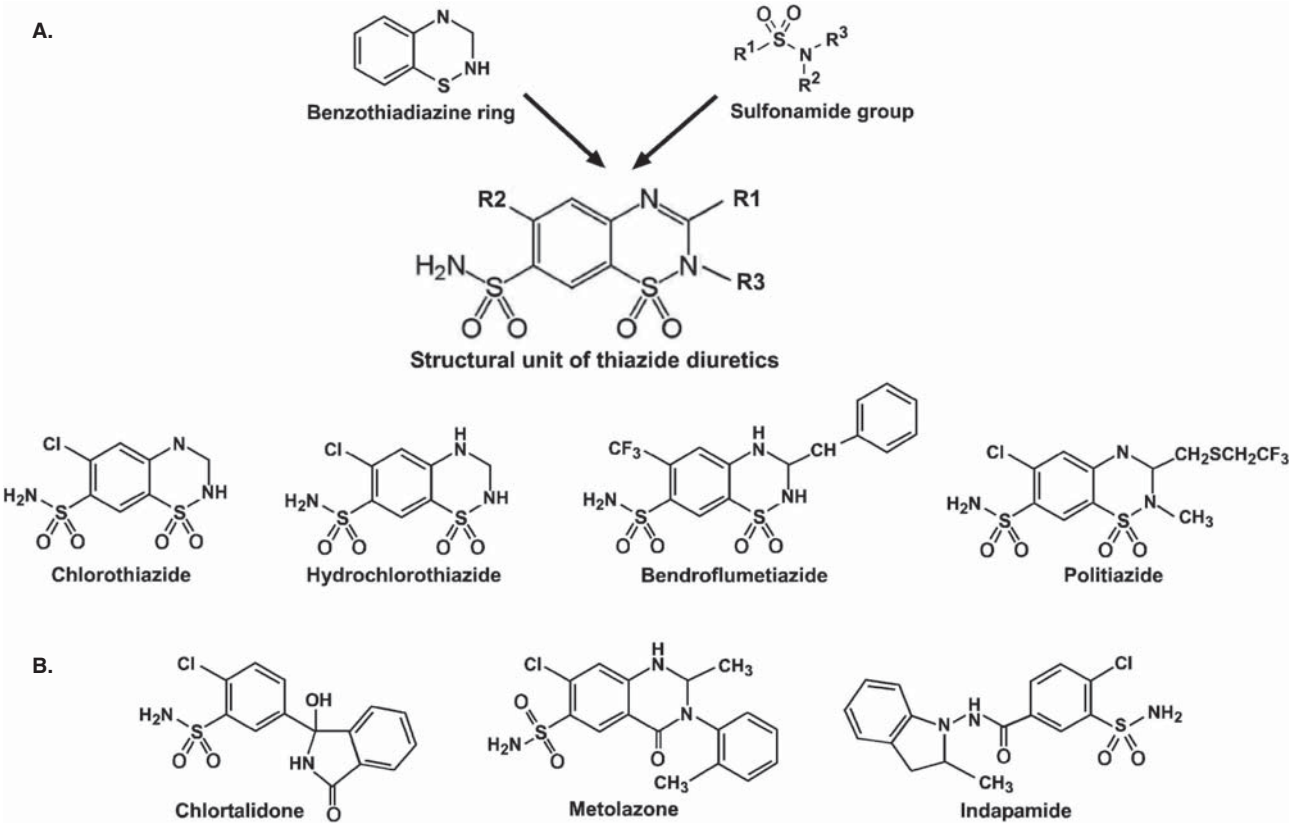

Figure 1. Schematic representation of the chemical structures of several thiazide and thiazide-like diuretics. A. Thiazide diuretics are analogs of 1,2,4-benzothiadiazine-1,1-dioxide. **B**. Chemical structure of thiazide-like diuretics is shown. They are a structurally diverse group of sulfonamide derivatives that contain the sulfonamide group but not the benzothiadiazine ring.

membrane that pumps Na^+ out of the epithelial cell, while Cl^- moves against its electrical gradient (inside of the cell is electronegative) and exits the cell across a Cl^- channel Kb (ClC-kb or CLCNKB) (**Figure 2**). At high doses, some thiazide diuretics also inhibit a membrane-bound form of carbonic anhydrase in the proximal convoluted tubule, an effect that increases HCO_3^- and phosphate excretion. This inhibition, however, does not contribute to the net diuresis, since the excess fluid delivered out of the proximal tubule is reabsorbed in the loop of Henle.

Additionally, thiazide diuretics increase the excretion of K^+, Mg^{2+} and H^+, due to an increased delivery of Na^+ to the distal tubule, producing a hypokalemic alkalosis. A major mechanism of renal K^+ secretion by the distal nephron is the generation of a lumen-negative potential by the reabsorption of Na^+ through the apical epithelial Na^+ channel (ENaC). This Na^+ reabsorption together with the activity of the basolateral Na^+-K^+-ATPase, which transports K^+ into the tubular epithelial cells against a concentration gradient generates the electrochemical gradient for K^+ excretion through the K^+ channels (ROMK1 and ROMK3) [14]. Thiazide diuretics can also activate flow-sensitive maxi-K channels [15] and can reduce the luminal Ca^{2+} concentration in the DCT, which activates ENaC and facilitates K^+ excretion [16]. Mg^{2+} excretion takes place in the DCT, although the mechanisms responsible for active Mg^{2+} transport remain incompletely understood. A possible explanation for the hypomagnesemia developed during chronic HCTZ administration is a downregulation of epithelial transient receptor potential cation channels (TRPM6) located in the apical membrane of the DCT which are highly permeable to Mg^{2+} [17]. Thiazides also increase H^+ excretion into the tubular lumen by increasing the distal delivery of Na^+ which stimulates the lumen H^+-ATPase at the level of type A intercalated cells of the collecting tubule. Additionally, the thiazide-induced activation of the renin-angiotensin-aldosterone system (RAAS) increases Na^+ conductance via epithelial channels (ENaC) located in the luminal membrane and Na^+ pump activity in the basolateral membrane, which increases transepithelial Na^+ transport and the lumen-negative transepithelial membrane potential. This latter effect increases the driving force for the excretion of H^+ and K^+ into the tubuli lumen.

The DCT is impermeable to water and, thus, when Na^+ and Cl^- are absorbed via the NCCT, an iso-osmotic amount

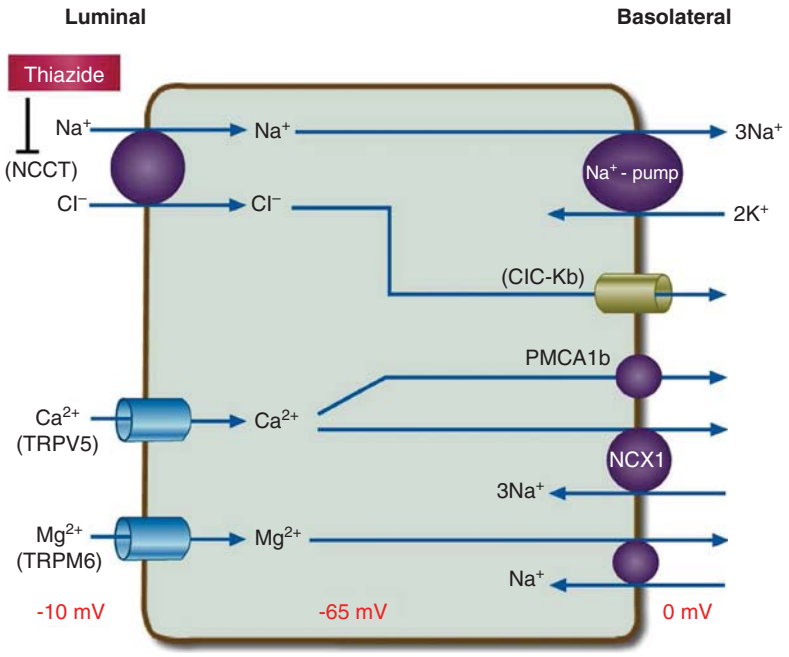

Figure 2. Mechanism of action of thiazide diuretics is shown.

ClC-Kb: Basolateral chloride channel; NCCT: Na^+–Cl- cotransporter located on the apical membrane of the distal convoluted tubules; NCX1: Na^+/Ca^{2+} exchanger; PMCa1b: Plasma membrane Ca^{2+}-ATPase; TRPM6: Transient receptor potential cation channels, subfamily M, member 6; TRPV5: Apical Ca^{2+}-selective channels.

of water is not absorbed but remains in the lumen accounting for the diluting function. When NCCT is inhibited, the fraction of filtered Na^+ and Cl^-, which is no longer absorbed, now interferes with the diluting function by osmotically including the water component. Therefore, thiazide diuretics reduce free water clearance and impair the ability of the kidneys to excrete dilute urine during water diuresis, an effect that predisposes the development of dilutional hyponatremia if treated patients ingest large quantities of water. At high doses, thiazide diuretics may impair renal diluting via additional mechanisms as they: i) decrease the extracellular fluid volume (ECV) and the estimated glomerular filtration rate (eGFR), which trigger a compensatory increase in proximal Na^+ reabsorption and reduce the delivery of fluid to the distal dilutes sites and the amount of water for excretion; ii) stimulates vasopressin release, which increases water reabsorption in the collecting ducts; and possibly iii) a direct effect on water flow in the collecting duct [18]. However, as the DCT is not involved in the mechanism generating a hypertonic medullary interstitium, thiazides do not alter the kidney's ability to concentrate urine during hydropenia.

Thiazides increase Ca^{2+} reabsorption by a double mechanism. Thiazide-induced renal salt and water loss results in contraction of the ECV, which triggers a compensatory increase in proximal Na^+ reabsorption. This would, in turn, enhance the electrochemical gradient, driving passive Ca^{2+} transport in the proximal tubule. Thiazides also stimulate Ca^{2+} reabsorption at the distal tubule, possibly due to the stimulation of the basolateral Na^+/Ca^{2+} exchanger (NCX1) and the Ca^{2+}-ATPase (PMCA1b) that extrude Ca^{2+} into the bloodstream. This reduces the intracellular $[Ca^{2+}]$ and increases the driving force for the reabsorption of Ca^{2+} into the cell via apical Ca^{2+}-selective channels (TRPV5) (**Figure 2**). There is also evidence that thiazides stimulate osteoblast differentiation and bone mineral formation independently of their renal actions [19]. All these effects can explain why in observational studies, chronic administration of thiazide diuretics decreases urinary Ca^{2+} excretion, increases bone mineral density and reduces age-related bone loss and the risk of hip fractures in the elderly [20,21].

Compared with loop diuretics, thiazide diuretics: i) produce a moderate natriuresis as most of the Na^+ originally filtered at the glomerulus has already been reabsorbed, but present a longer duration of action. However, loop diuretics reduce BP to a lesser extend than thiazide diuretics, which indicates that the antihypertensive effects of thiazides are not exclusively due to their diuretic effect. Furosemide and bumetanide present a short duration of action (~ 6 h), so that the initial natriuresis is followed by a period of antinatriuresis lasting up to 18 h/day when the drug is administered once daily. During this period of time, there is a post-diuretic Na^+ reabsorption in the nephron (*breaking*), an effect that can counteract the previous natriuresis, especially if Na^+ intake is not restricted; ii) with the exception of metolazone, thiazide diuretics are largely ineffective in patients with severe CKD (i.e., serum creatinine > 1.5 mg/dl, eGFR < 30 ml/min/m^2) [2,3,22,23]. This is partly because of a reduced secretion into the proximal tubule due to competition with endogenous organic acids produced in

renal insufficiency, which limits the delivery of thiazide diuretics to their site of action in the distal tubule. Additionally, progressive loss of renal function leads to both reduction in eGFR and tubular mass. Reduced GFR results in reduced filtered Na^+ load and volume expansion [24]. This latter effect should provoke reduced renal tubular Na^+ absorption, but failure to fully suppress Na^+ reabsorption would increase the ECV. Reduced tubular mass should also suppress Na^+ reabsorption per nephron; iii) pleiotropic effects: indapamide (or one metabolite) lowers BP at doses below those required to produce diuresis, an effect attributed to its L-type Ca^{2+} channel-blocking properties [25] and CTD exert other effects (e.g., decrease platelet aggregation, vascular endothelial growth factor-C levels and vascular permeability, and promote angiogenesis) [26]. However, other thiazide diuretics (i.e., HCTZ) do not present pleiotropic effects [27].

4. Pharmacodynamics

Thiazide diuretics do not lower BP in normotensive individuals but are effective in hypertensive subjects [28]. However, the mechanisms by which thiazides chronically lower BP are poorly understood but might be the final result of direct renal and endothelial and vascular effects and indirect regulatory mechanisms via a chronic response to the acute decrease in cardiac output. Interestingly, the role of some of these mechanisms can be different depending on the type of thiazide studied.

The initial BP lowering is related to the inhibition of the NCCT, which increases diuresis and natriuresis, decreases ECV and plasma volume and reduces venous return and cardiac output [29-32]. Indeed, during this acute phase re-expansion of plasma volume with dextran restores plasma volume and BP to pretreatment levels [33]. The reduction in cardiac output induces an increase in PVR due to an increase in sympathetic tone and activation of the RAAS that partly counteract the BP reduction [2,28,34-36]. In fact, the coadministration of a thiazide with an angiotensin-converting-enzyme inhibitor (ACEI) or an angiotensin II-receptor blocker (ARB) inhibits the increase in PVR and increases the antihypertensive response.

The decrease in BP observed during chronic administration of thiazides cannot be related to the decrease in plasma and ECV or cardiac output, which returns within 4 – 6 weeks to near-normal levels but can be related to a decrease in PVR [29-32,37,38]. Indeed, there is a poor correlation between the dose of thiazide required for diuresis and BP lowering [39] and loop diuretics do not lower BP to the same degree as thiazide diuretics, even though they are more effective diuretics than thiazides. Further, in patients treated with thiazides for > 2 months, the infusion of dextran infusion produces an expansion of body fluid volume but BP does not return to baseline. However, the observation that plasma renin activity decreases and body weight and plasma volume abruptly increase when long-term treatment with a thiazide is discontinued suggests that some depletion of ECV continues during long-term therapy [29,38].

4.1 Vasodilator effects of thiazide diuretics

The decrease in PVR indicates that thiazide diuretics exert direct or indirect vasodilator effects, but their role varies with the studied drug [40-42]. The main vasodilator mechanisms include: i) a reduction in vascular reactivity *in vitro* and in vasopressor responses *in vivo* to angiotensin II, norepinephrine and thromboxane A2 [4,37]. At supratherapeutic plasma levels, HCTZ (but not indapamide) exerts a direct vasodilator effect in the human forearm that is not dependent on BP and persists in patients with Gitelman's syndrome (due to loss-of-function mutations in *SLC12A3*, the gene that encodes NCCT) but is inhibited by tetraethylammonium. Thus, the vasodilator effect is mediated by activation of vascular K^+ channels and not by inhibition of a putative vascular NCCT [41]; ii) the opening of large-conductance Ca^{2+}-activated K^+ (BK_{Ca}) channels resulting in hyperpolarization of the vascular smooth muscle cell, reduction of the open probability of voltage-dependent L-type Ca^{2+} channels, fall in $[Ca^{2+}]_i$ and vasorelaxation [43,44]. The open probability of BK_{Ca} channels is also modulated by intracellular pH (pH_i), so that thiazide diuretics with carbonic anhydrase-inhibiting activity (e.g., HCTZ) can increase pH_i and activate BK_{Ca} channels [44]; iii) CTD and HCTZ attenuate agonist-induced vasoconstriction by Ca^{2+} desensitization, an effect related to inhibition of the RhoA–Rho kinase pathway [43,45]; iv) inhibition of voltage-dependent L-type Ca^{2+} channels, an effect that has been described with indapamide but not with other thiazide diuretics [25]; v) an endothelium-dependent mechanism involving endothelium-dependent relaxing factor/nitric oxide (NO) release. Indeed, endothelial removal or inhibition of NO synthase abolishes the vasodilator response induced by methyclothiazide in spontaneously hypertensive rats [46]; vi) an increased release of locally acting vasodilators, including prostaglandins E2 and F2α, has been described with indapamide [40] but not with HCTZ [43]. The role of the vasodilator effects of thiazide-like diuretics has been questioned as they appear at high (supratherapeutic) plasma levels; however, the accumulation of thiazides in the vascular wall during chronic administration can explain the discrepancy between plasma levels and those needed for their vasodilator effects [37].

Another explanation for the changes in PVR is the reverse whole-body regulation theory [47]. This hypothesis proposes that blood vessels adapt to the initial thiazide-induced plasma volume loss and decrease in cardiac output with a reactive vasoconstriction. After long-term administration cardiac output is regulated by tissular metabolic demands and vessels dilate to increase cardiac output toward baseline values. This transforms hypotension from hypovolemic to vasodilatatory [47].

4.2 Determinants of the antihypertensive response

As with other antihypertensive drugs in monotherapy, only 40 – 60% of individuals treated with thiazide diuretics achieve

an adequate BP control [22]. Predictors of greater BP responses include higher baseline BP level, female gender, shorter duration of diagnosed or treated hypertension, lower plasma renin activity (elderly, blacks, diabetics) and urinary aldosterone excretion and greater decrease in urinary sodium excretion [22,48-56]. Greater decrease in weight is a significant predictor of systolic BP (SBP) but not diastolic BP (DBP) response, and older age is a predictor of DBP but not SBP response [55]. However, the combined effects of all identified predictors accounted only for 38% of interindividual variation in SBP response and 20% of interindividual variation in DBP response.

Other possible predictors of BP response to a low-dose of thiazide-like diuretics include:

1) *Genetic variants*. Several studies have analyzed the potential effects of genetic variations in the antihypertensive response to thiazide diuretics. Gitelman's syndrome is an autosomal recessive hereditary renal disorder due to loss-of-function mutations in the *SLC12A3* gene encoding NCCT characterized by salt wasting and low BP, hypokalemia, metabolic alkalosis, hypomagnesemia and hypocalciuria [57]. Patients with *SLS12A3* mutations present SBP and DBP levels similar to those observed following the treatment with thiazide diuretics, but this hypotension is mediated by vasodilation and not by extracellular fluid depletion [58,59]. Type II pseudohypoaldosteronism (Gordon's syndrome or familial hyperkalemic hypertension) is an autosomal dominant disease caused by mutations in two genes (*WNK1 and WNK4*) encoding two serine/threonine kinases that increase NCCT activity [60]. Patients present low-renin hypertension, hyperkalemia, increased urinary calcium excretion and hyperchloremic metabolic acidosis and a marked sensitivity to the BP-lowering effects of thiazide diuretics. A loss-of-function mutation in *WNK4* gene (which inhibits NCCT activity by repressing its cell surface targeting) or a gain-of-function in *WNK1* gene (which relieves WNK4-induced inhibition) caused overactivation of NCCT [61]. Polymorphisms in *WNK1* made significant contributions for predicting ambulatory BP responses and account for 2 – 4% of variation in SBP and DBP responses to HCTZ [62]. Other genetic polymorphisms associated with interindividual differences in the BP response to thiazide diuretics are summarized in supplemental **Table 1**. However, polymorphisms in genes encoding aldosterone-synthase (*CYP11B2* -344T/C), angiotensinogen (*AGT* M235T), angiotensin II type 1 receptor (*AGT1R* 1166A/C), β2-adrenoceptor (*ADRB2* rs2400707), ENaC-γ (*SCNN1G* rs5723 and rs5729) and β-subunits (*SCNN1B)* or the mineralocorticoid receptor (*NR3C2*) do not predict the BP responses [62-65]. Thus, the study of genetic variants can provide a link in better understanding the variability in BP response and the mechanisms involved in their antihypertensive response to thiazide diuretics. However, much extensive characterization of genetic variations is required to generate the evidence needed to more accurately predict the individual variations in BP response to these drugs.
2) *Enhanced Na^+ reabsorption* at sites in the nephron other than the DCT, that is, proximal tubular reabsorption of Na^+.
3) *Changes in other BP control systems*. Depletion of intravascular volume activates counter-regulatory mechanisms, including an increase in sympathetic tone that produces a vasoconstriction of the afferent/efferent arterioles and decreases GFR, stimulates the release of renin by the juxtaglomerular cells and activates the RAAS leading to an increase in Na^+ reabsorption, increases the release of vasopressin which promotes water reabsorption across the collecting duct, and releases aldosterone that increases distal Na^+ reabsorption and K^+ and H^+ excretion. Patients with low plasma-renin activity and urinary aldosterone levels are more thiazide-responsive, while nonresponders show a greater degree of plasma volume depletion and activation of the RAAS [28,30]. The neurohumoral activation observed at high doses of thiazides may explain, at least partly, the observed flattening of the dose–response relationship.
4) *Pharmacokinetic differences*. CTD (and indapamide) present a longer half-life and a larger volume of distribution (Vd) than HCTZ because they are accumulated in red blood cells [66]. These differences are expected to correlate with a more prolonged antihypertensive effect of CTD and indapamide on BP and might provide greater antihypertensive effects particularly throughout nighttime hours [67-69]. These differences are not appreciated when the assessment of antihypertensive efficacy is based on daytime office BP readings alone but can be detected with 24-h ambulatory BP monitoring. Further, the post-diuretic period of antinatriuresis (*braking phenomenon*) will be less evident when a long-acting drug is prescribed. Because of the belief that it might have advantages related to its longer duration of action, trials sponsored by the National Heart, Lung, and Blood Institute used CTD.

5. Pharmacokinetics

Thiazide-like diuretics are rapidly absorbed from the gastrointestinal tract. Food intake increases, whereas HF or renal diseases decrease HCTZ absorption [70]. Thiazides are extensively bound to plasma proteins, which limit their glomerular filtration, and are excreted in the urine by proximal tubular secretion [2]. However, there are marked differences in their metabolism and renal excretion (**Table 1**). Diuresis appears within 1 – 3 h and lasts for 12 – 24 h. CTD presents a much longer half-life (50 – 60 h) and larger Vd than HCTZ because 98% of the drug is bound to erythrocyte

Table 1. Pharmacokinetic characteristics of thiazide-like diuretics.

	Bioavailability (%)	Onset (h)	Peak (h)	PPB (%)	Vd (l/kg)	Half-life (h)	Duration of action (h)	Renal excretion (%)	Dose (mg)
Hydrochlorothiazide	70	2	4 – 6	58	0.83	6 – 14	6 – 12	> 95	12.5 – 25 od
Hydroflumethiazide	50					17	12 – 18	40 – 80	12.5 – 25 od
Polythiazide	≈ 100					25		25	2 – 4 od
Chlorthalidone	65	2.5	2 – 6	98	0.14 – 3 – 13	47 (40 – 60)	40 – 72	65	12.5 – 50 od
Indapamide	95	1 – 4		79		14 – 18 (11 SR)	24	70 (7*)	1.25 – 2.5 od (1.5 SR)
Bendroflumethiazide	95	2	3 – 6	96	1 – 1.5	3 – 4	8 – 16	30	1.25 – 5 od
Metolazone (Microx)	65	1	2 – 4	96	1 – 1.5 (113)	8 – 24	24 – 48	80	2.5 – 10 od
Xipamide	95	1	1 – 2	98		5 – 8	12 – 20	30	5 – 40 od

*Recovered in the urine as unchanged drug.
H: Hours; PPB: Plasma protein binding; SR: Sustained-release formulation; Vd: Volume of distribution.

carbonic anhydrase, reaching 7 – 10 times greater concentrations in erythrocytes than in plasma [71]. Thus, red blood cells act as a reservoir from which the drug flows back to the plasma and is gradually eliminated from the plasma by tubular renal excretion [71,72]. Indapamide and metolazone also bound to erythrocyte carbonic anhydrase, present a large Vd and a longer half-life than HCTZ. Thus, the half-life of these compounds would be longer if blood, rather than plasma, is analyzed. Indeed, the whole blood:plasma ratio for indapamide is ~ 6:1 at the time of peak concentration. Because of this long half-life, CTD retains its efficacy when given less frequently than once daily and in patients who occasionally miss doses [73]. Thiazides are ineffective in patients with severe CKD because the reduced GFR limits the filtered Na^+ load reaching the distal tubule, and at this level is only modestly effective as compared with that in the large-capacity, thick ascending limb [18].

6. Antihypertensive effects

Thiazide diuretics have remained the cornerstone of antihypertensive treatment whenever possible since the first *Joint National Committee* (JNC) report in 1977 and remain as first-choice drugs to start the treatment in the JNC-7 [74] and the *World Health Organization* (WHO)/*International Society of Hypertension* (ISH) guidelines [75]. The current ESH/ESC guidelines confirm the use of low doses of thiazide diuretics (e.g., HCTZ 12.5 mg/day, CTD 12.5 mg/day, indapamide 1.5 mg/day) for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in combination with other antihypertensives to produce an additive decrease in BP and to reduce hypertension-related morbidity and mortality [2,22]. As compared with placebo, thiazide diuretics in monotherapy reduce SBP and DBP by 10 – 15 and 5 – 10 mmHg, respectively [2]. In a meta-analysis of 42 studies, the reduction in SBP with a thiazide used alone was 7.3 mmHg as compared with 9.3 mmHg with a β-blocker, 6.8 mmHg with an angiotensin-converting enzyme and 8.4 mmHg with a calcium channel blocker [76]. The *Blood Pressure Lowering Treatment Trialists' Collaboration* demonstrates that the magnitude of BP lowering is the most important determinant in reducing the cardiovascular (CV) risks associated with hypertension and that short-to-medium term effects on major CV events of BP-lowering regimens are broadly comparable for patients with and without diabetes [48-50]. As compared with placebo, thiazide-based regimens reduce the morbidity and mortality associated with hypertension, including stroke, coronary heart disease (CHD) and HF [76,77], and in randomized clinical trials (RCTs) [78-87] and in several meta-analysis, their benefit is similar to that of other antihypertensives in preventing CHD events and strokes [49-54,76,88-94]. However, in some of the trials included in this meta-analysis, the doses of thiazide diuretics included in the thiazide-based regimen were higher than those actually recommended.

In a meta-analysis of 18 RCTs and 48,220 patients, compared with placebo, low doses of a thiazide-based regimen (equivalent of 25 – 50 mg of HCTZ or 12.5 – 25 mg of CTD) reduce the incidence of stroke (34%), CHD (28%), congestive HF (42%) and total mortality (24%), whereas at high doses (CTD 50 mg, HCTZ 50 mg), it reduce strokes and HF by 51 and 83%, respectively [89]. However, the risk reduction for HF was derived from fewer trials but was not routinely reported in many trials. These differences between low doses and high doses of thiazides were thiazide-based regimens (19 RCTs) reduced mortality (risk ratio [RR] = 0.89), stroke (RR = 0.63), CHD (RR = 0.84) and CV events (RR = 0.70). However, whereas low-dose thiazides (8 RCTs) reduced CHD (RR = 0.72), high-dose thiazides (11 RCTs) did not (RR =1.01). Thus, first-line low-dose thiazides reduce all morbidity and mortality outcomes, whereas first-line high-dose thiazides are inferior to first-line low-dose thiazides. In the

elderly, a starting dose of 12.5 mg and a maximum dose of 25 mg HCTZ (or its equivalent) are recommended as they present a greater sensitivity to the volume-depleting effects of these drugs [68]. Another meta-analysis of 147 RCTs found that diuretics (including thiazides, CTD and indapamide) are as effective as other antihypertensive agents [94].

In a *post-hoc* subgroup analysis of the *The Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension* (ACCOMPLISH) trial, hypertensive patients who were at high risk of CV events were divided based on the body mass index (BMI) into obese (BMI ≥ 30), overweight (≥ 25 to < 30) or normal weight (< 25) categories [95]. They found that in patients treated with benazepril and HCTZ, the primary end point of CV death or nonfatal myocardial infarction (MI) or stroke (per 1000 patient-years) was 30.7 in normal weight, 21.9 in overweight and 18.2 in obese patients; however, in those treated with benazepril and amlodipine, the primary end point did not differ between the three BMI groups (18.2, 16.9 and 16.5, respectively). In obese individuals, primary event rates were similar with both benazepril and HCTZ and benazepril and amlodipine, but rates were significantly lower with benazepril and amlodipine in overweight patients and in those of normal weight. These findings indicated that CV deaths or nonfatal MI or stroke occur more frequently in normal weight than in obese hypertensive patients, suggesting that hypertension in obese and lean patients might be mediated by different mechanisms (i.e., in obese people, it seems to be characterized by increased plasma volume and cardiac output rather than vasoconstrictor mechanisms). Thus, it was hypothesized that a thiazide-based treatment would represent a logical approach for obese hypertensives, whereas thiazides are clearly less protective against CV events in lean patients, but this assessment merits further investigation. Further, whether these results can be extrapolated in patients with lesser CV risk profile remains uncertain. Thiazide diuretics are preferred in elderly people with isolated systolic hypertension [22,84] and for volume-overload conditions, such as HF and nephrotic syndrome, as they improve signs and symptoms of edema and congestion [18,22]. CKD is present in 3 – 4% of the adult population and most of these patients are hypertensive [23]. Additionally, hypertension in CKD remains poorly controlled despite the use of multiple antihypertensive drugs. Progressive loss of renal function decreases both the eGFR, which results in reduced filtered Na^+ load and ECV expansion, and tubular mass. Thus, hypervolemia is a major cause of hypertension in these patients. Thiazide diuretics decrease tubular Na^+ reabsorption, reverse ECV expansion and lower BP. The 2013 ESH/ESC guidelines recommend thiazide diuretics in hypertensives with eGFR ≥ 30 ml/min/1.73 m^2. Loop diuretics should replace thiazide diuretics if serum creatinine is 1.5 mg/dl or eGFR is < 30 ml/min/1.73 m^2 [22].

In patients with severe HF and insufficient response or resistant peripheral edema (and ascites), the combination of a loop and a thiazide diuretic (bendroflumethiazide or metolazone) can achieve an adequate diuresis. This combination is usually only needed for a few days and requires careful monitoring to avoid the risk of hypokalemia, renal dysfunction and hypovolemia [96].

6.1 Hydrochlorothiazide

HCTZ is the most widely used thiazide diuretic. But despite their well-established efficacy, the role of HCTZ in hypertensive patients is a matter of debate for several reasons [97,98]. In monotherapy, its antihypertensive response is variable, depending on the dose, age and race of the patient and Na^+ intake. Approximately 45% of patients respond initially to the lowest dose of HCTZ; increasing the dose of HCTZ from 12.5 to 25 mg/day may result in a response in an additional 20% (approximately) of patients; at 50 mg/day, 80 – 90% of patients had measurable decreases in BP [99]. In 53 RCTs, the additional BP reduction caused by HCTZ when given as a second-line drug averaged 6/3, 8/4 and 14/6 mmHg at doses of 1, 2 and 3 times the standard recommended starting dose, respectively [69]. These results confirm that HCTZ when given as a second-line drug have a dose-related effect to lower BP that is similar to when it is added as a first-line drug. Moreover, in younger whites (mean 51 years), only 32% respond to escalating doses of HCTZ over 1 year (40% in young blacks); in elderly people, these percentages increase to 52 and 58%, respectively. In two recent RCTs, low-dose HCTZ in combination with other medications showed less effectiveness as compared with the non-thiazide regimen. The *Second Australian National Blood Pressure Study Group*, a prospective, randomized, open-label study compared the outcomes in elderly hypertensives (65 – 84 years of age) treated with ACEIs or diuretics (even when the dose of HCTZ was not specified) [100]. After 4.1 years, BP decreased to a similar extent in both groups, but the rates of nonfatal CV events and MI were lower in the group receiving an ACEI-based regimen than in the group receiving a thiazide-based regimen, whereas a similar number of strokes occurred in each group (although there were more fatal strokes in the ACEI group). Thus, initiation of a treatment involving an ACEI in older subjects appears to lead to better outcomes than treatment with diuretic agents, despite similar reductions of BP. The ACCOMPLISH trial compared the benazepril-amlodipine and benazepril-HCTZ combinations in high-risk hypertensives. The trial was stopped prematurely after a mean follow up of 36 months because despite similar reductions in office and ambulatory BP values, the ACEI/amlodipine combination reduced the combined end point of CV death, myocardial infarction, and stroke by 20% compared with the ACEI/HCTZ combination [101]. Interestingly, 60% of patients were diabetic and a large percentage had evidence of underlying CHD [102]. These results suggest the superiority of a calcium channel blocker over a thiazide diuretic when used in conjunction with a RAAS inhibitor in this high-risk population. However, because previous studies comparing a calcium antagonist-based therapy with a

diuretic-based therapy never found a significant superiority of a calcium antagonist over a diuretic, these results need to be replicated. Until then, it remains uncertain whether they can be extrapolated to patients with a lesser CV risk profile. Possible explanations for the results of the ACCOMPLISH trial included the dose of HCTZ (12.5 – 25 mg/day), which was lower than those used in other placebo-controlled trials, or that the combination of benazepril–amlodipine decreases central SBP more effectively than the benazepril–HCTZ combination, deserve further investigation [103-105].

Even when clinical guidelines state that thiazide-like diuretics are as effective as other antihypertensive drugs in preventing CV complications in hypertensive patients [22,48-50], very recently, Messerli and Bangalore [106] suggested that HCTZ is an inappropriate first-line drug for the treatment of hypertension because: i) in a meta-analysis of 19 RCTs assessing 24-h BP, the antihypertensive efficacy of HCTZ (12.5 – 25 mg/day) decreases 24-h ambulatory BP by 6.5/4.5 mmHg which is significantly less than that observed with other drug classes, including ACEIs, ARBs, β-blockers and calcium channel blockers. However, at the dose of 50 mg, HCTZ reduced 24-h BP 12.0/5.4 mmHg and was comparable to other agents [98]. Moreover, in the ANBP2 trial, HCTZ was inferior to enalapril [78,79], and in the CAMELOT trial, HCTZ was not different from placebo [107]; ii) there is no evidence that low doses of HCTZ (12.5 – 25 mg) in monotherapy reduce MI, stroke or death. Indeed, the studies demonstrating that HCTZ reduces clinical outcomes in hypertensive patients were performed at higher doses (between 25 and 50 mg/day) than currently recommended or in combination with reserpine [76,77,108] or potassium-sparing diuretics [78,80-83]. Further, in the MRFIT trial, CTD might be more efficacious than HCTZ in reducing CV mortality [86,87]. Indeed, the only thiazide diuretics that have been found to reduce morbidity and mortality in hypertension are CTD [109] and indapamide [85]. However, these two drugs present important differences as compared with HCTZ, so that the findings observed with them cannot be extrapolated to HCTZ [97,98,106]. Indeed, HCTZ, CTD and bendroflumethiazide have markedly different potency, bendroflumethiazide being the most potent and HCTZ the least, both for BP lowering and for biochemical changes in serum K^+ and urate [109]. Based on this evidence, Messerli and Bangalore concluded that because outcome data at low doses of HCTZ are lacking, its antihypertensive efficacy is paltry, and adherence is poor, if a 'thiazide-type' diuretic is indicated, either CTD or indapamide should be selected instead of HCTZ [106].

Similarly, the NICE guidelines states that there is limited evidence confirming the benefit of initial therapy on clinical outcomes with low doses of HCTZ [110] and indicate that if diuretic treatment is to be initiated or changed, offer a thiazide diuretic, such as CTD (12.5 – 2.5 mg once daily [od]) or indapamide (1.5 mg sustained release [SR] od or in preference to a conventional thiazide diuretic such as bendroflumethiazide or HCTZ as step 1 therapy.

6.2 Chlorthalidone

CTD presents important pharmacodynamic/pharmacokinetic differences with HCTZ [10,68]. Both drugs are often incorrectly considered as equipotent, but CTD is ~ 1.5 – 2.0 times as potent as HCTZ and presents a much longer duration of action [68]. Thus, the dose of 25 mg of CTD and HCTZ results in a mean decrease in SBP of 18 and 12 mmHg, respectively. In a crossover short-term study in untreated hypertensive patients, after 8 weeks of treatment CTD (12.5 force-titrated to 25 mg/day) was approximately twice as potent in lowering SBP (12.4 vs 7.4 mmHg) as HCTZ (25 mg force-titrated to 50 mg/day), as evidenced by 24-h ambulatory BP; however, these differences were not apparent with office BP measurements [67]. These findings were attributed to the ability of CTD to maintain efficacy throughout the nighttime (13.5 vs 6.4 mmHg) and reduce the gradual rise in BP that may occur during the dose interval. Additionally, lower doses of CTD (12.5 mg and 25 mg/day) offer the best efficacy-to-side effect ratio with respect to hypokalemia [68].

The largest trials that primarily used CTD (12.5 – 25 mg od) as the initial therapy confirmed that the drug might be more efficacious than HCTZ with regard to antihypertensive efficacy or in reducing stroke, CV end points and all-cause mortality [80-82,111-114]. The *Systolic Hypertension in the Elderly Program* (*SHEP*) studied in elderly patients (mean age 72 years) with isolated systolic hypertension (mean baseline BP = 170/77 mmHg) the impact of CTD-based therapy compared with placebo on the incidence of stroke and other CV events. After 4.5 years, antihypertensive stepped-care drug treatment with low-dose CTD (12.5 – 25.0 mg/day) as step 1 reduced BP in > 50% of patients and the incidence of stroke (36%), MI (27%), HF (54%) and overall CV morbidity (32%) without significant untoward consequences [111].

Two recent retrospective analysis of the MRFIT study found that patients treated with CTD display significantly lower SBP, lower total cholesterol, low-density lipoprotein cholesterol and lower potassium and higher uric acid levels over time as compared with HCTZ [115]. More interestingly, both HCTZ and CTD reduce CV events compared with either drug, but CTD reduces CV events more than HCTZ (49 vs 35%, $p = 0.0016$). Further, left ventricular (LV) mass was significantly lower in men receiving CTD compared with HCTZ through 48 and 84 months of follow up [116]. These data suggest that CTD may be the preferred thiazide-type diuretic for hypertension in patients at high risk of CV events [115].

The *Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial* (ALLHAT) trial compared, in > 42,000 hypertensives with CVD or at least one other CHD risk factor, the initial treatment with CTD (12.5 mg/day), amlodipine or lisinopril. After 4.9 years, no significant differences were found between the CTD group and any other treatment group in the rate of the composite primary end point of fatal CHD or nonfatal MI or all-cause mortality. CTD was superior with respect to several predefined secondary end

points, including HF (vs amlodipine and lisinopril) and stroke (vs lisinopril only in blacks but no difference in non-black patients) [51,52]. In a retrospective updated analyses of this trial, neither lisinopril nor amlodipine were superior to CTD in preventing end-stage CKD overall, by diabetes status or by renal function level, as initial therapy for reduction of CV or renal risk [53]. This benefit can be attributed to the improved BP control maintained throughout the study in the patients receiving CTD as compared with those receiving other treatments.

6.3 Hydrochlorothiazide versus chlorthalidone

Because no RCTs have compared HCTZ and CTD head-to-head with respect to CV events, several recent meta-analysis have compared the effects of HCTZ and CTD. Law *et al.* performed a meta-analysis of seven thiazide diuretics grouped based on the standard daily dose (HCTZ 25 mg, CTD 25 mg and bendroflumethiazide 2.5 mg), and the standard dose of thiazide was found to reduce SBP by 8.8 (8.3 – 9.4)/4.4 (4.0 – 4.8) mmHg and plasma potassium levels by 0.38 mmol/l and to increase urate by 48 µmol/l [117]. Another meta-analysis of 26 RCTs compared the effects of HCTZ, CTD and bendroflumethiazide on BP, serum potassium and urate [109]. Meta-regression of the effect of thiazides on SBP showed a log–linear relationship with a potency series: bendroflumethiazide > CTD > HCTZ. The estimated dose of each drug predicted to reduce SBP by 10 mmHg was 1.4, 8.6 and 26.4 mg, respectively, but there was no evidence of a difference in maximum reduction of SBP by high doses of different thiazide diuretics. Potency series for DBP, serum potassium and urate were similar to those seen for SBP.

Roush *et al.* conducted a systematic review of nine RCTs in which one arm was based on either HCTZ (12.5 – 50 mg/day) or CTD (12.5 – 25 mg/day) followed by two types of network meta-analyses, a drug-adjusted analysis and an office SBP-adjusted analysis [118]. In the drug-adjusted analysis, the percentage of risk reduction in congestive HF for CTD versus HCTZ was 23 and in all CV events the percentage of risk reduction was 21. In the office SBP-adjusted analysis, the risk reduction in CV events for CTD versus HCTZ was 18%. When the reduction in office SBP was identical in both arms, the risk of CV events in HCTZ arms was 19% higher than in its non-diuretic comparator arms. This difference which was similar to that from the retrospective analysis of MRFIT trial [115] cannot be explained entirely by the lesser effect of HCTZ on office SBP but can be related to the pleiotropic effects of CTD or to the short duration of HCTZ action [118]. An equivalence analysis using data from 137 trials concluded that CTD generally produces slightly greater reductions in SBP and potassium than HCTZ. In the low-dose range of 12.5 – 25 mg, equivalence analysis reveals that the reductions in SBP are not equivalent between the two drugs [119]. However, within the same dosing range, reductions in potassium can be considered equivalent. Additionally, a recent re-analysis of MRFIT trial found that patients receiving CTD also had less LV hypertrophy, as assessed by Sokolow-Lyon, and LV mass criteria compared with HCTZ through 48 and 84 months of follow up [116].

6.4 Indapamide

Indapamide SR (1.5 mg) is as effective in reducing BP as HCTZ (25 mg) or amlodipine (5 mg) [120], more effective than enalapril (20 mg) to reduce LV mass index in hypertensive patients with LV hypertrophy [121] and equal to enalapril (20 mg) to reduce microalbuminuria in hypertensive patients with type 2 diabetes [122]. In elderly hypertensive patients with isolated systolic hypertension, indapamide SR 1.5 mg shows a similar efficacy to amlodipine 5 mg but a greater efficacy than HCTZ 25 mg in reducing SBP (-24.7 vs -23 and -18.5 mmHg, respectively [120]). In this subgroup, the normalization rate was relatively high for indapamide SR (84.2%), when compared with amlodipine (80.0%) and HCTZ (71.4%).

In hypertensive and non-hypertensive patients with a history of stroke or transient ischemic attack, the combination of indapamide and perindopril (4 mg od) for 4 years reduces BP by 12/5 mmHg and the risk of stroke by 43% [123]. However, single-drug therapy reduces BP by 5/3 mmHg and produces no reduction in stroke risk. In another trial enrolling 3845 very elderly (> 80 years) patients with entry SBP ≥ 160 mmHg, a indapamide SR-based regimen (1.5 mg), with or without perindopril (2 – 4 mg od) for 2 years, reduces BP (-15.0/6.1 mmHg), the risk of fatal or nonfatal stroke (30%), the rate of death from stroke (39%), all-cause mortality (21%), HF (64%) and any CV event (34%) compared with placebo [85].

7. Adverse effects

We have already mentioned that thiazide diuretics present a flat dose–response curve, so that lower dosages (e.g., HCTZ 12.5 – 25 mg/day) are as efficacious as higher dosages in lowering BP [11,99], whereas higher doses significantly increase the risk of hydroelectrolytic and metabolic adverse effects. Therefore, at the recommended low doses used in monotherapy, or in combination with other antihypertensives, the adverse effects of thiazide diuretics are mild and transient. Drug-related adverse effects are more common with longer-acting thiazide-like diuretics (CTD, metolazone), although indapamide seems to produce less metabolic disturbances than other thiazide and thiazide-like diuretics [124-126].

The most frequent adverse effects produced by thiazide diuretics are:

1) *Hydroelectrolyte disturbances*: dehydration, hypovolemia, hypokalemia, hypomagnesemia, hyponatremia, hypercalcemia and hypochloremic alkalosis. Excessive diuresis can cause fatigue and listlessness, hypovolemia, postural hypotension and decrease cardiac output. Thiazide diuretics block NaCl reabsorption in the DCT but do not interfere with the ability of the kidney to maximally concentrate urine. Thus, patients treated with thiazides

who consume large quantities of water can develop significant dilutional hyponatremia [127]. Restriction of water intake, reduction or discontinuation of the diuretic together with liberalization of Na^+ intake may correct hyponatremia. Hypovolemia, with risk of prerenal azotemia, can be lessened by reducing the starting dose of the diuretic. Thiazide diuretics can reduce the excretion of calcium, and hypercalcemia can be observed in patients with preexisting hyperparathyroidism or vitamin D-treated hypoparathyroidism.

2) *Cardiovascular*: thiazides can produce hypovolemia and postural hypotension, particularly in the elderly.
3) *Gastrointestinal*: anorexia, nausea, gastric irritation, and constipation.
4) *Central*: dizziness, vertigo, paresthesia, and headache.
5) *Metabolic*: thiazide diuretics dose-dependently increase new-onset diabetes, total cholesterol, low-density lipoprotein cholesterol and triglyceride plasma levels and the ratio of apolipoprotein B to A1, whereas high-density lipoprotein cholesterol levels may fall [128-130]. These lipid effects are more apparent in blacks, males, diabetics and nonresponders to thiazide therapy (probably because higher diuretic doses are used in such patients) [124,129]. The diuretic-induced dyslipidemia has been related to worsened insulin sensitivity and/or reflex activation of the sympathetic tone and RAAS in response to volume depletion [18,125]. Indeed, low doses of diuretics that do not increase neurohumoral activation do not increase lipid levels. Thus, during chronic thiazide therapy, blood lipids should be monitored and a lipid-lowering diet should be recommended. However, in some studies, lipid levels may return toward baseline after prolonged use [129,131,132]. The risk of dyslipidemia is lower with indapamide [126,132].

Thiazide-like diuretics decrease in urate clearance and can dose-dependently increase serum urate levels by up to 35% by a dual mechanism: they increase urate reabsorption in the renal proximal tubule as a result of diuretic-induced volume contraction and compete with uric acid for tubular secretion [124,133]. Indeed, thiazide diuretics are sulfonamide-related organic acids that like urate are secreted into the proximal tubule through rOAT1, both competing for the same transporter. Additionally, thiazide diuretics inhibit the ATP-dependent unidirectional efflux transporter, multidrug resistance protein 4 (MRP4) which contributes to the secretion of urate across the human proximal tubule apical membrane [134]. Diuretic-related hyperuricemia rarely provoke gout, except in patients with a previous history of gout or in whom serum urate concentrations routinely exceed 12 mg/dl [124,135]. In these patients, thiazide therapy can be coadministered with allopurinol, but the dose of allopurinol should be adjusted according to the level of renal function, since allopurinol-induced hypersensitivity reactions increase with the combination. In patients intolerant to allopurinol, the ARB losartan, which is a uricosuric compound, ameliorates thiazide-induced hyperuricemia [136,137]. Even at the doses of 1.25 or 2.5 mg od, indapamide is as effective as HCTZ at doses of 12.5 or 25 mg od to lower BP; however, indapamide produces modest reductions in serum potassium and increases in uric acid levels [126].

6) *Others*: thiazides rarely cause sulfonamide-type immune side effects, including rashes, dermatitis, eosinophilia, photosensitivity, intrahepatic cholestatic jaundice, necrotizing pancreatitis, blood dyscrasias and acute allergic interstitial nephritis. In the TOMHS and MRC trials, erectile dysfunction was more commonly observed with CTD or bendroflumethiazide than with other antihypertensives [80-82,138]. Thiazide diuretics cross the placental barrier and can cause fetal or neonatal abnormalities (thrombocytopenia, jaundice), hypovolemia and decrease placental perfusion. Therefore, they should be avoided in pregnancy (FDA Pregnancy Category B). Thiazides are excreted in breast milk but it is unlikely they are harmful, although large doses may suppress lactation.

7.1 Thiazide-induced hypokalemia

When thiazides were introduced in clinical practice, the high doses used were frequently associated with severe hypokalemia. However, at the present time, thiazide diuretics dose-dependently decrease plasma K^+ levels by 0.2 – 0.6 mmol/l [8,113,128,129,139]. Thiazide-induced hypokalemia results from: i) an increase in Na^+ delivery to the distal tubuli and collecting ducts. At this level, the reabsorption of Na^+ through apical ENaC channels depolarizes the luminal membrane voltage and increases the driving force for K^+ excretion through K^+ selective channels (ROMK); ii) an increase in flow-dependent distal nephron K^+ secretion by activating flow-sensitive maxi-K channels [140]; iii) the inhibition of carbonic anhydrase with a fall of the distal delivery of chloride; iv) a secondary hyperaldosteronism in response to hypovolemia, which stimulates the Na^+–K^+ exchanger, resulting in further loss of potassium [125]; v) last, thiazide diuretics decrease luminal Ca^{2+} concentration in the distal tubules which activates ENaCs (which are inhibited by Ca^{2+}) and favors K^+ secretion [141]. The risk of hypokalemia (3 – 3.5 mM/l) increases with the dose, particularly in the elderly and in polymedicated patients, as well as in patients with LV hypertrophy, congestive HF and/or CHD [125,142]. Conversely, the risk of hypokalemia decreases by using low doses of thiazides, dietary salt restriction, supplementary K^+ or the coadministration with a potassium-sparing diuretic or a RAAS inhibitor (ACEI, ARB or mineralocorticoid receptor antagonists). Potassium-sparing diuretics are preferred to K^+ supplementation as they correct both hypokalemia and hypomagnesemia.

In the ALLHAT study, CTD decreased the kalemia from 4.3 to 4.1 mmol/l over a 4-year period, and serum K^+ concentration was 0.3 – 0.4 mm/l lower in patients treated with CTD

12.5 – 25 mg/day than in those treated with amlodipine or lisinopril [113]. In the MRFIT trial, CTD displayed a lower potassium and a higher uric acid over time, compared with HCTZ [115]. In a meta-analysis of 26 trials, the dose–response relationship for serum K^+ is bendroflumethiazide > CTD > HCTZ and the doses predicted to reduce serum levels by 0.4 mM/l were 4.2, 11.9 and 40.5 mg, respectively [109]. Another meta-analysis of 108 trials did not observe, within the low-dose range currently recommended, any differences between HCTZ and CTD despite previous concerns about the CTD-induced K^+ losses [119]. In a comparative trial between indapamide (2.5 mg/day) and HCTZ (50 mg/day), indapamide produced less hypokalemia (0.46 vs 0.9 mEq/l) and hyperuricemia [143], which can be attributed to the high-dose of HCTZ.

Hypokalemia (and hypomagnesemia) causes symptoms (fatigue, muscle cramps, constipation, anorexia) and ECG abnormalities as well as supraventricular and ventricular arrhythmias. In hypertensive patients, some studies found that thiazide diuretic therapy may be associated with an increase in premature ventricular contractions (PVCs) [144-146], but most have failed to demonstrate a relationship between the frequency or severity of PVCs and serum K^+ concentration even in patients with echocardiographic evidence of LV hypertrophy [147,148]. In the MRFIT trial, an inverse relationship between the serum K^+ concentration and the frequency of PVCs was observed; however, in this trial, patients on CTD with the greatest decrease in K^+ levels had the best outcomes [144]. In the MRC trial, there was not a significant increase in the number of PVCs during short-term thiazide treatment; however, after 24 months of therapy, a highly significant correlation between number of PVCs and serum K^+ concentrations was observed [80-82,149]. One study found an association between increasing doses of thiazide diuretics and the occurrence of primary cardiac arrest in hypertensive patients without known cardiac disease [150], but the addition of a potassium-sparing diuretic to low-dose thiazide therapy reduced the risk of cardiac arrest.

Diuretic-induced hypokalemia can increase the risk of digoxin intoxication and of polymorphic ventricular tachycardia (torsades de pointes) and sudden death when coadministered with QT prolonging drugs (e.g., class IA and III antiarrhythmics, phenothiazines, antipsychotics and some macrolides and antihistamines). Thus, electrolytic balance should be carefully monitored to avoid severe hypokalemia, especially when diuretics are administered at high doses or in combination with loop diuretics or in patients with CKD. In hepatic impairment, hypokalemia induced by thiazides may precipitate coma and so their use should be avoided.

7.2 Thiazide-induced hyperglycemia

Epidemiological and clinical trials suggested that long-term thiazide diuretic treatment can lead to insulin resistance and glucose intolerance, increase the risk of new-onset type 2 diabetes and worsen diabetic control [113,151,152]. The risk of new-onset diabetes depends on the thiazide dose and the risk increases in patients with a familial history of diabetes, abdominal obesity or metabolic syndrome. As the metabolic syndrome can often be considered as a 'pre-diabetic' state, thiazide diuretics should be avoided or given only in low doses (HCTZ 12.5 mg or CTD 15 mg od) in this population.

It has been hypothesized that hypokalemia is the most likely cause of thiazide-induced hyperglycemia via several mechanisms as they [152,153]: i) decrease glucose uptake into skeletal muscle which metabolizes large amounts of glucose; ii) open BK_{Ca} channels in pancreatic β-cells leading to membrane hyperpolarization, inhibition of Ca^{2+} influx and in Ca^{2+}-dependent release of insulin; and iii) activates the RAAS and sympathetic activity [152,153]. Indeed, RAAS inhibitors attenuate both thiazide-induced hypokalemia and hyperglycemia [22].

In a meta-analysis of 22 RCTs, patients treated with thiazide diuretics had a higher risk of developing diabetes when compared with placebo groups; the risk also increased when thiazides are combined with β-blockers, carvedilol and nebivolol being the exceptions [154]. Another meta-analysis of 59 RCTs found a significant correlation between the degree of diuretic-induced hypokalemia and the increase in plasma glucose levels [152]. Interestingly, the trial arms that used any K^+ supplementation and/or potassium-sparing diuretics presented a smaller decrease of serum K^+ (0.23 mM/l) and a smaller increase in serum glucose (3.26 mg/dl). Conversely, among the trials that did not supplement K^+, there was a relatively larger rise in serum glucose (6.01 mg/dl), which correlated less strongly with a larger decrease in serum K^+ (0.37 mM/l).

In the SHEP trial, patients with isolated systolic hypertension treated with CTD have an increased incidence of diabetes as compared to placebo after a follow up of 14.3 years [155]. Diabetes that developed during the trial among subjects on placebo was associated with increased CV adverse outcome and total mortality rate, whereas diabetes that developed among subjects during diuretic therapy did not have significant association with CV mortality rate or total mortality rate. Further, diuretic treatment in subjects who had diabetes was strongly associated with lower long-term CV mortality rate and total mortality rate. Thus, CTD-based treatment improved long-term outcomes, especially among subjects who had diabetes. In a secondary analysis of the SHEP trial, in year 1, the incidence of diabetes was related to the severity of hypokalemia, even after adjusting for baseline glucose and the dose of diuretic, so that each 0.5-mEq/l decrease in serum potassium was independently associated with a 45% higher adjusted diabetes risk [156]. After year 1, CTD use was not associated with increased diabetes risk. Thus, thiazide-induced diabetes occurring early after initiating treatment appears to be mediated by changes in serum K^+ and might be prevented with K^+ supplementation, but this hypothesis should be tested in a randomized trial. In the ALLHAT trial, the incidence of new-onset diabetes occurred more frequently in patients

treated with CTD (11.5%) than in those treated with lisinopril and amlodipine (8.3 and 7.6%, respectively), but the rates of fatal and nonfatal MI were similar in all groups, suggesting that the development of diabetes do not obviate the benefit of the thiazide [157]. Conversely, in the VALUE trial, patients with new-onset diabetes during antihypertensive treatment had significantly higher cardiac morbidity, especially more congestive HF [158]. Thus, although a meta-analysis of 27 RCTs concluded that the short- to-medium-term effects on major CV events of the BP-lowering regimens are broadly comparable for patients with and without diabetes [49], new-onset diabetes in patients receiving thiazide-like diuretics remains a potential concern for long-term adverse effects on CV outcomes.

Nevertheless, several factors should be taken into consideration when evaluating the association between thiazide use and new onset diabetes, including that most are *post-hoc* finding and were not adequately powered to assess this association, new-onset diabetes was defined differently in many trials, new-onset diabetes was not a prespecified primary end point in most trials and the follow up was not long enough to fully assess the risk of hyperkalemia or to observe any adverse effects of new diabetes on outcome [125,131]. Thus, further studies should also focus on the very long-term follow up of cohorts of patients initially enrolled in fixed-term outcome studies. Further prospective RCTs are needed to analyze the long-term effects of low doses of thiazides on insulin sensitivity or glucose tolerance, whether thiazides independently cause or exacerbate hyperglycemia, whether preventing hypokalemia can reduce the risk of diuretic-induced hyperglycemia or diabetes, the mechanism of thiazide-induced hyperglycemia, the populations at higher risk of diuretic-induced hyperglycemia and to confirm whether serum K^+ is a marker or mediator of thiazide-induced diabetes mellitus [153].

7.3 Prevention of metabolic side effects

The incidence of hypokalemia, hypomagnesemia, hyperuricemia and glucose intolerance is much less common with low-dose diuretics (e.g., 12.5 mg of HCTZ) and both hypokalemia and glucose intolerance can be minimized by the coadministration of an ACEI or an ARB [22,90,152-156]. Therefore, if low doses of thiazide-like diuretics are insufficient to reduce BP rather than increasing the dose, a second antihypertensive drug, such as an ACEI or an ARB, which exert a synergistic reduction in BP and reduce the hypokalemia, should be added. The ARB losartan is a uricosuric compound that can be used in hypertensive patients with thiazide-induced hyperuricemia in patients who are intolerant to allopurinol [124].

7.4 Drug adherence to thiazide diuretics

In a meta-analysis of 17 studies, patients on thiazide diuretics exhibited the lowest adherence compared with the other drug classes [159], probably due to urinary frequency, erectile dysfunction, fatigue and leg cramps. In another study, after a follow-up of 1 year, only 39% of all patients who were started on a diuretic remained on therapy [160]. Thus, the low persistence rates, together with their effects on electrolyte and glucose metabolism, can be an argument against thiazide-like diuretics as first-line antihypertensive therapy [106]. However, at low doses and, particularly, when given in combination with RAAS inhibitors that reduce the incidence of metabolic side effects, thiazide diuretics are an effective and safe therapeutic approach to control BP in a very significant number of hypertensive patients.

8. Interactions

Thiazide-like diuretics exert an additive effect or potentiate the effects of other antihypertensives and increase the risk of postural hypotension when coadministered with alcohol, baclofen, barbiturates, MAO inhibitors, nitrates, opioids, tizanidine or tricyclic antidepressants [3]. An excessive reduction of BP can be observed following the administration of ACEIs or ARBs in patients on thiazide diuretics; the risk of hypotension can be minimized by either discontinuing or reducing the dose of the diuretic, gradual titration of the dose of RAAS inhibitors and careful monitoring of BP following institution of combined diuretic and ACEI or ARB therapy [23]. The BP-lowering effects of thiazides are attenuated by nonsteroidal anti-inflammatory drugs, presumably due to a decreased synthesis of renal vasodilator prostaglandins [100] and by causing Na^+ retention and can predispose to functional renal insufficiency. Thus, both BP and kidney functions should be monitored. Glucocorticoids and adrenocorticotropic hormone cause salt retention, hyperkalemia and hyperglycemia and antagonize the antihypertensive effect of thiazides. Bile acid sequestrants (cholestyramine and colestipol) reduce the oral absorption of thiazides and decrease their diuretic effect; to avoid this interaction, the thiazide should be taken 1 h before or 4 h after a dose of the resin. Thiazide-induced hypokalemia increases the risk of digitalis-induced arrhythmias and of ventricular tachycardia (including torsades de pointes) when given with QT prolonging drugs. Thiazides decrease renal Ca^{2+} excretion and increase the risk of hypercalcemia when combined with Ca^{2+} salts or vitamin D (cholecalciferol, ergocalciferol) preparations. The risk of hypokalemia increases when thiazides are coadministered with amphotericin B, β2-adrenergic agonists, carbenoxolone, loop diuretics or reboxetine [3]. Thiazides can produce hyperglycemia and inhibit the release of insulin release from the pancreas; thus, thiazide diuretics produce hyperglycemia, worsen glycemic control and reduce the effectiveness of insulin and other diabetic medications. The coadministration of thiazide diuretics with allopurinol increases the risk of severe allergic reactions in patients with CKD.

Thiazide diuretics decrease lithium renal excretion, increasing the risk of lithium toxicity; thus, lithium levels should be monitored closely. Chronic lithium therapy causes nephrogenic diabetes insipidus, which is, at least partly, associated with a downregulation of aquaporin-2 (AQP2), the

vasopressin-regulated water channel of the kidney collecting duct [161]. Under these circumstances, thiazide diuretics paradoxically decrease urine volume and increase urine osmolarity. It has been suggested that thiazide-induced Na^+ depletion causes a reduction in distal delivery associated with enhanced fractional water reabsorption in the collecting duct [162]. In rats with lithium-induced nephrogenic diabetes insipidus, HCTZ reverses lithium-induced AQP2 downregulation and upregulates NCCT and ENaC [163]. Upregulation of NCCT and ENaC would enhance Na^+ reabsorption along the distal segments of nephron; the increase in ENaC-mediated transport decreases luminal osmolarity in the cortical connecting tubule and collecting duct and increases the driving force for water reabsorption.

9. Contraindications and precautions

Thiazides are contraindicated in patients with anuria and hypersensitivity to sulfonamide-derived drugs. If BP control worsens or if volume expansion occurs as CKD progresses to stages 4 – 5 during treatment with a thiazide diuretic (either as monotherapy or as fixed-dose combination antihypertensive therapy) should be substituted by a loop diuretic [23]. Thiazide diuretics should be used with caution in patients with impaired hepatic function, as alterations of hydroelectrolyte balance (hypokalemia) may precipitate hepatic coma, and in patients with hypokalemia, hyponatremia, glucose intolerance, diabetes, symptomatic hyperuricemia and/or hypercalcemia [22]. Thiazide-induced hypokalemia may induce ventricular arrhythmias (including torsades de pointes) in patients with cardiac hypertrophy, HF or acute MI. Thiazide-like diuretics should be avoided on the day of surgery to avoid a potential adverse interaction with surgery-dependent fluid depletion [22]. Because retrospective data have shown an increased risk of malformations associated with thiazide diuretics, these drugs should be used during pregnancy only if clearly needed.

10. Drug combinations

When thiazide diuretics are not the first antihypertensive drug and when the target BP is not achieved, the addition of a thiazide to other antihypertensives exerts an additive BP-lowering effect because they exert a different, but complementary, effect on PVR and can counteract the increase in Na^+ and water retention produced by other antihypertensives [22,164]. There are numerous fixed combinations of HCTZ (6.25 – 25 mg/day) with β-blockers. Thiazides improve the antihypertensive efficacy of β-blockers in blacks and other populations with low-renin hypertension, whereas β-blockers attenuate the RAAS activation induced by thiazide diuretics, and the combination results in fully additive BP reduction [164,165]. However, this combination worsens glucose tolerance, facilitates new onset diabetes and produces fatigue, lethargy and sexual dysfunction [164]. Thus, β-blockers (with the exception of carvedilol and nebivolol) and thiazide diuretics should only be considered as additional drugs, preferably at low doses, in patients with diabetes or metabolic syndrome [22].

The preferred combination is a low-dose thiazide with a RAAS inhibitor (ACEI, ARB, mineralocorticoid receptor antagonists or aliskiren), because it leads to a fully additive BP reduction [164]. Thiazides induce a depletion of intravascular volume and activate the RAAS which causes Na^+ and water retention and vasoconstriction and RAAS inhibitors attenuate these counter regulatory responses. Moreover, RAAS inhibitors decrease thiazide-induced metabolic adverse effects (hypokalemia and glucose intolerance) and thiazide diuretics minimize racial differences usually observed in response to monotherapy with RAAS inhibitors [166]. Thus, if low doses of thiazide diuretics (i.e., HCTZ 12.5 – 25 mg/day) are insufficient to reduce BP, rather than increasing the dose, an ACEI or an ARAII should be added to obtain a synergistic reduction in BP and reduce the risk of hypokalemia [167-169]. Fixed-dose combinations of RAAS inhibitors are available with HCTZ (plus amiloride, triamterene or spironolactone) and CTD (with azilsartan). Another effective and safe combination is a low-dose indapamide SR with perindopril. The combination of a thiazide diuretic and a calcium channel blocker results in a partially additive BP reduction [164], presumably because the calcium channel blocker also increases renal Na^+ excretion. Further, even when this combination results in more vasodilation, it does not reduce the side effect profile of each drug.

Potassium-sparing diuretics (spironolactone, eplerenone, amiloride, triamterene) are useful when coadministered with thiazides diuretics working at more proximal nephron locations. This *sequential nephron blockade* attenuates the risk of hypokalemia and reduces the risk of cardiac arrhythmias and sudden death in hypertensive patients [150]. Potassium-sparing diuretics are preferred to K^+ supplements as they correct both hypokalemia and hypomagnesemia. Even at low doses (25 mg od), spironolactone can increase plasma Mg^{2+} and reduce the risk of ventricular and atrial premature beats and atrial fibrillation/flutter. The spironolactone/HCTZ combination improves BP lowering and is particularly interesting in obese patients [170], whereas the combination of HCTZ with amiloride reduces hypokalemia but results in variable BP reduction [164,171]. These combinations are recommended in patients with an eGFR > 50 ml/min/1.73 m^2; at lower GFR levels, the risk of hyperkalemia increases and decreases the diuretic efficacy of thiazide-like diuretics.

11. Expert opinion

Diuretics and, in particular, thiazide and thiazide-like diuretics are drugs that have been widely used in the treatment of arterial hypertension for more that 50 years. Used initially in monotherapy and at doses higher than those actually recommended in the guidelines, they constitute a relevant component of different fixed-dose combinations with two and

even three other antihypertensive drugs. In most cases, an inhibitor of RAAS (an ACEI, an ARB or a mineralocorticoid receptor antagonist) is the second component in combinations of two drugs, whereas amlodipine is the most frequent third component. Initially, thiazide and thiazide-like diuretics were used at unnecessarily high doses (e.g., HCTZ > 100 mg/day, CTD 25 – 100 mg/day) for the treatment of hypertension. This was accompanied by a significant increase in the incidence of dose-dependent electrolyte and metabolic disturbances without a concomitant increase in their antihypertensive effectiveness, which created an ambiance against the wide use of these types of diuretics. However, at lower doses actually recommended and/or their combination with a RAAS inhibitor diminished in great part these adverse hydroelectrolytic and metabolic adverse effects and contributed to a new era in the use of diuretics. Nowadays, the wide use of thiazide diuretics continues in particular in combination, even though not < 30% of the hypertensive population with no associated CV risk factors and elderly hypertensives can receive these drugs as first-step monotherapy. In the elderly, thiazide diuretics are particularly effective to control BP with many evidence favoring the use of indapamide in combination with a RAAS inhibitor in the next step. The recent debate related to the partial absence of effects of HCTZ and in favor of using CTD or indapamide is not based on a sufficient number of evidences because few studies have made an adequate head-to head comparison of these diuretics. On the other hand, most fixed combinations use HCTZ and we can either use free combinations or rely in the fixed combination of perindopril and indapamide that has demonstrated a reduction in morbidity and mortality in elderly hypertensives and in diabetic patients. CTD has the disadvantage of unavailability in many countries, albeit the new combination of azilsartan and CTD already available in USA opens a new interesting therapeutic alternative. In the presence of a preserved renal function, the effect of thiazide diuretics on volume overload can also be positive in patients with diabetes and in obese patients where a certain degree of Na^+ sensitivity exists. It is important to remember that these two types of patient monotherapy are almost always insufficient. When renal function gets to stage 3 or lower (eGFR < 60 ml/min), a diuretic is mandatory, but thiazide diuretics still remain active until eGFR falls to values < 30 ml/min/1.73 m^2. Afterward, loop diuretics will be the preferred type of diuretic, but it should be remembered that in some cases their association with a thiazide diuretic will greatly facilitate natriuresis and diuresis. In summary, thiazide diuretics have been, are and will be an excellent therapeutic strategy to control BP in a very significant number of hypertensive patients.

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Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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Supplementary material available online

Supplementary Table 1.