EDITORIAL COMMENT

Thiazides in chronic kidney disease: "back to the future"

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ABSTRACT

The thiazide class diuretics are first-line agents for managing hypertension either as monotherapy or as a fixed-dose combination with other antihypertensive drugs. However, despite the extensive experience with these drugs for >60 years, there is general reluctance to use these agents in patients with advanced chronic kidney disease (CKD) because of concerns about their efficacy and safety as kidney function declines. In this issue of *Clinical Kidney Journal*, Minutolo *et al.* performed an updated review of the pharmacological properties, efficacy and side effects and randomized controlled trials that tested these drugs in patients with CKD.

Keywords: chronic renal insufficiency, diuretics, heart failure, hypertension, thiazides

'You cannot connect the dots looking forward; you can only connect them looking backward'.

—Steve Jobs

The agonal picture of volume overload has been a matter of medical concern since the earliest days of recorded history. Nonetheless, the modern era of diuretics is quite recent and began in 1937 with the serendipitous finding that patients receiving one of the new antimicrobials, sulphanilamide, developed metabolic acidosis from the increased excretion of bicarbonate in urine. Twelve years later, William Benjamin Schwartz first reported the natriuretic effect of sulfanilamide in three patients with heart failure by inhibiting carbonic anhydrase in the proximal renal tubule, resulting in hydrogen retention and a concomitant reduction in sodium reabsorption [1]. Shortly after, in 1954, the carbonic anhydrase inhibitor acetazolamide was marketed. Almost concomitantly, the Renal Program of Merck Sharp & Dohme (MSD) discovered chlorothiazide while synthesizing new carbonic anhydrase inhibitors, but unexpectedly, this new agent increased chloride rather than bicarbonate excretion [2]. This finding revealed for the first time that other nephron segments than the proximal tubule could be therapeutically targeted [3]. A few years later, further structural modifications led to the discovery of more potent thiazides (hydrochlorothiazide in 1959 and bendroflumethiazide in 1960) and a closely related group of sulphonamide derivatives lacking the benzothiadiazole ring (chlorthalidone in 1960, metolazone in 1966 and indapamide in 1969). These findings revolutionized the treatment of congestion and hypertension and heralded the present era of oral diuretics (Figure 1).

After their initial discovery, thiazides and thiazide-like diuretics rapidly became first-line agents for the treatment of hypertension through their natriuretic and vasodilating properties. More importantly, beyond their efficacy as antihypertensive drugs, thiazides have been shown to reduce hypertension-related morbidity and mortality [4]. Nonetheless,
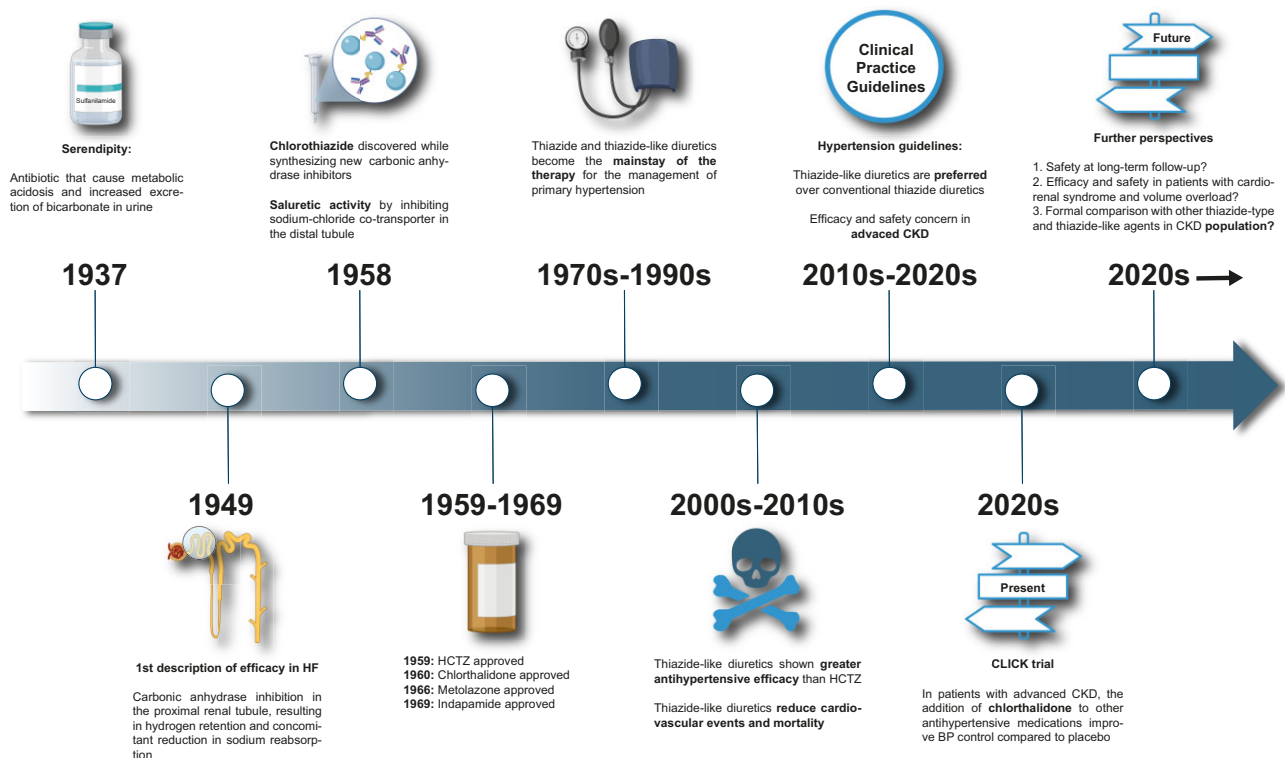
Figure 1: Historical development of thiazides and thiazide-like diuretics. HCTZ: hydrochlorothiazide; HF: heart failure.

there is general reluctance to use these agents in patients with advanced chronic kidney disease (CKD) because of concerns about their efficacy and safety as kidney function declines. In this issue of *Clinical Kidney Journal*, Minutolo *et al.* [5] elegantly reviewed published randomized trials to date of thiazides in this specific population, with a special focus on the Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease trial (CLICK) [6]. Based on the current literature, the authors conclude that thiazides may be useful among people with advanced CKD.

Although we overall agree, a fundamental question remains unanswered:

Is there a thiazide class effect that could eventually translate into a cardiorenal benefit?

The first aspect that needs to be contextualized is the well-known pharmacological differences between thiazide-type and thiazide-like agents. For instance, chlorthalidone is unique among thiazides due to its long elimination half-life (averaging 50–60 h with chronic dosing), as >90% of the drug is reversibly bound to erythrocyte carbonic anhydrase, which acts as a storage reservoir, allowing a constant flow back to the plasma (recycling effect) [7]. This property explains the drug's sustained diuretic and antihypertensive effects even when administered less frequently than once daily. Second, preliminary findings suggest differential pleiotropic properties and molecule-specific effects between agents beyond blood pressure control and natriuresis. For instance, chlorthalidone, but not bendroflumethiazide, decreases vascular endothelial growth factor C and transforming growth factor β3 transcription, both implicated in angiogenesis and vascular permeability [8]. Furthermore, chlortalidone exhibits a higher inhibition of carbonic anhydrases, favouring endothelial and smooth muscle relaxation [9]. Both indapamide and chlorthalidone appear to have a greater effect on

decreasing platelet aggregation than hydrochlorothiazide and bendroflumethiazide [10]. On the other hand, indapamide reduces oxidative stress [11] and exerts a non-diuresis-dependent reduction in blood pressure by blocking calcium channels [12]. Third, as CKD progresses, maintaining euvolemia becomes problematic because the kidney must excrete the same amount of sodium with fewer nephrons. Considering that the distal convoluted tubule reabsorbs only 5–10% of the filtered sodium [13], thiazides are generally not recommended (either as monotherapy or as fixed-dose combination antihypertensive therapy) in patients with advanced CKD if blood pressure control worsens or if volume overload occurs, due to efficacy concerns [14]. Nonetheless, the CLICK trial has recently challenged this notion by showing an adjusted change in 24-h systolic blood pressure from baseline to 12 weeks of ~11 mmHg [95% confidence interval (CI) −14 to −8] in patients with stage 4 CKD randomized to chlorthalidone, while no change (−0.5 mmHg) occurred in the placebo group [6]. Interestingly, and despite patients randomized to chlorthalidone exhibiting a greater reduction in the glomerular filtration rate (GFR) during the treatment period [between-group difference −2.2 ml/min/1.73 m^2 (95% CI −3.3 to −1.0)], the blood pressure–lowering effect of chlortalidone was associated with a 50% change (95% CI 37–60) in the urinary albumin:creatinine ratio from baseline to 12 weeks [6]. A similar efficacy profile was recently reported in patients with resistant hypertension (poorly controlled 24-h ambulatory blood pressure monitoring despite three or more antihypertensive agents) and stage G4 CKD randomized to either placebo or chlorthalidone 12.5 mg/day [15].

The preserved efficacy of chlorthalidone in this population may be a function of its long-acting nature and higher potency at standard doses. It is possible that these pharmacokinetic properties allow chlorthalidone to maintain stable plasma

concentrations more effectively. Furthermore, it has been observed that erythrocyte carbonic anhydrase levels are increased in patients with advanced CKD, potentially increasing the drug storage reservoir [16]. All these preliminary data suggest molecule-specific heterogeneity between agents, arguing against patterns of a class effect. However, although we may be tempted to speculate that these individual differences can lead to differential cardiorenal outcomes, this needs to be confirmed in larger randomized clinical trials.

PITFALLS OF EVIDENCE AND FURTHER PERSPECTIVES

Despite the promising antihypertensive effect of chlorthalidone in advanced CKD, several issues should be evaluated in further studies. First, larger studies comparing the long-term antihypertensive and kidney effects among different thiazides and other widely used diuretics and antihypertensive agents in the whole spectrum of CKD patients are warranted [5].

As Minutolo et al. [5] stated, thiazides may increase the risk of electrolytes disturbances (i.e. hypokalaemia, hyponatremia, hypomagnesemia), GFR decline and/or metabolic abnormalities (impaired glucose tolerance, hyperuricemia, acid-based alterations) in a dose-dependent manner. Although a low-dose strategy correcting hypokalaemia (key mediator in thiazide-related toxicity) is currently recommended to minimize their potential side effects [14, 17], the long-term safety profile of thiazides (specifically with longer-acting compounds such as chlorthalidone and metolazone) needs to be further evaluated in larger trials including patients with a higher risk of adverse events (i.e. cardiorenal syndrome, elderly and frail patients, concomitant use of loop diuretics). Additionally, evaluation of the long-term risk of skin cancer merits specific evaluation, a side effect reported mainly with the long-term use of hydrochlorothiazide [18].

Whether the observed reduction in the urinary albumin:creatinine ratio [6, 15] might translate into long-term kidney protection remains to be determined.

Robust data about the trajectory of kidney function over time and its efficacy in reducing the risk of adverse clinical events are scarce. Here we envision a greater benefit of thiazides, and specifically chlorthalidone, in patients with the coexistence of volume overload or prior heart failure (patients at higher risk of congestive nephropathy). In this setting, we believe sequential nephron blockade, adding thiazides to loop diuretics, may increase natriuresis, ameliorate renal congestion and translate into renal and clinical benefits [19]. Endorsing this postulate, in the Improve-HF trial that randomized 160 patients with acute heart failure and kidney dysfunction on admission (mean GFR 33.7 ± 11.3 ml/min/1.73 m^2), we found that those patients with greater congestion [assessed by high levels of circulating carbohydrate antigen 125 (CA 125)] benefited from a more aggressive diuretic strategy in terms of greater decongestion and better renal function at 72-h [20]. Interestingly, in the CA 125–guided arm, there was a statistical trend of a higher proportion of patients treated with intravenous furosemide plus chlorthalidone compared with the usual clinical diuretic arm (26.6% versus 14.8%; $P = .066$). However, this hypothesis needs to be confirmed in further studies to evaluate the clinical utility of different sequential nephron blockade strategies in cardiorenal patients across the different degrees of volume overload.

Formal comparisons among distal convoluted tubule diuretics in patients with advanced CKD (including hydrochlorothiazide, metolazone, chlorthalidone, indapamide and others such as xipamide) are warranted [21].

Further studies with close monitoring of safety issues are required to reveal the appropriate chlorthalidone regimen to minimize the risk of adverse events and maximize the efficacy in each specific patient. We believe close monitoring with dynamic up/down titration will show the best net clinical benefit. Additionally, the parameters to be used for this exercise of precision medicine also remain a matter of further examination.

In summary, although there is still some way to go, the revived interest in research with these old drugs [6, 21] makes us envision the future with enthusiasm. Hopefully current and future evidence will help us move from empiricism by finally looking backward and connecting the dots.

FUNDING

AUTHORS' CONTRIBUTIONS

All authors meet each of the following characteristics defined by the International Committee of Medical Journal Editors in the criteria for authorship of scientific articles: substantial contributions to the conception or design of the manuscript, drafting the work or revising it critically for important intellectual content, final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the manuscript are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

J.N. is a member of the *CKJ* editorial board. The other authors have no conflicts of interest to declare.

(See related article by Minutolo et al. Thiazide diuretics are back in CKD: the case of chlorthalidone. *Clin Kidney J* (2023) 16: 41–51.)

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