

Thiazide diuretics in chronic kidney disease: Is there still a role?

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"The young physician starts life with 20 drugs for each disease, and the old physician ends life with one drug for 20 diseases."

— William Osler

Hypertension is both a cause and consequence of chronic kidney disease (CKD). As such, the prevalence of hypertension is high among CKD patients and the incidence increases as their kidney disease progresses. Given the high risk of mortality, morbidity and risk of progression to end-stage renal failure, blood pressure management remains a key focus in managing CKD patients. However, without strong definitive evidence for blood pressure targets, or clear data to support the precise combination of antihypertensive medications, practice variance increases as the number of drugs available to treat hypertension increases and older drug classes may be overlooked.

Based on the latest available evidence from the Systolic Blood Pressure Intervention Trial (SPRINT) and Action to Control Cardiovascular Risk in Diabetes (ACCORD), the Kidney Disease Improve Global Outcomes (KDIGO) guideline in 2021 lowered the suggested systolic blood pressure target from 130 mmHg to less than 120 mmHg using standardised office reading for most people with CKD and not receiving dialysis.¹⁻³ They recommend antihypertensive drugs targeting the renin-angiotensin system (RAS) as first-line in CKD because of the antiproteinuric effect, slowing the progression of kidney disease.¹ RAS inhibitors include both angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers that act by blocking the conversion of angiotensin I to the potent vasoconstrictor peptide angiotensin II and angiotensin II receptors, respectively. The overall effect is a reduction in aldosterone secretion and peripheral vascular resistance, therefore reducing blood pressure. However, the mechanism contributing to hypertension in CKD become increasingly complex as the disease worsens, with patients experiencing volume overload, sympathetic overactivity, salt retention, endothelial dysfunction, and alterations in hormonal systems.⁴ As a result, most CKD patients eventually need a combination of therapies to achieve increasingly lower blood pressure targets.

The evidence for combination therapy is less robust and often limited to expert opinion, frequently developed by extrapolating from the general population. When RAS inhibition alone fails to achieve blood pressure targets in CKD, diuretic therapy is often added, either as second- or third-line agents. Mechanistically they help manage concomitant hypervolemia, hyperkalemia, and facilitate sodium removal. Loop diuretics are usually the drug of choice in advanced CKD,⁵ but they may fail because uremic anions compete for the tubular transporters that transfer this class of drugs from the peritubular circulation to the tubular lumen, and combined with the frequent coexistence of low serum albumin, their delivery to the site of action in kidney is often impaired.⁶

For many years, hypertension guidelines have recommended the use of thiazides in non-CKD patients. Thiazide diuretics are a pharmacologically heterogeneous class that acts primarily on the distal convoluted tubule, heterogeneous because the term includes thiazide-like antihypertensives, which are sulfonamide diuretics that behave like thiazide diuretics, but lack the benzothiazide molecular structure of thiazide-type diuretics, resulting in different pharmacokinetics; specifically, bioavailability, metabolism and half-life. Thiazides have been available since the 1950s, are safe, effective, well-tolerated and in most countries are the least expensive antihypertensive drugs. They have been shown to reduce risk of cardiovascular events, heart failure and stroke, and while treatment with thiazides may result in hypokalemia, hyponatremia and hypomagnesemia, using lower doses and concurrent RAS inhibitors or concurrent potassium-sparing agent manages these side effects. However, they have not been frequently used to in CKD patients, perhaps because they are assumed to be less efficient than relatively newer loop diuretics,⁷ despite recent evidence demonstrating that thiazides can achieve diuresis and sodium balance among patients with lower glomerular filtration rate.^{8,9}

Among them, was the double-blind randomised, placebo-controlled Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease (CLICK) trial, published in 2021, which reported improved

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blood pressure control in patients with stage 4 CKD and poorly controlled hypertension using chlorthalidone.⁹ As a thiazide-like diuretic, chlorthalidone has a longer half-life, close to 50 hours, because it is bound to erythrocyte carbonic anhydrase resulting in greater concentration in red blood cells,¹⁰ compared to thiazide-type diuretics which have a half-life of about 12 hours. This may explain why chlorthalidone is reported to have a more pronounced, and faster, blood pressure-reducing effect than other thiazides. Publication of the CLICK trial renewed interest in the role of thiazides in blood pressure management for patients with advanced CKD.

In this issue of *Annals*, Lin and colleagues present a large retrospective study evaluating the association between thiazide diuretics use and clinical outcomes among CKD patients using a national database in Taiwan.¹¹ The authors compared 8501 CKD patients on thiazide, or thiazide-like diuretics, by carefully matching them with a comparison group. In their cohort, 44.1% patients were treated with thiazide-type diuretics (bendroflumethiazide and hydrochlorothiazide), and the remaining with thiazide-like diuretics; 48.8% with indapamide, 2.2% with chlorthalidone, and 4.9% with metolazone. Most of the patients in the study received their diuretic in combination with RAS inhibitors, similar to the CLICK trial. Lin et al. were able to show that thiazide-type diuretics were associated with a mortality reduction in CKD stage 3 and 4 patients, and after adjusting for co-morbidities, these patients had a lower incidence of end-stage renal disease, congestive heart failure, peripheral arterial occlusive disease and stroke.

While promising, we should remember the limitation of findings from large retrospective cohorts, such as misclassification, lack of blood pressure details and lack of information of adverse events. Without the actual comparative BP readings between the group given thiazide or thiazide-like diuretics and the group that did not receive such treatment, it is possible that the favourable outcome is solely driven by better BP control. It is worth noting that only 8.9% of the comparator group was treated with a diuretic (a loop diuretic as they were in the non-THZ group). The percentage of patients being treated with a RAS blockade agent was also relatively low at 54.7% for a CKD population. The study does provide the answer if loop diuretics can be equally or even more effective than THZ diuretic and if more frequent use of RAS agents may alter the observed benefits. Despite these limitations, their study raises the important question: Should thiazide diuretics be prescribed more often to manage hypertension in patients with CKD? Unlike many studies, Lin

et al. focuses on a predominately Asian cohort, providing important information specific to those of us working within Asia, a demographic not always well represented in multicentre studies such as the CLICK trial,⁹ and the use of a national database allowed for a large cohort and long follow-up time.

At the very least, this robust registry study paves the way for randomised controlled trials, generating important new data with relatively old and established drugs. Until such studies are conducted, the study by Lin et al. makes an important contribution, there is little to be lost in adding, or keeping, thiazide-type and thiazide-like diuretics in our antihypertensive tool box for patients with CKD. As with any therapeutic decision, careful evaluation of the type of thiazide diuretics—considering individual patient characteristics, tolerability and preferences—is vital in determining the best individualised therapy for our CKD patients.

Keywords: bendroflumethiazide, chronic kidney disease, hydrochlorothiazide, hypertension, thiazides

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