Patients with advanced CKD have a high rate of cardiovascular disease and uncontrolled hypertension. Large hypertension trials have generally excluded patients with stage 4 CKD (GFR=15–30 ml/min), leaving the preferred treatment strategy of hypertension in this population unclear (1). There are over 1 million patients with stage 4 CKD in the United States, and given their high rates of morbidity and mortality, improving their cardiovascular health is a high priority (2). To date, there are high-quality data that renin-angiotensin system (RAS) antagonists slow CKD progression in patients with stage 4 CKD (3). Recent guidelines support the use of RAS inhibitors and loop diuretics in patients with stage 4 CKD, with the loop diuretic recommendation representing one on the basis of opinion (4). Although there is evidence that thiazide diuretics retain efficacy in CKD, they have not been routinely used in this patient population (5).

Because thiazide diuretics are beneficial in the general population with hypertension, and patients with stage 4 CKD have high rates of uncontrolled hypertension, the investigators of the Chlorthalidone in Chronic Kidney Disease (CLICK) study tested whether chlorthalidone is efficacious in patients with stage 4 CKD (6). The trial was a randomized controlled trial in patients with stage 4 CKD and uncontrolled hypertension (24-hour ambulatory BP >130/80 mm Hg while on at least one antihypertensive medication). Patients were randomized to placebo or chlorthalidone (12.5 mg); the doses were increased to a maximum of 50 mg if BP was not controlled. The primary end point was change in 24-hour ambulatory BP at 12 weeks, while secondary end points included change in urine albumin-creatinine ratio (UACR) at 12 weeks, plasma N-terminal pro B-type natriuretic peptide (NT-pro BNP) levels, and plasma renin and aldosterone levels.

The trial successfully enrolled 160 patients with stage 4 CKD. At baseline, there was good representation of Black and White participants, while the majority of participants were men. The mean eGFR was approximately 23 ml/min per 1.73 m² in both groups, and most patients had overt proteinuria (UACR >300 mg/g). On average, the participants were taking more than three antihypertensive medications, with near-universal use of RAS blockers and 60% use of loop diuretics. At entry, the mean 24-hour BP was 143/75 mm Hg in the chlorthalidone group and 140/73 mm Hg in the placebo group. After 12 weeks of therapy, chlorthalidone treatment led to a significant decrease in BP (11/5-mm Hg decrease) compared with placebo (0.5/1-mm Hg decrease). Chlorthalidone was also associated with a 1.2-kg weight loss, supporting the diuretic efficacy of chlorthalidone in patients with CKD. In addition to a significant change in the primary end point, chlorthalidone was associated with a significant reduction in proteinuria; UACR decreased by approximately 40%, an effect that persisted 2 weeks after discontinuation of chlorthalidone. In further support of diuretic efficacy, NT-pro BNP levels decreased more in the chlorthalidone group, and renin and aldosterone levels increased. The most common adverse effects seen with chlorthalidone were hypokalemia (10% versus 0%), hypomagnesemia (23% versus 16%), hyperuricemia (20% versus 9%), dizziness (25% versus 16%), and AKI (41% versus 13%). The episodes of AKI were consistent with prerenal AKI as they were reversible after chlorthalidone was withdrawn. Although the trial was not designed to evaluate hard end points, such as progression to kidney failure, the investigators followed most patients for 3 years after the trial and observed a trend toward decreased kidney failure or death.

The CLICK trial had several notable strengths, and it provides very useful data for those who care for patients with stage 4 CKD. Trials focusing on high-risk patients with stage 4 CKD are rare. A previous randomized controlled trial in patients with stage 4 CKD demonstrated that benazepril treatment decreased BP, proteinuria, and CKD progression (3). However, as seen in the baseline data study of the CLICK study, RAS inhibitors are not sufficient to control BP and proteinuria in many patients with stage 4 CKD; addition of chlorthalidone may be a useful additive therapy.

The trial was also notable for the rigorous techniques to assess BP. Ambulatory 24-hour BP measurements provide a highly sensitive tool for measuring BP and correlate better with CKD progression and left ventricular hypertrophy than clinic BP measurements (7). Ambulatory 24-hour BP measurements also allow for the assessment of the physiologic decrease in nocturnal BP (“dipping”). Absence of nocturnal dipping is correlated with adverse cardiac outcomes, but it is unclear if reversing nondipping status actually improves cardiovascular health in patients with CKD.
In this trial, chlorthalidone treatment was not associated with an increase in nocturnal diuring. The chlorthalidone-induced reduction in 24-hour BP is large and would likely be associated with a significant improvement in cardiovascular outcomes. A previous study showed that hydrochlorothiazide restored dipping status in patients with normal kidney function (8). It is unclear if the negative results in the CLICK trial are related to differences between chlorthalidone and hydrochlorothiazide or to differences between patients with CKD and patients without CKD. In addition to using 24-hour BP monitors, the investigators analyzed home BP measurements (performed twice daily in the week before the office visits) and standardized office BP measurements with an oscillometric monitor. The trial results indicated a close correlation between all three techniques, an important finding for clinical practice because some practitioners may not regularly use 24-hour BP monitors.

Although the trial was not designed to test hard end points of progression of kidney disease and cardiovascular events, it did assess secondary end points that are associated with these adverse outcomes. The large decrease in proteinuria is often associated with slower CKD progression and fewer cardiovascular events. Serum levels of NT-pro BNP, renin, and aldosterone also provide a plausible mechanism for the beneficial effects of chlorthalidone in CKD. NT-pro BNP decreased, whereas renin and aldosterone levels increased, supporting a volume-mediated effect of chlorthalidone. Further support for a volume-dependent mechanism came with the analysis 2 weeks after stopping chlorthalidone when NT-pro BNP increased and renin and aldosterone levels declined.

Despite the significant findings of the study, it is unclear how the results will translate to the wider population patients with stage 4 CKD. At baseline, the patients in the CLICK study had relatively well-controlled BP (average systolic BP between 140 and 145 mm Hg). The patients were also educated on a reduced sodium diet and had appropriately reduced 24-hour urine sodium values. Many patients with stage 4 CKD, especially those in underserved populations, are not seen in the clinic frequently, have higher baseline BP, and have significantly higher dietary sodium. Whether chlorthalidone would lead to a large decrease in BP and weight loss in these patients is unknown. Furthermore, although the adverse effects of chlorthalidone seen in the trial were predictable, it is possible that more widespread use of chlorthalidone in a less-monitored, higher-risk stage 4 CKD population may be associated with a higher rate of adverse events.

Frequently, nephrologists encounter patients with stage 4 CKD with overt volume overload and diuretic resistance. Diuretic resistance among patients taking a loop diuretic is often due to upregulation of the thiazide-sensitive sodium chloride transporter (NCC) channel (9). Because over 60% of trial participants were taking loop diuretics at baseline, thiazides may have further improved BP by targeting sodium retention by the kidneys in a different manner than loop diuretics. However, it is important to note that the participants in CLICK likely did not have symptomatic volume overload. Although chlorthalidone did lead to a modest weight decrease (1.2 kg) in patients, the CLICK trial was not designed to test whether chlorthalidone would overcome diuretic resistance in patients with overt volume overload.

Mineralocorticoid antagonists (MRAs) are often used for patients with CKD and residual proteinuria as well as patients with resistant hypertension. However, MRAs are not often initiated in patients with stage 4 CKD due to risk of hyperkalemia. Recent trials of MRAs have mainly studied patients with stage 3 CKD and found that MRAs led to only a slight reduction in BP (10). It is therefore unclear if MRAs would be preferred for patients with stage 4 CKD, proteinuria, and hypertension. On the basis of the CLICK trial, it could be argued that chlorthalidone would be the preferred agent for patients with stage 4 CKD and resistant hypertension given the proven efficacy and low risk of hyperkalemia. Because thiazide diuretics led to an increase in plasma aldosterone in this trial, it is also plausible that combination therapy with thiazides and MRAs may provide benefit to patients with stage 4 CKD.

In summary, the CLICK trial was a high-quality randomized controlled trial that supports the use of chlorthalidone to reduce BP in patients with stage 4 CKD and hypertension, especially those with significant proteinuria. Although reducing BP is an important outcome, further studies will be necessary to determine if reductions in BP are associated with improvement in “harder” outcome, such as cardiovascular events and/or progression of CKD. The safety signals observed in the CLICK study raise concerns that the risks may outweigh benefits in the entire population of patients with stage 4 CKD.

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S.B. Furgeson and S. Linas conceptualized the study; S.B. Furgeson and S. Linas wrote the original draft; and S.B. Furgeson and S. Linas reviewed and edited the manuscript.

References


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