EDITORIALS

Chlorthalidone in Advanced Chronic Kidney Disease — Have We Missed a Trick?

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Control of hypertension is central to the management of chronic kidney disease, both to preserve residual kidney function and to reduce the associated high risk of cardiovascular events. International guidelines recently updated by the Kidney Disease: Improving Global Outcomes Organization recommend that patients with chronic kidney disease and hypertension be treated to reduce standardized office systolic blood pressure to less than 120 mm Hg, unless there are obvious reasons not to do so.[1] This ambitious target is difficult to achieve with currently available antihypertensive medications, particularly in patients with more advanced chronic kidney disease (stages 4 and 5).[2] In principle, any blood-pressure–lowering agents can be used to control hypertension in this clinical setting, although the strongest evidence supports the use of angiotensin-converting–enzyme (ACE) inhibitors or angiotensin-receptor blockers, particularly when proteinuria is present.[3] Several trials, many conducted more than 20 years ago, which included patients with either diabetic or nondiabetic kidney disease, showed that preservation of kidney function was better with ACE inhibitors or angiotensin-receptor blockers than with placebo or active comparators.[4] On the basis of these trials, these drug classes are endorsed in the guidelines,[1] although blood pressure is rarely adequately controlled with the use of a single agent, particularly in the context of advanced chronic kidney disease. The choice of a second- or third-line agent is more difficult, largely because of a lack of relevant clinical evidence.

Although thiazide and thiazide-like diuretics have reduced the risks of stroke, heart failure, and other cardiovascular events in trials involving patients with "essential hypertension,"[5] there has been a general reluctance to use these agents in patients with advanced chronic kidney disease, largely because of concerns that they lose diuretic efficacy as kidney function declines; the more potent loop diuretic agents are usually preferred.[6] In this issue of the *Journal*, Agarwal et al. challenge this perception with data from their Chlorthalidone in Chronic Kidney Disease (CLICK) trial.[7]

In the double-blind CLICK trial, 160 patients with stage 4 chronic kidney disease (mean [±SD] estimated glomerular filtration rate, 23.2±4.2 ml per minute per 1.73 m^2 of body surface area), 76% of whom had diabetes, were randomly assigned in a 1:1 ratio to receive chlorthalidone or placebo and were followed over a 14-week period. The patients were already receiving a mean of 3.4±1.4 antihypertensive agents, which, in all but two patients, included either an ACE inhibitor or an angiotensin-receptor blocker. The protocol allowed for an increase in the dose of the trial drug at every 4 weeks, from an initial dose of 12.5 mg per day to a maximum dose of 50 mg per day; this maximum was not reached (the mean dose at 12 weeks was 23.1 mg in the chlorthalidone group and 37.2 mg in the placebo group). The primary outcome of the trial was the change in 24-hour ambulatory systolic blood pressure from baseline to 12 weeks. The results showed reductions of –11.0 mm Hg (95% confi-

dence interval [CI], –13.9 to –8.1) in the chlorthalidone group and –0.5 mm Hg (95% CI, –3.5 to 2.5) in the placebo group, with a between-group difference of –10.5 mm Hg (95% CI, –14.6 to –6.4) (P<0.001).

These results should dispel concerns that chlorthalidone is "ineffective" as an antihypertensive agent in patients with stage 4 chronic kidney disease, but what are the clinical benefits? The CLICK trial was too small and too short to inform us whether this substantial blood-pressure reduction translates to cardiorenal benefits. However, the signals are encouraging, with a percent change in the urinary albumin-to-creatinine ratio from baseline to 12 weeks (a secondary outcome) that was 50 percentage points lower in the chlorthalidone group than in the placebo group, which could indicate kidney protection. Adverse events included a greater reduction in the estimated glomerular filtration rate (eGFR) at 12 weeks with chlorthalidone than with placebo, but it was reassuring that this was reversed on discontinuation of trial drug. This reversible acute drop in eGFR, along with the reduction in albuminuria, suggests that chlorthalidone might reduce intraglomerular pressure in the same way as other classes of drugs with proven renoprotective actions, namely ACE inhibitors, angiotensin-receptor blockers, and sodium–glucose cotransporter inhibitors.[8] As expected from the known side-effect profile of chlorthalidone, higher rates of hypokalemia, hyperglycemia, and hyperuricemia were observed in the patients in the chlorthalidone group.[5]

These findings showing that chlorthalidone is an effective blood-pressure–lowering agent in patients with advanced chronic kidney disease are welcome news, particularly because this agent is relatively inexpensive and widely available. However, as noted by the authors, whether the addition of chlorthalidone to a regimen of ACE inhibitors or angiotensin-receptor blockers will further slow the progression of kidney disease and reduce cardiovascular risk without important safety concerns should be determined through the assessment of clinical outcomes in a larger trial of longer duration. If the results of such a trial were favorable, chlorthalidone could prove to be a valuable addition to the growing number of therapeutic agents of established clinical benefit in the management of chronic kidney disease.[9]

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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