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Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease

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Abstract

BACKGROUND—Little evidence has been available to support the use of thiazide diuretics to treat hypertension in patients with advanced chronic kidney disease.

METHODS—We randomly assigned patients with stage 4 chronic kidney disease and poorly controlled hypertension, as confirmed by 24-hour ambulatory blood-pressure monitoring, in a 1:1 ratio to receive chlorthalidone at an initial dose of 12.5 mg per day, with increases every 4 weeks if needed to a maximum dose of 50 mg per day, or placebo; randomization was stratified according to previous use of loop diuretics. The primary outcome was the change in 24-hour ambulatory systolic blood pressure from baseline to 12 weeks. Secondary outcomes were the change from baseline to 12 weeks in the urinary albumin-to-creatinine ratio, N-terminal pro–B-type natriuretic peptide level, plasma renin and aldosterone levels, and total body volume. Safety was also assessed.

RESULTS—A total of 160 patients underwent randomization, of whom 121 (76%) had diabetes mellitus and 96 (60%) were receiving loop diuretics. At baseline, the mean (±SD) estimated glomerular filtration rate was 23.2±4.2 ml per minute per 1.73 m^2 of body-surface area and the mean number of antihypertensive medications prescribed was 3.4±1.4. At randomization, the mean 24-hour ambulatory systolic blood pressure was 142.6±8.1 mm Hg in the chlorthalidone group and 140.1±8.1 mm Hg in the placebo group and the mean 24-hour ambulatory diastolic blood pressure was 74.6±10.1 mm Hg and 72.8±9.3 mm Hg, respectively. The adjusted change in 24-hour systolic blood pressure from baseline to 12 weeks was −11.0 mm Hg (95% confidence 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. The between-group difference was −10.5 mm Hg (95% CI, −14.6 to −6.4) (P<0.001). The percent change in the urinary albumin-to-creatinine ratio from baseline to 12 weeks was lower in the chlorthalidone group than in the placebo group by 50 percentage points (95% CI, 37 to 60). Hypokalemia, reversible increases in serum creatinine level, hyperglycemia, dizziness, and hyperuricemia occurred more frequently in the chlorthalidone group than in the placebo group.

CONCLUSIONS—Among patients with advanced chronic kidney disease and poorly controlled hypertension, chlorthalidone therapy improved blood-pressure control at 12 weeks as compared with placebo. (Funded by the National Heart, Lung, and Blood Institute and the Indiana Institute of Medical Research; CLICK ClinicalTrials.gov number, NCT02841280.)

Hypertension, a common risk factor for both cardiovascular disease and chronic kidney disease, is often poorly controlled, especially in patients with advanced chronic kidney disease.[1] Thiazide or thiazide-like diuretics are important agents for lowering blood pressure in patients with essential hypertension. [2] Chlorthalidone, a thiazide-like diuretic, reduces cardiovascular morbidity, such as the incidence of stroke and heart failure, and cardiovascular mortality.[3–5] However, its efficacy and safety among patients with advanced chronic kidney disease remain poorly understood.[6] Several studies suggest that these drugs might be effective for treating hypertension in patients with chronic kidney disease.[7,8] On the basis of preliminary evidence of an effect on blood pressure in patients with chronic kidney disease,[9] we hypothesized that among patients with advanced chronic kidney disease and uncontrolled hypertension, chlorthalidone would decrease the 24-hour ambulatory

systolic blood pressure. We also hypothesized that chlorthalidone would reduce the degree of albuminuria over 12 weeks and provide preliminary evidence that chlorthalidone is renoprotective and cardioprotective.

METHODS

TRIAL SETTING

The Chlorthalidone in Chronic Kidney Disease (CLICK) Trial was a double-blind, randomized, placebo-controlled trial of chlorthalidone in patients with advanced chronic kidney disease and treated but poorly controlled hypertension. The trial design was published previously[10]; the trial protocol, with the statistical analysis plan, is available with the full text of this article at NEJM.org. The trial was approved by the institutional review board of Indiana University and the Research and Development Committee of the Richard L. Roudebush Veterans Affairs (VA) Medical Center. Patients were recruited from the Indiana University Hospitals, Eskenazi Hospital, and the Richard L. Roudebush VA Medical Center. All the patients provided written informed consent before participation.

An independent data and safety monitoring committee oversaw patient safety; no interim analyses were planned or conducted. The first author designed the trial, wrote the manuscript, and made the decision to submit the manuscript for publication. The first five authors collected the data. The first and last two authors analyzed the data and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PATIENTS

Eligible patients had stage 4 chronic kidney disease (estimated glomerular filtration rate [GFR], 15 to <30 ml per minute per 1.73 m^2 of body-surface area) and uncontrolled hypertension, as confirmed by 24-hour ambulatory blood-pressure monitoring after a 2-week period during which antihypertensive medications were standardized and patients received a placebo. We standardized medications through the use of a preferred drug in each class of antihypertensive drug.

Uncontrolled hypertension was defined as a mean 24-hour ambulatory blood pressure of 130 mm Hg or higher (systolic) or 80 mm Hg or higher (diastolic) while receiving at least one antihypertensive drug. We excluded patients who had a 24-hour ambulatory blood pressure of 160 mm Hg or higher (systolic) or 100 mm Hg or higher (diastolic), had had a stroke or myocardial infarction, had been hospitalized for heart failure within 12 weeks before randomization, were receiving high-dose loop diuretics (>200 mg of furosemide daily or >100 mg of torsemide daily), or had received a thiazide or a thiazide-like diuretic within 12 weeks before randomization. The patients were required to be receiving an angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker or a beta-blocker at the time of randomization. The active trial drug (chlorthalidone, Mylan Pharmaceuticals) and placebo (microcrystalline cellulose) were encapsulated at a compounding research pharmacy (Richard L. Roudebush VA Medical Center) to ensure identical taste and appearance.

TRIAL VISITS

There were nine prespecified trial visits — four took place over a 3-week period before randomization, and four over a 12-week period after randomization; a final visit took place 2 weeks after the assigned regimen was discontinued (Fig. S1 in the Supplementary Appendix). At every visit, seated and standing blood pressures were measured with a digital oscillometric sphygmomanometer (Model HEM-907, Omron Healthcare). Seated blood pressure was measured in the clinic (clinic blood pressure) after the patient had rested for 5 minutes without an observer in the room. The blood pressure was measured in triplicate in close succession in both arms after an appropriately sized cuff was applied. Patients were provided a blood-pressure monitor (Model 791IT, Omron Healthcare) and were instructed to measure blood pressure at home (home blood pressure) in triplicate after 5 minutes of seated rest twice daily for 1 week before the scheduled clinic visit.

At the second visit, which took place 1 week after the first, the patients were given written instructions to consume a diet containing less than 100 mmol of sodium per day. A 2-week run-in period with placebo was initiated for all patients at this time, and the patients antihypertensive regimens were standardized to the preferred regimens within each drug class as follows: lisinopril (20 to 40 mg daily) was given in place of an angiotensin-converting–enzyme inhibitor, losartan (50 to 100 mg daily) was given in place of an angiotensin-receptor blocker (if angiotensin-converting–enzyme inhibitors were contraindicated in the patient), amlodipine (10 mg daily) was given in place of a dihydropyridine calcium-channel blocker, atenolol (25 to 100 mg daily) was given in place of a beta-blocker, and torsemide (10 to 20 mg daily) was given in place of a loop diuretic.

At the third visit, which occurred 2 weeks after the second, a blood sample was obtained for the measurement of levels of electrolytes, glucose, renin, aldosterone, and N-terminal pro–B-type natriuretic peptide (NT-proBNP) and for use in kidney-function tests. A urine sample was obtained to measure albumin and creatinine levels. Total body volume (the volume of air displaced by the body in a pressure-regulated closed chamber) was measured by means of air-displacement plethysmography (CosMed). During the ensuing 24 hours, a urine sample was collected to measure sodium and creatinine levels, and blood pressure was measured with a Spacelabs 90207 ambulatory monitor (Spacelabs Healthcare). At the fourth visit, patients underwent randomization.

RANDOMIZATION

Patients were randomly assigned in a 1:1 ratio to receive either chlorthalidone or placebo. Randomization was stratified according to previous use of loop diuretics. Random block sizes were used to avoid an imbalance in the number of patients receiving chlorthalidone or placebo. The trial pharmacist, who did not interact with patients, dispensed the trial drug or placebo in a blinded manner, according to the randomization sequence for the appropriate stratum, after confirming eligibility with the principal investigator. The trial-group assignments were concealed from the investigator, the treating physician, the patient, and the outcome assessor.

DOSE ADJUSTMENT AND ANNUAL FOLLOW-UP STUDY

The dose used in the assigned regimen was doubled every 4 weeks if, at that time, the patient had a home blood pressure of 135 mm Hg or higher (systolic) or 85 mm Hg or higher (diastolic): at week 4, the dose was doubled from 12.5 mg once daily to 25 mg once daily, and at week 8, the dose was doubled to 50 mg once daily (maximum dose). The dose was not increased if the patient had symptomatic orthostatic hypotension, hypercalcemia, moderate hypokalemia (potassium level, <3 mmol per liter), acute gout, or recent hospitalization for poorly controlled diabetes. In these instances, the dose was either maintained or decreased, as determined by the investigator.

The assigned regimen was discontinued or the dose was reduced if a patient had a rash that was considered by the trial investigator to have been induced by chlorthalidone or placebo, had acute kidney injury, or had other adverse events potentially attributable to chlorthalidone or placebo. Poorly controlled hypertension led to withdrawal from the trial if the home blood pressure (averaged over a 1-week period) exceeded 179/109 mm Hg and remained at 180/110 mm Hg or higher 1 week after the dose was increased. Alternatively, the patient was withdrawn from the trial if the home blood pressure was 160 to 179/100 to 109 mm Hg and was not reduced to below 160/100 mm Hg by 4 weeks after the dose was increased.

Patients who completed the final visit at 2 weeks after the assigned regimen was discontinued were invited to participate in an annual follow-up study for up to 3 years. At these follow-up visits, any clinically significant outcome event such as long-term renal-replacement therapy was recorded.

TRIAL OUTCOMES

The primary outcome was the change in 24-hour ambulatory systolic blood pressure from baseline to 12 weeks. Secondary outcomes were the change from baseline to 12 weeks in the urinary albumin-to-creatinine ratio, NT-proBNP level, plasma renin and aldosterone levels, and total body volume.

STATISTICAL ANALYSIS

Assuming that 20% of the patients would discontinue the trial, we calculated that a total sample of 160 patients would ensure that at least 128 patients would complete the assigned trial regimen at 12 weeks and have a 24-hour ambulatory blood-pressure recording that could be evaluated. On the basis of our preliminary data, we used a two-sided t-test at the 0.05 significance level to estimate that a sample of 64 patients in each trial group would provide the trial with at least 80% power to detect a difference of 6 mm Hg in the change in blood pressure from baseline.

All the analyses were based on the intention-to-treat approach. The primary analysis was performed with a mixed model for repeated measures that included the 24-hour ambulatory systolic blood pressure measured at baseline and at 12 weeks as the response variables. The model included the trial-group assignment indicator (chlorthalidone or placebo), time (4 and 12 weeks), and use of loop diuretics at baseline as independent variables, as well as the two-way and three-way interactions of trial group by time, time by use of loop diuretics at

baseline, trial group by use of loop diuretics at baseline, and use of loop diuretics at baseline by trial group by time. The model included a random patient effect and an unstructured variance–covariance matrix to accommodate the potential correlations among the repeated measures within the same patient.

We first examined the statistical significance of the three-way interaction term. If the three-way interaction was not significant, we planned to remove the term from the model and report the time trend of the blood-pressure change according to trial groups, with adjustment for use of loop diuretics at baseline. Multiple imputation was used in the primary analysis to account for missing data. Specifically, we imputed the final ambulatory blood pressure using the following variables: ambulatory blood pressure at baseline, trial-group assignment, use of loop diuretics at baseline, and the interaction of the two terms.

Similar mixed models for repeated measures were used to analyze the changes in blood pressure from baseline and their 95% confidence intervals; the models were adjusted for the use of loop diuretics at baseline. Modification of the treatment effect is reported for prespecified subgroups. A complete case analysis and additional sensitivity imputation analyses were performed to validate the trial findings. The urinary albumin-to-creatinine ratio and the NT-proBNP, renin, and aldosterone levels were logarithmically transformed to correct the skewed distribution for the purpose of inference; point estimates and 95% confidence intervals were back-transformed so that results could be interpreted on the original scale. All the between-group differences were calculated as the change from baseline in the value in the chlorthalidone group minus the change from baseline in the value in the placebo group.

RESULTS

PATIENTS

A total of 2849 patients underwent screening (Fig. S2). Of the 403 patients who had provided consent, 160 (40%) underwent randomization — 81 were assigned to the chlorthalidone group and 79 to the placebo group. A total of 140 patients (88% of the enrolled patients) completed the 12-week trial period. Selected baseline characteristics of the patients who underwent randomization are provided in Table 1. At baseline, the patients were receiving a mean (±SD) number of 3.4±1.4 antihypertensive medications, 96 patients (60%) were receiving loop diuretics, and all except 2 patients (1%) were receiving an angiotensin-converting–enzyme inhibitor, an angiotensin-receptor blocker, or a beta-blocker (Table S1). The mean estimated GFR was 23.2±4.2 ml per minute per 1.73 m^2 of body-surface area.

In the chlorthalidone group, the mean dose received per day was 11.5 mg at 4 weeks after the initiation of the regimen, 18.3 mg at 8 weeks, and 23.1 mg at 12 weeks. In the placebo group, the mean dose received per day was 12.3 mg at 4 weeks after the initiation of the regimen, 21.9 mg at 8 weeks, and 37.2 mg at 12 weeks. The chlorthalidone group received a median cumulative dose of 1063 mg, and the placebo group received a median cumulative dose of 2163 mg. The cumulative distributions of the total dose of chlorthalidone or placebo received by trial groups are provided in Figure S3.

The time course of seated clinic systolic blood pressure is shown in Figure 1A. At 4 weeks after the initiation of the assigned regimen, the chlorthalidone group had a decrease in the seated clinic systolic blood pressure of 9.2 mm Hg, and the placebo group had an increase of 2.7 mm Hg (between-group difference, −11.9 mm Hg; 95% CI, −17.1 to −6.7). The change from baseline was −10.6 mm Hg in the chlorthalidone group and 5.1 mm Hg in the placebo group at 8 weeks (between-group difference, −15.7 mm Hg; 95% CI, −21.0 to −10.5) and −12.6 mm Hg and 2.4 mm Hg, respectively, at 12 weeks (between-group difference, −15.1 mm Hg; 95% CI, −19.4 to −10.7). Two weeks after the assigned regimen was discontinued, the change from baseline in the seated clinic systolic blood pressure was −7.0 mm Hg in the chlorthalidone group and 5.3 mm Hg in the placebo group (between-group difference, −12.3 mm Hg; 95% CI, −17.5 to −7.2). Similar changes in blood pressure were observed in the home blood-pressure recordings (Fig. S4).

The change from baseline in body weight was −1.2 kg in the chlorthalidone group and 0.3 kg in the placebo group at 4 weeks (between-group difference, −1.5 kg; 95% CI, −2.2 to −0.8); −1.7 kg and 0.3 kg, respectively, at 8 weeks (between-group difference, −2.0 kg; 95% CI, −2.7 to −1.3); and −1.9 kg and 0.2 kg, respectively, at 12 weeks (between-group difference, −2.1 kg; 95% CI, −2.8 to −1.4) (Fig. 1B). Two weeks after the assigned regimen was discontinued, the change from baseline in body weight was −0.9 kg in the chlorthalidone group and 0.5 kg in the placebo group (between-group difference, −1.4 kg; 95% CI, −2.4 to −0.5).

PRIMARY OUTCOME

At randomization, the mean 24-hour ambulatory systolic blood pressure was 142.6±8.1 mm Hg in the chlorthalidone group and 140.1±8.1 mm Hg in the placebo group and the mean 24-hour ambulatory diastolic blood pressure was 74.6±10.1 mm Hg and 72.8±9.3 mm Hg, respectively (Table 2). At 12 weeks after randomization, 140 recordings of the 24-hour ambulatory blood pressure were available. The adjusted change in the 24-hour ambulatory systolic blood pressure from baseline to 12 weeks was −11.0 mm Hg in the chlorthalidone group and −0.5 mm Hg in the placebo group, for a mean difference of −10.5 mm Hg (95% CI, −14.6 to −6.4) ($P<0.001$), and similar reductions were observed during the day and night. The adjusted change in the 24-hour ambulatory diastolic blood pressure from baseline to 12 weeks was −4.9 mm Hg in the chlorthalidone group and −1.0 mm Hg in the placebo group, for a mean difference of −3.9 mm Hg (95% CI, −6.3 to −1.5), and similar reductions were observed during the day and at night.

There was no significant effect of previous use of loop diuretics on the change from baseline in 24-hour ambulatory systolic blood pressure. The percentage of patients who had a nocturnal dip in systolic blood pressure of more than 10% from the daytime value did not change substantially from baseline to 12 weeks. The treatment effect was similar across all prespecified subgroups (Fig. S5).

SECONDARY OUTCOMES

The percent change in the urinary albumin-to-creatinine ratio from baseline was −41% in the chlorthalidone group and −7% in the placebo group at 4 weeks after the initiation of

the assigned regimen (between-group difference, −36 percentage points; 95% CI, −49 to −21); −45% and −3%, respectively, at 8 weeks (between-group difference, −43 percentage points; 95% CI, −54 to −28); and −52% and −4%, respectively, at 12 weeks (between-group difference, −50 percentage points; 95% CI, −60 to −37) (Fig. 2A). Two weeks after the assigned regimen was discontinued, the percent change in urinary albumin-to-creatinine ratio was −38% in the chlorthalidone group and −6% in the placebo group (between-group difference, −34 percentage points; 95% CI, −48 to −16).

The percent change in NT-proBNP level was −25% in the chlorthalidone group and −14% in the placebo group at 4 weeks after the initiation of the assigned regimen (between-group difference, −13 percentage points; 95% CI, −29 to 6); −32% and 5%, respectively, at 8 weeks (between-group difference, −35 percentage points; 95% CI, −48 to −20); and −30% and −11%, respectively, at 12 weeks (between-group difference, −21 percentage points; 95% CI, −35 to −4) (Fig. S6). Two weeks after the assigned regimen was discontinued, the percent change in the NT-proBNP level was −14% in the chlorthalidone group and 8% in the placebo group (between-group difference, −20 percentage points; 95% CI, −36 to −1).

Changes in plasma renin and aldosterone levels over time in the chlorthalidone group were consistent with the changes in body volume over time, which decreased during the treatment period and then increased after the regimen was discontinued (Figs. S7 and S8). The time trends of the changes in total body volume were consistent with a diuretic effect of chlorthalidone (Fig. S9).

ADVERSE EVENTS

Adverse events that occurred during the period from the time of randomization to the discontinuation of the regimen were recorded in 74 patients (91%) in the chlorthalidone group and in 68 patients (86%) in the placebo group (Table 3). Adverse events known to be associated with chlorthalidone therapy occurred more frequently in the chlorthalidone group than in the placebo group. These adverse events included increases in the serum creatinine level, hypokalemia, hypomagnesemia, hyponatremia, hyperglycemia, dizziness, and hyperuricemia. The assigned regimen was permanently discontinued because of adverse events in 5 patients — 4 in the chlorthalidone group (bullous pemphigoid in 1 patient, hypercalcemia and acute kidney injury in 1 patient, and poorly controlled hypertension in 2 patients) and 1 in the placebo group (pancreatitis).

The change from baseline in the estimated GFR was −2.7 ml per minute per 1.73 m^2 in the chlorthalidone group and 0 in the placebo group at 4 weeks after the initiation of the assigned regimen (between-group difference, −2.7 ml per minute per 1.73 m^2, 95% CI, −3.9 to −1.6); −2.7 ml per minute per 1.73 m^2 and 0.3 ml per minute per 1.73 m^2, respectively, at 8 weeks (between-group difference, −3.0 ml per minute per 1.73 m^2; 95% CI, −4.2 to −1.9); and −22.7 ml per minute per 1.73 m^2 and −0.5 ml per minute per 1.73 m^2, respectively, at 12 weeks (between-group difference, −2.2 ml per minute per 1.73 m^2; 95% CI, −3.3 to −1.0) (Fig. 2B). At 2 weeks after the assigned regimen was discontinued, the change from baseline in the estimated GFR was −0.3 ml per minute per 1.73 m^2 in the chlorthalidone group and −0.5 ml per minute per 1.73 m^2 in the placebo group (between-group difference, 0.2 ml per minute per 1.73 m^2; 95% CI, −1.0 to 1.4).

From the time of randomization to the end of the trial, increases in the serum creatinine level greater than 25% from baseline were observed in 33 of 74 patients (45%) in the chlorthalidone group and in 10 of 77 patients (13%) in the placebo group. Among those who were not receiving loop diuretics at baseline, 6 of 28 patients (21%) in the chlorthalidone and 4 of 32 patients (13%) in the placebo group had such increases. In contrast, among those who were receiving loop diuretics at baseline, 27 of 46 patients (59%) in the chlorthalidone group and 6 of 45 patients (13%) in the placebo group had such an increase. The odds ratio for an increase in the creatinine level greater than 25% was 1.9 (95% CI, 0.4 to 10.3) among patients who were not receiving loop diuretics at baseline and 9.2 (95% CI, 3.0 to 31.3) among those who were.

A serious adverse event that led to hospitalization occurred in 8 patients in the chlorthalidone group and in 11 in the placebo group. In the chlorthalidone group, 1 patient underwent long-term renal-replacement therapy after a urinary tract infection and pneumonia, and another patient died after a cardiac arrest outside the hospital.

OBSERVATIONAL FOLLOW-UP STUDY

Over the course of the observational follow-up period of up to 3 years, which started 2 weeks after the assigned regimen was discontinued, 49 patients (29 in the placebo group and 20 in the chlorthalidone group) had a decrease in the estimated GFR to below 10 ml per minute per 1.73 m^2, underwent long-term dialysis, or died. The hazard ratio (chlorthalidone vs. placebo) for a decrease in the estimated GFR to below 10 ml per minute per 1.73 m^2, long-term dialysis, or death (whichever occurred first), with adjustment for use of loop diuretics at baseline, was 0.63 (95% CI, 0.36 to 1.12) (Fig. S10).

DISCUSSION

In this double-blind, randomized trial involving patients with stage 4 chronic kidney disease and poorly controlled hypertension who were receiving a mean number of 3.4 antihypertensive drugs at baseline, the difference between the chlorthalidone group and the placebo group in the reduction in the 24-hour systolic ambulatory blood pressure from baseline to 12 weeks was −10.5 mm Hg in favor of the chlorthalidone group, and the corresponding value for diastolic blood pressure was −3.9 mm Hg in favor of the chlorthalidone group. Decreases in blood pressures recorded at home and in the clinic were similar to those in ambulatory blood pressure. The time course of the blood-pressure changes suggests that most of the reduction in blood pressure occurred within 4 weeks after therapy with 12.5 mg of chlorthalidone was initiated (in addition to other antihypertensive medications).[11] Reductions in body weight, body volume, and NT-proBNP levels and increases in plasma renin and aldosterone levels within 4 weeks after starting chlorthalidone therapy suggest that the mechanism of blood-pressure reduction is consistent with the changes in effective arterial blood volume over time, which decreased during the treatment period and then increased after the regimen was discontinued. Two weeks after chlorthalidone therapy was discontinued, 44% of the reduction in seated clinic systolic blood pressure and 53% of the peak weight loss that was observed at the end of the 12-week treatment period remained. The reported half-life of chlorthalidone is 45 to 60

hours, and the duration of action is even longer at 48 to 72 hours.[12] The persistent effects on blood pressure and weight loss are consistent with the long duration of action of chlorthalidone or a modifying effect of the drug on kidney disease. The large reduction in blood pressure is likely to have occurred because chlorthalidone is three times as potent as hydrochlorothiazide.[13]

The reversible changes in the estimated GFR that occurred in the chlorthalidone group were probably due to better blood-pressure control, which has been observed in other trials.[14] At 2 weeks after chlorthalidone therapy was discontinued, the blood pressure remained below the baseline value, but the estimated GFR returned to approximately the baseline value, which suggests the additional involvement of tubuloglomerular feedback.[15] In a long-term, phase 3 trial (the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [ALLHAT]), kidney failure outcomes in patients who were randomly assigned to receive chlorthalidone were similar to those observed in patients who were assigned to receive amlodipine or lisinopril.[16] Observational follow-up in ALLHAT did not reveal a clinically significant increase in the risk of severe, persistent reduction in kidney function, receipt of dialysis, or death. The other adverse effects observed in our trial were similar to those reported in patients without chronic kidney disease who received chlorthalidone in other trials.[17,18]

The reduction in the degree of albuminuria in the chlorthalidone group occurred within 4 weeks after the initiation of the regimen and may be explained by a hemodynamic effect or a diuretic-induced potentiation of antialbuminuric effects of renin–angiotensin system inhibitors.[19] The increase in the urinary albumin-to-creatinine ratio from the time chlorthalidone therapy was discontinued to 2 weeks later suggests that the mechanism of the reduction in the degree of albuminuria is at least in part hemodynamically mediated. The persistent reduction in the degree of albuminuria with the use of chlorthalidone suggests that the drug has the potential to provide cardiovascular and kidney protection in patients with chronic kidney disease.[20] There is some evidence that among the thiazide-type diuretics, chlorthalidone might be especially useful in reducing cardiovascular complications in patients without chronic kidney disease.[21,22]

Chlorthalidone should be used with caution in patients receiving loop diuretics, especially because of the risk of an increase in the serum creatinine level. The lowest dose of chlorthalidone produced most of the blood-pressure-lowering effect, and this might be the safest dose to use. A reduction in the dose of the loop diuretic might be needed.

Our trial has several limitations. The trial was relatively small and had an underrepresentation of women (36 of 160 patients [22%] were women). In addition, very few patients were Asian or Hispanic.

The strengths of our trial are the high percentage of patients in whom ambulatory blood-pressure recordings were completed and the inclusion of many Black patients (64 of 160 patients [40%] were Black). The participation of three distinct practices — a Veterans Health Administration hospital, a hospital that provides care for underserved populations, and a university hospital — improves the generalizability of the findings. The reduction in

the degree of albuminuria points to an early effect of target-organ protection. Phase 3 trials are needed to support the use of chlorthalidone in patients with advanced chronic kidney disease.

In this placebo-controlled trial involving patients with advanced chronic kidney disease and poorly controlled hypertension, chlorthalidone therapy improved blood-pressure control at 12 weeks as compared with placebo.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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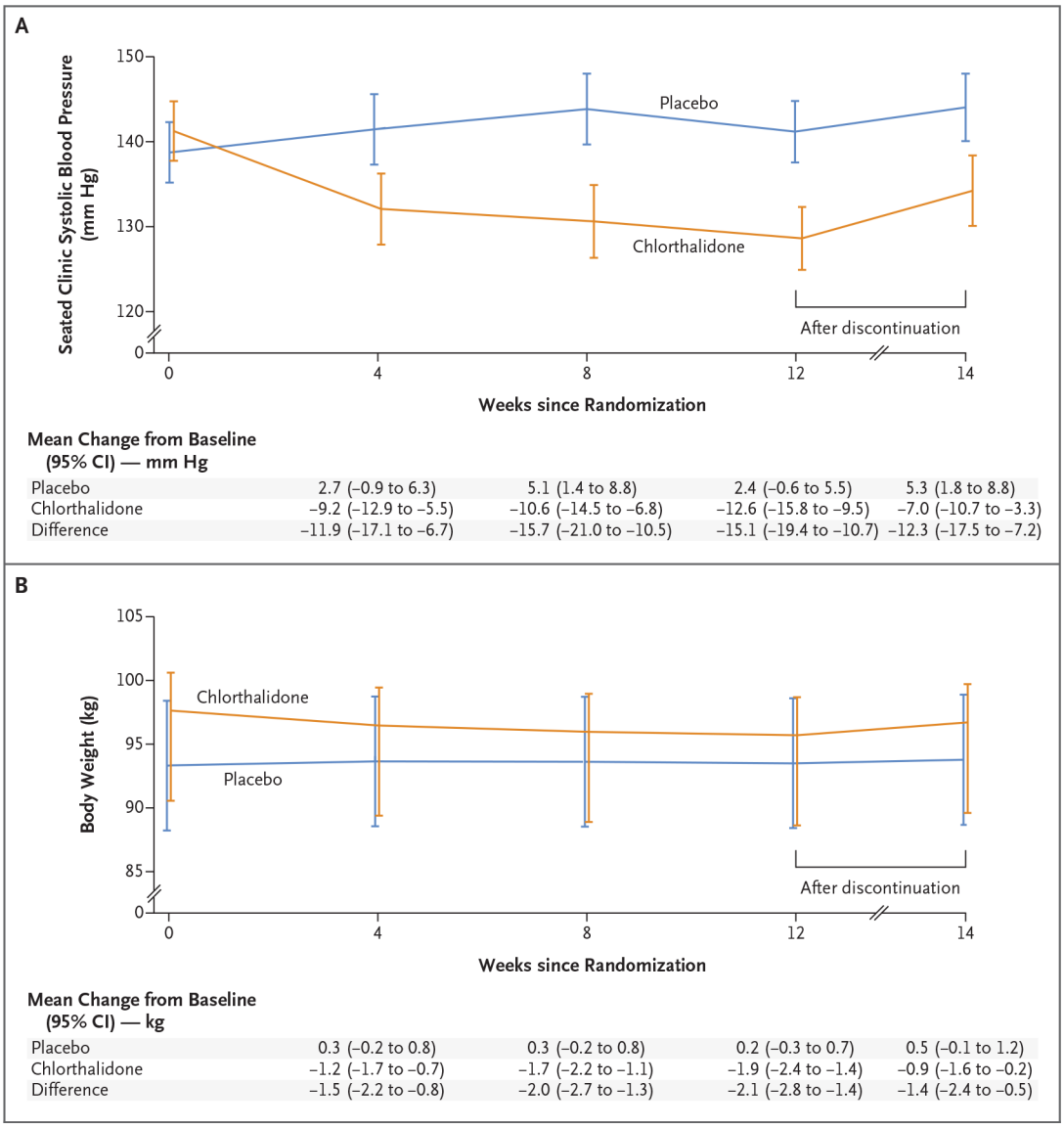
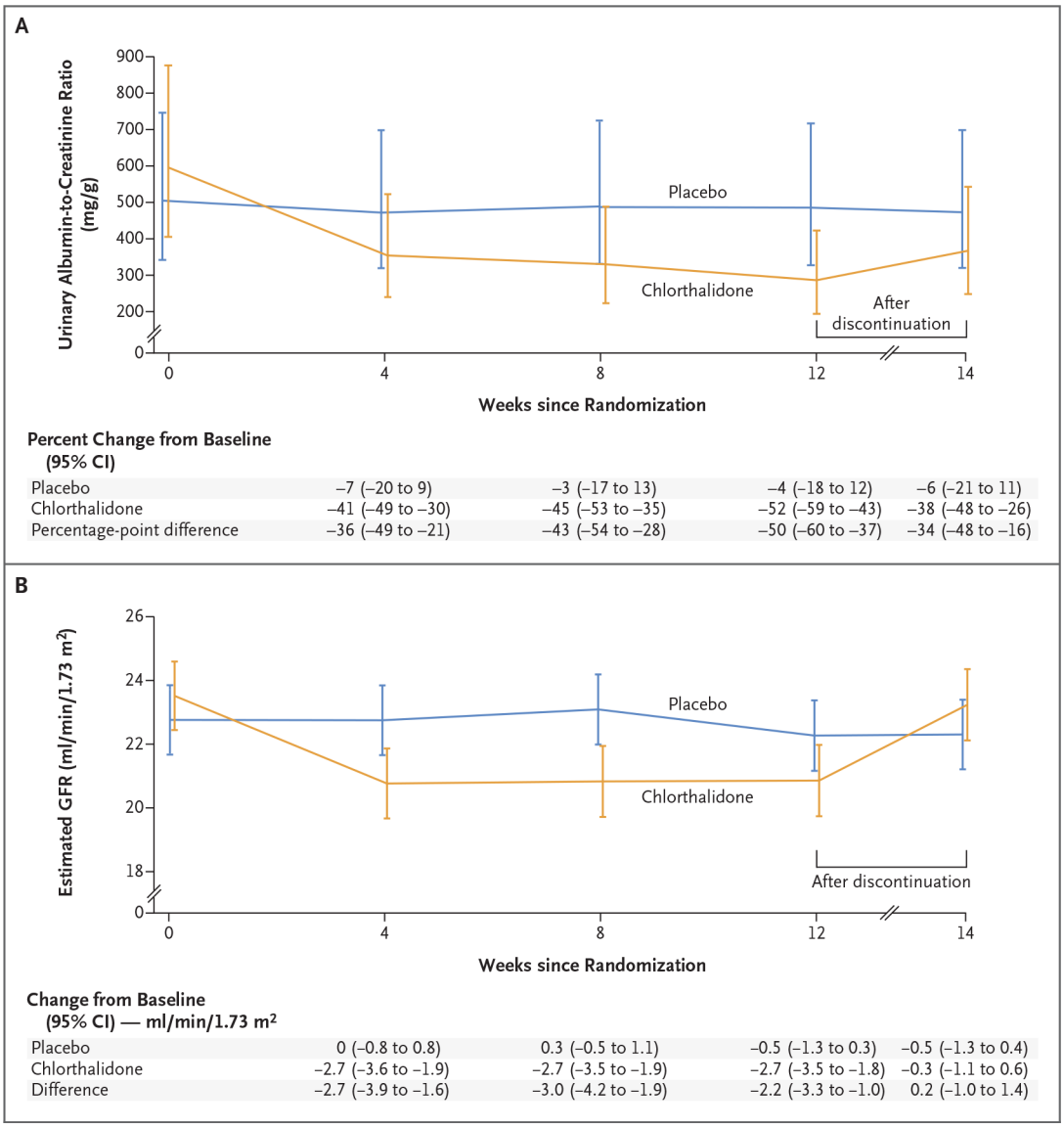


Mean Change from Baseline (95% CI) — mm Hg				
Placebo	2.7 (–0.9 to 6.3)	5.1 (1.4 to 8.8)	2.4 (–0.6 to 5.5)	5.3 (1.8 to 8.8)
Chlorthalidone	–9.2 (–12.9 to –5.5)	–10.6 (–14.5 to –6.8)	–12.6 (–15.8 to –9.5)	–7.0 (–10.7 to –3.3)
Difference	–11.9 (–17.1 to –6.7)	–15.7 (–21.0 to –10.5)	–15.1 (–19.4 to –10.7)	–12.3 (–17.5 to –7.2)

Mean Change from Baseline (95% CI) — kg				
Placebo	0.3 (–0.2 to 0.8)	0.3 (–0.2 to 0.8)	0.2 (–0.3 to 0.7)	0.5 (–0.1 to 1.2)
Chlorthalidone	–1.2 (–1.7 to –0.7)	–1.7 (–2.2 to –1.1)	–1.9 (–2.4 to –1.4)	–0.9 (–1.6 to –0.2)
Difference	–1.5 (–2.2 to –0.8)	–2.0 (–2.7 to –1.3)	–2.1 (–2.8 to –1.4)	–1.4 (–2.4 to –0.5)

Figure 1. Systolic Blood Pressure and Body Weight in the Trial Groups over the Trial Period.

Shown are the changes in the least-squares mean seated clinic systolic blood pressure (Panel A) and body weight (Panel B) over the 14-week trial period. At 12 weeks, the assigned regimen was discontinued. I bars indicate 95% confidence intervals. The between-group difference was calculated as the value in the chlorthalidone group minus the value in the placebo group. Values are offset from each other at each time point for readability.



Percent Change from Baseline (95% CI)

Placebo	–7 (–20 to 9)	–3 (–17 to 13)	–4 (–18 to 12)	–6 (–21 to 11)
Chlorthalidone	–41 (–49 to –30)	–45 (–53 to –35)	–52 (–59 to –43)	–38 (–48 to –26)
Percentage-point difference	–36 (–49 to –21)	–43 (–54 to –28)	–50 (–60 to –37)	–34 (–48 to –16)

Change from Baseline (95% CI) — ml/min/1.73 m²

Placebo	0 (–0.8 to 0.8)	0.3 (–0.5 to 1.1)	–0.5 (–1.3 to 0.3)	–0.5 (–1.3 to 0.4)
Chlorthalidone	–2.7 (–3.6 to –1.9)	–2.7 (–3.5 to –1.9)	–2.7 (–3.5 to –1.8)	–0.3 (–1.1 to 0.6)
Difference	–2.7 (–3.9 to –1.6)	–3.0 (–4.2 to –1.9)	–2.2 (–3.3 to –1.0)	0.2 (–1.0 to 1.4)

Figure 2. Changes in Urinary Albumin-to-Creatinine Ratio and Estimated GFR in the Trial Groups over the Trial Period.

Shown are the changes in the geometric mean of the urinary albumin-to-creatinine ratio (Panel A) and the least-squares mean estimated glomerular filtration rate (GFR) (Panel B) over the 14-week trial period. At 12 weeks, the assigned regimen was discontinued, and the measurements at week 14 were taken after the patients had been off their assigned regimen for 2 weeks. I bars indicate 95% confidence intervals. The between-group difference was calculated as the value in the chlorthalidone group minus the value in the placebo group. The percent changes in urinary albumin-to-creatinine ratio were back-transformed and may not total to the percentage-point difference because of rounding. Values are offset from each other at each time point for readability.

Table 1.

Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Chlorthalidone (N = 81)	Placebo (N = 79)
Age — yr	66.2±10.8	66.7±10.8
Male sex — no. (%)	62 (77)	62 (78)
Race or ethnic group — no. (%)†		
White	46 (57)	47 (59)
Black	32 (40)	32 (41)
Asian	2 (2)	0
Hispanic	1 (1)	0
Medical history — no. (%)		
Diabetes mellitus	60 (74)	61 (77)
Sleep apnea	36 (44)	39 (49)
Coronary artery disease	26 (32)	25 (32)
Hospitalization for heart failure	26 (32)	27 (34)
Gout	20 (25)	24 (30)
Stroke	20 (25)	16 (20)
Myocardial infarction	17 (21)	22 (28)
Percutaneous coronary revascularization	17 (21)	13 (16)
Coronary-artery bypass graft	10 (12)	7 (9)
Peripheral vascular bypass	3 (4)	7 (9)
Cause of chronic kidney disease — no. (%)		
Diabetes	42 (52)	42 (53)
Hypertension	26 (32)	26 (33)
Glomerulonephritis	3 (4)	5 (6)
Obstructive uropathy	3 (4)	2 (3)
Polycystic kidney disease	1 (1)	1 (1)
Other	6 (7)	3 (4)
Current smoking — no. (%)	21 (26)	19 (24)
Height — cm	171.7±11.3	173.0±8.6
Weight — kg	97.4±23.6	95.8±23.5

Characteristic	Chlorthalidone (N = 81)	Placebo (N = 79)
Body-mass index‡	33.0±7.0	32.0±7.4
Hip circumference — cm	115.9±14.9	114.6±15.0
Waist circumference — cm	115.3±17.0	115.4±16.6
Waist-to-hip ratio	1.011±0.078	0.998±0.074
Systolic blood pressure — mm Hg	141.2±15.1	138.7±16.0
Diastolic blood pressure — mm Hg	69.2±12.3	67.9±13.9
Pulse rate — beats/min	66.5±11.7	64.3±11.1
Median spot urinary albumin-to-creatinine ratio (IQR)§	862 (187–2274)	812 (128–2022)
Urinary albumin-to-creatinine ratio category — no. (%)§		
<30	5 (6)	9 (11)
30 to <300	19 (23)	19 (24)
≥300	56 (69)	51 (65)
Estimated GFR — ml/min/1.73 m^2	23.5±4.2	22.8±4.2
Median NT-proBNP (IQR) — pg/ml	545 (189–1342)	636 (274–1601)
Median plasma renin (IQR) — pg/ml	2276 (1160–4702)	2611 (1198–4870)
Median plasma aldosterone (IQR) — pg/ml	313 (181–519)	321 (189–499)
Median urine sodium excretion (IQR) — mmol/24 hr	115 (82–142)	96 (77–129)

*Plus–minus values are means ±SD. To convert the values for plasma aldosterone to picomoles per liter, multiply by 2,774. GFR denotes glomerular filtration rate, IQR interquartile range, and NT-proBNP N-terminal pro–B-type natriuretic peptide.

†Race or ethnic group was reported by the patients.

‡The body-mass index is the weight in kilograms divided by the square of the height in meters.

§The urinary albumin-to-creatinine ratio was calculated with albumin measured in milligrams and creatinine measured in grams.

Table 2.

Ambulatory Blood Pressure at Randomization and at 12 Weeks (End of the Assigned Regimen).*

Variable	Chlorthalidone (N = 81)	Placebo (N = 79)	Treatment Effect (95% CI)†
Systolic blood pressure			
24-hr blood pressure — mm Hg			
At randomization	142.6±8.1	140.1±8.1	
Adjusted change at 12 wk (95% CI)	−11.0 (−13.9 to −8.1)	−0.5 (−3.5 to 2.5)	−10.5 (−14.6 to −6.4)‡
Daytime blood pressure — mm Hg			
At randomization	145.2±8.8	142.7±8.8	
Adjusted change at 12 wk (95% CI)	−11.3 (−14.4 to −8.3)	−0.7 (−3.9 to 2.5)	−10.6 (−15.0 to −6.3)
Nighttime blood pressure — mm Hg			
At randomization	138.0±10.0	135.4±10.2	
Adjusted change at 12 wk (95% CI)	−10.5 (−15.2 to −5.8)	0.6 (−3.0 to 4.2)	−11.1 (−16.6 to −5.6)
Diastolic blood pressure			
24-hour blood pressure — mm Hg			
At randomization	74.6±10.1	72.8±9.3	
Adjusted change at 12 wk (95% CI)	−4.9 (−6.6 to −3.2)	−1.0 (−2.8 to 0.7)	−3.9 (−6.3 to −1.5)
Daytime blood pressure — mm Hg			
At randomization	77±10.6	75.1±9.5	
Adjusted change at 12 wk (95% CI)	−5.4 (−7.3 to −3.6)	−1.3 (−3.1 to 0.6)	−4.2 (−6.8 to −1.6)
Nighttime blood pressure — mm Hg			
At randomization	70.4±10.5	68.9±10.2	
Adjusted change at 12 wk (95% CI)	−4.7 (−7.5 to −2.0)	−0.6 (−2.8 to 1.6)	−4.1 (−7.4 to −0.9)
Patients with a nocturnal dip in systolic blood pressure §			
At randomization — no./total no. (%)	14/79 (18)	18/79 (23)	
At 12 wk — no./total no. (%)	14/65 (22)	13/72 (18)	1.15 (0.72 to 1.84)

*Plus–minus values are means ±SD. Data on final ambulatory blood pressure were imputed for 20 patients who had missing values for the 24-hour blood pressure and the daytime blood pressure and for 23 patients who had missing values for the nighttime blood pressure. In addition, 2 patients had missing data on the baseline nighttime ambulatory blood pressure, and therefore the values could not be imputed.

†The treatment effect is expressed as a mean difference with a 95% confidence interval for all the variables except nocturnal dip in systolic blood pressure, for which the effect is expressed as an odds ratio with a 95% confidence interval.

[‡] $P<0.001$.

[§] A nocturnal dip in systolic blood pressure indicates a decrease of more than 10% from the daytime value.

Table 3.

Adverse Events and Serious Adverse Events That Occurred during the Treatment Period.

Event	Chlorthalidone (N = 81)		Placebo (N = 79)	
	no. of patients with event (%)	*no. of events*	*no. of patients with event (%)*	*no. of events*
Adverse events				
Total	74 (91)	330	68 (86)	219
Infection	6 (7)	6	10 (13)	10
Cardiovascular event	2 (2)	2	3 (4)	3
Other	42 (52)	57	39 (49)	64
Event of interest	69 (85)	265	56 (71)	142
Hypokalemia	8 (10)	10	0	0
Hypomagnesemia	19 (23)	35	13 (16)	26
Hyponatremia	9 (11)	12	6 (8)	6
Hypocalcemia	1 (1)	1	1 (1)	3
Hypercalcemia	2 (2)	3	2 (3)	3
Hyperglycemia	13 (16)	18	4 (5)	5
Hyperuricemia	16 (20)	32	7 (9)	9
Hyperkalemia	5 (6)	5	7 (9)	8
Hypernatremia	0	0	1 (1)	1
Acute gout	2 (2)	2	3 (4)	3
Syncope	2 (2)	2	1 (1)	1
Orthostatic hypotension [*]	8 (10)	12	5 (6)	8
Dizziness [†]	20 (25)	33	13 (16)	24
Asymptomatic orthostatic hypotension [‡]	21 (26)	39	18 (23)	33
Acute kidney injury	33 (41)	61	10 (13)	12
Serious adverse events [§]				
Infection	2 (2)	3	1 (1)	1
Cardiovascular event	3 (4)	3	5 (6)	7
Renal event	1 (1)	1	1 (1)	1
Event of interest	3 (4)	4	0	0
Other	3 (4)	3	5 (6)	6

Event	Chlorthalidone (N = 81)		Placebo (N = 79)	
	no. of patients with event (%)	*no. of events*	*no. of patients with event (%)*	*no. of events*
Total	8 (10)	14	11 (14)	15

[*] Orthostatic hypotension was defined as a decrease in the standing systolic blood pressure greater than 20 mm Hg, accompanied by a feeling of dizziness or light-headedness.

[†] Dizziness was recorded when the patient felt dizzy when standing from a seated position but did not have a decrease in the systolic blood pressure greater than 20 mm Hg.

[‡] Asymptomatic orthostatic hypotension was defined as a decrease in the standing systolic blood pressure greater than 20 mm Hg that was not accompanied by a feeling of dizziness or light-headedness.

[§] Some patients had multiple serious adverse events. The four events of interest that occurred among the three patients in the chlorthalidone group were orthostatic hypotension, acute kidney injury, hyperglycemia, and hypokalemia.