Parallel-Group 8-Week Study on Chlorthalidone Effects in Hypertensives With Low Kidney Function

Massimo Cirillo, Fabiana Marcarelli, Alessandra A. Mele, Massimo Romano, Cinzia Lombardi, Giancarlo Bilancio

Abstract—Short-term effects of chlorthalidone are unknown in low kidney function. The effects of 8-week treatment with 25-mg chlorthalidone on the top of ongoing treatment were compared between control hypertensives and low kidney function hypertensives as assessed by estimated glomerular filtration rate <60 mL/minx1.73 m². Screening period consisted of 2 visits for patient selection and pretreatment laboratory evaluations (baseline). Inclusion criteria were uncontrolled hypertension on nondiuretic antihypertensive treatment. Exclusion criteria were chlorthalidone contraindications, refused consent, treatment with >3 antihypertensive drugs, severe hypertension, severe comorbidities, unreliable estimated glomerular filtration rate. Treatment period consisted of 5 visits (weeks 1, 2, 4, 6, and 8). Post-treatment laboratory evaluations were performed 3 to 4 days before week-8 visit. The 2 groups differed for baseline estimated glomerular filtration rate (low kidney function and control: n=60 and 60; mean, 39 and 76; range, 15–59 and 60–104) but not for sex, age, and baseline blood pressure. Week-8 blood pressure changes were a decrease in both groups (low kidney function and control: systolic pressure, −20 and −23; 95% confidence interval, −22/−18 and −26/−19; diastolic pressure, −9 and −10, −11/−7, and −13/−8) without significant between-group differences. Incidence of adverse events was similar in the 2 groups (15.0% and 16.7%). Baseline estimated glomerular filtration rate did not predict blood pressure changes and adverse events in either groups (P>0.6). In both groups, post-treatment changes were a decrease for estimated glomerular filtration rate and serum potassium, an increase for serum uric acid (P<0.01). Data show that short-term chlorthalidone effects were not reduced in hypertensives with low kidney function. (Hypertension. 2014;63:00-00.) ● Online Data Supplement

Key Words: chlorthalidone ■ clinical trial ■ creatinine ■ glomerular filtration rate ■ hypertension ■ kidney

Cardiovascular risk and renal risk are high in hypertensives of both sexes with low kidney function.①② The 2012 guidelines of the Kidney Disease: Improving Global Outcomes state that blood pressure control is fundamental to the care of chronic kidney disease.③ The US and European guidelines recommend that blood pressure be reduced to lower levels in chronic kidney disease.④⑤ Thiazides and thiazide-like diuretics are recommended as initial or additional antihypertensive drug for most patients but are conventionally considered ineffective in low kidney function in the absence of research data.⑥⑦⑧ Chlorthalidone is a highly effective thiazide-like diuretic.⑨⑩ Long-term effects of a hydrochlorothiazide-based therapeutic regimen and of a chlorthalidone-based therapeutic regimen are investigated by large trials that included hypertensives with low kidney function also.⑪⑫⑬⑭⑮⑯ The antihypertensive effects of the diuretics per se are of difficult interpretation in those 2 trials because the design of both trials pursued an effective control of hypertension and, to this aim, allowed the sequential addition of other drugs besides the diuretic under investigation. Data about short-term effects in low kidney function were reported by small studies for hydrochlorothiazide,⑰⑱⑲⑳ The antihypertensive effects of chlorthalidone are unknown in low kidney function. One parallel-group study investigated the 8-week effects of chlorthalidone without giving separate data for hypertensives with low kidney function.①②③ The present study focused on the 8-week effects of chlorthalidone as additional drug in hypertensives with low kidney function when compared with hypertensives without low kidney function.

Methods

This was a prospective, parallel-group, single-blind, single-center study for comparison of the effects of 25-mg chlorthalidone between hypertensives with low kidney function and hypertensives without low kidney function as assessed by estimated glomerular filtration rate (eGFR).②③ The study was registered in the public registry of the Italian Drug Agency (Agenzia Italiana del FArmaco, unique identifying number ID 671), was approved by the institutional review committee (Hospital Ethical Committee), and required the written informed consent of the participants. All procedures were in accordance with institutional guidelines, and the study adhered to the principles of the Declaration of Helsinki and Title 45 of US Code of Federal Regulations. The study comprised a 1- to 2-week screening period and an 8-week treatment period. The first screening visit was for the collection of medical history by questionnaires, the general physical examination, the measurements of anthropometry, pulse, systolic and diastolic blood
pressure (SBP and DBP, respectively). Inclusion criteria were uncontrolled hypertension (SBP ≥ 140 or DBP ≥ 90) in the presence of regular treatment with nondiuretic antihypertensive drug(s) since ≥3 months; completion of diagnostic work-up for hypertension and kidney disease with ≥1 eGFR assessment 3 to 6 months before first screening visit; both sexes; age 25 to 74 years; written informed consent. Exclusion criteria were chlorthalidone contraindications, treatment with diuretics of any class; treatment with ≥4 antihypertensive drugs; severe hypertension (SBP ≥ 180 or DBP ≥ 110 mm Hg); renal artery stenosis; conditions associated with risk of unreliable eGFR; recent diagnosis of cardiovascular disease; severe comorbidities (malignancy, malabsorption, liver failure, and respiratory failure). Eligible patients were prescribed laboratory evaluations to be completed within 1 to 2 weeks for re-evaluation of eGFR and for assessment of chlorthalidone contraindications in laboratory parameters. The second screening visit was performed 1 to 2 weeks after the first screening visit and included a re-evaluation of blood pressure. Patients who fulfilled the eligibility criteria and had no exclusion criteria also at the second screening visit were enrolled and split into the following 2 groups on the basis of eGFR values: the group of hypertensives with ≥2 eGFR values consistently ≤60 mL/min×1.73 m² in the last 3 months (<60 group); the group of hypertensives with ≥2 eGFR assessments consistently ≤60 mL/min×1.73 m² in the last 3 months (control group). Patients were excluded from the study if with eGFR nonconsistently <60 or ≥60 mL/min×1.73 m². Enrolled patients were prescribed 25-mg chlorthalidone per day to be taken at morning wake-up. Data of second screening visit were taken as pretreatment data (baseline). Follow-up visits were performed at weeks 1, 2, 4, 6, and 8 from baseline. Screening visits and follow-up visits were conducted between 14:30 and 18:00. Vital signs, weight, blood pressure, pulse, treatment compliance, and adverse events were assessed at all visits. Chlorthalidone effects on laboratory parameters were assessed by laboratory evaluations that were repeated 3 to 4 days before week-8 visit as in the screening period. Study design was based on the continuation of the patients’ habitual unrestricted diet and of the ongoing treatments. Dosage of chlorthalidone and other drug(s) was maintained constant during the study. The design did not allow the initiation of new treatment(s). The initiation of new treatment(s) or the change in the dosage of chlorthalidone or of other antihypertensive drug(s) implied the exclusion from the study. Treatment with chlorthalidone was suspended in case of patient’s request, adverse events, or hypotension (SBP<110 or DBP<60 mm Hg). In case of chlorthalidone suspension, the patient was offered the opportunity of a postdiscontinuation visit with laboratory evaluation 1 to 2 weeks after chlorthalidone suspension. Figure S1 in the online-only Data Supplement summarizes study design.

Trained physicians blind to the treatment measured blood pressure after the World Health Organization protocol with the use of mercury sphygmomanometer and cuffs of appropriate size (12x22, 16x30, or 16x36 cm). Blood pressure measurements initiated after participants had been comfortably and quietly seated for 5 minutes with the arm supported at heart level. Three readings were made, 1 minute apart, and the mean of the last 2 readings was used for analyses. Standing blood pressure was measured in patients reporting symptoms of orthostatic hypotension. Orthostatic hypotension was defined as a fall of ≥20 mm Hg SBP or 10 mm Hg DBP within 3 minutes of standing position. eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaborative equation.25–27 Urinary creatinine excretion was used as marker of creatinine generation.28 Serum total calcium was expressed with correction for serum albumin concentration.29 Acute kidney injury was defined as doubling of baseline serum creatinine or halving of baseline eGFR or low urine output.30

Statistics
The primary outcome was the 8-week change in blood pressure. ANOVA was used for calculation of the between-group least squares mean difference with 95% confidence interval. The mean±SD of the chlorthalidone-induced SBP reduction in hypertensives without low kidney function is approximately 20±15 mm Hg.2–11 Thus, 57 patients per group were required for a power of 80% with a non-inferiority limit of 7 mm Hg, α=5%, 1-sided test.31 Between-group comparison of baseline and week-8 data were done using ANOVA or χ² analysis. Baseline data were compared with 8-week data by paired t test. Efficacy analyses were limited to the per-protocol set. Safety analyses were done in the whole set of enrolled patients.

Results
Descriptive Statistics
The study initiated in November 2012 and ended in May 2013. Sixty patients were enrolled for each group. Diagnoses in the <60 group included glomerular disease (n=17), diabetic nephropathy (n=9), polycystic disease (n=10), pyelonephritis (n=8), and others (n=6). Diagnoses in the control group included essential hypertension (n=49), glomerular disease (n=7), and others (n=4). Table 1 reports baseline descriptive statistics.

Analyses on Efficacy
The number of hypertensives in the per-protocol set was 58 in the <60 group and 57 in the control group because 5 hypertensives autonomously decided to discontinue chlorthalidone before study end. Blood pressure decreased in both groups starting from week-1 visit, but the maximal decrease was achieved from week-2 visit onward (Figure). The 8-week change in SBP and DBP was a significant decrease without significant between-group differences (Table 2). Findings were similar in analyses by sex and in analyses with control for sex, age, body mass index, other antihypertensive drugs, and baseline blood pressure (data not shown).

In analyses limited to the <60 group, baseline values of eGFR and urinary albumin did not correlate with 8-week changes in blood pressure (R²<0.12; P>0.3). The 8-week changes in blood pressure did not differ among the subgroup of 21 hypertensives with eGFR 59 to 45 mL/min×1.73 m² (mean of 8-week change in SBP/DBP, −18.7/−7.1 mm Hg), the subgroup of 28 hypertensives with eGFR 44 to 30 mL/min×1.73 m² (−19.2/−9.3 mm Hg), and the subgroup of 9 hypertensives with eGFR 29 to 15 mL/min×1.73 m² (−20.3/−8.9 mm Hg; P>0.5 by ANOVA for contrast among subgroups and P>0.4 for linearity along subgroups). At the individual level, the 8-week change was a decrease in all 58 patients for SBP and in 48 patients for DBP.

The week-8 change in weight was a decrease in both groups but significant only in the <60 group (Table 2). The week-8 change in weight was 4× greater in patients of the <60 group with baseline edema than in patients of the <60 group without baseline edema (mean, −3.0 and −0.6 kg; least squares mean difference, −2.4 kg; 95% confidence interval, −3.1/−1.7; P<0.001).

Compared with baseline, the week-8 change in both groups was an increase in serum creatinine (<60 group and control group, +0.14 and +0.07 mg/dL; P<0.001 versus baseline) and serum uric acid (+59 and +54 µmol/L; P<0.001) but was a decrease in eGFR (−2.1 and −5.1 mL/min×1.73 m²; P<0.001) and serum potassium (−0.2 and −0.2 mmol/L; P<0.001). The week-8 change was not significant for urinary albumin (−19.9 and +3.0 mg/24 hours; P>0.26) and other laboratory parameters (not shown). The week-8 changes in laboratory parameters were not significantly different between groups with exception of the greater eGFR decrease in the control group (least squares mean difference, −3.0 mL/min×1.73 m²; P=0.030).
Adverse Events

The overall incidence of adverse events and the incidence of single adverse events were not significantly different between 2 groups (Table 3). Hypotension was the reported cause of chlorthalidone discontinuation in the 5 patients who did not complete the study. Symptoms of orthostatic hypotension were reported by 4 patients who did not have orthostatic hypotension at follow-up visits. Acute kidney injury was not observed in any patient. Within the <60 group, hypertensives with adverse events differed from hypertensives without adverse events only for lower baseline body mass index (mean, 25.4 and 27.8 kg/m²; n=9 and 51; P=0.033). The difference in body mass index was also found within the control group but was not significant (25.8 and 27.9 kg/m²; n=10 and 50; P=0.173).

The 5 patients with chlorthalidone discontinuation and the 14 patients with laboratory abnormalities at week-8 evaluation underwent an additional visit with repetition of laboratory evaluations 1 week after chlorthalidone discontinuation. Hypotension and laboratory abnormalities were resolved in all patients after chlorthalidone discontinuation (data not shown).

Discussion

This study about short-term effects of chlorthalidone in low kidney function indicates that the addition of 25-mg chlorthalidone on the top of the ongoing nondiuretic antihypertensive treatment had similar antihypertensive efficacy in patients with low kidney function and in patients without low kidney function. Chlorthalidone effects were generally similar between the 2 groups of hypertensives also for laboratory indices and adverse events.

Before the initiation of chlorthalidone treatment (baseline), the <60 group and the control group differed substantially for eGFR values and other indices related to kidney function. Baseline blood pressure was similar in the groups although the mild difference in the number of antihypertensive drugs could point to more severe or more resistant hypertension in the <60 group.
Time-course and magnitude of blood pressure effects of 25-mg chlorthalidone overlapped between 2 groups and were characterized by a stable reduction of ≈20 mm Hg SBP and ≈9 mm Hg DBP after 2-week treatment. Considering the study power and the mean of SBP reduction in the control group, data prove that the chlorthalidone-induced SBP reduction in the <60 group averaged >14 mm Hg, an effect that seemed consistent also in subgroups with severely reduced kidney function. Results about laboratory parameters and adverse events further supported the idea of similar chlorthalidone effects between the <60 and the control group. The definition of the mechanism(s) underlying the effects of chlorthalidone in low kidney function was beyond the aims of this clinical study. The possibility that the well-known natriuretic effects of chlorthalidone were preserved in low kidney function also was coherently supported by data about incidence of hypotension and hypokalemia in the <60 group adverse events that are typical of effective natriuretic agents. The same is true for the post-chlorthalidone weight reduction in patients of the <60 group and, in particular, in those ones with baseline edema because weight is an index of sodium balance in the presence of sodium retention.

The comparison of the present results with previous studies is difficult because data are not published about short-term antihypertensive effects of chlorthalidone in low kidney function. The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) study reported that a long-term therapeutic regimen based on the use of chlorthalidone has favorable effects on renal and cardiovascular outcomes also in hypertensives with an eGFR<60 mL/min×1.73 m². However, the ALLHAT results are of difficult interpretation with regard to the specific antihypertensive effects of chlorthalidone per se because that study allowed the sequential addition of other 3 different drugs on the top of chlorthalidone. Another study investigated on the short-term effects of chlorthalidone in hypertensives, including patients with creatinine clearance >30 mL/min, but did not report separate data for the subgroup with low kidney function.

The main limitations of the study are the lack of a placebo-treated group, of data about true glomerular filtration rate, data with various chlorthalidone dosages, laboratory evaluations in first week of treatment, and data for ambulatory blood pressure monitoring. The use of placebo in high-risk patients with uncontrolled hypertension was inadmissible in the authors' opinion. However, it is unlikely that a placebo effect played a major confounding in the present observation of similar chlorthalidone effects in hypertensives with low kidney function and hypertensives without low kidney function. First, there are not data or plausible mechanisms in support of the possibility that the placebo effect on blood pressure could be higher in hypertensives with low kidney function. Actually, the higher number of antihypertensive drugs at baseline in the <60 group was against this possibility. Second, the chlorthalidone effects in low kidney function hypertensives included changes in weight and laboratory indices, hence in variables for which the placebo effect should be minor or null. For the lack of data about true glomerular filtration rate, kidney function was assessed by eGFR derived from serum creatinine, a method that is the most diffuse in the real world and in accordance with current guidelines.

The risk of misclassification because of the use of eGFR seemed low considering the evidence of laboratory alterations typical of low kidney function in the group of hypertensives with eGFR<60 mL/min×1.73 m² (Table 1). The lack of data with various chlorthalidone dosages did not allow to exclude that the dose–response curve to chlorthalidone could differ between the 2 groups, a point that was beyond the study aims. Transient adverse events could have been missed because laboratory evaluation was not performed also in the first week of treatment.

Table 2. Effects of 8-Week Treatment With 25-mg Chlorthalidone on Blood Pressure, Pulse, and Weight in Hypertensives With Baseline eGFR<60 mL/min×1.73 m² (<60 group) and Hypertensives With eGFR≥60 mL/min×1.73 m² (control group)

<table>
<thead>
<tr>
<th>Blood Pressure, Pulse, and Weight</th>
<th>8-Week Changes in &lt;60 group</th>
<th>8-Week Changes in Control group</th>
<th>Between-Group LSM Difference</th>
<th>P Value for LSM Difference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of hypertensives completing the study</td>
<td>57</td>
<td>58</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>−19.2† (−21.4/−17.0)</td>
<td>−21.6† (−24.8/−18.5)</td>
<td>−2.5 (−6.3/+1.4)</td>
<td>0.205</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>−8.4† (−10.4/−6.5)</td>
<td>−9.3† (−11.4/−7.3)</td>
<td>−0.9 (−3.7/+1.9)</td>
<td>0.534</td>
</tr>
<tr>
<td>Pulse rate, breaths/min</td>
<td>−1.7‡ (−4.3/+0.8)</td>
<td>+2.9† (−0.3/+6.2)</td>
<td>−4.6 (−1.1/+10.3)</td>
<td>0.122</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>−0.88‡ (−1.19/−0.57)</td>
<td>−0.22‡ (−0.49/+0.4)</td>
<td>−0.66 (−1.07/+0.26)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Mean change at week-8 visit (calculated as value at week-8 visit minus baseline value) and between-group LSM difference in hypertensives of the per-protocol set (95% confidence interval). eGFR indicates estimated glomerular filtration rate; and LSM, least squares mean.

*ANOVA.
†P<0.001 by paired t test for change over baseline.
‡Not significant by paired t test for change over baseline.
when the chlorthalidone effects are bigger on extracellular volume. Finally, the lack of data about ambulatory blood pressure monitoring did not allow to exclude that the present results represented an overestimate of true chlorthalidone antihypertensive effects because of a regression-toward-the-mean effect.

Hypotension was the most common cause of treatment discontinuation in both groups, and hyponatremia is the most common adverse event in the <60 group. Frequency and severity of adverse events could differ during long-term treatment. The functional nature of these effects and of other adverse events was proved by their rapid reversibility after chlorthalidone discontinuation. This observation is in agreement with the concept that a titration phase is needed for individually tailoring the best diuretic dose with reduction of adverse effects. The inclusion of a titration phase for chlorthalidone would have required a longer duration of the study and a higher number of patients for both groups at different dosages. Previous data for dietary or pharmacological treatment of chronic kidney disease suggested that a mild eGFR reduction in the first week of treatment could predict favorable long-term effects against the progression of kidney disease. Long-term effects of chlorthalidone and thiazides in kidney disease are debated. The ALLHAT study reported that the long-term incidence of cardiovascular and renal events did not differ between a therapeutic regimen based on chlorthalidone and other regimens based on amlopidine or lisinopril. The avoiding cardiovascular events through combination therapy in patients living with systolic hypertension (ACCOMPLISH) study reported that, in combination with an angiotensin-converting enzyme inhibitor, hydrochlorothiazide was less effective than amlopidine in reducing cardiovascular events and progression of kidney disease, a conclusion that could reflect also the lower antihypertensive efficacy of hydrochlorothiazide in comparison with chlorthalidone.

**Perspectives**

In conclusion, this short-term study showed that 25-mg chlorthalidone has a significant antihypertensive efficacy in low kidney function. The study also showed chlorthalidone effects on weight and laboratory indices, which suggest the preservation of the natriuretic action of chlorthalidone in low kidney function. Study results should not generalized to hydrochlorothiazide and other thiazides. The practical implications of the study are potentially relevant to the subgroup of hypertensives with eGFR <60 mL/min×1.73 m² (ie, to a subgroup of hypertensives who account for ≤20% of hypertensives in the general population). Within the group of hypertensives with low kidney function, the antihypertensive effect of chlorthalidone was more constant for SBP than for DBP and did not associate with adverse events in patients with higher body mass index. Thus, data point to a favorable benefit/risk ratio of chlorthalidone in patients with low kidney function, systolic hypertension, and overweight. Altogether, the data are in contrast with the idea of reduced efficacy of chlorthalidone in low kidney function and suggest the need of long-term trials about chlorthalidone effects in chronic kidney disease.

**References**

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Novelty and Significance

What Is New?
• Short-term data on chlorthalidone effects in hypertensives with low kidney function.

What Is Relevant?
• Chlorthalidone is effective in patients with low kidney function.

Summary
In patients with low kidney function, 25-mg chlorthalidone per day lowers blood pressure and modifies weight and laboratory indices as expected with the use of natriuretic drugs. The antihypertensive effect of chlorthalidone was more constant for systolic blood pressure than for diastolic blood pressure and did not associate with adverse events in patients with higher body mass index. Data point to a favorable benefit/risk ratio of chlorthalidone in patients with low kidney function, systolic hypertension, and overweight.
Parallel-Group 8-Week Study on Chlorthalidone Effects in Hypertensives With Low Kidney Function

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PARALLEL-GROUP 8-WEEK STUDY ON CHLORTHALIDONE
EFFECTS IN HYPERTENSIVES WITH LOW KIDNEY FUNCTION.

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Running title: Chlorthalidone in hypertensives with low eGFR.

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EXPANDED METHODS

This was a prospective, parallel-group, single-blind, single-center study for comparison of the effects of 25 mg chlorthalidone (CTD) between hypertensives with low kidney function and hypertensives without low kidney function as assessed by estimated glomerular filtration rate (eGFR) (1).

The study was registered to the public registry of the Italian Drug Agency (Agenzia Italiana del FArmaco, AIFA, unique identifying number ID 671), was approved by the institutional review committee (Hospital Ethical Committee) and required the written informed consent of the participants. The study adhered to the principles of the Declaration of Helsinki and Title 45 of U.S. Code of Federal Regulations. Patients were selected, enrolled, and followed-up at the outpatient Clinic of the Unit of Hypertension and Metabolic Nephropathies - University Hospital (Salerno, Italy).

The study comprised of two periods: a 1-2 week screening period and an 8-week treatment period. The first screening visit was for the collection of medical history by standard questionnaires, the general physical exam, the measurements of anthropometry, pulse, systolic and diastolic blood pressure (SBP and DBP). The criteria for inclusion in the study were: uncontrolled hypertension (SBP ≥140 and/or DBP ≥90) in the presence of regular treatment with non-diuretic antihypertensive drug(s) since at least three months; completion of diagnostic work-up for hypertension and kidney disease with at least one eGFR assessment 3-6 months prior to first screening visit; both sexes; ages 25-74 years; written informed consent. Exclusion criteria were as follows: CTD contraindications (dehydration, anuria, gout, uric acid urolithiasis, allergy or intolerance to CTD or related molecules); treatment with diuretics of any class; treatment with four or more antihypertensive drugs; severe hypertension (SBP ≥180 and/or DBP ≥110 mmHg); renal artery stenosis; conditions associated with risk of unreliable eGFR (2,3); treatment with restricted diets; pregnancy or lactation; ages <25 years or ≥75 years; dementia or other cognitive impairment; alcoholism or drug use; use of non-steroidal anti-inflammatory drugs; recent diagnosis of cardiovascular disease; severe co-morbidities (malignancy, malabsorption, liver failure, respiratory failure). Eligible patients were prescribed lab evaluations to be completed within 1-2 weeks for re-evaluation of eGFR and for assessment of CTD contraindications in lab parameters as listed in the summary product characteristics (creatinine clearance <30 mL/min, serum sodium <135 mmol/L, serum potassium <3.5 mmol/L, serum calcium >2.62 mmol/L, and liver insufficiency). The second screening visit was performed 1-2 weeks after the first screening visit and included a re-evaluation of blood pressure.

Patients who fulfilled the eligibility criteria and had no exclusion criteria also at the second screening visit were enrolled and split into the following two groups on the basis of eGFR values: the group of hypertensives with at least two eGFR values consistently <60 mL/min x 1.73 m² in the last three months (<60group); the group of hypertensives with at least two eGFR assessments consistently ≥60 mL/min x 1.73 m² in the last three months (controlgroup) (2,3). Patients were excluded from the study if with eGFR non-consistently <60 mL/min x 1.73 m² or ≥60 mL/min x 1.73 m². Enrolled patients were prescribed 25 mg CT/day to be taken at morning wake-up. CTD was supplied by the National Health System (Igroton 25 mg tablets, Amdipharm Ltd). Data of second screening visit were taken as pre-treatment data (baseline). Follow-up visits were performed at week 1, 2, 4, 6 and 8 from baseline. Screening visits and follow-up visits were all conducted in the afternoon between 14:30 and 18:00. Vital signs, weight, blood pressure, pulse, treatment compliance, and adverse events were assessed at all visits. CTD effects on lab parameters were assessed by lab evaluations which were repeated 3-4 days before week-8 visit as in the screening period.

Study design was based on the continuation of the patients’ habitual unrestricted diet and of the ongoing treatments. Dosage of CTD and other drug(s) was maintained constant during the study. The design did not allow the initiation of new treatment(s). The initiation of new treatment(s) and the change in the dosage of CTD or of other antihypertensive drug(s) implied the
exclusion from the study. Treatment with CTD was suspended in case of patient’s request, adverse events, or hypotension (SBP <110 or DBP <60 mmHg). In case of CTD suspension, the patient was offered the opportunity of a post-discontinuation visit with lab evaluation 1-2 week after CTD suspension. Figure S1 summarizes study design.

Trained physicians blind to the treatment measured blood pressure following the WHO protocol with the use of mercury sphygmomanometer and cuffs of appropriate size (12 x 22, 16 x 30 or 16 x 36 cm). Blood pressure measurements initiated after participants had been comfortably and quietly seated for five minutes with the arm supported at heart level. Three readings were made, one minute apart, and the mean of the last two readings was used for analyses. Standing blood pressure was measured in patients reporting symptoms of orthostatic hypotension. Orthostatic hypotension was defined as a fall of 20 mmHg SBP or 10 mmHg DBP within three min of standing position.

eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaborative equation with the use of gender, age, ethnicity, and plasma creatinine measured by an assay traceable to isotope dilution mass spectrometry (IDMS-traceable assay) (4-6). Urinary creatinine excretion was used as marker of creatinine generation (7). Serum total calcium was expressed with correction for serum albumin concentration (8). Acute kidney injury was defined as doubling of baseline serum creatinine or halving of baseline eGFR or low urine output (9).

Statistics
The primary outcome was the 8-week change in blood pressure. Analysis of variance (ANOVA) was used for calculation of the between-group least squares mean difference (LSM difference) with 95% confidence interval (95%CI). The mean±standard deviation (mean±SD) of the CTD-induced SBP reduction in hypertensives without low kidney function is approximately 20±15 mmHg (10-14). Thus, 57 patients per group were required for a power of 80% with a non-inferiority limit of 7 mmHg, α=5%, one-sided test (15). Between-group comparison of baseline and week-8 data were done using ANOVA or chi-square analysis. Baseline data were compared to 8-week data by paired t-test. Efficacy analyses were limited to the per-protocol-set. Safety analyses were done in the whole set of enrolled patients.

REFERENCES


Figure S1. Design of the study.