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Chlorthalidone vs. Hydrochlorothiazide for Hypertension–Cardiovascular Events

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ABSTRACT

BACKGROUND

Whether chlorthalidone is superior to hydrochlorothiazide for preventing major adverse cardiovascular events in patients with hypertension is unclear.

METHODS

In a pragmatic trial, we randomly assigned adults 65 years of age or older who were patients in the Department of Veterans Affairs health system and had been receiving hydrochlorothiazide at a daily dose of 25 or 50 mg to continue therapy with hydrochlorothiazide or to switch to chlorthalidone at a daily dose of 12.5 or 25 mg. The primary outcome was a composite of nonfatal myocardial infarction, stroke, heart failure resulting in hospitalization, urgent coronary revascularization for unstable angina, and non–cancer-related death. Safety was also assessed.

RESULTS

A total of 13,523 patients underwent randomization. The mean age was 72 years. At baseline, hydrochlorothiazide at a dose of 25 mg per day had been prescribed in 12,781 patients (94.5%). The mean baseline systolic blood pressure in each group was 139 mm Hg. At a median follow-up of 2.4 years, there was little difference in the occurrence of primary-outcome events between the chlorthalidone group (702 patients [10.4%]) and the hydrochlorothiazide group (675 patients [10.0%]) (hazard ratio, 1.04; 95% confidence interval, 0.94 to 1.16; $P=0.45$). There were no between-group differences in the occurrence of any of the components of the primary outcome. The incidence of hypokalemia was higher in the chlorthalidone group than in the hydrochlorothiazide group (6.0% vs. 4.4%, $P<0.001$).

CONCLUSIONS

In this large pragmatic trial of thiazide diuretics at doses commonly used in clinical practice, patients who received chlorthalidone did not have a lower occurrence of major cardiovascular outcome events or non–cancer-related deaths than patients who received hydrochlorothiazide. (Funded by the Veterans Affairs Cooperative Studies Program; ClinicalTrials.gov number, NCT02185417.)

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The prevalence of hypertension has been increasing.[1,2] Hypertension increases the risk of complications and death from cardiovascular disease.[3] Thiazide diuretics are first-line antihypertensive agents that lower blood pressure and prevent adverse cardiovascular outcomes.[4] Early studies suggested that chlorthalidone was superior to hydrochlorothiazide in patients with hypertension[5,6]; however, more recent observational studies have shown that the two drugs reduced cardiovascular events at a similar rate.[7-9] Chlorthalidone may be associated with an increased risk of adverse events, including hypokalemia.[7-9]

In 2020, Part D Medicare expenditures showed that approximately 1.5 million persons received prescriptions for chlorthalidone as compared with 11.5 million who received prescriptions for hydrochlorothiazide,[10] despite guidelines that recommended chlorthalidone as the preferred agent. The discrepancy between guideline recommendation and real-world use is possibly related to the belief that chlorthalidone has a greater risk of adverse effects without clear evidence for differences in cardiovascular outcomes.[7-9]

The Diuretic Comparison Project aimed to evaluate whether chlorthalidone, as compared with hydrochlorothiazide, would reduce the risk of major nonfatal cardiovascular disease outcomes and non–cancer-related deaths in older patients with hypertension who were receiving hydrochlorothiazide at baseline. We incorporated the pragmatic methods used by the Department of Veterans Affairs (VA) Healthcare System to provide a real-world assessment of the effectiveness of chlorthalidone as compared with hydrochlorothiazide in routine clinical care.

Methods

Trial Design and Oversight

This trial was a multicenter, pragmatic, open-label trial. The trial protocol and statistical analysis plan are available with the full text of this article at NEJM.org. The trial was approved by the VA central institutional review board. The sponsor was the VA Cooperative Studies Program.

The trial was designed and overseen by academic investigators who were employed by the VA health care system. Interim results were reviewed by an independent data and safety monitoring board twice yearly. Trial staff were responsible for data collection, storage, and analysis. The first author wrote the first draft of the manuscript. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Patients

The trial design has been published previously.[11] Briefly, participants were adults who were at least 65 years of age and had hypertension, a systolic blood pressure of at least 120 mm Hg at their most recent clinical visit, and an active prescription for hydrochlorothiazide at a dose of 25 or 50 mg per day (Table S1 in the Supplementary Appendix, available at NEJM.org). Patients taking blood-pressure medication that contained hydrochlorothiazide combined with other agents were excluded, as were patients who did not provide consent.

Pragmatic Trial Design

This comparative-effectiveness trial used a point-of-care approach[12-14] to embed the trial procedures in electronic health records (EHRs) in the VA Healthcare System. This approach enabled us to conduct trial-related interactions and randomization with the use of data in the EHRs, centralize recruitment efforts without the use of site staff, eliminate the need for trial-related visits and procedures, and centralize data capture from administrative databases.

All the primary care providers within participating VA Healthcare Systems were identified and were approached by means of an electronic informed consent form within the EHRs that explained the purpose and risks of participation. After providers gave consent, their patients' records were electronically screened for eligibility, and eligible patients were mailed a recruitment letter and an informed-consent document. Centralized study recruiters telephoned potential participants to review the documents. Oral informed consent was obtained if the patient agreed to participate. Nurses at a central location reviewed the EHR to confirm eligibility before a patient underwent randomization.

After informed consent was obtained, the patient's provider was sent an electronic order to sign if the provider assented to the patient undergoing randomization. Patients were randomly assigned to continue receiving hydrochloro-

thiazide or to switch to chlorthalidone. If a provider declined to assent to a patient undergoing randomization, the patient was notified of the decision and the patient's data were not included in the trial.

Patients who were assigned to the hydrochlorothiazide group continued to receive the medication according to their current prescription. Patients who were assigned to switch to chlorthalidone were assigned medication orders prescribing chlorthalidone and discontinuing hydrochlorothiazide; the orders were placed in the EHR and sent to the patient's provider for electronic signature. Patients in the chlorthalidone group for whom hydrochlorothiazide had been prescribed at a daily dose of 25 or 50 mg were switched to receive chlorthalidone at a daily dose of 12.5 or 25 mg, respectively. All the patients who underwent randomization were included in the intention-to-treat analysis. Patients and providers were aware of the group assignments.

All subsequent activities were considered to be usual care, including filling the first and subsequent trial-drug prescriptions, hypertension management, changes in medication, and adverse-event monitoring. The trial did not mandate clinic visits or data reporting.

A computer-generated, site-stratified assignment schedule (a 1:1 ratio, with a block size of six) was used. The schedule was created before the trial began and remained concealed until randomization.

PRIMARY AND SECONDARY OUTCOMES

The primary outcome was the first occurrence of a composite outcome consisting of a nonfatal cardiovascular disease event or non–cancer-related death, assessed in a time-to-event analysis. Nonfatal cardiovascular disease events were nonfatal myocardial infarction, stroke, hospitalization for heart failure, or urgent coronary revascularization for unstable angina. Secondary outcomes were the individual components of the primary outcome. Secondary analysis included the effect of treatment on the primary outcome within a priori subgroups. Safety outcomes, including electrolyte abnormalities, hospitalizations, and acute kidney injury, are shown in Table S2.

DATA COLLECTION AND OUTCOME ASCERTAINMENT

All baseline data were extracted from the EHR and consisted of the data most proximal to, but recorded before, the randomization date. Coexisting conditions were identified with the use of VA claims data. Follow-up blood-pressure data were extracted from the records of routine outpatient clinic visits. Data with regard to medication prescription fills were obtained from the VA outpatient pharmacy service. Ascertainment of primary, secondary, and safety outcomes was made with the use of administrative and clinical data obtained from VA EHRs through June 1, 2022, from records of Medicare claims obtained from the Centers for Medicare and Medicaid Services (CMS) through 2021, and from National Death Index (NDI) records through 2019. Outcomes data from CMS and NDI will continue to accrue until all final data (through 2022) become available. Trial outcomes were ascertained with the use of validated EHR phenotypes and, when needed, manual adjudication.[11] Manually adjudicated outcomes were evaluated by investigators and staff who were unaware of group assignments.

Patients were followed until they withdrew from the trial or died, or until the end of the trial. Follow-up continued beyond the time that the primary-outcome event occurred in order to determine secondary, safety, and recurrent outcomes.

STATISTICAL ANALYSIS

We calculated that 1055 primary-outcome events would provide the trial with 90% power to detect a 17.5% lower hazard for the primary outcome in the chlorthalidone group at a two-sided alpha level of 0.049, assuming a 3% annual incidence of the primary outcome in the hydrochlorothiazide group. A planned interim analysis of the primary hypothesis was performed after 500 primary-outcome events had occurred, with a type I error rate of 0.01.

Primary analyses were performed with the use of unadjusted log-rank tests that were stratified according to VA health care system. Secondary analyses and analysis of the time to hospitalization for hypokalemia were performed with the use of a competing-risk model.[15] Adjusted Cox proportional-hazards models were also used for secondary analyses that were controlled for age, sex, race, estimated glomerular filtration rate (GFR), baseline diabetes, and history of myocardial infarction or stroke.[5] Prespecified subgroup analyses were conducted

with the use of baseline data with regard to median age, race (Black or non-Black), estimated GFR (<60 or ≥60 ml per minute per 1.73 m^2 of body-surface area), sex, presence or absence of diabetes, history of myocardial infarction or stroke, and median systolic blood pressure.

Because the statistical analysis plan did not include a provision for multiplicity when tests were conducted for secondary or other outcomes, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals were not adjusted for multiplicity, so intervals should not be used in place of hypothesis testing. All the analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

From June 2016 through October 2021, a total of 72 VA health care systems (which encompassed 537 locations) were enlisted in the trial (Fig. S1 in the Supplementary Appendix). A total of 6188 primary care providers were approached for participation, and 4128 (67%) consented. A total of 16,595 patients consented to participate, and 13,523 underwent randomization (6756 assigned to the chlorthalidone group and 6767 to the hydrochlorothiazide group). Informed consent was withdrawn by 12 patients in the chlorthalidone group and by 7 patients in the hydrochlorothiazide group. Vital status was confirmed for all the remaining patients. Thus, our large pragmatic trial was carried out within the framework of the VA point-of-care program; the score on the basis of eight PRECIS-2 (Pragmatic–Explanatory Continuum Indicator Summary) criteria (with each criterion scored on a scale from 1 to 5, with higher scores indicating greater pragmatism) was 37 out of 40 (Fig. S3).[16]

The characteristics of the patients at baseline were similar in the two groups (Table 1). The mean age of the patients was 72 years, 13,092 of the patients who underwent randomization (97%) were men, 2027 (15%) were Black, 1455 (10.8%) had a history of stroke or myocardial infarction, and 6122 (45%) resided in rural areas. At baseline, a total of 12,781 patients (94.5%) received a prescription for hydrochlorothiazide at a daily dose of 25 mg. The mean systolic blood pressure at baseline was 139 mm Hg, and the mean number of medications that patients were receiving for blood-pressure control was 2.6. Blood pressure, as measured at outpatient follow-up, remained similar in the two groups (Fig. 1 and Table S3).

OUTCOMES

At a median follow-up of 2.4 years, a primary composite outcome event had occurred in 1377 patients — 702 (10.4%) in the chlorthalidone group and 675 (10.0%) in the hydrochlorothiazide group (hazard ratio, 1.04; 95% confidence interval [CI], 0.94 to 1.16; P=0.45) (Table 2 and Fig. 2). The observed annual event rate was 4.5% in the chlorthalidone group (702 events over 15,653 person-years) and 4.3% in the hydrochlorothiazide group (675 events over 15,683 person-years). There was no difference between the groups in the individual components of the primary outcome: the hazard ratio for myocardial infarction was 1.01 (95% CI, 0.80 to 1.28); for stroke, 1.00 (95% CI, 0.74 to 1.36); for hospitalization for heart failure, 1.04 (95% CI, 0.87 to 1.25); for revascularization for unstable angina, 1.54 (95% CI, 0.77 to 3.10); and for non–cancer-related death, 1.01 (95% CI, 0.88 to 1.17). A total of 446 patients (6.6%) in the chlorthalidone group and 448 (6.6%) in the hydrochlorothiazide group died from any cause (hazard ratio, 1.00; 95% CI, 0.87 to 1.13) (Table 2). There was no difference between the groups in the adjusted analysis (Table S4).

Subgroup analysis of the primary outcome showed a qualitative interaction[17] between treatment assignment and a history at baseline of myocardial infarction or stroke (Fig. 3). Patients in the chlorthalidone group who had a history of myocardial infarction or stroke had a lower incidence of the primary outcome (105 of 733 patients [14.3%]) than patients in the hydrochlorothiazide group (140 of 722 patients [19.4%]) (hazard ratio, 0.73; 95% CI, 0.57 to 0.94). Patients in the chlorthalidone group who did not have a history of myocardial infarction or stroke had a slightly higher incidence of the primary outcome (597 of 6023 patients [9.9%]) than patients in the hydrochlorothiazide group (535 of 6045 patients [8.9%]) (hazard ratio, 1.12; 95% CI, 1.00 to 1.26). Other subgroups did not have analysis results that differed from the main results (Fig. 3).

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Chlorthalidone (N=6756)	Hydrochlorothiazide (N=6767)
Age — yr	72.4±5.4	72.5±5.3
Male sex — no. (%)	6536 (96.7)	6556 (96.9)
Race or ethnic group — no. (%)†		
Black	1004 (14.9)	1023 (15.1)
White	5229 (77.4)	5225 (77.2)
Other	523 (7.7)	519 (7.7)
Not Hispanic or Latino	6281 (93.0)	6268 (92.6)
Resided in rural area — no. (%)‡	3043 (45.0)	3079 (45.5)
Body-mass index§	31.7±5.8	31.8±5.9
Medical history — no. (%)		
Diabetes	2967 (43.9)	3062 (45.2)
Heart failure	525 (7.8)	526 (7.8)
MI	230 (3.4)	258 (3.8)
Stroke	534 (7.9)	495 (7.3)
MI and stroke¶	733 (10.8)	722 (10.7)
Estimated GFR <60 ml/min/1.73 m^2 — no. (%)	1550 (22.9)	1547 (22.9)
Current smoker — no. (%)	1520 (22.5)	1437 (21.2)
Receiving hydrochlorothiazide at a daily dose of 25 mg — no. (%)	6379 (94.4)	6402 (94.6)
Systolic blood pressure — mm Hg	139±14	139±14
No. of antihypertensive drugs prescribed	2.6±1.0	2.6±1.1
Antihypertensive medications — no. (%)		
Hydrochlorothiazide alone	889 (13.2)	866 (12.8)
Hydrochlorothiazide plus one additional blood-pressure medication	2352 (34.8)	2284 (33.8)
Hydrochlorothiazide plus two additional blood-pressure medications	2180 (32.3)	2221 (32.8)
Hydrochlorothiazide plus three additional blood-pressure medications	1061 (15.7)	1090 (16.1)
Hydrochlorothiazide plus four additional blood-pressure medications	274 (4.1)	306 (4.5)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. GFR denotes glomerular filtration rate, and MI myocardial infarction.
† Race or ethnic group was reported by the patient.
‡ Place of residence was defined according to the Veterans Affairs urban–rural–highly rural classification system.
§ Body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ At baseline, 31 patients in each group had had both an MI and stroke.

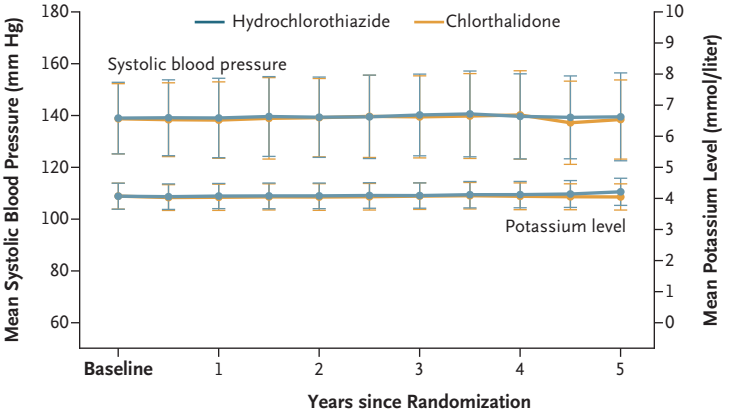
SAFETY OUTCOMES AND ADVERSE EVENTS

There was no between-group difference in the incidence of hospitalization for any cause (1825 patients [27.0%] in the chlorthalidone group and 1826 patients [27.0%] in the hydrochlorothiazide group; P=0.98). On average, patients in the chlorthalidone group underwent more laboratory studies for potassium levels in the first year of the trial (mean [±SD] number of tests, 3.5±4.6) than patients in the hydrochlorothiazide group (3.3±4.1). Hospitalizations for hypokalemia were slightly more common with chlorthalidone (in 1.5% of the patients) than hydrochlorothiazide (in 1.1%) (hazard ratio, 1.35; 95% CI, 1.00 to 1.82) (Table 2 and Fig. S3). Similarly, a potassium level of less than 3.1 mmol per liter at follow-up was more common in the chlorthalidone group (in 5.0% of the patients) than in the hydrochlorothiazide group (in 3.6%) (P<0.001). All the patients in the two groups

Table 2. Primary, Secondary, and Safety Outcomes.*

Outcome	Chlorthalidone (N=6756)	Hydrochlorothiazide (N=6767)	Hazard Ratio (95% CI)†
Primary composite outcome — no. (%)‡	702 (10.4)	675 (10.0)	1.04 (0.94–1.16)§
Secondary outcomes: components of the primary outcome — no. (%)			
MI	142 (2.1)	140 (2.1)	1.02 (0.80–1.28)
Stroke	83 (1.2)	83 (1.2)	1.00 (0.74–1.36)
Hospitalization due to heart failure	242 (3.6)	232 (3.4)	1.04 (0.87–1.25)
Unstable angina leading to urgent coronary revascularization	20 (0.3)	13 (0.2)	1.54 (0.77–3.10)
Non–cancer-related death	359 (5.3)	354 (5.2)	1.01 (0.88–1.17)
Death from any cause — no. (%)	446 (6.6)	448 (6.6)	1.00 (0.87–1.13)
Expected adverse events — no. (%)			
New allergic or adverse reaction to thiazide-type diuretic	109 (1.6)	21 (0.3)	5.23 (3.28–8.35)
Hypokalemia	406 (6.0)	298 (4.4)	1.38 (1.19–1.60)
As primary cause of hospitalization	98 (1.5)	73 (1.1)	1.35 (1.00–1.82)
Potassium level <3.1 mmol/liter	335 (5.0)	243 (3.6)	1.39 (1.18–1.64)
Hospitalization for acute kidney injury	495 (7.3)	512 (7.6)	0.95 (0.85–1.09)

* Detailed definitions of outcomes are shown in Table S5.
† Hazard ratios were estimated with the use of a Cox proportional-hazards model for the primary outcome and a Fine–Gray model of competing risk[15] for the secondary outcomes and for the outcome of hospitalization for hypokalemia. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of a hypothesis test.
‡ The primary outcome was a composite of nonfatal MI, stroke, heart failure resulting in hospitalization, urgent coronary revascularization for unstable angina, and non–cancer-related death.
§ P=0.45 by the log-rank test.



Percentage of Patients Receiving Potassium Supplement

Hydrochlorothiazide	11.1	11.9	12.3	11.8	11.9	12.2	11.7	10.9	11.0	11.7	8.8
Chlorthalidone	10.8	12.1	13.0	12.6	13.0	14.0	13.4	13.1	13.0	14.9	13.6

Figure 1. Systolic Blood Pressure, Potassium Level, and Potassium Supplementation over Time.
Laboratory values for potassium include both serum and plasma measurements. I bars indicate confidence intervals.

had recovered to a potassium level higher than 3.1 mmol per liter within 6 months after their first low level was detected; the median time to recovery was 31 days in the chlorthalidone group and 33 days in the hydrochlorothiazide group. Prescriptions for potassium supplements were issued more often to patients in the chlorthalidone group than to those in the hydrochlorothiazide group (Fig. 1).

ADHERENCE TO TRIAL MEDICATION

Over the course of the trial, 1039 patients (15.4%) who had been assigned to receive chlorthalidone were switched back to treatment with hydrochlorothiazide; 260 patients (3.8%) who had been assigned to continue treatment with hydrochlorothiazide were switched to chlorthalidone. The mean medication possession ratio, defined as the sum of the days that a patient was supplied with filled prescriptions of the assigned drug divided by the number of days in the trial, was 79.5% (interquartile range, 58.3 to 103.1) in the chlorthalidone group and 79.1% (interquartile range, 65.3 to 99.2) in the hydro-

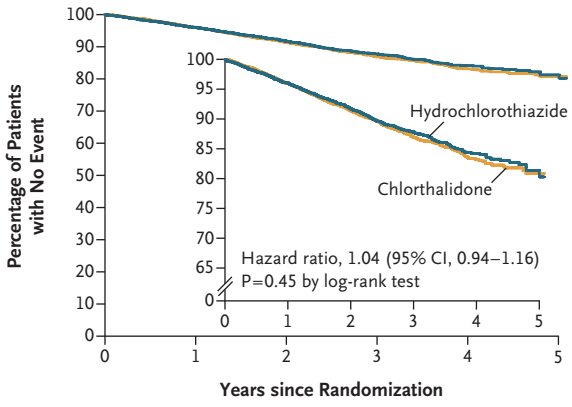


Figure 2. Kaplan–Meier Survival Curve for the Primary Outcome.

A primary composite outcome event (a composite of nonfatal myocardial infarction, stroke, heart failure that resulted in hospitalization, urgent coronary revascularization for unstable angina, and non–cancer-related death) occurred in 1377 patients: 702 (10.4%) in the chlorthalidone group and 675 (10.0%) in the hydrochlorothiazide group. The observed annual event rate was 4.5% in the chlorthalidone group and 4.3% in the hydrochlorothiazide group. The inset shows the same data on an expanded y axis.

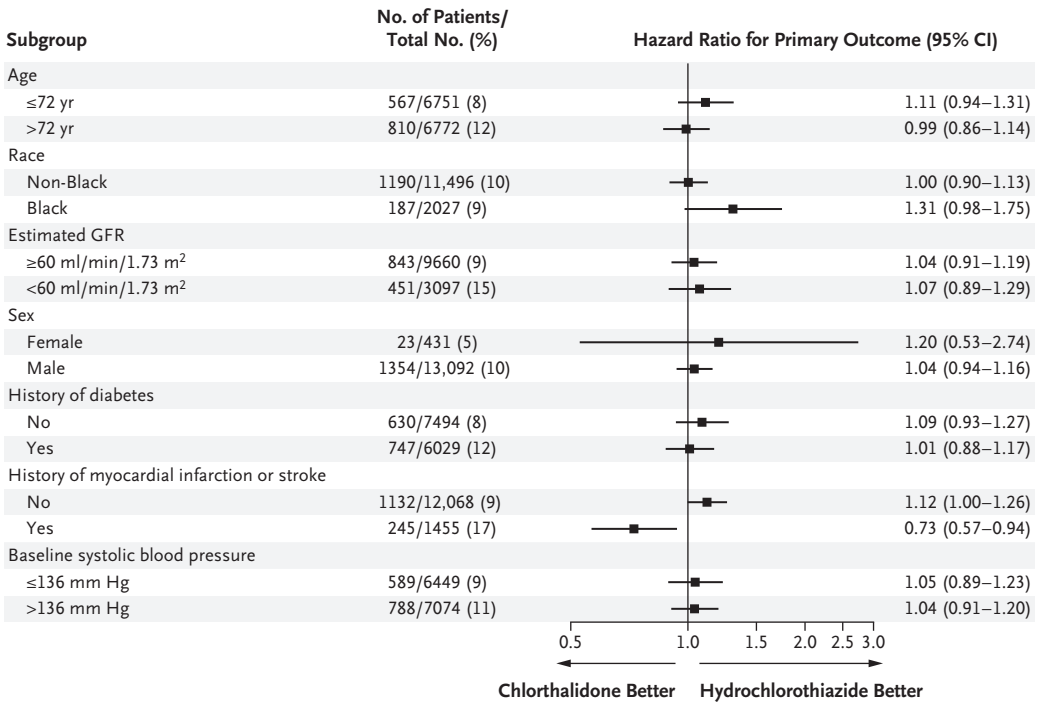


Figure 3. Subgroup Analysis of the Primary Composite Outcome.

Race was reported by the patient. GFR denotes glomerular filtration rate.

chlorothiazide group. The median average daily dose was 12.3 mg in the chlorthalidone group and 23 mg in the hydrochlorothiazide group.

DISCUSSION

In this large, VA point-of-care, comparative-effectiveness trial in which the Diuretic Comparison Project protocol was integrated into the usual care of patients with hypertension, there was no difference in effectiveness between chlorthalidone and hydrochlorothiazide therapy with regard to the risks of the primary composite outcome (P=0.45) or the individual components of the primary outcome. There was a qualitative interaction in a prespecified subgroup that was defined according to the history of myocardial infarction or stroke and treatment-group assignment. Patients in the chlorthalidone group who had no history of myocardial infarction or stroke had a modestly higher risk of a primary-outcome event than patients in the hydrochlorothiazide group, but patients who had a history of myocardial infarction or stroke and were assigned to receive chlorthalidone had a lower risk of a primary-outcome event than patients with this history in the hydrochlorothiazide group. Because the trial did not show a difference in the risk of the primary outcome between treatment groups overall, this difference is probably a chance finding and should not be overinterpreted.

Chlorthalidone therapy was associated with a small increase in the incidence of hospitalizations for hypokalemia and in the incidence of laboratory-identified hypokalemia, almost all cases of which resolved with usual care. Patients in the chlorthalidone group were more likely to either switch to the other trial drug or discontinue thiazide agents than patients in the hydrochlorothiazide group. These findings were probably a consequence of the trial design. Patients were required to have already been receiving hydrochlorothiazide to be eligible for the trial. At baseline, almost all the patients were receiving hydrochlorothiazide without unacceptable side effects or hypokalemia. We speculate that patients who had been assigned to receive chlorthalidone underwent a greater number of potassium measurements within the first 6 months after randomization than those who continued taking hydrochlorothiazide because they were receiving a new medication. Additional monitoring probably identified a greater number of hypokalemic events in the chlorthalidone group. Patients in the chlorthalidone group probably had new symptoms related to the receipt of chlorthalidone, which prompted a switch back to hydrochlorothiazide. The open-label design may have also contributed to a greater number of patients in the chlorthalidone group reverting to hydrochlorothiazide therapy.

Thiazides reduce the risk of cardiovascular outcomes, but the choice of which thiazide to use is controversial. Previous studies have suggested that chlorthalidone is superior to hydrochlorothiazide in preventing cardiovascular outcomes. Evidence suggests that chlorthalidone has a longer duration of action, with improved 24-hour blood-pressure control[18,19] and other pleotropic effects.[20] Several observational studies have suggested various effects on cardiovascular outcomes, from no effect to an increased risk of cardiovascular events with chlorthalidone as compared with hydrochlorothiazide,[7-9] and an increased risk of adverse effects (i.e., electrolyte abnormalities and acute kidney injury) with chlorthalidone as compared with hydrochlorothiazide. Results from the present trial suggest no difference between the drugs with regard to cardiovascular outcomes, with potential disparate results in the primary outcome caused by the presence or absence of a history of stroke or myocardial infarction at baseline. Those assigned to the chlorthalidone group were more likely to switch to the other trial drug than those assigned to the hydrochlorothiazide group. Patients assigned to receive chlorthalidone had a greater incidence of hypokalemia than those assigned to receive hydrochlorothiazide.

We conducted this large pragmatic trial within the VA point-of-care program, with a PRECIS-2 score of 37 out of 40.[16] The trial was embedded within the VA EHR system, which allowed centralized identification and recruitment. We enrolled more than 4000 providers and 13,500 patients at 537 clinics and assessed all outcomes with the use of EHR and claims data. The trial was conducted in the context of usual care with no trial-specific procedures (including case-report forms) or trial-specific visits. All data were extracted from administrative databases, which dramatically reduced the total cost of the trial. Centralized recruitment allowed participa-

tion from many smaller VA sites that traditionally have been excluded from clinical trials owing to lack of research infrastructure. The percentages of patients from rural areas (45%)[21] enhanced the pragmatic nature of the trial and its generalizability.

We believe that this trial provides several lessons that can be used in the conduct of large pragmatic trials. Large, embedded trials are clinically and operationally feasible. They can be incorporated into the clinical workflow of providers by means of leveraging EHR systems and other existing clinical and informatics infrastructure. It is possible to centrally identify, recruit, randomly assign, and retain a large number of patients. Patients with no contact from the trial personnel continued to take the trial medications at a high level consistent with real-world adherence. Although the trial temporarily paused recruitment during the coronavirus disease 2019 pandemic, once recruitment resumed, the centralized design allowed for no interruptions to trial procedures, and we immediately resumed recruitment at the prepandemic rate of approximately 100 patients per week.

This trial had several important limitations. Because it was open label and, by design, included patients who were receiving hydrochlorothiazide at baseline, there was a greater likelihood that the patients assigned to the chlorthalidone group might switch back to hydrochlorothiazide. We planned to follow patients for a mean of 3 years or until 1055 primary-outcome events had occurred. The target number of total events occurred before 3 years had elapsed, which led us to stop the trial. Follow-up by way of the EHRs is planned through the end of 2022. Because only a subset of follow-up data from Medicare and NDI were available at the time of publication, we expect the total number of outcomes to change.

The dose levels of the two diuretics were also an important limitation of this pragmatic trial. Previous trials that showed the benefits of these medications on cardiovascular outcomes used higher target doses (≥50 mg of hydrochlorothiazide or ≥25 mg of chlorthalidone).[22,23] However, most patients currently treated with hydrochlorothiazide, including the VA population, receive 12.5 to 25 mg, and only 5% of the patients in this trial had been receiving 50 mg of hydrochlorothiazide at baseline. Therefore, the primary comparison in this trial was between 25 mg of hydrochlorothiazide and 12.5 mg of chlorthalidone. These results should not be extrapolated to other doses of these medications.

In this large pragmatic trial, chlorthalidone did not lead to a lower incidence of major cardiovascular outcomes or non–cancer-related deaths than hydrochlorothiazide at doses commonly used in clinical practice.

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

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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