Long-Term Effects of Chlorthalidone Versus Hydrochlorothiazide on Electrocardiographic Left Ventricular Hypertrophy in the Multiple Risk Factor Intervention Trial

Michael E. Ernst, James D. Neaton, Richard H. Grimm, Jr, Gary Collins, William Thomas, Elsayed Z. Soliman, Ronald J. Prineas, for the Multiple Risk Factor Intervention Trial Research Group

See Editorial Commentary, pp XX–XX

Abstract—Chlorthalidone (CTD) reduces 24-hour blood pressure more effectively than hydrochlorothiazide (HCTZ), but whether this influences electrocardiographic left ventricular hypertrophy is uncertain. One source of comparative data is the Multiple Risk Factor Intervention Trial, which randomly assigned 8012 hypertensive men to special intervention (SI) or usual care. SI participants could use CTD or HCTZ initially; previous analyses have grouped clinics by their main diuretic used (C-clinics: CTD; H-clinics: HCTZ). After 48 months, SI participants receiving HCTZ were recommended to switch to CTD, in part because higher mortality was observed for SI compared with usual care participants in H-clinics, whereas the opposite was found in C-clinics. In this analysis, we examined change in continuous measures of electrocardiographic left ventricular hypertrophy using both an ecological analysis by previously reported C- or H-clinic groupings and an individual participant analysis where use of CTD or HCTZ by SI participants was considered and updated annually. Through 48 months, differences between SI and usual care in left ventricular hypertrophy were larger for C-clinics compared with H-clinics (Sokolow-Lyon: −93.9 versus −54.9 μV, P=0.049; Cornell voltage: −68.1 versus −35.9 μV, P=0.019; Cornell voltage product: −4.6 versus −2.2 μV/V, P=0.071; left ventricular mass: −4.4 versus −2.8 g, P=0.002). At the individual participant level, Sokolow-Lyon and left ventricular mass were significantly lower for SI men receiving CTD compared with HCTZ through 48 months and 84 months of follow-up. Our findings on left ventricular hypertrophy support the idea that greater blood pressure reduction with CTD than HCTZ may have led to differences in mortality observed in the Multiple Risk Factor Intervention Trial. (Hypertension. 2011; 58:00-00.)

Key Words: hydrochlorothiazide ■ chlorthalidone ■ left ventricular hypertrophy ■ hypertension ■ blood pressure ■ electrocardiography

Lowering of blood pressure with a diuretic-based regimen has decreased stroke, heart failure, and cardiovascular disease events in several outcome-based clinical trials.1 Most of these studies used the thiazide-like diuretic chlorthalidone (CTD), yet 95% of thiazide prescriptions are for hydrochlorothiazide (HCTZ).2 There has been little direct comparison of the 2 agents on measures other than blood pressure reduction.3 One source of comparative data comes from the Multiple Risk Factor Intervention Trial (MRFIT), which used both CTD and HCTZ in a nonrandomized manner.4 Almost 5 years into the trial, a recommendation was made by the external data and safety monitoring committee (ie, the MRFIT Policy Advisory Board) to switch all of the hypertensive participants in the special intervention (SI) group who were taking 50 or 100 mg/d of HCTZ to 50 mg/d of CTD.5 This protocol change was prompted by an ecological analysis revealing that coronary heart disease mortality rates for the SI group were significantly higher than for usual care (UC) participants in clinics where HCTZ was predominantly used (ie,
H-clinics). Conversely, mortality rates were lower for SI compared with UC participants in clinics with high use of CTD (ie, C-clinics). After the protocol change, this unfavorable mortality pattern for SI compared with UC participants reversed during follow-up, giving relevance of the ecological association identified earlier. Although choice of diuretic was believed to have influenced the findings, conclusions about the specific impact of CTD or HCTZ in MRFIT remain speculative.

A small, prospective study suggested that CTD can sustain reductions in blood pressure throughout a 24-hour period more effectively than HCTZ, probably because of its longer half-life. These data led us to investigate the effects of CTD and HCTZ on electrocardiographic left ventricular hypertrophy (LVH) in MRFIT. LVH is strongly influenced by blood pressure and is an established risk factor for coronary heart disease. Differences in LVH may yield further insight into the MRFIT findings.

Methods

Study Cohort

The design and methods of MRFIT have been reported extensively. Briefly, MRFIT was a large randomized primary prevention trial designed to determine effects on coronary heart disease mortality of a multifaceted intervention targeting smoking cessation, reduction in serum cholesterol, and stepped-care treatment of hypertension. Men aged 35 to 57 years were invited to attend 3 screening examinations in 22 clinical centers located in 18 US cities. Participants were selected based on their having an above-average risk of developing coronary heart disease, as determined from a risk score calculated as a function of serum cholesterol, diastolic blood pressure, and cigarette smoking. Participants who were free of coronary heart disease by history and examination, including a resting ECG, were eligible for randomization.

After providing consent, 12,866 men were randomly assigned to 2 groups, SI or UC. The SI program included counseling on smoking cessation, advice on dietary modifications to reduce cholesterol, and treatment for hypertension, whereas the UC group received treatment of their risk factors as considered on an individual basis by their usual sources of care within the community. Of those randomized, 8012 (62%) were classified as hypertensive at baseline, defined as average diastolic blood pressure level of ≥90 mm Hg or those who had been receiving antihypertensive drugs on entry. These 8012 men, also the focus of earlier reports, are included in this analysis.

Intervention

Hypertension treatment for SI participants used a stepped-care approach, which included moderate salt reduction, weight loss, and antihypertensive drugs. Initial medication was an oral diuretic, either CTD or HCTZ, at a dose of 50 or 100 mg daily (the standard doses used at the time MRFIT was carried out). This was followed by stepwise addition of antihypertensive drugs or a β-blocker (step 2), an arteriolar vasodilator (step 3), and an β-blocker (step 4), designed to achieve and maintain a diastolic blood pressure goal of 80 to 89 mm Hg. The choice of which diuretic to initiate in SI participants was left to the discretion of the individual physician. Within many clinics there was a tendency to use predominantly one diuretic or the other, which enabled clinics to be categorized in earlier ecological analyses according to the diuretic predominantly used in that clinic (C-clinics: CTD; H-clinics: HCTZ).

Blood Pressure and Electrocardiographic Measurements

A random 0 sphygmomanometer was used to measure clinic blood pressure in the seated position after 5 minutes of rest, as detailed elsewhere. Two measurements were recorded at each of the second and third screening visits and annually thereafter throughout follow-up.

Procedures have been reported for recording resting electrocardiograms and for computerized measurements, including different measures of LVH. Briefly, standard 12-lead resting electrocardiograms were recorded at the second and third screening visits and then annually for the duration of follow-up. Standard limb electrodes were placed on the torso to permit exercise, as well as resting electrocardiograms, at baseline (at the third of 3 screening visits before randomization). This lead configuration was maintained for recording resting electrocardiograms at annual visits after randomization. The electrocardiograms were recorded on magnetic tape cassettes with standard 3-channel ECG machines (Marquette series 3500, Marquette Inc, Milwaukee, WI). The analog cassettes were processed by computer algorithm at the Computer ECG Center (Dalhousie University, Halifax, Nova Scotia, Canada) and were also visually coded at the ECG Coding Center at the University of Minnesota.

The following continuous measurements were used to define LVH: Sokolow-Lyon voltage (μV) = SV1 + max RV5/S6; Cornell voltage (μV) = SV1 = RaVL; and Cornell voltage product (μV/ms) = Cornell voltage * QRS duration. The following computer measurements were used to calculate left ventricular mass (in grams) for whites: 0.023 Cornell voltage + 0.010 Sokolow-Lyon + 1.32 weight + 10.6, and for blacks: 0.0018 Cornell voltage + 0.51 JVP + 1.45 weight + 17.4. In MRFIT, ~3% of hypertensive men reported their race as something other than white or black, and left ventricular mass for these men is determined using the formula for whites.

Statistical Analysis

We assessed the association between CTD and HCTZ use and LVH using 2 types of analyses, an ecological analysis, with the 22 MRFIT clinics classified (as in previous reports) as C-clinics, H-clinics, or SI or UC. The individual participant analysis, with use of CTD, HCTZ, or antihypertensive medication other than CTD or HCTZ considered time-dependent covariates and updated annually. Both analyses were restricted to men hypertensive at baseline. The ecological analysis was carried out through 4 years of follow-up, the last measurement before the recommendation to switch all of the participants to 50 mg of CTD; it used information from both SI and UC participants who were hypertensive at entry into C- or H-clinics. The individual participant analysis was performed for the same 4-year period and also for the duration of the trial (84 months) taking into account individual changes in CTD and HCTZ prescriptions; it used information for all of the SI hypertensive men, including those in the switching clinics but not men in the UC group. Both the ecological and individual participant analyses were repeated excluding participants with major conduction defects, as evidenced by QRS ≥120 ms.

Ecological Analysis

The ecological analysis takes advantage of the randomization to SI and UC, which was carried out within clinic. As a consequence, SI and UC men within clinic are similar, on average, with respect to baseline characteristics, both those measured and not measured. For the ecological analysis, the estimand used to quantify differences between CTD and HCTZ for blood pressure and LVH is the difference in “intention-to-treat” estimates (SI/UC for C-clinics versus H-clinics) (ie, a difference of differences). Two potential limitations of this estimand are that the grouping variable, CTD or HCTZ, determined postrandomization, may be a marker for a factor other than CTD or HCTZ that is related to LVH, and there is the possibility of misclassification within clinic grouping (eg, not all SI participants in the C-clinics were treated for hypertension, and some used HCTZ). To assess the likelihood that the clinic label of C- or H- was because of another factor related to LVH, we carried out an analysis for men who were normotensive at entry. Because fewer of these men were initiated on antihypertensive drugs during follow-up, we hypothesized that differences among C- and H-clinics would be
Table 1. Baseline Characteristics of MRFIT Participants Hypertensive at Entry, by Clinic Grouping

<table>
<thead>
<tr>
<th>Variable</th>
<th>C-Clinics</th>
<th>H-Clinics</th>
<th>Switching Clinics</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>2112</td>
<td>3399</td>
<td>2501</td>
<td>8012</td>
</tr>
<tr>
<td>Age, y*</td>
<td>46.8 (5.8)</td>
<td>46.7 (5.9)</td>
<td>46.6 (5.9)</td>
<td>46.7 (5.9)</td>
</tr>
<tr>
<td>Black, %</td>
<td>10.0</td>
<td>10.7</td>
<td>5.5</td>
<td>8.9</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>58.6</td>
<td>56.1</td>
<td>50.9</td>
<td>55.1</td>
</tr>
<tr>
<td>Serum cholesterol, mg/dL*</td>
<td>249.3 (36.6)</td>
<td>249.7 (36.6)</td>
<td>251.7 (34.4)</td>
<td>250.2 (35.9)</td>
</tr>
<tr>
<td>Body mass index, kg/m²*</td>
<td>27.8 (3.4)</td>
<td>28.0 (3.5)</td>
<td>28.0 (3.5)</td>
<td>28.0 (3.5)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg*</td>
<td>142.0 (13.1)</td>
<td>141.5 (13.1)</td>
<td>140.2 (12.5)</td>
<td>141.2 (12.9)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg*</td>
<td>95.8 (6.9)</td>
<td>95.5 (6.7)</td>
<td>95.3 (6.6)</td>
<td>95.5 (6.7)</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>4.36 (0.46)</td>
<td>4.37 (0.48)</td>
<td>4.38 (0.44)</td>
<td>4.37 (0.46)</td>
</tr>
<tr>
<td>On antihypertensive medication, %</td>
<td>31.3</td>
<td>31.0</td>
<td>30.9</td>
<td>31.1</td>
</tr>
<tr>
<td>Left ventricular hypertrophy, by Minnesota code, %</td>
<td>2.3</td>
<td>2.7</td>
<td>2.3</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Electrocardiographic measurement

| Absolute maximum of R amplitude V5/6, μV* | 1702.0 (515.4) | 1677.8 (530.9) | 1726.1 (525.2) | 1699.4 (525.4) |
| Absolute S amplitude V1, μV*           | 947.4 (461.5)  | 979.3 (461.6)  | 921.3 (445.4)  | 952.7 (457.2)  |
| R amplitude aVL, μV*                   | 290.3 (251.3)  | 271.0 (251.5)  | 268.4 (240.8)  | 275.3 (248.3)  |
| Absolute S amplitude V3, μV*           | 1031.3 (467.6)| 1065.2 (467.6)| 1019.6 (463.7)| 1042.0 (466.8) |
| QRS duration, ms                       | 85.3 (9.4)     | 84.7 (9.6)     | 85.5 (9.3)     | 85.1 (9.4)     |

Criteria for electrocardiographic left ventricular hypertrophy

| Sokolow-Lyon, μV*                    | 2649.4 (789.4)| 2657.3 (788.3)| 2647.3 (786.4)| 2652.1 (782.3) |
| Cornell voltage, μV*                 | 1322.1 (527.0)| 1336.2 (528.5)| 1288.1 (517.6)| 1317.4 (525.1) |
| Cornell voltage product, μV/ms*      | 113.9 (49.8)  | 114.5 (50.7)  | 111.3 (49.1)  | 113.3 (50.0)   |
| Left ventricular mass, g*            | 178.0 (21.6)  | 177.4 (22.6)  | 178.9 (21.4)  | 178.0 (21.9)   |

Results

Study Cohort

Of the 8012 hypertensive men enrolled in MRFIT, 2112 (1046 SI and 1066 UC) were randomly assigned by 6 clinics that predominantly used CTD (ie, C-clinics); 3399 (1725 SI and 1674 UC) were randomly assigned by 9 clinics that predominantly used HCTZ (ie, H-clinics); and 2501 (1248 SI and 1253 UC) were randomly assigned by 7 clinics that initially used CTD and then switched to HCTZ during the first 4 years of the study (ie, switching clinics). As reported previously, the characteristics of SI and UC hypertensive men were well balanced at baseline. This was also the case for the SI-UC comparison within the 3 groups of clinics (data not shown).

Table 1 summarizes the baseline characteristics for the hypertensive participants overall and by clinic grouping. Baseline characteristics, including continuous measures of LVH, were similar for participants in C- and H-clinics. Participants in the switching clinics were less likely to be black and to smoke. Overall, average systolic and diastolic
Use of CTD, HCTZ, and Other Antihypertensives in MRFIT

Figure 1 gives the percentage of SI participants prescribed CTD, HCTZ, or other treatment (neither CTD nor HCTZ) by month of follow-up, irrespective of clinic grouping. Use of CTD declined during the first 4 years, from 33.4% at 12 months to 26.6% at 48 months, whereas use of HCTZ increased from 27.4% at 12 months to a high of 42.5% at 48 months. After the protocol change, which occurred after all of the participants had completed the 48-month visit, use of CTD increased (to 50.8% by 84 months), whereas use of HCTZ declined to 14.7% by 84 months.

At 48 months, of SI hypertensive participants, 80% in C-clinics, 75% in H-clinics, and 76% in switching clinics were prescribed antihypertensive medication. The distribution of CTD and HCTZ use according to clinic grouping is summarized in Figure 2. Among C-clinics, use of CTD ranged from 43% to 58% (average: 48%), whereas among H-clinics, use of HCTZ ranged from 40% to 61% (average: 49.5%). In the switching clinics, 49.7% of SI participants were prescribed HCTZ and 21.2% were prescribed CTD. After the protocol change (ie, by the 72-month follow-up visit), these percentages were approximately reversed, among SI participants in the switching clinics, 51.4% were prescribed CTD and 16.8% were prescribed HCTZ (data not shown). Less than 10% of UC participants were prescribed CTD in each of the clinic groupings, and ~35% were prescribed HCTZ at 48 months.

Additional antihypertensive medication was added to the diuretic used to achieve blood pressure goal. In C-clinics, 52.9% of SI participants at 48 months were prescribed a step 2 drug, 13.2% were prescribed step 3, and 0.6% were prescribed step 4. In SI participants of H-clinics, the corresponding percentages were 42.4%, 12.0%, and 0.7%.

Blood pressure levels were 141.2 and 95.5 mm Hg, respectively. Approximately 31% were taking antihypertensive medications at entry.

Blood Pressure and LVH Measures Through 48 Months According to C- or H-Clinic

Changes in systolic and diastolic blood pressures were greater for SI compared with UC participants in both the C- and H-clinics. The SI-UC differences were greater within C-clinics compared with H-clinics for systolic (−10.4 versus −8.6 mm Hg; P=0.001 for clinic difference) and diastolic blood pressure (−6.5 versus −5.1 mm Hg; P<0.001 for clinic difference; Table 2). All of the continuous LVH measures were significantly lower in the SI compared with the UC group, regardless of clinic designation. Mean differences between SI and UC in these measures were all uniformly of greater magnitude in the C- compared with the H-clinics (P values for interaction between C- and H-clinics: Sokolow-Lyon, P=0.049; Cornell voltage, P=0.019; Cornell voltage product, P=0.071; left ventricular mass, P=0.002).

Analyses were also carried out for the men who were normotensive at entry to determine whether differences between C- and H-clinics were evident in this subgroup. Participants randomized to SI with repeated diastolic blood pressure ≥90 mm Hg during follow-up were placed on antihypertensives. Overall, the percentage of SI men who were normotensive at entry receiving antihypertensives at 48 months was much smaller (22.2%) than for men hypertensive at entry (76.5%). Likewise, although differences in use of CTD and HCTZ were evident among clinics (13.4% used CTD and 9.3% used HCTZ among C-clinics and 5.0% used CTD and 12.9% used HCTZ among H-clinics at 48 months), the percentages using these drugs were much smaller than for hypertensive men. Consequently, SI-UC differences in blood pressure change were smaller. Differences in systolic blood pressure for SI-UC averaged −2.6 mm Hg (SE=0.46) for C-clinics and −3.0 mm Hg (SE=0.34) for H-clinics (P=0.56 for difference), whereas SI-UC differences in diastolic blood pressure averaged −1.8 mm Hg (SE=0.30 mm Hg) and −2.1 mm Hg (SE=0.22 mm Hg), respectively, for C- and H-clinics (P=0.48 for difference). Differences in SI-UC in LVH did not vary significantly by C- or H-clinic grouping.
Systolic blood pressure, mm Hg
Criteria for electrocardiographic left ventricular hypertrophy (versus CTD) among hypertensive men at 48 months (ie, the was to determine factors associated with the use of HCTZ (versus CTD) among hypertensive men at 48 months (ie, the

**Table 2.** Mean Blood Pressure, Potassium, and Electrocardiographic Changes From Baseline Through 48 mo by Treatment Group for C- and H-Clinics in MRFIT

<table>
<thead>
<tr>
<th>Variable</th>
<th>C-Clinics</th>
<th>SI UC Difference (SE)</th>
<th>H-Clinics</th>
<th>SI UC Difference (SE)</th>
<th>P for Interaction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>−19.7</td>
<td>−9.4</td>
<td>−10.4 (0.4)</td>
<td>−18.1</td>
<td>−9.5</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>−11.5</td>
<td>−5.0</td>
<td>−6.5 (0.3)</td>
<td>−11.3</td>
<td>−6.3</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>−0.42</td>
<td>−0.08</td>
<td>−0.33 (0.02)</td>
<td>−0.31</td>
<td>−0.08</td>
</tr>
</tbody>
</table>

Electrocardiographic measurement

<table>
<thead>
<tr>
<th></th>
<th>SI</th>
<th>UC</th>
<th>SI-UC Difference (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R amplitude aVL, μV</td>
<td>−13.3</td>
<td>7.1</td>
<td>−20.4 (4.6)</td>
</tr>
<tr>
<td>S amplitude Vp, μV</td>
<td>−136.1</td>
<td>−88.7</td>
<td>−47.4 (8.5)</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>0.7</td>
<td>−0.3</td>
<td>1.0 (0.2)</td>
</tr>
</tbody>
</table>

Criteria for electrocardiographic left ventricular hypertrophy

<table>
<thead>
<tr>
<th>Electrocardiographic left ventricular hypertrophy</th>
<th>SI UC Difference (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sokolow-Lyon, μV</td>
<td>−346.3 −252.4 −93.9 (15.1)</td>
</tr>
<tr>
<td>Cornell voltage, μV</td>
<td>−149.5 −81.4 −68.1 (9.6)</td>
</tr>
<tr>
<td>Cornell voltage product, μV/ms</td>
<td>−11.9 −7.4 −4.6 (0.9)</td>
</tr>
<tr>
<td>Left ventricular mass, g</td>
<td>−8.4 −4.1 −4.4 (0.4)</td>
</tr>
</tbody>
</table>

**SI indicates special intervention; UC, usual care; MRFIT, Multiple Risk Factor Intervention Trial; C-clinic, chlorthalidone clinic; H-clinic, hydrochlorothiazide clinic.**

*The P value for interaction assesses whether the SI-UC differences for C- and H-clinics differ significantly from one another.

(Sokolow-Lyon, P=0.35; Cornell voltage, P=0.12; Cornell voltage product, P=0.26; left ventricular mass, P=0.49). Only a small number of participants had a QRS duration ≥120 mm (11 participants at baseline and ≤12 at each annual visit). Exclusion of these participants did not impact the results.

**Individual Participant Analysis With Time-Updated Use of CTD and HCTZ: All SI Hypertensives**

Table 3 summarizes differences between CTD and HCTZ for the individual participant analysis of SI men, it is based on all of the annual follow-up measures of LVH through 48 and 84 months. For comparison, the estimand based on the clinic analysis shown in Table 2 is given in the last column. Similar to the clinic-level analysis, differences in blood pressure and in most measures of LVH significantly favored participants taking CTD. However, for Cornell voltage product, the CTD-HCTZ differences were significant in the opposite direction of the ecological analysis, and no significant difference was observed for the Cornell voltage measure between CTD and HCTZ. In contrast to the clinic analyses, we also found that QRS duration (the multiplicant to convert Cornell voltage to Cornell voltage product) was greater for CTD compared with HCTZ. Unadjusted (no covariate adjustment) estimates of the CTD-HCTZ differences were similar to those in Table 3 (data not shown). Likewise, when the covariate adjustment was expanded to include use of step 2, 3, and 4 drugs, the CTD-HCTZ differences in blood pressure and measures of LVH were similar.

A propensity score analysis that compares CTD and HCTZ for each of the LVH measures at 48 months is summarized in the online Data Supplement (please see http://hyper.ahajournals.org). The first step in this analysis was to determine factors associated with the use of HCTZ (versus CTD) among hypertensive men at 48 months (ie, the propensity for using HCTZ). Older age and use of antihypertensive treatment at entry were significantly associated with less use of CTD than HCTZ. No factor other than clinic was significantly associated with the use of HCTZ versus CTD. After adjustment of CTD versus HCTZ, differences in blood pressure, and LVH for propensity score, the results for LVH measures were similar to Table 3.

To explore the differences between clinic and individual participant analyses for Cornell voltage and product, we carried out a subgroup analysis according to the use of antihypertensive treatment at entry, the most important predictor of using CTD in the propensity score analyses. For the individual participant analyses, interaction P values were 0.22 for Cornell voltage and 0.29 for Cornell voltage product; for the clinic analyses, the interaction P values were 0.16 for Cornell voltage and 0.20 for Cornell voltage product.

Blood pressure reductions in the SI group with hypertension at entry were associated with decreases in each of the LVH measures (P<0.001 for each measure). The association of blood pressure change with LVH change was similar for SI participants in C- and H-clinics and for UC participants.

**Discussion**

The presence of LVH in MRFIT has been independently associated with an increased risk of cardiovascular death.13–15 Our primary analysis found that SI-UC differences in continuous measures of electrocardiographic LVH were of greater magnitude in C-clinics than in H-clinics, suggesting a differential benefit in favor of treatment with CTD compared with HCTZ. When examined at the individual participant level, those receiving CTD also had less LVH, as assessed by Sokolow-Lyon and left ventricular mass criteria, than those receiving HCTZ. These findings occurred when both CTD and HCTZ were widely used through 48 months and persisted after participants were switched to CTD through long-term
ever, unlike the individual participant analysis, confounding
grouping (ie, not all SI participants in the C-clinics were
H-clinics and the potential for misclassification within clinic
noted. Diuretic assignment in MRFIT was not randomized,
between regimens occurring over an entire 24-hour period.

Importantly, office blood pressure measure-
differences for CTD versus HCTZ observed at the individual
participant level. Differences were also consistent with
UC groups was 1.7 mm Hg greater in participants of C-clinics
than H-clinics; these differences were also consistent with
LVH.13 It is possible that the differences in LVH
reductions in blood pressure were associated with a reduced
incidence of LVH.13 It is possible that the differences in LVH
were used in MRFIT than what are currently used. Given
hypertensive men were affected differently by use of CTD
were used in MRFIT than what are currently used. Given
established potency differences between the 2 agents, it is not
possible that the differences in LVH between CTD and HCTZ
may have occurred as a consequence of improved blood pressure control in participants
receiving CTD compared with HCTZ. The change in systolic
blood pressure from baseline to 48 months between SI and
UC groups was 1.7 mm Hg greater in participants of C-clinics
than H-clinics; these differences were also consistent with
differences for CTD versus HCTZ observed at the individual
participant level. Importantly, office blood pressure measure-
ments were taken in MRFIT during daytime hours and may not
have reflected potentially larger blood pressure differences
between regimens occurring over an entire 24-hour period.

Several limitations typical of post hoc analyses should be
noted. Diuretic assignment in MRFIT was not randomized,
leading to heterogeneity of diuretic use within the C-
and H-clinics and the potential for misclassification within clinic
grouping (ie, not all SI participants in the C-clinics were
treated for hypertension, and some received HCTZ). How-
ever, unlike the individual participant analysis, confounding
within the clinic designation is protected by overall random-
ization to SI or UC group. The results of the ecological
analysis are further strengthened by the absence of differ-
ences in LVH between SI and UC groups in the analysis of
men normotensive at entry, which supports the notion that
hypertensive men were affected differently by use of CTD
versus HCTZ. Second, higher doses of both CTD and HCTZ
were used in MRFIT than what are currently used. Given
established potency differences between the 2 agents, it is not
clear whether the lower doses of CTD and HCTZ in common
use today would give similar results. Third, LVH was
assessed using electrocardiography rather than by echocardi-
ography or MRI. Although these newer methods of cardiac
imaging may be more sensitive, electrocardiographically
determined LVH remains an established predictor of cardio-
vascular disease risk in both MRFIT and elsewhere.8,9,12–15

Lastly, the findings for Cornell voltage and product in the
individual participant analysis were not consistent with those
of the ecological (clinic-level) analysis. We conducted sen-
sitivity analyses of the individual components of the Cornell
LVH measures and observed that the discrepancy may result,
in part, from a significant increase in QRS duration found in
individual participant analysis were not consistent with those
of the ecological (clinic-level) analysis. We conducted sen-
sitivity analyses of the individual components of the Cornell
LVH measures and observed that the discrepancy may result,
in part, from a significant increase in QRS duration found in
individual participant analyses but not in clinic analyses. We
also assessed whether the CTD and HCTZ differences varied
by use of antihypertensive treatment at entry, and the evi-
dence for subgroup heterogeneity was weak.

### Table 3. Mean Differences in Blood Pressure, Potassium, and Electrocardiographic LVH Through 48 and 84 mo for Individual SI Participants Who Were Hypertensive at Baseline and Comparison With Differences Between C- and H-Clinic SI-UC Differences Through 48 mo

<table>
<thead>
<tr>
<th>Variable</th>
<th>Through 48 mo</th>
<th>Through 84 mo</th>
<th>SI-UC Difference for C- vs H-Clinics (Through 48 Mo)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C-H Difference*</td>
<td>95% CI</td>
<td>P</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>−1.6</td>
<td>−2.1, −1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>−0.7</td>
<td>−1.0, −0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>−0.23</td>
<td>−0.3, −0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure, mm Hg</strong></td>
<td><strong>−0.7</strong></td>
<td><strong>−1.0, −0.4</strong></td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td><strong>Potassium, mmol/L</strong></td>
<td><strong>−0.23</strong></td>
<td><strong>−0.3, −0.2</strong></td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td><strong>Through 48 mo</strong></td>
<td><strong>−1.7</strong></td>
<td><strong>−2.1, −1.3</strong></td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td><strong>Through 84 mo</strong></td>
<td><strong>−1.4</strong></td>
<td><strong>−1.9, −0.9</strong></td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td><strong>SI-UC Difference for C- vs H-Clinics (Through 48 Mo)</strong></td>
<td><strong>−0.8</strong></td>
<td><strong>−1.8, 0.2</strong></td>
<td><strong>&lt;0.001</strong></td>
</tr>
</tbody>
</table>

SI indicates special intervention; UC, usual care; MRFIT, Multiple Risk Factor Intervention Trial; C-clinic, chlorthalidone clinic; H-clinic, hydrochlorothiazide clinic; LVH, left ventricular hypertrophy.

*Data show change in systolic and diastolic blood pressures adjusted for baseline blood pressure level and for age, race, and baseline serum cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, antihypertensive use, glucose, creatinine, potassium, proteinuria, uric acid, drinks per week, body mass index, and smoking status. Change in electrocardiographic level adjusted for baseline electrocardiographic level and for age, race, and baseline systolic blood pressure, LVH, left ventricular hypertrophy.

†Data were adjusted for baseline level only.

(84 months) follow-up. Our analyses offer new insight into
the recent report from MRFIT concluding that CTD is more
effective at reducing cardiovascular events than HCTZ.24

Our study results are consistent with earlier reports from
MRFIT that have shown that overall LVH incidence was
lower in the SI compared with the UC group and that
reductions in blood pressure were associated with a reduced
incidence of LVH.11 It is possible that the differences in LVH
between CTD and HCTZ may have occurred as a conse-
quence of improved blood pressure control in participants
receiving CTD compared with HCTZ. The change in systolic
blood pressure from baseline to 48 months between SI and
UC groups was 1.7 mm Hg greater in participants of C-clinics
than H-clinics; these differences were also consistent with
differences for CTD versus HCTZ observed at the individual
participant level. Importantly, office blood pressure measure-
ments were taken in MRFIT during daytime hours and may not
have reflected potentially larger blood pressure differences
between regimens occurring over an entire 24-hour period.

Several limitations typical of post hoc analyses should be
noted. Diuretic assignment in MRFIT was not randomized,
leading to heterogeneity of diuretic use within the C-
and H-clinics and the potential for misclassification within clinic
grouping (ie, not all SI participants in the C-clinics were
treated for hypertension, and some received HCTZ). How-
ever, unlike the individual participant analysis, confounding
within the clinic designation is protected by overall random-
ization to SI or UC group. The results of the ecological
analysis are further strengthened by the absence of differ-
ences in LVH between SI and UC groups in the analysis of
men normotensive at entry, which supports the notion that
hypertensive men were affected differently by use of CTD
versus HCTZ. Second, higher doses of both CTD and HCTZ
were used in MRFIT than what are currently used. Given
established potency differences between the 2 agents, it is not
clear whether the lower doses of CTD and HCTZ in common
use today would give similar results. Third, LVH was
assessed using electrocardiography rather than by echocardi-
ography or MRI. Although these newer methods of cardiac
imaging may be more sensitive, electrocardiographically
determined LVH remains an established predictor of cardio-
vascular disease risk in both MRFIT and elsewhere.8,9,12–15

Lastly, the findings for Cornell voltage and product in the
individual participant analysis were not consistent with those
of the ecological (clinic-level) analysis. We conducted sen-
sitivity analyses of the individual components of the Cornell
LVH measures and observed that the discrepancy may result,
in part, from a significant increase in QRS duration found in
individual participant analyses but not in clinic analyses. We
also assessed whether the CTD and HCTZ differences varied
by use of antihypertensive treatment at entry, and the evi-
dence for subgroup heterogeneity was weak.
Perspectives
Previous MRFIT reports have documented a lower incidence of LVH for SI compared to UC men, but these analyses did not assess possible differences related to use of CTD versus HCTZ. In ecological analyses, we found that SI-UC differences in electrocardiographically defined continuous measures of LVH were of greater magnitude in clinics with high use of CTD compared with those where HCTZ predominated. At the individual participant level for all of the SI hypertensives, both Sokolow–Lyon and left ventricular mass measures were also lower in users of CTD compared with HCTZ. Given the strong association between LVH and blood pressure, our findings suggest that differences in blood pressure lowering may explain the variation in mortality observed between CTD and HCTZ in MRFIT and also underscore the need for a randomized clinical outcome trial comparing the 2 agents.

Acknowledgments
We express appreciation to the MRFIT study participants and the many investigators who contributed to the design and conduct of the study.

Sources of Funding
The Multiple Risk Factor Intervention Trial was supported by a contract and grants from the National Heart, Lung, and Blood Institute. This funding included R01-HL68140.

Disclosures
None.

References
17. Molloy TJ, Okin PM, Devereux RB, Kligfield P. Electrocardiographic detection of left ventricular hypertrophy by the simple QRS voltage-duration product. J Am Coll Cardiol. 1992;20:1180–1186.
Long-Term Effects of Chlorthalidone Versus Hydrochlorothiazide on Electrocardiographic Left Ventricular Hypertrophy in the Multiple Risk Factor Intervention Trial


Hypertension. published online October 24, 2011;

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/early/2011/10/24/HYPERTENSIONAHA.111.181248

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2011/10/25/HYPERTENSIONAHA.111.181248.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/
LONG-TERM EFFECTS OF CHLORTHALIDONE VS HYDROCHLOROTHIAZIDE ON ELECTROCARDIOGRAPHIC LEFT VENTRICULAR HYPERTROPHY IN THE MULTIPLE RISK FACTOR INTERVENTION TRIAL

Michael E. Ernst, PharmD; James D. Neaton, PhD; Richard H. Grimm, Jr, MD, PhD; Gary Collins, MS; William Thomas, PhD; Elsayed Z. Soliman, MD, MSc, MS; Ronald J. Prineas, MD, PhD; for the MRFIT Research Group

Online Supplement
**S1.** Logistic regression of being on chlorthalidone at month 48 on selected baseline variables, adjusted for clinic for SI hypertensive participants on chlorthalidone or hydrochlorothiazide at month 48.

<table>
<thead>
<tr>
<th>Baseline Variables</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (5 year difference)</td>
<td>0.91 (0.84, 0.99)</td>
<td>.03</td>
</tr>
<tr>
<td>Black race</td>
<td>1.04 (0.76, 1.43)</td>
<td>.82</td>
</tr>
<tr>
<td>Body mass index (4 kg/m$^2$ difference)</td>
<td>1.01 (0.90, 1.12)</td>
<td>.91</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.92 (0.75, 1.14)</td>
<td>.45</td>
</tr>
<tr>
<td>Diastolic blood pressure (25 mmHg difference)</td>
<td>1.25 (0.80, 1.95)</td>
<td>.34</td>
</tr>
<tr>
<td>Systolic blood pressure (50 mmHg difference)</td>
<td>1.28 (0.80, 2.06)</td>
<td>.30</td>
</tr>
<tr>
<td>On antihypertensive meds</td>
<td>0.76 (0.61, 0.95)</td>
<td>.02</td>
</tr>
<tr>
<td>Glucose (20 mg/dl difference)</td>
<td>1.05 (0.92, 1.19)</td>
<td>.48</td>
</tr>
<tr>
<td>Creatinine (0.2 mg/dl difference)</td>
<td>0.96 (0.85, 1.09)</td>
<td>.54</td>
</tr>
<tr>
<td>Potassium (mg/dl)</td>
<td>0.85 (0.68, 1.05)</td>
<td>.12</td>
</tr>
<tr>
<td>Proteinuria (+1 or greater)</td>
<td>0.71 (0.46, 1.11)</td>
<td>.14</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>1.04 (0.97, 1.12)</td>
<td>.25</td>
</tr>
<tr>
<td>Drinks per week (7 drink difference)</td>
<td>1.02 (0.96, 1.07)</td>
<td>.59</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>0.88 (0.76, 1.02)</td>
<td>.08</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.05 (0.96, 1.15)</td>
<td>.25</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.99 (0.86, 1.15)</td>
<td>.93</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.05 (0.92, 1.20)</td>
<td>.46</td>
</tr>
</tbody>
</table>
S2. Mean differences in blood pressure, potassium, and electrocardiographic LVH through 48 and 84 months, adjusted for propensity score with stratification by site for SI participants who were hypertensive at baseline.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Through 48 Months</th>
<th>Through 84 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C-H difference</td>
<td>95% CI</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>-1.7</td>
<td>-2.3, -1.2</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>-0.7</td>
<td>-1.1, -0.4</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>-0.23</td>
<td>-0.25, -0.21</td>
</tr>
</tbody>
</table>

**Electrocardiographic Measurement**

| Absolute maximum of R amplitude V5,6 (μV) | -24.8 | -38.3, -11.2 | < .001 | -8.2 | -17.8, 1.4 | .09 |
| Absolute S amplitude V1 (μV)            | -12.7 | -25.1, -0.3  | .05    | -16.2 | -25.5, -6.9 | < .001 |
| R amplitude aVL (μV)                    | 4.3   | -2.2, 10.8   | .20    | 3.3   | -1.4, 8.0   | .17 |
| Absolute S amplitude V3 (μV)            | 0.1   | -10.9, 11.2  | .98    | -5.1  | -12.9, 2.8  | .21 |
| QRS duration (ms)                       | 1.0   | 0.6, 1.3     | < .001 | 0.9   | 0.6, 1.1    | < .001 |

**Criteria for Electrocardiographic Left Ventricular Hypertrophy**

<p>| Sokolow-Lyon (μV)                      | -38.8 | -57.9, -19.7 | &lt; .001 | -26.8 | -40.6, -12.9 | &lt; .001 |</p>
<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>95% CI</th>
<th>SD</th>
<th>95% CI</th>
<th>Mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cornell voltage (µV)</td>
<td>3.7</td>
<td>-8.8, 16.3</td>
<td>.56</td>
<td>-1.3</td>
<td>-10.3, 7.8</td>
<td>.78</td>
</tr>
<tr>
<td>Cornell voltage product</td>
<td>1.7</td>
<td>0.5, 3.0</td>
<td>.008</td>
<td>1.3</td>
<td>0.3, 2.2</td>
<td>.008</td>
</tr>
<tr>
<td>(µV/ms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular mass</td>
<td>-0.6</td>
<td>-1.0, -0.1</td>
<td>.02</td>
<td>-0.5</td>
<td>-0.8, -0.2</td>
<td>.003</td>
</tr>
<tr>
<td>(gm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for baseline level and propensity score

Formulas:

- Sokolow-Lyon voltage (µV) = |SV₁| + max |RV₅/V₆|
- Cornell voltage (µV) = SV₃ + RaVL
- Cornell voltage product (µV/ms) = Cornell voltage * QRS duration
- Left ventricular mass (white men): 0.023 Cornell voltage + 0.010 Sokolow-Lyon + 1.32 weight + 10.6
- Left ventricular mass (black men): 0.0018 Cornell voltage + 0.51 JV₅ + 1.45 weight + 17.4