Unexpected effects of treating hypertension in men with electrocardiographic abnormalities: a critical analysis

LEWIS H. KULLER, M.D., DR. P.H., STEPHEN B. HULLEY, M.D., M.P.H., JEROME D. COHEN, M.D., AND JAMES NEATON, PH.D.

ABSTRACT The relationship between diuretic therapy and possible increased risk of coronary heart disease (CHD), especially sudden death, is controversial. The initial report from the Multiple Risk Factor Intervention Trial (MRFIT) raised the possibility that the increased CHD mortality observed in a subset of special intervention men with hypertension and certain electrocardiographic abnormalities on their baseline examination might be an unexpected adverse effect of diuretic therapy. Subsequent reports from the MRFIT have revealed a stronger association of CHD mortality to hydrochlorothiazide than to chlorthalidone. There was no consistent relationship of CHD mortality to the dose of either drug, to the most recent serum potassium level, or to the presence of ventricular premature beats. Unfavorable trends of the same magnitude were also seen among similar white men in the Hypertension Detection and Follow-up Program and in the Oslo hypertension trial, although the sample sizes in these two studies were too small to yield clearcut conclusions. Clinical studies have shown an increased risk of CHD death among hypertensive men with left ventricular hypertrophy. Such men are also noted to have a higher frequency of ventricular premature beats, even in the absence of diuretic therapy. Other studies have shown that diuretic-induced hypokalemia is accentuated in the presence of epinephrine and that low potassium levels decrease the threshold for ventricular fibrillation. Thus, although the evidence is still incomplete, it is possible that the excess CHD mortality among MRFIT special intervention men with electrocardiographic abnormalities may have been caused by a combination of increased left ventricular mass in the presence of coronary atherosclerosis, and hypokalemia caused by good compliance with diuretic therapy and accentuated by stress-induced increases in circulating catecholamines. Given the very large population of patients receiving diuretic therapy, further evaluation of this possibility is important.


THE INITIAL RESULTS of the Multiple Risk Factor Intervention Trial (MRFIT) were published in September 1982 and showed a nonsignificant 7.1% difference in coronary heart disease (CHD) mortality between special intervention (SI) and usual care (UC) groups. Three possible explanations were suggested for the failure to achieve a significant reduction in CHD mortality in the SI group as compared with the UC group:

1. The overall intervention program under the circumstances of the Trial did not affect CHD mortality.
2. The intervention used does affect CHD mortality but the benefit was not observed in this Trial of seven years average duration with lower than expected mortality and with considerable risk factor change in the UC group.
3. Measures to reduce cigarette smoking and lower blood cholesterol may have reduced CHD mortality within subgroups of the SI cohort with a possible unfavorable response to antihypertensive drug therapy in certain but not all hypertensive subjects."

This last possibility, which was considered in need of further investigation, was based on the observation that approximately 30% of the MRFIT participants were hypertensive and had resting abnormalities on their baseline electrocardiograms (ECGs). There were 36 (29.2/1000) CHD deaths in the SI group and 21 (17.7/1000) in the UC group, a 65% excess in the SI group. "

The 1984 report of the Joint National Commission on Detection, Evaluation and Treatment of High Blood
Pressure noted that the controversy remains about whether all patients with diastolic blood pressure between 90–94 mm Hg should receive pharmacological therapy if nonpharmacologic measures do not control blood pressure adequately. One of the concerns about drug therapy is the potential for long-term adverse effects that could minimize or negate the salutary short-term effects that have been demonstrated. The MRFIT did not alter mortality rates in SI hypertensive men when compared with the UC men, and this may be due to the adverse effect observed in the subgroup of SI men with abnormal baseline resting ECGs.

In this article the unexpected outcome of antihypertensive drug therapy in the MRFIT will be further evaluated by examining the subgroup findings in more detail, by comparing the MRFIT results with those of the Hypertension Detection and Follow-up Program (HDFP), and by reviewing other information related to this issue.

The MRFIT results

In January 1985, a more detailed analysis of the relationship between baseline resting ECG abnormalities, antihypertensive treatment, and mortality in the MRFIT trial was published and summarized as follows: (1) The most common baseline resting ECG abnormalities were high R waves and nonspecific ST-T wave changes. (2) The CHD mortality differential (between the SI and UC groups) was similar in the subgroup with these abnormalities and in a subgroup with other ECG abnormalities at rest. (3) The apparent excess CHD mortality among hypertensive SI men with ECG abnormalities at rest was manifested chiefly as sudden death within 1 hr. (4) The association between resting baseline ECG abnormalities and CHD mortality among hypertensive men was independent of the baseline level of blood pressure or the results of the exercise ECG. (5) A possible explanation for the SI-UC difference in CHD mortality was an unexpected low UC mortality rate in men with baseline resting ECG abnormalities.

The lower than expected mortality in the UC group cannot be the entire explanation, however, because regression analysis within the SI group revealed an interaction between the ECG abnormalities and diuretic treatment. The risk of CHD death for men receiving diuretic drugs, relative to men not receiving diuretic drugs, was estimated at 3.32 among men with baseline resting ECG abnormalities, and 0.95 among men without such abnormalities (table 1). No such effect was found in the UC men, perhaps because they took lower doses of diuretics or different diuretics than SI men.

### Table 1

<table>
<thead>
<tr>
<th>ECG abnormalities</th>
<th>Nonhypertensive at entry</th>
<th>Hypertensive at entry</th>
<th>All men</th>
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<tbody>
<tr>
<td>Absent</td>
<td>1.08</td>
<td>0.80</td>
<td>0.95</td>
</tr>
<tr>
<td>Present</td>
<td>2.49</td>
<td>6.66&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.32&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>p < .01.

### Serum potassium and magnesium.

Sherwin evaluated the relationship between serum potassium and CHD mortality. A larger proportion of SI men were treated with antihypertensive drugs and larger doses of diuretics were used in the SI group. The serum potassium levels were lower in SI men than in UC men and three times as many SI as UC men had serum potassium levels of 3.5 meq/dl or less. However, SI participants who died of CHD had higher average serum potassium levels at their last visit to the clinic before death when compared with surviving participants at comparable visits.

Low serum magnesium levels had also been suggested as a potential risk for CHD death among thiazide diuretic users. Serum magnesium was not routinely measured during the trial; however, during the latter years of the trial, serum magnesium levels were measured among SI participants only in two clinics. SI participants receiving diuretics had lower average magnesium levels and a higher percentage (15%) at lower levels of 1.8 mg/dl or less than SI participants not receiving diuretics.

### Arrhythmias.

The incidence of ventricular premature beats (VPBs) was greater in hypertensive SI men than among comparable UC men. The increased risk of VPBs in SI participants was independent of the presence of resting ECG abnormalities at baseline. The risk of developing VPBs was approximately 20% higher among diuretic users in both the SI and UC groups. There was, however, no significant relationship between change in serum potassium level from baseline and the incidence of VPBs.

### Hydrochlorothiazide vs chlorothalidone.

Bartsch et al. recently reported that when the 22 MRFIT clinics were divided into tertiles by frequency of hydrochlorothiazide use as the step 1 diuretic, the odds ratio for SI as compared with UC CHD deaths was 1.39, 1.12, and 0.62 (p = .006) from the highest to the lowest tertile of hydrochlorothiazide use in SI participants. An analysis based on individuals rather than clinic center revealed similar findings: SI participants receiving hydroclo-
rothiazide were estimated to be at a twofold higher risk of CHD death as compared with the SI participants prescribed chlorthalidone (p = .12).

**Nonfatal myocardial infarction.** In addition to the mortality findings discussed above, MRFIT data on nonfatal myocardial infarction are now available. Two blinded measures of nonfatal myocardial infarction were defined: one was based on the annual visit ECG, and the other on a review of hospitalization records. For men who had a myocardial infarction and survived, this myocardial infarction end point is a nearly independent test of a possible subgroup effect. If the SI-UC difference in CHD mortality in relationship to the baseline ECG abnormalities were due to chance alone then we would not expect to find a similar pattern in men with nonfatal myocardial infarction.

Among the MRFIT hypertensive participants without baseline ECG abnormalities, the rate of nonfatal myocardial infarction (excluding those who subsequently died of CHD) was 40/1000 in the SI group and 49/1000 in the UC group, an 18% difference. Among those who had baseline ECG abnormalities, the rates were 51/1000 in the SI group and 50/1000 in the UC group, a 1% difference in the other direction. These findings are consistent with the previously described mortality results, although not of the same magnitude (p = .28 for this contrast in relative risk [SI/UC] estimates). MRFIT hypertensive SI participants with baseline ECG abnormalities did not do as well as those without such ECG abnormalities, compared with their UC counterparts, when considering both for CHD deaths and nonfatal myocardial infarction.

This relatively small subgroup of hypertensive men with ECG abnormalities, approximately 19% of the total MRFIT cohort, appears to have had a major impact on the overall MRFIT results. Exclusion of the hypertensive men with baseline resting ECG abnormalities changes the SI/UC difference in the rate of a first major CHD events (myocardial infarction and/or CHD death) from 8% to 15%, a difference that was very nearly what had been estimated based on the risk factor changes.

**Implications.** The implications of these findings have generated much discussion. There are an estimated 60 million Americans who have elevated blood pressure that increases their risk of illness and premature death. Of these persons, approximately 35 million are believed to need continuing treatment and the remaining 25 million may require some treatment.6

“The Food and Drug Administration Fourth Annual Review of Drug Usage in the Continental United States” noted that among specific drug chemicals in 1982, hydrochlorothiazide ranked first with 78.2 million prescriptions; Dyazide was the number one prescription drug, based on drug store acquisition cost.9

Clearly, if 20 or 30 million people are currently taking thiazide-like diuretic therapy, even a small adverse effect among those with ECG abnormalities could involve large numbers of individuals. On the other hand, diuretics have been the successful cornerstone of effective antihypertensive drug therapy and are probably a major factor in the substantial reduction in hypertension and stroke mortality, congestive heart failure, aneurysm, and kidney disease that has been observed in the United States and several other countries. These considerations make it vitally important to examine evidence from other studies in an effort to decide whether the MRFIT subgroup findings represent chance phenomena or whether they truly represent an adverse effect of this antihypertensive treatment in a subgroup of the hypertensive population.

**Comparison between MRFIT and HDFP**

It is important to note that the comparisons between treatment groups in either the HDFP stepped care (SC) vs referred care (RC) or MRFIT SI vs UC are measures of the effect of differences in the extent of treatment, rather than being a trial of drug therapy compared with no treatment. There was no placebo control group in either study. By the fifth year of the HDFP trial, 75.6% of SC and 56.9% of RC white men were receiving treatment for hypertension,10 whereas in MRFIT at 6 years, 58% of the SI and 47% of the UC were taking antihypertensive drug therapy.1 The lower percentages in MRFIT as compared with HDFP reflected the fact that only about two-thirds of the MRFIT participants were hypertensive at entry to the study.

The MRFIT trial included predominantly white men (93%). The results of the MRFIT trial are therefore compared primarily with similar hypertensive white men in the HDFP trial. There were 1502 SC and 1470 RC white men in the HDFP trial who were in stratum 1; diastolic blood pressure between 90 to 104 mm Hg.10 The 1090 (72.5%) SC and 1063 (72.3%) RC men who were not on antihypertensive medication11 at entry to the trial and were free of specific end organ damage at baseline were considered most comparable to the 4018 SI and 3993 UC MRFIT hypertensive participants. The results of MRFIT are similar whether the 7% black men are included or excluded.

Among these HDFP participants so defined,11 631 (29.3%) of 2153 had baseline resting ECG abnormalities according to MRFIT criteria as compared with
TABLE 2

<table>
<thead>
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<th>ECG abnormalities</th>
<th>Present</th>
<th>Absent</th>
<th>Total</th>
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<tr>
<td></td>
<td>SI (SC)</td>
<td>UC (RC)</td>
<td>SI (SC)</td>
</tr>
<tr>
<td>MRFIT</td>
<td>36</td>
<td>29.2</td>
<td>21</td>
</tr>
<tr>
<td>HDFP</td>
<td>11</td>
<td>35.1</td>
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2418 (30.1%) of the 8011 MRFIT hypertensive participants. The type and frequency of baseline resting ECG abnormalities were similar in both studies.2, 11

Intergroup findings. The CHD mortality rates by presence or absence of baseline resting ECG abnormalities among these defined HDFP and MRFIT participants are shown in table 2.2, 11 In both MRFIT and HDFP, hypertensive participants with baseline resting ECG abnormalities had approximately a 60% higher mortality rate in the intervention groups (SI and SC) than in the comparison groups (RC and UC). Men without resting ECG abnormalities at baseline, on the other hand, had a lower CHD mortality rate in the intervention groups than in the comparison groups (24% in MRFIT and 30% in HDFP). Thus the results with regard to ECG abnormalities and CHD mortality in HDFP and MRFIT are very similar. Furthermore, there are no differences in CHD mortality rates between the intervention and comparison groups for all hypertensive men combined in either MRFIT or HDFP (table 3).

Intragroup findings. One of the major difficulties in interpreting the MRFIT findings has been the low CHD mortality among the UC hypertensive participants with baseline ECG abnormalities. In table 3, the ratio of CHD mortality for those with or without baseline ECG abnormalities is shown for both MRFIT and HDFP participants. It is clear that in both MRFIT and HDFP, SI and SC participants with baseline ECG abnormalities have a substantially higher CHD mortality as compared with those without ECG abnormalities. The HDFP RC men with baseline ECG abnormalities also had a somewhat higher mortality than those without baseline ECG abnormalities. However, among MRFIT UC participants, CHD mortality was slightly lower for those with baseline ECG abnormalities.

The impact of baseline ECG abnormalities remains far greater in the special intervention groups of both studies, and the ratio of this impact (SI or SC to UC or RC) is similar in both studies, that is 1.8 divided by 0.86 in MRFIT (2.15) and 3.41 divided by 1.49 in HDFP (2.29) (table 3). This observation is further substantiated by including all of the race/sex groups in the HDFP. The differences in CHD mortality between those with and without ECG abnormalities was 2.1 times higher in the SC group than in the RC group. Thus the low risk associated with baseline ECG abnormalities in the "control" group compared with the "treated" group does not appear to be unique to MRFIT. The HDFP results are similar.

All-cause mortality. The major differences between the HDFP and MRFIT findings are in the total mortality findings.2, 11 In HDFP all-cause mortality was lower in the SC group than in the RC group irrespective of ECG abnormalities (for those without ECG abnormalities 28.3/1000 in SC vs 38.9/1000 in RC and for those with ECG abnormalities 67.1/1000 in SC and 72.3/1000 in RC). In MRFIT the total mortality was higher in SI men with baseline ECG abnormalities (60.0/1000 in SI vs 39.7/1000 in UC). However, as noted in table 4, the difference in total mortality between MRFIT and HDFP is limited to the noncardiovascular causes of death, i.e., deaths due most likely to cancer, accidents, and infectious diseases, which are less likely to be related to the effects of antihypertensive drug therapy.

Effect of socioeconomic status. A more recent report from the HDFP trial further supports the possibility of a differential effect of antihypertensive treatment by

<table>
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<th>ECG abnormalities</th>
<th>Intervention</th>
<th>Comparison</th>
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<tr>
<td></td>
<td>SI or UC</td>
<td>UC or RC</td>
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TABLE 4
Comparison of total CHD, CVD, and all other deaths between HDFP white men and MRFIT hypertensive subjects by presence or absence of baseline ECG abnormalities

<table>
<thead>
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<th>Cause of death</th>
<th>HDFP Baseline ECG abnormalities</th>
<th>MRFIT Baseline ECG abnormalities</th>
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<tr>
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<td>CHD</td>
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<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
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</tr>
</tbody>
</table>

*Includes CHD, stroke, and other cardiovascular diseases.

race. For those with less than a high school education, the RC mortality was 9% and the SC approximately 7%, whereas for those with a greater than high school education, the mortality was 4.5% in RC and 6.3% in SC. Data classified by sex and race were not provided, but the majority of those with a high school education are most likely white. This group would be similar to most of the MRFIT participants, of whom 84% had a high school education.

The interpretation of these findings from both within MRFIT as well as between MRFIT and HDFP has a certain scientific liability. Neither trial alone provides enough information to differentiate between an unexpected and potentially adverse effect in a specific subgroup and the possibility of a chance observation. Further information from other clinical trials, from observational studies, and from animal experimental investigations are therefore reviewed below.

**Other clinical trials.** The Oslo Study of mild hypertension randomly assigned 785 men, aged 40 to 49 years, to hydrochlorothiazide treatment (50 mg/day) or to a control group and followed them for 5 years. The average difference in blood pressure between the two groups was 17/10 mm Hg (systolic/diastolic). Despite the difference in blood pressure there was no difference in CHD incidence between the treated and control groups. With the MRFIT criteria for ECG abnormalities, 32.8% in the treatment group and 40.6% in the control group had such abnormalities present. Among men without such abnormalities there were 12 coronary events in the treatment group (4.4%) and eight in the control group (3.6%). For men with baseline resting ECG abnormalities there were eight events (6.0%) vs five events (3.2%) in the treatment and control groups, respectively. Thus no benefit in CHD incidence was seen in the treated groups either with or without ECG abnormalities.

In a report by Morgan et al., 172 men with mild hypertension (95 to 109 mm Hg) were randomly assigned to four groups and followed-up for 200 to 2000 days. One group received no treatment, the second was placed on low sodium diets (70 meq/day), the third received chlorthiazide (500 mg/day) without potassium supplementation, and the fourth was treated with propranolol (80 to 320 mg in divided doses). The mortality rates in all treatment groups except one were similar and close to that predicted from life tables for a normal population. The patients who received diuretics had a higher mortality rate, primarily because of a larger number of fatal myocardial infarctions and sudden deaths. There were 13 deaths among the 55 men on thiazides compared with 13 deaths among the 117 in the other three groups combined. Of the 14 deaths due to myocardial infarction, nine were in the thiazide group and only five in the other three groups combined.

Because of the variability in follow-up length and drug exposure, total mortality rates were calculated in terms of deaths per 100,000 person-days at risk (on drugs). These rates were similar for the three groups not receiving thiazide (9.25, 8.00, and 7.66), whereas for the thiazide group the rate was 19.23 deaths per 100,000 person-days at risk. The difference was most striking for those under 60 years old and most of the increased mortality was observed during the first 1000 days on drug therapy. The last known serum potassium level was 4.4 meq/liter for the decedents and there was no difference in serum potassium levels between the survivors and decedents. The authors concluded that "the possibility must exist that thiazide therapy was the factor which influenced the increase in the mortality rate.”

A substudy of the Medical Research Council Mild Hypertension Trial using 24 hr ambulatory ECG monitoring has shown an increase in ventricular arrhythmias when comparing thiazide to a placebo con-

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In patients studied for at least 6 months, the prevalence of daytime and night time ventricular ectopic beats greater than five per hour was 32% and 23% in patients on bendrofluazide 5 mg bid as compared with 20% and 9% in the placebo group. The incidence of ventricular ectopic beats was positively correlated with age (p ≤ .001) and inversely with the serum potassium levels (p = .04). No data related to end points and ECG abnormalities have yet been presented from this study.

Possible mechanisms for mortality results

Studies of left ventricular hypertrophy. Clinical, epidemiologic, and animal experimental studies provide further evidence for a possible relationship between diuretics, electrocardiographic abnormalities, and CHD mortality, especially sudden death. ECG abnormalities associated with excess mortality in MRFIT and HDFP are frequent among hypertensive patients. They are more prevalent in black than white hypertensive patients, and they are more common among Japanese. They are found very commonly in hypertensive populations in which the frequency of coronary atherosclerosis is relatively low, such as Japanese living in northern Japan or blacks in the West Indies. The ECG abnormalities are probably related to left ventricular hypertrophy or an increase in left ventricular mass. The correlation, however, between the electrocardiographic abnormalities and actual increase in left ventricular mass as measured by echocardiography is not very high.

Left ventricular hypertrophy, whether measured by electrocardiographic criteria, chest x-rays, or echocardiography, is associated with a substantial increased risk of sudden death and heart attack. The presence of left ventricular hypertrophy by ECG criteria was associated with a sixfold increase risk of sudden death in the Framingham Heart Study. Furthermore, autopsy studies have demonstrated that individuals who die suddenly from CHD have greater heart weights than control subjects who died from other causes.

Most sudden cardiac death victims with cardiac hypertrophy, at least in the United States, also probably have significant coronary artery disease. However, patients with myocardial hypertrophy due to nonhypertensive causes, e.g., aortic stenosis, coartation of the aorta, and hypertrophic cardiomyopathy, also have an increased risk of sudden death. In both experimental and clinical studies the relationship between hypertension and left ventricular hypertrophy has been observed to involve more factors than blood pressure level alone. Increases in left ventricular wall thickness and mass develop early in the evolution of the disease and can be made to regress in a relatively short period with some but not all forms of equally potent antihypertensive therapy. In the HDFP and MRFT, treatment of hypertension reduced the risk of the development of left ventricular hypertrophy and resulted in regression of existing left ventricular hypertrophy.

The heterogeneity of cardiac hypertrophy is now well recognized. Recent studies have demonstrated a wide spectrum of variations of hypertensive left ventricular hypertrophy. It is possible that some of the factors that lead to the development of left ventricular hypertrophy among hypertensive patients also may be the same determinants for sudden death or heart attacks among patients on diuretic therapy.

Left ventricular hypertrophy increases the vulnerability to tachyarrhythmias. Messerli et al. conducted 24 hr continuous ambulatory ECG and arterial blood pressure monitoring on 14 normotensive subjects, 10 hypertensive patients without left ventricular hypertrophy, and 16 hypertensive patients with left ventricular hypertrophy by ECG criteria. Patients with left ventricular hypertrophy had significantly more VPBs than both those without left ventricular hypertrophy and normotensive subjects. Five patients with left ventricular hypertrophy had episodes of more than 30 VPBs per minute. None of the patients were being treated with diuretic drugs at the time of the study. It is therefore probable that left ventricular hypertrophy, even in the absence of diuretic therapy, increases the risk of ventricular arrhythmias and this may cause, at least in part, the increased rate of sudden death noted earlier.

Left ventricular hypertrophy has also been associated with a reduction in coronary vascular reserve. Tarazi noted that balance between coronary perfusion pressure and myocardial mass may be of critical importance. A reduction in blood pressure without a concomitant reduction in hypertrophy can upset the balance and thereby reduce coronary reserve.

Studies of hypokalemia. Another possible mechanism for the increased risk of coronary heart disease deaths among hypertensive SI or SC participants with ECG abnormalities in MRFIT or HDFP is a decrease in potassium with resultant cardiac arrhythmias secondary to the use of thiazide-like diuretic drugs. Bigger and Weld have reviewed the relationship between drugs and sudden cardiac deaths. Arrhythmias associated with hypokalemia may be caused in part by enhanced automaticity by increasing both the rate and magnitude of spontaneous phase four depolarization of the His-Purkinje system.
The importance of diuretic-induced hypokalemia has been a much debated topic, especially in recent years. In spite of the lack of solid scientific data for its benefit, potassium supplementation is widely prescribed. Approximately 24 million prescriptions for potassium supplementation and 35 million for potassium sparing diuretics were issued in 1981 according to the National Disease and Therapeutic Index. The average cost of each prescription was $8.00 to $11.00 and estimated total cost was over $250 million. Furthermore, the use of potassium supplementation is increasing. The findings of the MRFIT trial as well as those from other clinical trials have contributed relatively little to our understanding of the value of potassium supplementation on risks of CHD mortality or morbidity. Decreased serum potassium levels among users of diuretics are common in all of these trials, but the relationship between lower potassium levels and subsequent risk of disease is unsubstantiated.

Cooper et al. showed that the incidence of arrhythmias, including ventricular fibrillation, ventricular tachycardia, and frequent ventricular ectopic beats after a myocardial infarction, was inversely related to the initial serum potassium levels. The lower the level of potassium the higher the frequency of complications. Hypokalemia was also significantly more common in patients previously treated with diuretics.

Struthers determined that thiazide diuretics cause the serum potassium level to fall to even lower levels during increased sympathoadrenal activity. They infused epinephrine into six healthy subjects after pretreatment for 7 days with either bendrofluazide (5 mg) or placebo. The bendrofluazide therapy resulted in a fall of serum potassium to 3.4 meq/liter compared with 3.8 meq/liter in the placebo; after infusion of epinephrine the levels were 2.7 vs 3.1 meq/liter. This transient, profound hypokalemia associated with sympathoadrenal activity could increase the risk of ventricular arrhythmias in patients on diuretic therapy and predispose to ventricular tachyarrhythmia and possible sudden death in those with underlying heart disease. Measurement of the resting serum potassium levels, as done in MRFIT and the other clinical trials, may therefore substantially underestimate this potential risk of hypokalemia especially when the last measurement of serum potassium was remote in time from the occurrence of sudden death or myocardial infarction.

Lown has further evaluated the effect of hypokalemia on ventricular arrhythmias in a canine preparation. Ligation of the left anterior descending coronary artery resulted in ischemia and decreased the threshold for ventricular fibrillation from 25 to 12 mA. The presence of hypokalemia in addition to ischemia further reduced the threshold to 7 mA.

Summary of the evidence. The mechanism suggested by these clinical and animal experimental studies could explain the apparent increased CHD mortality among the SI hypertensive MRFIT participants with baseline ECG abnormalities. First, the baseline resting ECG abnormalities are most likely related to changes in left ventricular mass or hypertrophy. Second, the MRFIT participants, who were at above-average risk for CHD at entry, are likely to have had substantial coronary atherosclerosis considering their age and high coronary risk status. Third, the use of diuretics at initial doses of 50 to 100 mg/day plus the excellent compliance among the SI participants resulted in a substantial frequency of hypokalemia. These three factors (increased left ventricular mass, advanced coronary artery disease, and chronic hypokalemia) provide a milieu for even lower serum potassium levels related to stress and catecholamines and thereby predispose to ventricular arrhythmias and sudden death.

These potential adverse effects occur in the context of the substantial benefit of hypertensive therapy in reducing left ventricular hypertrophy and the complications of hypertensive disease. The balance between benefit and risk largely determines the outcomes in clinical trials involving the drug treatment of hypertension. The adverse effects, if present, are probably a function of the duration and intensity of diuretic therapy and its effects on potassium and possibly magnesium. The data are compatible with direct toxic effect.

Future research directions

The major research questions that have emerged from the MRFIT findings are: (1) whether diuretics have an adverse effect on CHD death rates in patients with resting ECG abnormalities (and perhaps in other subpopulations of people with hypertension) and (2) whether hydrochlorothiazide has a less beneficial effect than chlorothalidone on reducing CHD death rates. These questions can be answered in part by analyzing data from existing studies and in part by conducting new investigations.

Further analyses in MRFIT and HDFP. First, and most important, data are needed related to a longer mortality follow-up of both the MRFIT and HDFP cohorts. In both studies, the SC or SI men were referred back to their community physicians at the termination of the trial. Because the apparent adverse effects in both of these trials were predominantly limited to men in SI and SC, we would hypothesize that the excess in CHD morbidity and mortality in those with ECG abnormalities...
ties would gradually disappear with the cessation of the intensive stepped care antihypertensive treatment program after the end of the trial.

With regard to the question of relative effects of different diuretics, most SI men for MRFIT were systematically switched to chlorthalidone before the termination of the trial. There is a need to evaluate the impact of the switch from hydrochlorothiazide to chlorthalidone with a longer mortality follow-up, which is currently underway.

Subgroup analyses in other trials. A second important approach is to carry out similar analysis on data from other large existing trials of antihypertensive treatment. One trial that provides an additional opportunity to test the interaction hypothesis is the Australian Mild Hypertension Study. This study, however, is also not large enough to have a substantial degree of power, particularly in those under age 50. A study with much more power for this purpose is the British Medical Research Council Mild Hypertension Trial. In this trial, men were randomly assigned to receive thiazide, β-blocker, or placebo. The preliminary results of that trial have recently been published. There was a reduction in stroke incidence and mortality. The effect was greater for bendrofluazide than propranolol. Treatment made no difference in the overall rate of coronary events. For fatal coronary events the rate per 1000 patient-years on bendrofluazide was 4.6, propranolol 3.4, and placebo 3.9. These results for white men with regard to total CHD mortality are consistent with both MRFIT and the HDFP trials.

It will obviously be of considerable interest to further evaluate the relationship between ECG abnormalities and outcome in relation to drug therapy and placebo. This analysis will be different than MRFIT or HDFP because the comparison will be between two drugs or placebo. However, the information will still be extremely useful in evaluating the reasons for the apparent ineffectiveness of diuretics in reducing CHD as compared with stroke mortality.

Analyses in observational studies. Another approach to analysis of existing data sets is to examine associations in observational cohort studies. Although such analyses are susceptible to confounding, the results may contribute useful information. One such analysis has recently been reported from the Framingham Study, suggesting a relatively high rate of sudden death in men treated with diuretics relative to men with similar blood pressure levels who were not so treated, regardless of the presence or absence of resting ECG abnormalities. Similar analysis could be undertaken on other existing cohort studies, examining the effects of treatment in the presence or absence of resting ECG abnormalities while controlling for level of blood pressure and other measures of the extent of disease before treatment was undertaken.

The research questions generated by the MRFIT are suitable for study by case-control designs. For example, cases of sudden death defined in the same way as in the MRFIT and drawn from similar populations of men attending hypertension clinics could be compared with age- and blood pressure–matched men attending the same clinics who did not die. The analysis would examine treatment with diuretics and prior ECG abnormalities as predictors of outcome, both separately and combined. This research design would be particularly useful for addressing the important question of the comparative efficacy of different diuretics, e.g., hydrochlorothiazide and chlorthalidone.

Clinical studies of mechanisms. The availability of ambulatory ECG monitoring, echocardiographic measurement of left ventricular mass, and improved techniques for measuring both intracellular as well as extracellular electrolyte levels enhance the ability to do more precise clinical studies. Further studies of the frequency of arrhythmias among patients with echocardiographic evidence of left ventricular hypertrophy with and without diuretic therapy and the specific effects of potassium and/or magnesium or other supplementation will be extremely useful.

Summary

This report has reviewed the published evidence from the MRFIT on the possible adverse effect of antihypertensive treatment in SI men with ECG abnormalities at baseline. This finding is not due solely to an unusually low mortality in comparable UC men because it is present in an analysis within the SI group as well as in the SI/UC contrasts. A similar pattern of findings have been reported from the HDFP trial, and evidence from other clinical studies supports the possibility that patients with left ventricular hypertrophy, advanced atherosclerosis, and chronic diuretic-induced hypokalemia accentuated by circulating catecholamines may be susceptible to arrhythmias and sudden death. Further studies are needed to investigate whether these possible adverse effects of diuretics are real and whether the choice or dose of diuretic drug is an important factor.

The importance of these further studies to better delineate the possible relationships between ECG abnormalities, left ventricular hypertrophy, ischemia, and diuretic therapy stems from the extremely large
number of patients currently on such therapy. The value of specific stepped-care therapy in reducing many of the complications of hypertension, particularly left ventricular hypertrophy, and stroke has been established. On the other hand, there is considerable uncertainty about the ability of antihypertensive therapy to reduce mortality and morbidity specifically by coronary artery disease. The recently reported Medical Research Council Trial does not demonstrate substantial benefits in reducing CHD or total mortality, and the Medical Research Council Working Party concluded that "evidence produced by the trial does not unequivocally support the need to introduce such a policy of active intervention on a national scale and would not justify the costs which would be incurred."

There is a need to evaluate the potential for adverse effects of these drugs among subsets of hypertensive patients. The recent studies reviewed in this report should serve to stimulate a major research effort and to better understand the complications of hypertension and to provide safer and more effective treatment.

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