Observed Benefits of Antihypertensive Drug Treatment
Results of the Trials of Traditional Therapy

Controlled Clinical Trials of Drug Treatment for Hypertension
A Review

Jeffrey A. Cutler, Stephen W. MacMahon, and Curt D. Furberg

We reviewed the designs and major results of 17 large-scale, controlled, clinical trials that reported the effects of drug treatment for hypertension on morbidity or mortality. Seven trials conducted in study populations with more-severe hypertension (diastolic blood pressures 100–120 mm Hg or higher), including the more-severe stratum of the Veterans Administration Trial, showed large reductions in stroke, other "hypertensive" events, and, in one trial, total mortality. Of 11 trials in populations with less-severe hypertension (diastolic blood pressures predominantly below 105 mm Hg), including the less-severe stratum of the Veterans Administration Trial, nine met the criteria for pooling of results. Among the aggregate 43,000 patients in the nine trials who were followed up for an average of 5.6 years, mean diastolic blood pressure reduction was 5.8 mm Hg, and a significant 11% reduction in total mortality was observed. This benefit was largely attributable to a 38% reduction in fatal strokes; nonfatal strokes were similarly reduced. Coronary heart disease mortality was 8% lower in drug treatment than in control groups, but this difference was not significant. A similar result was observed for combined coronary mortality and nonfatal myocardial infarction. A possible explanation for the inconclusive result regarding coronary end points was an adverse trend, observed in several trials, in a subgroup with baseline resting electrocardiographic abnormalities. Because all the trials except the propranolol arm of the Medical Research Council trial used drug regimens based on thiazide-like diuretic agents, and because there are now several new drug classes proposed as initial therapy, additional large-scale clinical trials may need to be considered. (Hypertension 1989;13(suppl I):I-36–I-44)

Three conditions are generally considered necessary to justify a systematic effort by the health care system to detect and treat a risk factor for common and serious diseases such as cardiovascular disease: 1) the risk factor has a high prevalence, 2) the risk factor has a strong association with the disease, and 3) treatment has been shown to be efficacious as well as safe, tolerable, and affordable by society. Other articles in this supplement have summarized the evidence establishing the first two of these conditions for primary hypertension. This article introduces and reviews the principal evidence regarding the efficacy of antihypertensive drug treatment in reducing morbidity and mortality, namely, the evidence from large-scale, long-term, randomized, controlled, clinical trials. The approach is quasihistorical: the earlier trials that dealt predominantly with more-severe hypertension are summarized first, and then the more recent widely debated trials in less-severe hypertension are discussed in greater detail. Except for this crude stratification by level of blood pressure (BP), this review does not address important further questions including whom to treat, what drugs to use, or the balance of benefits and costs (medical and financial). These topics have been previously addressed and are considered further in other contributions to this supplement. A discussion of the relation between baseline electrocardiographic abnormalities and treatment effects is also included.
Trials in More-Severe Hypertension (Diastolic Blood Pressure 100–120+ mm Hg)

The beginnings of randomized, controlled, clinical trials in hypertension can be traced to a double-blind placebo-controlled trial conducted by the Veterans Administration (VA) in hypertensive men of all severity levels and first reported in 1960. This trial was not designed to detect the effects of treatment on morbidity and mortality; rather, the trial apparently served as a pilot study for the landmark VA trial that separately reported the results for severe and less-severe hypertension in 1967 and 1970, respectively. Before the 1967 VA report, two other trials in middle-aged subjects with predominantly severe hypertension were completed by Hamilton et al and by Wolfe and Lindeman; another trial was reported several years afterward by Barratclough et al.

All these trials used a variety of drug classes, including the thiazides, but only the VA trial had a standardized initial regimen (a combination of hydrochlorothiazide, reserpine, and hydralazine). The VA trial was also the only one of the four trials that was double-blind as well as placebo controlled. The Hamilton trial was potentially more subject to bias than the others because alternate allocation rather than randomization was used for assignment to drug treatment or no treatment (without placebo).

Each trial produced a large net reduction of diastolic BP in the treatment group. However, with the modest sample sizes (61–143 participants) and relatively short follow-up periods (only Hamilton’s trial went beyond 18 months), there were neither enough deaths nor coronary heart disease (CHD) events, even in the aggregate, to evaluate the effects of treatment on these end points. Specifically, there were six deaths in treated groups and 10 in the control groups (total from all four trials). Three of the trials also reported “hypertensive” events (strokes, congestive heart failure, dissecting aneurysm, or nephropathy). The results, which indicated substantial benefits (>50%), have been discussed in detail in a previous review.

Three other long-term randomized trials in more-severe hypertension have been conducted in populations differing in major ways from those described above. Carter’s trial in 99 patients with a previous stroke demonstrated a statistically significant 57% reduction in total mortality, largely attributable to fewer recurrent strokes. Treatment in this trial consisted mainly of use of the thiazides and sodium restriction. Sprackling et al reported the results of a trial conducted in 123 very elderly patients (mean age, 81 years) randomized to methyldopa or no treatment. Mortality was very high (90%) in both randomized groups, and survival was not significantly affected by treatment. Finally, Coope and Warrender recently reported the results of another trial in the elderly, aged 60–79 years, with qualifying diastolic BP of 105–120 mm Hg or systolic BP more than 170 mm Hg. Eight hundred eighty-four subjects were randomized to active treatment (with atenolol, bendrofluazide, or both drugs) or no treatment and were followed up for 4.4 years on average. There was a significant reduction in fatal and nonfatal stroke incidence (20 vs. 39); the favorable trends in CHD events and total mortality were not significant.

In summary, seven controlled clinical trials that were designed with various degrees of rigor, that studied a variety of moderately-to-severely hypertensive populations, and that used various treatment regimens showed reductions in hypertensive events, especially stroke. Although there was some suggestion of benefit, there were too few deaths and CHD events to reliably determine moderate treatment effects on these end points.

Trials in Less-Severe Hypertension

Beginning with the initial report on the less-severe stratum of the VA trial, results have been published from nine randomized trials that enrolled subjects with entry diastolic BP as low as 85–95 mm Hg and that also met the following inclusion criteria for this review: 1) the trial objective was to test the effect of BP reduction on morbidity or mortality (i.e., the trial was not limited to comparing active drugs); 2) the focus was on primary prevention, so that most subjects enrolled were free of clinical cardiovascular disease; 3) allocation to treatment groups was by randomization of individual subjects; and 4) data were reported for one or more of the following end points: total mortality, stroke, and major CHD events (CHD death or nonfatal myocardial infarction) by “intention-to-treat” analysis (i.e., with inclusion of events occurring throughout follow-up in all subjects by original randomization group). In the interest of drawing unbiased conclusions and maximizing use of available information from the trials collectively, studies that met the above criteria were not excluded or subgrouped by such features as demographic characteristics of subjects, drug doses, or second-step and subsequent drugs. These subset issues are discussed in a previous report.

Information from the nine trials about study designs, drug regimens, adherence to assigned regimens, and BP results is summarized in Table 1. Other than the VA trial, these trials include the US Public Health Service (PHS) Hospitals Cooperative study, the VA National Heart, Lung, and Blood Institute (VA-NHLBI) Feasibility study, the mild hypertension trial of the Oslo study, the Australian National Blood Pressure (ANBP) study, the trial of the European Working Party on Hypertension in the Elderly (EWPHE), the British Medical Research Council (MRC) trial of treatment of mild hypertension, the Hypertension Detection and Follow-up Program (HDFP), and the hypertensive stratum (entry diastolic BP 90–114 mm Hg or on antihypertensive medication) of the Multiple
### Table 1. Randomized Drug Treatment Trials in Less-Severe Hypertension: Design Features and Protocol Implementation

<table>
<thead>
<tr>
<th>Study, year reported</th>
<th>Number of participants</th>
<th>Study population</th>
<th>Length of follow-up (years)</th>
<th>Design-control(s)</th>
<th>Step 1 drug(s)</th>
<th>DBP effect (mm Hg)</th>
<th>Maximum % crossover</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA, 1970</td>
<td>380</td>
<td>Mean, 52</td>
<td>90-114</td>
<td>3.8</td>
<td>DB-placebo</td>
<td>+HCTZ +RES +HDRZ</td>
<td>104 - 19</td>
</tr>
<tr>
<td>PHS, 1977</td>
<td>389</td>
<td>21-55</td>
<td>90-114</td>
<td>6.5-9.0</td>
<td>DB-placebo</td>
<td>CTZ</td>
<td>99 - 10</td>
</tr>
<tr>
<td>VA-NHLBI, 1978</td>
<td>1,012</td>
<td>21-50</td>
<td>85-105</td>
<td>1.5</td>
<td>DB-placebo</td>
<td>CTLD</td>
<td>93 - 7</td>
</tr>
<tr>
<td>Oslo, 1980</td>
<td>785</td>
<td>40-49</td>
<td>95-109</td>
<td>5.5</td>
<td>Open-untreated</td>
<td>HCTZ</td>
<td>97 - 10</td>
</tr>
<tr>
<td>ANBP, 1980</td>
<td>3,427</td>
<td>30-69</td>
<td>95-109</td>
<td>4.0</td>
<td>SB-placebo</td>
<td>CTZ</td>
<td>100 - 6</td>
</tr>
<tr>
<td>EWPHE, 1985</td>
<td>840</td>
<td>Mean, 72</td>
<td>90-119</td>
<td>4.7</td>
<td>SB-placebo</td>
<td>HCTZ +TMTR</td>
<td>101 - 10</td>
</tr>
<tr>
<td>MRC, 1985</td>
<td>17,354</td>
<td>35-64</td>
<td>90-109</td>
<td>5.5</td>
<td>SB-placebo</td>
<td>BDFZ or PROP</td>
<td>98 - 6</td>
</tr>
<tr>
<td>HDFP, 1979</td>
<td>10,940</td>
<td>30-69</td>
<td>90+</td>
<td>5.0</td>
<td>Open-refined</td>
<td>CLTD</td>
<td>101 - 5</td>
</tr>
<tr>
<td>MRFIT, 1982</td>
<td>8,012</td>
<td>35-57</td>
<td>90-114</td>
<td>7.0</td>
<td>Open-usual</td>
<td>CLTD or HCTZ</td>
<td>96 - 4</td>
</tr>
</tbody>
</table>

**DBP, diastolic blood pressure; VA, Veterans Administration; PHS, US Public Health Service Hospitals Cooperative Study; VA-NHLBI, VA National Heart, Lung, and Blood Institute Feasibility Study; Oslo, Oslo study; ANBP, Australian National Blood Pressure Study; EWPHE, European Working Party on Hypertension in the Elderly; MRC, British Medical Research Council trial; HDFP, Hypertension Detection and Follow-up Program; MRFIT, Multiple Risk Factor Intervention Trial; DB, double-blind; SB, single-blind; HCTZ, hydrochlorothiazide; RES, reserpine; HDRZ, hydralazine; CTZ, chlorothiazide; CTLD, chlorthalidone; TMTR, triamterene; BDFZ, bendrofluazide; and PROP, propranolol.**

Risk Factor Intervention Trial (MRFIT). 21,22 MRFIT is the only one of these trials with additional interventions by design (lipid-lowering diet and smoking cessation), and its exclusion would not materially affect the review findings.

The study populations of these trials ranged in size from 380 in the VA trial to more than 17,000 in the MRC trial. All trials included predominantly young-to-middle-aged adults except for the EWPHE, which enrolled men and women aged 60 years and older. The other trials also admitted subjects of either gender, with the exception of the VA, Oslo, and MRFIT trials. Generally, entry diastolic BP had to be in the 90-114-mm-Hg range. Some subjects of the Oslo trial had isolated systolic hypertension; some in the VA-NHLBI trial had borderline diastolic hypertension. Follow-up periods were generally about 4–7 years.

The three earliest trials had double-blind placebo-controlled designs. Three later studies, the ANBP, EWPHE, and MRC trials, used a single-blind approach with placebo controls. The other three studies had open designs, with the Oslo trial providing monitoring and treatment as necessary for control subjects through the research clinic, while in the HDFP and MRFIT, control subjects were referred at the outset to community sources of care for decisions about management. All trials used a thiazide or a thiazide-like diuretic agent (e.g., hydrochlorothiazide, chlorothiazide, chlorthalidone, or bendrofluazide) as the mainstay of treatment except for the propranolol arm of the MRC trial. (Comparison of the effects of diuretic agents and β-blockers is the subject of the article by Furberg and Cutler in this supplement.) 22 With the use of these drugs, as well as designated “step-up” drugs in most trials, net changes in mean diastolic BP of 4–19 mm Hg were achieved. The mean change in diastolic BP for participants in all trials was 5.8 mm Hg. An additional feature of the implementation of these protocols, which is important for understanding the BP changes and interpreting trial results, is shown in the last two columns of Table 1. In all trials, a substantial proportion of control subjects were receiving active treatment or were of unknown treatment status at the end of follow-up. This proportion ranged from 14% in the VA trial to 58% and 65% in the HDFP and MRFIT, respectively. The high “drop-in” was inherent in the design of the latter studies; the maintenance of substantial diastolic BP differences, nevertheless, was in part due to the relatively low dropout rates from the active treatment groups (22% and 23%). The proportion classified as dropouts or of unknown treatment status in the other seven trials ranged from 1% (Oslo) to 40% (MRC).

Morbidity and mortality data are presented in Figures 1, 2, and 3 for the nine trials individually and collectively (as pooled results). The rationale for combining results was to estimate any effect of treatment as precisely as possible, as well as to provide maximal statistical power to detect an effect of modest size, as there may be for CHD (see MacMahon et al 24 for details). To avoid bias in the estimates, it is important that 1) all relevant trials are included and 2) in each trial, all morbidity events
FIGURE 1. Bar graph showing estimates (×) with approximate 95% confidence intervals (—) of the relative difference in total mortality between intervention and control groups. The numbers in parentheses are the numbers of events (intervention/control). VA, Veterans Administration; PHS, US Public Health Service Hospitals Cooperative Study; VA-NHLBI, VA National Heart, Lung, and Blood Institute Feasibility Study; OSLO, Oslo study; ANBP, Australian National Blood Pressure study; EWPHE, European Working Party on Hypertension in the Elderly; MRC, British Medical Research Council; HDFP, Hypertension Detection and Follow-up Program; and MRFIT, Multiple Risk Factor Intervention Trial.

FIGURE 2. Bar graph showing estimates (×) with approximate 95% confidence intervals (—) of the relative difference in fatal and nonfatal stroke between intervention and control groups. The numbers in parentheses are the numbers of events (intervention/control). See the legend to Figure 1 for explanation of abbreviations.
have been reported. With regard to the first point, we have endeavored to include all published trials meeting the review criteria stated above; we have not sought data from unpublished trials. With regard to the second point, all trials provided data on cause-specific mortality and, with one exception, on nonfatal CHD and stroke by intention to treat. The statistical method for combining results is that of Yusuf et al. This procedure, which ensures that treatment and control subjects are compared only within each trial and not between trials, provides a "typical" odds ratio as the weighted mean estimate of effect, a Z statistic and corresponding \( p \) value, and a 95% confidence interval (CI). Similar statistics are provided for each individual trial; in Figures 1, 2, and 3, the odds ratios are presented as percent differences in risk of end points.

Total mortality was lower in the intervention than in the control groups in six of the nine trials (Figure 1). In one (HDFP), the difference was statistically significant (i.e., the 95% CI does not overlap zero). The finding for this trial population, which was drawn by probability sampling from residential areas, may be the most generalizable to the US population with due consideration of the BP reduction achieved in clinical practice. Also, the estimated relative benefit for the HDFP trial falls within the confidence limits of all other trials. Three trials (VA, ANBP, and HDFP) showed distinctive favorable point estimates of a 17-50% reduction, while four trials (Oslo, EWPHE, MRC, and MRFIT) showed small differences (8% benefit to 4% harm). The two remaining trials reported very few deaths. The pooled results demonstrated a statistically significant 11% reduction in total mortality (95% CI: −19%, −2%).

The results for the incidence of fatal and nonfatal stroke from each trial are shown in Figure 2 except that the EWPHE trial contributed data on fatal strokes only for this intention-to-treat analysis. There were fewer strokes in the group randomized to active treatment in all trials, except for one (VA-
NHLBI) that reported no such events and the MRFIT, in which there was essentially no difference in stroke rates. In three trials, the VA, MRC (nonfatal stroke only), and HDFP, the differences were significant. The pooled estimates from all trials are a 38% reduction in stroke mortality (95% CI: −21%, −55%) and a 36% (±10%) reduction in combined fatal plus nonfatal stroke (data not shown in the figure).

The data for CHD events are presented in Figure 3. Judgments were required regarding inclusion of data from two trials. In the HDFP, nonfatal myocardial infarctions were ascertained by three methods: 1) new pathological Q waves on electrocardiograms recorded at the 2nd and 5th years of follow-up, 2) Rose questionnaire at the same intervals, and 3) an annual query to participants about diagnosed heart attacks. As the last two measures are wholly subjective, we were concerned about bias in this unblinded trial. There was some evidence of overascertainment of nonfatal myocardial infarction (false-positives) when these were included, because the ratio of nonfatal myocardial infarction to fatal CHD was twice as high in the referred-care group compared with control groups in other trials. Therefore, we have included only those myocardial infarctions as ascertained by serial electrocardiogram from the HDFP trial, with the recognition that the rates would be substantially underestimated in both groups but without serious bias (although the proportion with no follow-up electrocardiogram was 6% higher in the referred-care than in the stepped-care group).

The other issue concerns the reporting of cardiac rather than coronary mortality from the EWPHE trial. It is reasonable to assume that the reduction in cardiac mortality in this trial was at least partly due to a reduction in mortality from congestive heart failure. However, because most of the deaths were probably from CHD, we included the EWPHE mortality data in our CHD analysis; however, we excluded nonfatal myocardial infarctions from the EWPHE, as these events were not reported by intention to treat.

The results for CHD death and for nonfatal myocardial infarction from individual trials are similarly distributed on both sides of the zero-difference line, although somewhat more trials show favorable trends for mortality than for nonfatal myocardial infarction (Figure 3). For CHD mortality alone, the pooled estimate is a reduction of 8% (95% CI: −21%, +5%); only the EWPHE trial showed a significant benefit (see the qualification noted above). For fatal and nonfatal CHD combined, the pooled treatment effect is estimated as −9%, a favorable trend, but the 95% CI ranges from −19% to +1%.

Two other drug trials in mild-to-moderate hypertension were not included in the pooled analyses because they did not meet one of the review criteria. The Hypertension-Stroke Cooperative Study26 enrolled only those subjects with a recent clinical history of cerebrovascular disease, so this trial was not focused on primary prevention. In this trial, differences between drug treatment and control groups for stroke, CHD, and total mortality were not significant, although they were in a favorable direction and are quite consistent with our pooled estimates of effect. In Morgan et al’s27 trial, men were allocated to four treatment arms on randomly chosen weeks rather than individually. End-point events, primarily CHD deaths, were few, with more deaths in the combined-drug treatment groups (thiazide or propranolol) than in control groups. This finding was attributed to a significant increase in the thiazide-treated group; mortality was not different between propranolol-treated and control groups.

**Hypotheses Regarding Effects of Treatment on Coronary Heart Disease**

The inconclusive results of the trials with regard to treatment effects on CHD have stimulated much debate and analysis. The article by MacMahon et al28 considers in some detail the question of whether the observed effects of treatment are consistent with those that might reasonably be expected with the achieved reduction in BP. It has been suggested that reliable detection of plausible treatment effects on CHD would have required somewhat larger numbers of patients than were present and randomized, collectively, in the trials. However, the effects of treatment in the trials might actually be less than those expected on the basis of BP reduction alone, as the thiazide diuretic agents are known to produce several metabolic changes that could offset some benefits of BP reduction. Diuretic drugs appear to increase blood cholesterol levels by about 3–5%,28,29; this increase is primarily in low density lipoprotein cholesterol. During these trials, such an effect on blood cholesterol might be expected to increase the risk of CHD by about 6–10%.30 Clearly, this effect alone could substantially offset the potential benefits of BP reduction on CHD, which might have been as great as a 15–20% reduction in risk.

Furthermore, treatment with diuretic agents is known to increase ventricular ectopic activity,31 perhaps due to effects on serum levels of potassium and magnesium, and the possibility that this effect may subsequently produce an excess of sudden CHD deaths has been raised. On the basis of data from the MRFIT, it has been suggested that such an effect of treatment might be greater in those who already have minor abnormalities on the resting electrocardiogram. In that study, treatment with diuretic agents in the special-intervention group was associated with a significantly greater risk of CHD death in those with an abnormal baseline electrocardiogram than in those with a normal electrocardiogram (Table 2). Such nonrandomized comparisons are, of course, potentially subject to bias. However, a similar interaction was also suggested in the randomized comparisons of the special-intervention group and the usual-care control group.
TABLE 3. Mortality From Coronary Heart Disease for Subsets of MRFIT and HDFP Cohorts

<table>
<thead>
<tr>
<th>Electrocardiogram status</th>
<th>MRFIT (hypertensive subjects)</th>
<th>HDFP (&quot;MRFIT-like&quot; subgroup)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Special intervention</td>
<td>Usual care</td>
</tr>
<tr>
<td>Normal</td>
<td>15.8</td>
<td>20.7</td>
</tr>
<tr>
<td></td>
<td>(44)</td>
<td>(58)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>29.2</td>
<td>17.7</td>
</tr>
<tr>
<td></td>
<td>(36)</td>
<td>(21)</td>
</tr>
</tbody>
</table>

*Based on randomized groups and the presence or absence of resting electrocardiographic abnormalities at baseline. Rates are per 1,000 person-years. Other risk factors are age (years), baseline diastolic blood pressure (mm Hg), baseline and annual cigarette smoking (yes/no) and serum cholesterol (mg/dl), adjusted by Cox proportional-hazards model. 
†p<0.01 for the difference between these relative risks.
‡p=0.08 for the difference between the corresponding relative risks.
§p=0.15 for the difference between the corresponding relative risks.
MRFIT, Multiple Risk Factor Intervention Trial.
malties. On this basis, a case may be made for alternate drug and nondrug treatments. There is also a need to consider the feasibility of conducting trials to test whether such alternate treatment strategies can reduce the incidence of CHD.

As impressive as these results are for stroke and total mortality, they are not generally regarded as a mandate to treat pharmacologically all individuals who could have qualified for these trials. There is the important consideration of absolute benefit of treatment, which cannot be easily estimated from trials due to subject selection and to the considerable use of active therapy in control groups. Rather, information is required from more representative populations about the risks of cardiovascular disease at different levels of blood pressure (for details, see Browner and Hulley, this supplement). The application of estimates of likely treatment effects to these morbidity or mortality rates is likely to provide the best estimate of the absolute effects of treatment. Decisions about treatment must also, of course, take into account the costs of treatment and the side effects of antihypertensive drugs. It may be concluded that treatment for hypertension is warranted, principally if the likely benefits of the expected reduction in risks of vascular disease warrant the costs of treatment and outweigh any adverse effects of treatment on the quality of life.

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Lancet 1981;2:539–543


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