Diuretic Agents Versus β-Blockers
Comparison of Effects on Mortality, Stroke, and Coronary Events

Curt D. Furberg and Jeffrey A. Cutler

Three recently concluded large randomized clinical trials have compared the preventive effects of diuretic agents and β-blockers in the treatment of approximately 22,000 subjects with hypertension. In the Medical Research Council trial, bendrofluazide (10 mg daily) was compared with a dose of propranolol (as much as 240 mg daily), a nonselective β-blocker without intrinsic sympathomimetic activity. Two selective β-blockers, atenolol (100 mg daily) and metoprolol (200 mg daily), were compared with bendrofluazide (5–10 mg daily) and hydrochlorothiazide (50–100 mg daily) in the Heart Attack Primary Prevention in Hypertension trial. In the International Prospective Primary Prevention Study in Hypertension, 160 mg of slow-release oxprenolol, a β-blocker with intrinsic sympathomimetic activity, was compared with a diuretic-based regimen not containing β-blockers. In each trial, similar reductions in mean diastolic blood pressure were achieved with diuretic and β-blocker treatment that lasted for several years. All-cause mortality and fatal and nonfatal stroke and coronary event rates were also similar in the treatment groups. Thus, it appears that β-blockers are as effective as diuretic agents in improving survival and in preventing major morbid events. Regarding cigarette smoking and stroke incidence, observations based on post hoc subgroup analyses of the Medical Research Council trial were not supported by subgroup findings in the Heart Attack Primary Prevention in Hypertension and the International Prospective Primary Prevention Study in Hypertension trials, and these observations should not form the basis for any treatment recommendations. (Hypertension 1989;13[suppl I]:I-57–I-61)

In hypertensive subjects, the risk of coronary heart disease (CHD) and stroke increases with elevated diastolic blood pressure (DBP). The benefit of treatment for stroke prevention can almost be predicted by the degree of lowering in DBP. However, the same close relation does not exist between the predicted and observed benefits of DBP reduction in the prevention of fatal CHD or nonfatal myocardial infarction. The apparent benefit is only one third of that expected. One of the proposed explanations for this discrepancy is that the beneficial effect of DBP reduction in the prevention of coronary disease is blunted by the opposing mechanisms of action of the class of drugs most commonly tested, that is, diuretic agents. It has been speculated that other blood pressure–lowering agents that lack the potentially negative effects of diuretic agents on lipids, lipoproteins, and electrolytes (potassium and magnesium) may exert a more favorable effect on the risk of CHD in hypertensive patients. For example, β-adrenergic receptor blockers (β-blockers) have, in postinfarction patients, been shown to convey a so-called cardioprotective effect, presumably mediated by an elevated threshold for ventricular fibrillation, which in turn, reduces the risk of sudden cardiac death. On the other hand, most β-blockers have been shown to increase serum triglycerides and to decrease high density lipoprotein cholesterol levels. A direct comparison of the thiazide diuretic agents and β-blockers in a randomized trial of hypertensive subjects in whom DBP reduction was identical would elucidate any role of the ancillary properties of β-blockers. The purpose of this report is to review the findings of three large randomized trials that compared diuretic agents and β-blockers and to determine whether any consistent differences were observed across the trials with respect to treatment effect on all-cause mortality and on the combined incidence of fatal and nonfatal stroke and coronary events.
Subjects and Methods

The major features of the three trials are listed in Table 1. A randomized double-blind design was used in the International Prospective Primary Prevention Study in Hypertension (IPPPSH) and in the Heart Attack Primary Prevention in Hypertension (HAPPHY) trials; the Medical Research Council (MRC) trial was single-blind. In contrast to the other trials, the MRC trial had a placebo group. However, only the two active treatment groups in the MRC trial are considered here. The MRC and IPPPSH trials enrolled men and women, while the HAPPHY trial was limited to men. The age ranges were similar, with a lower limit of 35 or 40 years and an upper limit of 64 years. The qualifying DBP varied among the trials: 90–109 mm Hg (MRC), 100–130 mm Hg (HAPPHY), and 100–125 mm Hg (IPPPSH). The entry DBP in the MRC trial was defined as the mean of two to four readings on three occasions; the baseline DBP in the HAPPHY trial was the mean of four readings at two visits; in the IPPPSH trial, readings at two of three visits had to be within a predefined range. In the MRC and HAPPHY trials, no patients were receiving any antihypertensive therapy at the time of randomization. Approximately one half of the IPPPSH subjects were receiving antihypertensive drugs at the time of entry into the trial. Patients with severe end-organ manifestations were excluded from participation in all three trials. The target of treatment was to reduce DBP to below 90 mm Hg (MRC) or 95 mm Hg (HAPPHY and IPPPSH). Supplementary treatment was added if the target DBP was not reached. Methyldopa was the main supplement in the MRC trial, hydralazine in the HAPPHY study, and methyldopa and hydralazine in the IPPPSH study. In contrast to the other two trials, diuretic agents were an acceptable supplemental treatment in the β-blocker group of the IPPPSH study. Bendrofluazide (10 mg daily) was evaluated in the MRC trial, and bendrofluazide (5–10 mg daily) or hydrochlorothiazide (50–100 mg daily) were evaluated in the HAPPHY trial. Any diuretic drug, including potassium-sparing agents, was used in the IPPPSH trial. Propranolol (as much as 240 mg daily), a nonselective β-blocker without intrinsic sympathomimetic activity, was tested in the MRC trial; two selective β-blockers were tested in the HAPPHY trial (atenolol [100 mg] or metoprolol [200 mg]); and a nonselective β-blocker with intrinsic sympathomimetic activity (160 mg slow-release oxprenolol) was tested in the IPPPSH trial. Approximately 22,000 patients were randomized into the three trials and were treated for a mean period of 3.1–5.5 years.

All results are presented according to the intention-to-treat principle. An arbitrator, blinded to treatment group assignment, classified the major events in the MRC trial according to World Health Organization criteria. An independent committee classified the major outcome events in the HAPPHY and IPPPSH
TABLE 2. Randomized Treatment Trials in Less Severe Hypertension Comparing Diuretic Agents and β-Blockers: 
Mortality, Stroke, and Coronary Events*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trial</th>
<th>MRC</th>
<th>HAPPHY</th>
<th>IPPPSH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D</td>
<td>BB</td>
<td>D</td>
<td>BB</td>
</tr>
<tr>
<td>Total mortality</td>
<td>6.0</td>
<td>5.5</td>
<td>8.3</td>
<td>7.7</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.8</td>
<td>1.9</td>
<td>3.4</td>
<td>2.6</td>
</tr>
<tr>
<td>Coronary events</td>
<td>5.6</td>
<td>4.8</td>
<td>9.5</td>
<td>10.6</td>
</tr>
</tbody>
</table>

*Rate per 1,000 patient-years.
MRC, Medical Research Council; HAPPHY, Heart Attack Primary Prevention in Hypertension; IPPPSH, International Prospective Primary Prevention Study in Hypertension; D, diuretic therapy; and BB, β-blocker therapy.

Trials. The classification criteria across the trials were similar but not identical. In this review, stroke is defined as the combined incidence of fatal and nonfatal strokes, and coronary events are defined as the combined incidence of CHD including sudden death and nonfatal definite myocardial infarction.

Post hoc subgroup analyses in the MRC trial suggested that the treatment effects were related to smoking status. To elucidate this suggested interaction, the subgroup data by smoking status from the HAPPHY and IPPPSH trials were compared with the MRC observations.

The process of randomization created, as expected in trials of this size, treatment groups that were highly comparable. In this report, therefore, adjustments have not been made for any minor imbalances in risk factors at baseline.

Results

Blood Pressure
The mean baseline DBP were substantially higher in the IPPPSH and HAPPHY trials (108 and 107 mm Hg, respectively) compared with that of the MRC trial (98 mm Hg). With antihypertensive therapy, the mean DBP in all three trials and in the two treatment groups decreased to 90 mm Hg or slightly below that value at the last visit (Table 1). The difference between the diuretic- and β-blocker-treated groups in each trial was within ± 1 mm Hg.

Approximately 40% of the MRC patients were not taking their study drug at the trial conclusion after 5.5 years. About 85% of the HAPPHY trial patients were taking the scheduled treatment at their last clinic visit. In the IPPPSH trial, approximately one quarter of the patients were withdrawn from their double-blind treatment at the trial termination.

All-Cause Mortality
The mortality results expressed as the mortality rate/1,000 patient-years are shown by trial and treatment groups in Table 2. The rates are higher in the IPPPSH and HAPPHY trials than in the MRC trial. The β-blocker-treated patients in all three trials had a slightly lower all-cause mortality than did the diuretic-treated patients. The relative differences of 5–10% are far from significant.

Fatal and Nonfatal Stroke Events
The overall event rate for stroke was also lower in the MRC trial than in the other two trials (Table 2). The observed rate of stroke in the diuretic-treated group compared with the β-blocker–treated group was lower in the MRC trial, higher in the HAPPHY trial, and virtually the same in the IPPPSH trial. Only in the MRC trial did the group difference reach significance (p<0.01).

Fatal and Nonfatal Coronary Events
Coronary events were more common in the HAPPHY and IPPPSH trials than in the MRC trial (Table 2). In the MRC and IPPPSH studies, the rates were slightly lower in the β-blocker groups, approximately 10%. The reverse findings were seen in the HAPPHY study. None of the between-group differences were significant.

Post Hoc Subgroup Analyses
The effect of diuretic drugs and β-blockers on the incidence of stroke and coronary events was examined in post hoc analyses (Table 3). A consistent pattern is the two- to threefold higher rates among smokers compared with nonsmokers, regardless of treatment group. An exception among the 12 comparisons is noted among patients assigned to diuretic therapy in the MRC trial. The stroke rate among smokers appears low and inconsistent with the findings in the HAPPHY and IPPPSH trials. No p values are shown because it is not possible to assign proper significance levels for statistical testing of post hoc analyses. The pattern of the findings across the trials shows no consistency with respect to treatment effect on stroke and coronary events among smokers and nonsmokers.

Discussion
From a methodological viewpoint, comparing two active agents in a single trial is difficult in itself, and attempting such a comparison across trials adds to the complexity. For a drug-to-drug comparison to be fair, optimal doses (efficacy and tolerability) of each agent should be used. Dose–response studies are rare when the outcome of interest is mortality or a major morbid event. Equipoise among individual drugs of a class of agents is rarely known, as
difference in the outcome measures, that is, a lower risk of fatal and nonfatal stroke as well as on all-cause mortality and because most trials evaluated a thiazide, it is reasonable to extrapolate that \( \beta \)-blockers exert similar benefits. However, the \( \beta \)-blockers do not seem to convey an additional cardioprotective effect. To ascertain whether there is such an action, much larger trials of longer duration are required.

Post hoc analyses of subsets of patients enrolled in a trial represent an important step in the generation of new hypotheses for testing. Unfortunately, many investigators go beyond this point and are prepared to issue claims of treatment effects based on post hoc analyses. Regardless of the reason, such practice can be counterproductive or misleading. The methodological issues of post hoc analyses relate to the difficulty of assigning a proper significance level for statistical testing and the problem of multiple testing (i.e., by conducting 100 analyses, five comparisons with \( p<0.05 \) could be expected to occur by chance). Moreover, trials are designed to answer an overall question with reasonable power, so it follows that any subgroup analyses have limited power. It is helpful in the interpretation of intriguing post hoc findings to look for replications. The post hoc findings from the MRC trial for smokers and nonsmokers were not seen in the HAPPHY and IPPPSH trials. Therefore, it is quite possible that the MRC observations are spurious findings resulting from random variability and, therefore, they should not form the basis for treatment recommendations.

**Addendum**

Another report on the comparison of a \( \beta \)-blocker and thiazide diuretic agents in hypertension was published after the submission of our manuscript. The mortality results from the Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) study were published in *JAMA* 1988;259:1976–1982. The 3,234 hypertensive subjects in the MAPHY study comprise the HAPPHY participants randomized to metoprolol and approximately one half of those randomized to the diuretic group. The report revealed several major limitations and raised many
questions (JAMA 1988;260:1713–1716). For example, no good reason for continuing follow-up of the metoprolol component was given, nor a stated hypothesis, power calculations, and information of intended duration of treatment and stopping rules. Several unexplained changes were made, for example, in authorship and the method for survival analysis. The latter may be critical because it is unlikely that the statistical method used in the original study would have yielded significant results in MAPHY. The many methodological limitations include the post hoc selection of the median follow-up time for comparison of treatment group differences. Due to all these deficiencies, we believe that the reported MAPHY results should not form the basis for treatment recommendations.

References

Key Words • prevention • clinical trials • diuretic therapy • β-blockers
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