Metoprolol Versus Thiazide Diuretics in Hypertension
Morbidity Results From the MAPHY Study

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The present study in hypertensive men (40–64 years old) with untreated diastolic blood pressure above 100 mm Hg was aimed at investigating whether metoprolol (n = 1,609) given as initial treatment would lower the risk for coronary events (sudden death and myocardial infarction) more effectively than thiazide diuretics (n = 1,625). A substantial part of this study was the metoprolol arm of the Heart Attack Primary Prevention in Hypertension (HAPPHY) study. The HAPPHY study was a pooling of the effect of different β-blockers, mainly metoprolol and atenolol, in which no favorable effect in relative risk was observed for atenolol as compared with diuretics. In the present study, 255 patients suffered definite coronary events during follow-up; 25% of these events were fatal, 39% were acute myocardial infarctions, and 36% were silent myocardial infarctions. The risk for coronary events was significantly lower in patients on metoprolol than in patients on diuretics (111 versus 144 cases, p = 0.001, corresponding to 143 versus 18.8 cases/1,000 patient years and a relative risk of 0.76 at the end of the trial; 95% confidence interval 0.58–0.98). This difference in risk has potentially important implications for clinical practice because of the large number of hypertensive patients who are at increased risk for coronary events. Because a placebo group, for ethical reasons, could not be included, relative risk can only be expressed in relation to diuretics. There was no difference between the two treatment groups in baseline characteristics, blood pressure during follow-up, or stroke rates. Thus, the difference in risk for coronary events is probably mediated via mechanisms other than blood pressure control. However, present data might suggest that different β-blockers may have different efficacy in preventing coronary events. The reasons for this possibility are as yet unknown. (Hypertension 1991:17:579–588)

Controlled studies with thiazide diuretics in mild-to-moderate hypertension have demonstrated an approximately 40% reduction in strokes as compared with placebo. However, because pooled analyses of all studies performed with thiazide diuretics have only shown a modest 8–10% beneficial effect on coronary events, comparative trials to assess the effects of other antihypertensive drugs are needed. These are of particular interest since the risk for coronary events is much greater than the risk for stroke.1–4

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Data are available from four randomized studies where thiazide diuretics have been compared with four β-blockers: propranolol (nonselective, relatively lipophilic); oxprenolol (nonselective with intrinsic sympathomimetic activity, relatively lipophilic); atenolol (β₁-selective, hydrophilic), and metoprolol (β₂-selective, relatively lipophilic). When the studies were planned, it was postulated that the β-blocker probably had the same effect on stroke as the diuretics and a possible additional effect on coronary events (sudden death and myocardial infarction) by an action that was independent of the reduction in blood pressure.

The present comparison, the Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) study, aimed at analyzing whether metoprolol given as initial antihypertensive treatment would prevent coronary events more effectively than diuretics in men with untreated diastolic blood pressure above 100 mm Hg. The first report from this study showed a significantly lower total mortality for metoprolol than for thiazide diuretics. The main purpose of the present paper is to present the nonfatal coronary events and stroke events observed in the study.

The publication of the mortality report aroused great interest but also critical comment. These latter arose from several issues: first, the results were conceived as a subgroup analysis of the HAPPHY study and second, the results were interpreted as contradicting the results from the Medical Research Council (MRC) and International Prospective Primary Prevention Study in Hypertension (IPPPSH) studies. In addition, the results suggested the possibility that metoprolol and atenolol may differentially affect the risk in hypertensive patients. The present article briefly addresses these issues by presenting the trial design in more detail in the Methods section and by considering the results from the other studies in context in the Discussion section.

Methods

The Original Study—“β-Blockade Versus Saluretics in Hypertension”

Plans were drawn up in 1975 in Gothenburg, Sweden, for a study comparing β-blockade with thiazide diuretic treatment in hypertensive patients. This study entitled “β-Blockers Versus Saluretics in Hypertension” is the parent trial for both the MAPHY study and the HAPPHY study. For reasons of statistical power, it was decided to only include patients at increased risk for coronary events: male patients with untreated diastolic blood pressure at or above 100 mm Hg. Recruitment was aimed at 20,000 patient years with a statistical power of α=0.05 and β=0.90 for the detection of a hypothesized 30% difference in coronary events. When the study was initiated, data existed to show that in hypertensive men with diastolic blood pressure above 100 mm Hg, thiazide diuretics reduced the risk for stroke. For ethical reasons, therefore, a placebo group could not be included. The original protocol from 1976 stipulated that patients should be randomly assigned to treatment with a thiazide diuretic (hydrochlorothiazide or bendroflumethiazide) or one of the two β-blockers metoprolol or propranolol. A fixed therapeutic schedule should be used to reach the treatment goal of diastolic blood pressure less than 95 mm Hg. Propranolol was used in only one center with a total of 88 patients (Table 1). Thus, the study following the original protocol essentially compared metoprolol and thiazide diuretics.

The HAPPHY Study—Pooling of Metoprolol, Propranolol, and Atenolol Data

In 1978, more than 2 years after the first patient was randomly assigned according to the original protocol, atenolol had become available in many countries, and the original protocol was modified to allow for centers that could randomly assign patients to either atenolol or diuretics (Figure 1). After 1981, the joint study was called HAPPHY. Results from 5,569 men covering 20,000 patient years with the pooled data, known as the HAPPHY study, were initially analyzed and published in 1987. The mean follow-up time was considerably shorter in the atenolol part as compared with the metoprolol and propranolol parts (Figure 1, Table 1).

The MAPHY Study

In 1985, it was decided to close the HAPPHY study since the pooled data had accumulated 20,000 patient years. However, follow-up continued at metoprolol centers with the following background. In 1985, the results of the MRC study and the IPPPSH performed in both men and women, were published (Table 1). The results, in the two sexes combined, suggested that β-blocker therapy was not effective in terms of reducing coronary events. However, at that time, and as summarized in the original mortality report from MAPHY, evidence was accumulating to suggest that certain β-blockers had various actions that indicated the potential for antiatherosclerotic and cardioprotective effects. In addition, the long-term postinfarct studies with timolol, propranolol, and metoprolol had produced positive results. Furthermore, there was some evidence in data published in 1985 from MRC and IPPPSH that in men, relative risk was lower on β-blockade as compared with a mainly thiazide diuretic-based schedule (Table 1). However, 60% of those on β-blockade in IPPPSH also received a diuretic, making it hard to compare drug effects in a valid way. Accordingly, it could be considered that the MRC and IPPPSH had failed to yield positive results for a num-
TABLE 1. Blood Pressure Inclusion Criteria, Mean Follow-up Time, and Mortality Rate in the Atenolol and Propranolol Arms of the HAPPHY Study and in the MRC, MAPHY, IPPPSH, and HDFP Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion diastolic BP (mm Hg)</th>
<th>Mean follow-up time (yr)</th>
<th>Mortality rate (deaths/1,000 patient years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol arm, HAPPHY (men only)</td>
<td>100–130</td>
<td>3.0</td>
<td>...</td>
</tr>
<tr>
<td>Randomized to diuretics</td>
<td></td>
<td></td>
<td>5.5</td>
</tr>
<tr>
<td>Randomized to atenolol</td>
<td></td>
<td></td>
<td>6.9</td>
</tr>
<tr>
<td>MRC (men and women)</td>
<td>90–109</td>
<td>4.9</td>
<td>6.0</td>
</tr>
<tr>
<td>Randomized to diuretics</td>
<td></td>
<td></td>
<td>7.5</td>
</tr>
<tr>
<td>Randomized to propranolol</td>
<td></td>
<td></td>
<td>6.7</td>
</tr>
<tr>
<td>MAPHY (men only)</td>
<td>100–130</td>
<td>5.0</td>
<td>...</td>
</tr>
<tr>
<td>Randomized to diuretics</td>
<td></td>
<td></td>
<td>10.3</td>
</tr>
<tr>
<td>Randomized to metoprolol</td>
<td></td>
<td></td>
<td>8.0</td>
</tr>
<tr>
<td>IPPPSH (men and women)</td>
<td>100–125</td>
<td>4.1</td>
<td>8.8</td>
</tr>
<tr>
<td>Randomized to non-β-blocker*</td>
<td></td>
<td></td>
<td>12.7</td>
</tr>
<tr>
<td>Randomized to exprenolol</td>
<td></td>
<td></td>
<td>8.3</td>
</tr>
<tr>
<td>HDFP (white men and women)</td>
<td>90–above</td>
<td>5.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Randomized to referred care</td>
<td></td>
<td></td>
<td>13.5</td>
</tr>
<tr>
<td>Randomized to stepped care</td>
<td></td>
<td></td>
<td>10.9</td>
</tr>
<tr>
<td>Randomized to propranolol</td>
<td></td>
<td></td>
<td>11.5</td>
</tr>
</tbody>
</table>

Studies are presented in increasing value of mortality rate in the male control groups. BP, blood pressure; HAPPHY,7,8 Heart Attack Primary Prevention in Hypertension; MRC, Medical Research Council trial; MAPHY,9 Metoprolol Atherosclerosis Prevention in Hypertensives; IPPPSH,6 International Prospective Primary Prevention Study in Hypertension; HDFP,13 Hypertension Detection and Follow-up Program.

*Mainly diuretics.
†There were only nine deaths in this center, four in patients given diuretics and five in patients given propranolol.8

number of reasons, one of which was that women with a low absolute risk for coronary events had been included and had diluted the results; and also because the number of events in the men was not sufficiently large to allow for a powerful statistical analysis. With this in mind and knowing the animal and postinfarct data,9 it was decided that follow-up should continue at the metoprolol/thiazide diuretic centers. The aim of this follow-up was to obtain additional data regarding the possible cardioprotective benefits of metoprolol.9 No information was available whatsoever about end points in the two treatment groups in HAPPHY when the decision to continue follow-up was made in 1985.9 The study with the extended follow-up was stopped in February 1987. The data showed an increasing use of β-blockade in the diuretic group as the follow-up period lengthened.9 The mortality results covering 16,180 patient years were published as the MAPHY study.9,22,23 This study strictly followed in all parts the original protocol of "β-Blockade Versus Saluretics in Hypertension" as defined in 1976, although the aim of having data on 20,000 patient years was not achieved.

**FIGURE 1. Schematic of design of Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) study9 and Heart Attack Primary Prevention in Hypertension (HAPPHY) study.7,8,10** For reasons of simplicity the single propranolol center has not been illustrated (information on this center is given in Table 1).8 R, randomization.
Main End Points and Classification of End Points

The main end points were total mortality, sudden cardiac death, the pooled incidence of fatal and nonfatal coronary events, and stroke. A classification of all reported fatal and nonfatal symptomatic events was made by the Independent End Point Committee. This classification, the Minnesota coding of electrocardiograms (ECGs) (see below) and data quality were audited by the Independent Data Audit Committee. All cases were judged without any knowledge of actual treatment or of the treatment to which the patients had originally been randomly assigned. Details on the classification of cause-specific mortality have been presented in the mortality reports.9,22,23

Nonfatal Myocardial Infarctions

Acute myocardial infarction. For a diagnosis of an acute myocardial infarction to be confirmed, at least two of the following three criteria were to be fulfilled: central chest pain of more than 15 minutes’ duration, transient elevation of enzymes indicating myocardial necrosis, or typical ECG changes. If myocardial infarction was suspected but only one criterion was fulfilled, the condition was reported as a possible myocardial infarction.

Silent myocardial infarction. A 12-lead resting ECG was recorded at randomization, repeated on a yearly basis, and sent to the administrative center at the Sahlgrenska Hospital, Gothenburg University, for Minnesota coding.24 Altogether 16,987 ECGs were each coded by two independent technicians: 8,575 from patients randomly assigned to metoprolol and 8,412 from patients randomly assigned to diuretics. The occurrence of a new major Q/QS item (Minnesota code 1:1 or 1:2) without other clinical signs of myocardial infarction was defined as a definite silent myocardial infarction. Similarly, a new minor Q/QS item (code 1:3) was defined as a possible silent myocardial infarction.

Nonfatal Stroke

For a diagnosis of nonfatal stroke to be recorded, unequivocal signs of focal or global neurological deficit with sudden onset, which were of a duration greater than 24 hours and were thought to be vascular in origin, were to be present.

Statistical Methods

All data were analyzed according to the original randomized allocation, even if actual treatment deviated from this (intention-to-treat). With the Gehan-Wilcoxon nonparametric test for survival analysis, the null hypothesis was tested (i.e. that there was no difference between the two treatments in risk).25,26 The Gehan-Wilcoxon test does not assume a constant ratio between the hazard functions of the two groups during follow-up and therefore cannot be used to calculate risk ratios and confidence intervals. Even so, in an attempt to quantitatively illustrate the difference between the two treatment regimens in relative risk, crude risk ratios and confidence intervals for relative risk have been given at the median follow-up time (4.2 years) and at the end of the study (10.8 years) for all first definite coronary events and cardiovascular events, using the Fisher statistics.25,26 In patients with an event, patient years have been calculated to the time of the first event, otherwise to the last follow-up date. In a post hoc subgroup analysis, data were analyzed according to smoking status at randomization to allow comparison with data presented from the MRC and IPPPSH reports.5,6 Furthermore, data were analyzed according to the occurrence of resting ECG abnormalities at randomization. The ECG abnormalities were defined as any of the codes 1:1-3 (Q or QS items); 2:1 (left axis deviation); 4:1-3 (S-T changes); 5:1-3 (T wave changes); 7:1 or 7:2 (left or right bundle branch block).

Values of p<0.05 (two-sided tests) were considered significant and all probability values referring to the Gehan-Wilcoxon statistics refer to the total study period until the end of the trial (10.8 years).

Results

Clinical characteristics at randomization and during follow-up were given in the mortality report.9 Baseline characteristics were very similar in the two treatment groups as was blood pressure during follow-up: 142/89 mm Hg in the metoprolol group (n=1,609) and 143/90 mm Hg in the diuretic group (n=1,625).

Definite Coronary Events

Fatal and nonfatal coronary events. Two hundred and fifty-five patients suffered definite coronary events during follow-up: 25% of these events were fatal, 39% were acute myocardial infarctions, and 36% were silent myocardial infarctions. The risk for coronary events was significantly lower in patients on metoprolol than in patients on diuretics (111 versus 144 cases, p=0.001, corresponding to 14.3 versus 18.8 cases/1,000 patient years and a relative risk of 0.76 at the end of the trial; 95% confidence interval 0.58-0.98). The lower risk for coronary events was due to differences in risk both for symptomatic events (sudden death and fatal and nonfatal acute myocardial infarction, p=0.024) as well as for definite silent myocardial infarctions (p=0.016). In one patient in the metoprolol group and three patients in the diuretic group, the first definite coronary event had been preceded by a nonfatal stroke (Table 2).

Nonfatal myocardial infarctions. The incidence of all first definite nonfatal myocardial infarctions was significantly lower in patients on metoprolol than in patients on diuretics (p=0.0034, 10.6 versus 14.3 cases/1,000 patient years at the end of the trial, Table 2).
TABLE 2. All First Definite and Definite Plus Possible Coronary Events and Cardiovascular Events

| Events                  | Metoprolol | Diuretics | | Metoprolol | Diuretics | | All first coronary events | | All first CV events* | |
|-------------------------|------------|-----------|---------------------|------------|-----------|---------------------|---------------------|---------------------|---------------------|
|                         | n          | Rate      | p value†            | n          | Rate      | p value†            | n          | Rate      | p value†            |
| Fatal                   |            |           |                     |            |           |                     |            |           |                     |
| Coronary                | 29         | 3.7       |                      | 35         | 4.6       |                      | 29         | 3.7       | 34*       | 4.5       |
| Stroke                  | ...        | ...       | ...                 | ...        | ...       | ...                 | ...        | ...       | ...                 | ...                 |
| Other CV‡               | ...        | ...       | ...                 | ...        | ...       | ...                 | ...        | ...       | ...                 | ...                 |
| Definite nonfatal       |            |           |                     |            |           |                     |            |           |                     |
| Acute MI§               | 44         | 5.7       |                      | 54         | 7.1       |                      | 44         | 5.7       | 53*       | 7.0       |
| Silent MI§              | 38         | 4.9       |                      | 55         | 7.2       |                      | 37*        | 4.8       | 54*       | 7.1       |
| Acute and silent MI     | 82         | 10.6      | 0.034               | 109        | 14.3      |                      | 82         | 10.6      | 0.034    | 109       |
| Nonfatal stroke         | ...        | ...       | ...                 | ...        | ...       | ...                 | 21         | 2.7       | 18        | 2.4       |
| All definite            | 111        | 14.3      | 0.0010              | 144        | 18.9      |                      | 134        | 17.3      | 0.0099   | 170       |
| Definite and possible   | 157        | 20.5      | 0.0015              | 202        | 27.0      |                      | 178        | 23.3      | 0.0011   | 228       |

Observe that fatal cases preceded by definite nonfatal cardiovascular events have not been given in the table. Cardiovascular events include coronary events, stroke events, and also deaths from other cardiovascular causes. Only one event (the first) counted in each patient. For full information on fatal cardiovascular events see References 9, 22, and 23. CV, cardiovascular; Rate, events/1,000 patient years of follow-up; MI, myocardial infarction. *A nonfatal stroke preceded a definite coronary event in one patient in the metoprolol group and three patients in the diuretic group. †Probability values refer to the difference in risk during the entire study period. ‡For details see Reference 9. §New major Q/QS items (1:1 or 1:2 according to the Minnesota code,24 in annual electrocardiograms). Only silent events (p=0.016) are given in the table (see Methods section for details). Altogether 57 major Q/QS items were coded in the metoprolol group and 73 in the diuretic group (p=0.014).

**Definite Cardiovascular Events**

The incidence of all first definite cardiovascular events was significantly lower in patients on metoprolol than in patients on diuretics (Tables 2 and 3). First stroke events accounted for 16% of these events: 23 cases in the metoprolol group (two fatal and 21 nonfatal) and 25 cases in the diuretic group (seven fatal and 18 nonfatal) (Figure 2). The incidence of all first definite cardiovascular events was significantly lower in patients on metoprolol in both patients with and patients without resting ECG abnormalities present at randomization (ECG changes absent, p=0.008; 16.7 versus 21.8 cases/1,000 patient years at the end of the trial; ECG changes present, p=0.03; 19.4 versus 24.6 cases/1,000 patient years at the end of the trial).

**Subgroup Analysis by Smoking Status at Randomization**

The incidence of all first definite coronary events and also definite cardiovascular events was significantly lower in nonsmoking patients on metoprolol than in nonsmoking patients on diuretics (Figure 3, Table 4). Total and coronary heart disease mortality were significantly lower in smokers on metoprolol than in smokers on diuretics (p=0.012 and p=0.021, respectively). In addition, the risk for fatal and definite nonfatal coronary events combined tended to be lower in smokers on metoprolol, although the difference in risk did not reach the level of formal statistical significance (p=0.09, Table 4).

In the whole study population as well as in subgroups of nonsmokers and smokers, the incidence of all first definite and possible coronary events and also definite and possible cardiovascular events was significantly lower in patients on metoprolol compared with patients on diuretics (Tables 2 and 4).

**Noncardiovascular Deaths**

There were 23 noncardiovascular deaths in the metoprolol group and 26 in the diuretic group. One noncardiovascular death in the metoprolol group and 2 noncardiovascular deaths in the diuretic group.

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**Table 3. Relative Risk (Metoprolol/Diuretics) and Confidence Intervals for Relative Risk for All First Definite Coronary Events and All First Definite Cardiovascular Events at the Median Follow-up Time (4.2 Years) and at the End of the Trial (10.8 Years)**

<table>
<thead>
<tr>
<th>Definite events</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary events</td>
<td>0.38</td>
<td>0.41-0.80</td>
<td>0.76</td>
<td>0.58-0.98</td>
</tr>
<tr>
<td>CV events</td>
<td>0.60</td>
<td>0.44-0.81</td>
<td>0.77</td>
<td>0.61-0.98</td>
</tr>
</tbody>
</table>

Cardiovascular events include coronary events, stroke events, and also deaths from other cardiovascular causes. CV, cardiovascular.
two noncardiovascular deaths in the diuretic group were preceded by definite cardiovascular events.

**Coronary Artery Bypass Surgery**

There were few cases of coronary artery bypass surgery performed during the course of the trial: six in patients on metoprolol and eight in patients on diuretics.

**Discussion**

The results from the present study in white men (40–64 years old) with untreated diastolic blood pressure above 100 mm Hg showed that metoprolol given as initial antihypertensive treatment was associated with a lower risk for coronary events than diuretics. This was due to differences for both symptomatic coronary events as well as silent myocardial infarctions. The data from the Framingham study showed that 38% of all first coronary events among treated hypertensive men were unrecognized or silent, a figure with which our results accord well.

Baseline characteristics, blood pressure during follow-up, and stroke rates were very similar in the two treatment groups. Therefore, the difference in risk is probably due to mechanisms other than blood pressure control. Because a placebo group, for ethical reasons, could not be included, relative risk can only be expressed in relation to diuretics. Thus, relative risk expresses both benefits of ß-blockade as well as any negative effects caused by the diuretics.

There are many possible mechanisms apart from the antihypertensive effect by which a ß-blocker may lower the risk for coronary events. These include cardiac anti-ischemic effects, antiarrhythmic effects, antithrombotic effects, and antiatherosclerotic effects.9-22-27-47 There was no difference between the two treatment groups in serum cholesterol at randomization.9 Serum cholesterol decreased significantly in the metoprolol group during follow-up and was significantly lower (0.17 mmol/l) for metoprolol than for diuretics at the end of follow-up, a finding that might contribute in part to the difference that was observed in coronary

<table>
<thead>
<tr>
<th>Events</th>
<th>Metoprolol</th>
<th>Rate</th>
<th>p value†</th>
<th>Diuretics</th>
<th>Rate</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsmokers*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary</td>
<td>50</td>
<td>9.7</td>
<td>0.0008</td>
<td>80</td>
<td>16.1</td>
<td></td>
</tr>
<tr>
<td>All CV</td>
<td>64</td>
<td>12.5</td>
<td>0.001</td>
<td>94</td>
<td>18.9</td>
<td></td>
</tr>
<tr>
<td>Smokers*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary</td>
<td>84</td>
<td>16.5</td>
<td>0.0072</td>
<td>117</td>
<td>24.0</td>
<td></td>
</tr>
<tr>
<td>All CV</td>
<td>97</td>
<td>19.2</td>
<td>0.0066</td>
<td>131</td>
<td>26.9</td>
<td></td>
</tr>
</tbody>
</table>

Cardiovascular events include coronary events, stroke events, and deaths from other cardiovascular causes. Rate, events/1,000 patient years of follow-up; CV, cardiovascular.

*For definition of nonsmokers and smokers see References 9 and 22. Information on smoking habits was missing in 72 patients, two of whom had a definite nonfatal cardiovascular event.

†Probability values refer to the difference in risk during the entire study period.
events.\textsuperscript{9,22} Even if controlled studies with diuretics have demonstrated irrefutable decreases in the risk for stroke and cardiovascular mortality in the type of patients we studied, it may also be argued that negative effects of diuretic treatment may have adversely affected outcome in individual patients randomly assigned to thiazide diuretics.\textsuperscript{4,48} However, pooled analyses of all studies performed with thiazide diuretics have not given any evidence that thiazide treatment increases the risk for coronary events, in fact a modest 8–10% beneficial effect on coronary events has been observed.\textsuperscript{1}

In a misleading commentary by Moser and Sheps,\textsuperscript{12} it was argued that the mortality in the diuretic-treated patients in MRC, IPPPSH, and also in the Hypertension Detection and Follow-up Program (HDFP) was considerably less than in the MAPHY study. They suggested that an exceptionally high absolute risk in the diuretic group could explain the results of the MAPHY study. As illustrated in Table 1, however, in comparable groups (i.e., in men) both IPPPSH and HDFP showed higher mortality rates. Thus, there is no reason to believe that the MAPHY diuretic-treated male patients by chance\textsuperscript{12} fared badly and represented an extreme sample of the population under investigation and that this would explain the difference in risk between the \( \beta \)-blocker group and the diuretic group.

The HAPPHY study showed no difference in mortality between \( \beta \)-blocker (metoprolol, atenolol, and propranolol pooled) and thiazide diuretic treatment.\textsuperscript{7} Data later published, however, showed a lower mortality in those patients on metoprolol than in those on diuretics and a nonsignificant opposite trend for atenolol, which explains the lack of difference from the pooled data.\textsuperscript{6}

The mean follow-up time was shorter and the overall risk lower in the patients enrolled in the atenolol part of the HAPPHY study as compared with male patients in the other studies performed (Table 1). However, neither the low mortality rate nor the shorter mean follow-up time can explain why atenolol had no positive effect. To partly illustrate this, figures have been given separately for the high risk Finnish centers\textsuperscript{40} and for the other countries in MAPHY in Figure 4. At a similar mortality rate in the diuretic group in the MAPHY study as in the diuretic group in the atenolol part of the HAPPHY study, there was a decrease in relative risk with metoprolol (see Figure 4, data at 842 days in all countries except Finland: 3.4 versus 6.2 deaths/1,000 patient years). Furthermore, at exactly the same mean follow-up time in the MAPHY study as in the atenolol part of the HAPPHY study (3.0 years, Table 1) there were 22 deaths in the group given metoprolol and 41 deaths in that given diuretics,\textsuperscript{9} corresponding to 4.6 versus 8.5 deaths/1,000 patient years (i.e., a decrease in relative risk with metoprolol). This has to be compared with the 33 deaths in the group given atenolol and 26 deaths in the group given diuretics, corresponding to 6.9 versus 5.5 deaths/1,000 patient years (i.e., an opposite trend in relative risk with atenolol).\textsuperscript{8} The reason atenolol did not show data in favor of \( \beta \)-blockade can only be sought in additional studies.\textsuperscript{33,36,45}

Without supporting evidence, no study ought to be judged as definite. Supporting evidence for a cardioprotective effect of \( \beta \)-blockade has been published from a large number of animal experiments.\textsuperscript{31–33,35,36,38,41,43,45–47} Results from two recently published nonrandomized clinical studies indicate a lower risk for coronary events in hypertensive patients on \( \beta \)-blockade than in patients on regimens not including \( \beta \)-blockers.\textsuperscript{50,51} Furthermore, post hoc subgroup analysis from the MRC study showed that the risk for coronary events (fatal and nonfatal) was significantly lower in nonsmoking men given propranolol than in nonsmoking men given placebo.\textsuperscript{52} The coronary event rates in nonsmoking men given placebo and diuretics were very similar. The IPPPSH showed a significantly lower risk for coronary events in male nonsmokers randomly assigned to oxprenolol compared with the men randomly assigned to a non-\( \beta \)-blocker, mainly thiazide diuretic-based, treatment schedule.\textsuperscript{6} The incidence of coronary events was also significantly lower in nonsmoking patients randomly assigned to the \( \beta \)-blocker than in nonsmoking patients randomly assigned to diuretics in the MAPHY study (Figure 3). Results in male nonsmokers are consistent accordingly in three randomized clinical trials
with relatively lipophilic $\beta$-blockers and furthermore are supported by one observational study. $^{30}$

No effect was seen for coronary events in male smokers randomly assigned to $\beta$-blockade in MRC and IPPPSH. $^{5,6}$ In the MAPHY study, on the other hand, total and coronary mortality were significantly lower in male smokers on $\beta$-blockade than in those on diuretics. $^{9,22}$ The possibility that the risk reduction in smokers is due to the fact that metoprolol also is cardioselective has been discussed in a separate paper. $^{22}$ Even so, the mortality risk in the smokers was much higher than in nonsmokers, which emphasizes the importance of measures to help smokers stop smoking. $^{22}$

Is it possible then that similar $\beta$-blockers could have differential effects on therapeutic outcome because there is no "class effect"? $^{32}$ It is of interest that animal studies designed to assist in the understanding of the mode of action of $\beta$-blockade have shown effects on atherogenesis in animals using lipophilic $\beta$-blockers (propranolol and metoprolol) $^{31,32,35,41}$ and reduction in spontaneous ventricular fibrillation with metoprolol but not atenolol. $^{45}$ There is a paucity of data on atherogenesis using the hydrophilic $\beta$-blockers, although this subject has been recently reviewed by Cruickshank. $^{54}$ Furthermore, although intravenous atenolol has been shown to reduce the risk for cardiac rupture in the acute phase of a myocardial infarction, $^{55}$ effects on ventricular fibrillation, asystole, and coronary events are less apparent. $^{55,56}$ Long-term benefits of $\beta$-blockade on sudden death in post-myocardial infarction patients have only been demonstrated for the lipophilic drugs timolol, propranolol, and metoprolol. $^{16-20}$

In conclusion, the present study has shown that it may be preferable to initiate treatment with a $\beta$-blocker rather than a thiazide diuretic in the group of patients studied (i.e., middle-aged, moderately hypertensive men who are at increased absolute risk for coronary events). Because no placebo data are available in the present study, the relative risk can only be judged relative to thiazide diuretics. The relative benefits have been attributed to $\beta_1$-blockade, and evidence has been presented to suggest that the lipophilic $\beta$-blockers are best documented. Among these the choice of a $\beta_1$-selective $\beta$-blocker is suggested since this may be an advantage for the risk reduction in those who smoke. $^{9,22}$ and also in reducing the risk of suffering adverse events. $^{57,58}$ The relevance of these observations to women, older patients, and other ethnic groups is a matter for speculation. There is no reason to believe, however, that the difference in risk between $\beta$-blockade and thiazide diuretics would be less in these other patient groups if they are at increased absolute risk for coronary events. However, available data do not indicate that relative risk would be lower in patients with a low absolute risk for coronary events such as middle-aged white women with uncomplicated hypertension.

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**References**


8. MAPHY and the two arms of HAPPHY (Letters to the Editor). *JAMA* 1989;262:3272-3274


13. Wilhelmsen L, Berglund G, Elmfeldt D, Wedel H: $\beta$-Blockers versus diuretics in hypertensive women: Comparison of total...

14. Veterans Administration Cooperative Study Group on Anti-hypertensive Agents: Effect of treatment on morbidity in hypertension: II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *JAMA* 1970;213:1143–1152

15. Hypertension Detection and Follow-up Program Cooperative Group: Five-Year Findings of the Hypertension Detection and Follow-up Program: II. Mortality by Race-Sex and Age. *JAMA* 1979;242:2572–2577


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