Decreased Coronary Heart Disease in Hypertensive Smokers
Mortality Results From the MAPHY Study

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The present primary prevention study aimed at investigating whether metoprolol given as initial antihypertensive treatment would lower cardiovascular complications of high blood pressure to a greater extent than thiazide diuretics. Patients were randomized to metoprolol (n=1,609, 8,110 patient-years) or a thiazide diuretic (n=1,625, 8,070 patient-years). At randomization, 535 patients in the metoprolol group and 524 patients in the diuretic group were classified as smokers. Blood pressure control during follow-up was equally effective regardless of smoking habits at randomization. Cardiovascular and coronary heart disease mortality was three to four times higher in smokers than in nonsmokers, underlining the importance of smoking as a risk factor. Total and cardiovascular mortality were significantly lower for the metoprolol group than for the thiazide diuretic group in the whole study population (p=0.028 and p=0.012), as well as in smokers (p=0.013 and p=0.016). Coronary heart disease mortality was significantly lower for patients on metoprolol than for patients on diuretics in the whole study population (p=0.048) as well as in smokers (p=0.021). The results suggest that initial antihypertensive therapy with metoprolol is associated with a lesser incidence of total, cardiovascular, and coronary heart disease mortality as compared with initial diuretic treatment, both in the whole study population and in smokers. The favorable effect of metoprolol must be mediated via mechanisms other than the blood pressure-lowering effect of metoprolol because equal blood pressure control was achieved with both types of medication, irrespective of smoking habits at randomization. (Hypertension 1989;13:773-780)

Smoking is an undisputed major independent risk factor for coronary heart disease. The serious adverse effects of smoking on a spectrum of cardiovascular complications to hypertension have been highlighted in numerous studies, and life table analyses have shown that the incidence of coronary heart disease is at least threefold higher in smoking hypertensive men than in nonsmokers. Thus, for reasons of statistical power, it is extremely difficult to show a reduction in overall mortality in intervention studies in hypertension unless an effect on coronary heart disease is achieved in smoking men. Studies of diuretics and several β-blockers as first-line treatment for hypertension have failed to provide evidence that they can reduce the increased risk for coronary heart disease in smokers.

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The present randomized primary prevention study attempts to investigate whether metoprolol given as initial antihypertensive treatment leads to a lesser incidence of cardiovascular complications of high blood pressure as compared with initial thiazide diuretic treatment. Before randomization, patients were stratified according to coronary heart disease risk factors, including smoking habits. This report discusses the results with respect to coronary heart disease mortality in smokers in the Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) Study.

Subjects and Methods
Details on patient characteristics and study methods are presented in the first report of this study.

Study Population
The study included 3,234 patients, 1,609 randomized to the metoprolol group and 1,625 to the diuretic group. A total of 535 patients in the metoprolol group and 524 patients in the diuretic group were classified as smokers at randomization. Stratification for smoking was performed in the MAPHY Study (see below), an exsmoker being defined as a smoker who had stopped at least 1 month previously. Exsmokers were considered as a part of the nonsmoking group in our present analysis.

All outpatients were men 40-64 years of age. At randomization, diastolic blood pressure in the sitting position was 100 mm Hg or greater but less than or equal to 130 mm Hg (calculated as the mean of two readings taken 2 weeks apart and including two readings on each occasion). Because this was a primary prevention study, patients with previous myocardial infarction, angina pectoris, or stroke were excluded. Additional exclusion criteria were secondary hypertension, second- and third-degree atrioventricular block, cardiac failure, obstructive lung disease not well controlled by \( \beta \)-2-stimulants, diabetes mellitus (defined as two separate positive dipstick tests for glucosuria and a fasting blood glucose level >6.8 mmol/l, i.e., >123 mg/dl), gout, and serious diseases like malignant neoplasms or severe alcoholism.

Study Design
The study design was defined in 1975. The original protocol stated that after stratification according to risk for coronary heart disease (age, systolic blood pressure, serum cholesterol, and smoking habits), patients should be randomly assigned to treatment with metoprolol (200 mg/day) or a thiazide diuretic (50 mg/day hydrochlorothiazide or 5 mg/day bendroflumethiazide). Propranolol was also defined as an optional \( \beta \)-blocker in the protocol but was used at only one center and only in 46 patients. The protocol stated that additional drugs (but not \( \beta \)-blockers or thiazide diuretics) should be given, if necessary, to reach the treatment goal of diastolic blood pressure less than 95 mm Hg. In 1978, more than 2 years after the first patient was randomized in the present study, the protocol was changed to allow for additional centers that could randomize patients to atenolol or diuretics. Thus, the original study protocol did not include atenolol as an optional \( \beta \)-blocker. Pooled results from all metoprolol centers, all atenolol centers, and the propranolol center existing until December 31, 1985 (the Heart Attack Primary Prevention in Hypertensives [HAPPHY] Trial), have been published separately. The present analysis thus deals with the outcome exclusively in the centers that used metoprolor or thiazide diuretics as baseline drugs.

Follow-up and Administrative Routines
Every patient entered on the randomization list was included in the follow-up, regardless of treatment status during follow-up; that is, the mortality data were conservatively analyzed according to the intention-to-treat principle. The start of treatment was defined as the date of randomization. For living patients, the end of the study was defined as the day of the last follow-up interview. The first patient was randomized in Gothenburg, Sweden, in March 1976, and the study was closed on February 28, 1987.

Classification of Cause-Specific Mortality
At the end of the study, 3,085 patients were confirmed to be alive and 148 were dead. One patient was unavailable for follow-up (randomized to diuretic). A decision regarding cause of death was made by the Independent End-Point Committee for each of the 148 deaths. All cases were judged without any knowledge of the actual treatment or the treatment to which the patient had originally been randomly assigned. Mortality classifications were subsequently scrutinized and approved in every case by the Independent Data Audit Committee, also without any knowledge of the actual treatment or randomization group.

Statistical Methods
All data were analyzed at the Computing Centre of Gothenburg University, Sweden, with the SAS program. With the Gehan-Wilcoxon nonparametric test for survival analysis, the null hypothesis was tested; that is, there was no difference between the two treatments in death rates.\(^8\) Survival analysis methods are necessary in trials in which subjects are entered over a long period of time and in which individual follow-up times vary. These methods permit comparison of the entire survival experience during the follow-up.\(^9\) The \( p \) value, however, does not permit calculation of a confidence interval describing the mean percentage difference between the two groups during follow-up because the survival test does not demand a constant difference in death rates between the two groups during follow-up. In an attempt to illustrate the extent of the possible differences in the outcome between the two treatment regimens, percentage differences in
cause-specific mortality rates between the two randomization groups have been given at the median follow-up time of 4.2 years and at the end of the study. The median follow-up time was chosen because it was a well-defined point during the follow-up and was also suitable for comparisons with the majority of earlier published randomized secondary preventive studies in post–myocardial infarction patients and intervention studies in hypertensive subjects, most of whom have had a follow-up time of 3–5 years (Figure 1). An on-treatment analysis was not attempted because of the inherent problems in interpreting this type of analysis. The observed crossover of treatments, however, (see below) would tend to underestimate rather than overestimate the difference between the metoprolol and diuretic group.

Results

Duration of Follow-Up

In total, data for 16,180 patient-years were accumulated: 8,110 patient-years in 1,609 patients randomized to metoprolol, of which 2,660 were patient-years in 535 patients classified as smokers at the randomization; and 8,070 patient-years in 1,625 patients randomized to diuretics, of which 2,540 were patient-years in the 524 patients being classified as smokers at randomization.

Antihypertensive Treatment

The mean daily dose of metoprolol in patients randomized to β-blockade was 174 mg, and the mean daily doses of hydrochlorothiazide and bendroflumethiazide in patients randomized to diuretics were 46 mg and 4.4 mg, respectively. The corresponding figures for smokers were 181 mg of metoprolol, 47 mg of hydrochlorothiazide, and 4.4 mg of bendroflumethiazide, respectively. Approximately one third of patients were receiving combination therapy, which was irrespective of random-

TABLE 1. Clinical Characteristics of Smokers and Nonsmokers at Entry and at Last Follow-Up Visit According to Smoking Habits at Entry

<table>
<thead>
<tr>
<th></th>
<th>Entry</th>
<th>Last follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Smokers</td>
<td>Nonsmokers</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
<td>Diuretics</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>168.2 (n=533)</td>
<td>169.0 (n=524)</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>108.1</td>
<td>108.0</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>79.8</td>
<td>78.5</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.3</td>
<td>52.4</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>82.4</td>
<td>81.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.1</td>
<td>26.8</td>
</tr>
<tr>
<td>S cholesterol (mmol/l)</td>
<td>6.36</td>
<td>6.32</td>
</tr>
<tr>
<td>S creatinine (µmol/l)</td>
<td>91.5</td>
<td>91.7</td>
</tr>
<tr>
<td>S potassium (mmol/l)</td>
<td>4.32</td>
<td>4.33</td>
</tr>
<tr>
<td>S urate (µmol/l)</td>
<td>343</td>
<td>340</td>
</tr>
<tr>
<td>S potassium &lt;3.6 mmol/l (%)</td>
<td>5.4</td>
<td>3.9</td>
</tr>
<tr>
<td>S urate &gt;450 µmol/l (%)</td>
<td>10.1</td>
<td>8.8</td>
</tr>
<tr>
<td>Glucosuria (%)</td>
<td>1.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Albuminuria (%)</td>
<td>3.2</td>
<td>4.5</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Major Q wave (%)</td>
<td>2.3</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Metoprolol, patients randomized to metoprolol; Diuretics, patients randomized to diuretics; p value, between group comparison at last follow-up visit; SBP, systolic blood pressure, DBP, diastolic BP; HR, heart rate; BMI, body mass index; S, serum.

*1:1 or 1:2 according to Minnesota coded ECG.
Cardiovascular mortality rates in non-smokers and smokers at the median follow-up time of 4.2 years

![Bar graph of cardiovascular mortality in nonsmokers and smokers at the median follow-up time (4.2 years) in the two randomization groups. Values of p refer to the survival experience between the two randomization groups at 4.2 years.](image)

The use of β-blockade in patients classified as smokers at randomization and randomized to diuretics increased as the follow-up time lengthened, from 9% at the median follow-up time of 4.2 years to 19% in patients followed up for more than 6.2 years (fourth quartile). The corresponding figures for use of diuretics in patients randomized to β-blockade were 6% and 10%, respectively.

Clinical Characteristics at Randomization and During Follow-Up

In subgroups of smokers and nonsmokers, the two randomization groups were well matched in major clinical characteristics at entry as well as at the last follow-up visit (Table 1). Approximately 30% of patients classified as smokers at randomization reported that they had stopped smoking during the last follow-up (Table 1). As expected, and independently of smoking habits at randomization, heart rate was lower with β-blockade during follow-up. Furthermore, during follow-up, serum potassium concentrations were lower, and serum uric acid concentrations were higher in patients randomized to diuretics. There was a slight increase in body weight in patients randomized to β-blockade. There was a decrease in serum cholesterol during follow-up in patients randomized to metoprolol ($p<0.0001$), and serum cholesterol was significantly lower with metoprolol treatment than with diuretics at the last follow-up visit.

Total and Cause-Specific Mortality

Smokers versus nonsmokers. Cardiovascular mortality was three to four times higher in smokers than in nonsmokers (Figure 2). The excess cardiovascular mortality in smokers was mainly due to more deaths from coronary heart disease (Table 2). There were very few fatal strokes, less than one fatal stroke for 10 deaths from coronary heart disease. Noncardiovascular mortality also tended to be higher in smokers than in nonsmokers.

Metoprolol versus diuretics. In the whole study population, total mortality was significantly lower in patients randomized to metoprolol than in patients randomized to diuretics ($p=0.028$), 48% at the median follow-up time of 4.2 years and 22% at the end of the study.

Total, cardiovascular, and coronary heart disease mortalities were significantly lower in smokers randomized to metoprolol than in smokers randomized to diuretics ($p=0.013$, $p=0.016$, and $p=0.021$, respectively) (Figure 3 and Table 2). Cardiovascular mortality in smokers was 56% lower with metoprolol treatment than with diuretics at the median follow-up time of 4.2 years and 36% lower at the end of the trial. There were four fatal strokes in patients classified as smokers at randomization; all

### Table 2. Cause-Specific Mortality at Median Follow-up Time and at End of Study in Patients Classified as Smokers at Entry

<table>
<thead>
<tr>
<th></th>
<th>Median follow-up (4.2 years)</th>
<th>End of study (10.8 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Metoprolol</td>
<td>Diuretics</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>All deaths</td>
<td>15</td>
<td>31</td>
</tr>
<tr>
<td>All cardiovascular</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>Noncardiovascular</td>
<td>5</td>
<td>9</td>
</tr>
</tbody>
</table>

Metoprolol, patients randomized to metoprolol; Diuretics, patients randomized to diuretics. $p$ values refer to the entire survival experience between the two treatment groups.
occurred in the patients randomized to diuretics (Table 2). The results regarding cardiovascular mortality in the two treatment groups, although statistically nonsignificant, indicated that the beneficial effect of metoprolol treatment was also exerted in nonsmokers (Figures 2 and 4). Although the mortality rates in smokers (deaths/1,000 patient-years) differed substantially between different populations, the percentage difference in mortality between patients randomized to metoprolol and to diuretics indicated that the benefit was spread over different geographical regions with different risks (Finland 31.2 vs. 17.5 per 1,000 patient-years; Sweden 17.5 vs. 12.7; and the other countries 16.5 vs. 11.3). This type of subgroup analysis must, however, be interpreted with great caution.

Discussion

The MAPHY Study with metoprolol is the first primary preventive study in hypertensive patients to show a significant effect on total mortality (conservatively analyzed according to the intention to treat principle). This effect depended partly on the substantial reduction in coronary heart disease mortality that was achieved in smoking men. A large number of landmark studies with diuretics and certain other β-blockers have clearly shown the benefits of antihypertensive treatment in reducing several cardiovascular complications although no effect has been observed on coronary heart disease mortality in smokers. The importance of the effect on coronary heart disease in smoking men for the outcome of any primary preventive trial can be exemplified in the following way: Of all cardiovascular deaths due to hypertension in middle-aged patients in the community, approximately 20% occur in women and 80% in men. Approximately one third of male patients are smokers, but their risk is tripled, accounting for 48% of all cardiovascular deaths, of which 90% are due to coronary heart disease. Accordingly, in the two sexes combined, approximately 40–50% of all cardiovascular deaths in hypertensive patients are due to coronary heart disease in smoking men (Figure 5). Thus, for reasons of statistical power, it is extremely difficult to show a reduction in overall mortality in primary preventive studies in hypertension unless an effect on coronary heart disease is achieved in smoking men. The arguments outlined above, as well as the results from the present study, emphasize the increased risk in smokers and also the importance of measures to help smokers stop smoking.

The pathophysiological mechanisms explaining the increased incidence of coronary heart disease in smokers are complex. Repeated and sustained sympathoadrenomedullary activation, stemming from psychosocial stress and reinforced especially by smoking, may negatively influence cardiovascular control, thromboembolic mechanisms, and atherosclerosis development. Metoprolol has been shown in experimental studies to favorably affect several of the pathophysiological mechanisms involved in cardiovascular disease development, both regarding reduced sympathetic nerve activity and direct myocardial protection, as well as thrombosis formation, prostacyclin synthesis, and cholesterol accumulation in the arterial vessel wall.
patients randomized to metoprolol (-2.8%) and slightly increased in those randomized to diuretics (+1.1%) (Table 1). One percent change in serum cholesterol might possibly explain a 2% change in coronary heart disease morbidity and mortality. Therefore, it cannot be excluded that the difference in effect on cholesterol might contribute in part to the difference in coronary heart disease mortality that was seen between the two treatment groups.

One factor of importance when interpreting the results of the MAPHY Study is the level of risk among the patients. The MAPHY Study included only men while the Medical Research Council Working Party (MRC) trial and the International Prospective Primary Prevention Study in Hypertension (IPPPSH) recruited both men and women. In women, low rates of events, particularly for coronary heart disease and total mortality, substantially reduce the likelihood of detecting any reduction in the event rate attributable to the treatment under study.

Cardiovascular deaths, hypertensives (middle-age)

Women 20%

Men 80% → 2/3 Non-smokers 32%

1/3 Smokers, risk tripled 48%

of which 90% is CHD

In the MRC primary preventive trial, results in favor of propranolol in comparison with placebo were achieved in nonsmoking men without any clear effect on cardiovascular end points in smoking men. These findings partially contrast with the present results. One possible explanation is that smoking leads to an increase in adrenaline, which, in smokers receiving a nonselective β-blocker like propranolol, might lead to unopposed α-constriction in peripheral resistance vessels interfering with blood pressure control. The reduction in event rates in nonsmoking men in the MRC trial was found in spite of the fact that nonsmoking men, regardless of randomization group, had a substantially lower risk than the smokers. It therefore seems unlikely, although plausible, that the lack of effect in smoking men observed in the MRC trial can be attributed to the lower risk in MRC smoking men compared with smokers in the MAPHY Study. The data from the present study also indicate that the benefit was spread over different geographic regions with very large differences in risks.

Finally, we want to stress that in the MRC and the IPPPSH trials no stratification for smoking status was done at randomization, and therefore, in these trials subgroups of smokers and nonsmokers were not fully comparable. In the MAPHY Study, careful stratification for smoking was done to minimize the bias stemming from differences in smoking habits between the randomization groups.

Primary and secondary preventive studies with different β-blockers have not shown uniform results. Pharmacologically, the most convenient explanation for differences in outcome between trials lies with the differences in the pharmacological action of the different β-blocker drugs. Postinfarction studies with lipophilic β-blockers have demonstrated a reduction in sudden cardiac death and prevention of ventricular fibrillation. Thus, the clinical relevance of certain pharmacological qualities, like lipophilicity and β₁-selectivity,
have to be further explored. At present, however, the evidence on the issue of specific pharmacological properties of metoprolol is too inconclusive to justify extensive speculation about mechanisms. More research is needed in this field.

The ability of antihypertensive drugs to exert an effect on cardiovascular risk has become one of the most important considerations in the selection of antihypertensive treatment. In the present study, the beneficial effect of metoprolol was due to factors in addition to blood pressure reduction because similar blood pressure levels were achieved in both treatment groups. Future research is bound to be influenced by the possibility that drugs with different pharmacological profiles, which lower blood pressure to a similar extent, may have differential effects on therapeutic outcome. Clinical trials have not yet produced long-term prognostic data on the effects of some of the newer antihypertensive agents like the α-blockers, angiotensin converting enzyme (ACE) inhibitors, or calcium antagonists on cardiovascular complications and mortality in hypertensive patients. The experience from earlier long-term studies with diuretics and certain β-blockers in hypertensive patients and from studies with calcium antagonists in secondary prevention after myocardial infarction has clearly shown that we cannot take for granted that any antihypertensive agent will prevent coronary heart disease and sudden death. Further long-term large-scale randomized trials are therefore needed to define the usefulness of α-blockers, ACE inhibitors, and calcium antagonists for this purpose.

In conclusion, the results from the present study suggest that initial antihypertensive therapy with metoprolol is associated with a lesser incidence of total, cardiovascular, and coronary heart disease mortality compared with initial diuretic treatment in the whole study population and in smokers. The favorable effect of metoprolol must be mediated via mechanisms other than the blood pressure-lowering effect of metoprolol because equal blood pressure control was achieved with both types of medication, irrespective of smoking habits at randomization.

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