Preinfarction Blood Pressure and Smoking Are Determinants for a Fatal Outcome of Myocardial Infarction

A Prospective Analysis From the Finnmark Study

Inger Njølstad, MD, PhD; Egil Arnesen, MD

Background: Serum cholesterol levels, blood pressure, and smoking are the classic coronary risk factors, but what determines whether a myocardial infarction will be fatal or not?

Objective: To investigate cardiovascular risk factors that may influence survival in subjects with coronary heart disease (myocardial infarction and sudden death).

Subjects and Methods: All inhabitants aged 35 to 52 years in Finnmark County, Norway, were invited to a cardiovascular survey in 1974-1975 and/or 1977-1978. Attendance rate was 90.5%. A total of 6995 men and 6320 women were followed up for 14 years with regard to incident myocardial infarction and sudden death. Predictors for 28-day case fatality rate after first myocardial infarction were analyzed.

Results: During 186,643 person-years, 635 events among men and 125 events among women were registered. The case fatality rate was 31.6% in men and 28.0% in women (P = .50). Among men (women) with baseline systolic blood pressure lower than 140 mm Hg, the 28-day case fatality rate was 24.5% (22.6%), among those with systolic blood pressure of 140 through 159 mm Hg, the case fatality rate was 35.6% (28.2%), and among those with systolic blood pressure of 160 mm Hg or higher, the case fatality rate was 48.2% (41.7%). Of the 760 subjects with myocardial infarction, 348 died during follow-up. In Cox regression analysis, systolic blood pressure at baseline was strongly related to death (relative risk per 15 mm Hg, 1.22; 95% confidence interval, 1.13-1.31). Daily smoking at baseline (relative risk, 1.40; 95% confidence interval, 1.07-1.85) and age at time of event (relative risk per 5 years, 1.12; 95% confidence interval, 1.01-1.24) were additional significant risk factors, while total serum and high-density lipoprotein cholesterol levels were unrelated to survival. Similar results were obtained with diastolic blood pressure in the model.

Conclusions: Preinfarction blood pressure was an important predictor of case fatality rate in myocardial infarction. Daily smoking and age were additional significant predictors.

Great efforts have been made to reduce in-hospital fatality rate due to myocardial infarction (MI), but more than 50% of coronary deaths occur suddenly and outside of hospitals. Therefore, one should identify those factors that influence the risk of dying of a heart attack and, if possible, intervene on such factors before the event occurs. Smoking, serum cholesterol levels, and blood pressure are the classic coronary risk factors, but so far no firm conclusion has been drawn as to their role for a fatal outcome in MI. Factors that are known to influence the case fatality rate are an advanced age, previous infarct, and diabetes mellitus. Some studies claim that women fare better or worse than men after a major heart attack, while others found no independent effect of sex. The size and location of an infarct are important immediate predictors for subsequent death.

However, several studies of predictors for case fatality and survival rates in MI were hospital based. Some studies included only subjects who initially survived a heart attack, measured risk factors after the first event, or included first and recurrent attacks, although a study among survivors may not reveal the most important causes of a fatal outcome in MI. Community-based studies of risk factors for case fatality and survival rates after heart attacks are few. To our knowledge, only the Framingham Study and the British Regional Heart Study present data on predictors of the case fatality rate in MI in a general population with standardized pre-event measurements of
SUBJECTS AND METHODS

SUBJECTS

In Finnmark County, northern Norway, all residents aged 35 to 49 years and a sample of those aged 20 to 34 years were invited to participate in a cardiovascular survey in 1974. The survey was conducted by the National Health Screening Service (Oslo, Norway) in cooperation with the University of Tromsø (Tromsø, Norway) and local health authorities. Three years later the survey was replicated. Details of study design and procedures have been published. A total of 22,612 individuals were invited to complete the first and/ or second survey through a personal, mailed letter, and 19,308 attended. The present analysis was limited to the 35- to 52-year age group, in which all residents were invited and 13,412 men and women attended either or both surveys. Attendance rate was 90.5% in this age group. Subjects with a previous MI (62 men and 6 women) or stroke (16 men and 13 women) were excluded, leaving 6995 men and 6320 women for the present analysis. Fifty percent were of Norse, 17% of Finnish, and 14% of Sami origin, while the remaining subjects were of mixed or unknown ethnicity.

SCREENING DATA AND PROCEDURES

On the reverse of the invitation letter was a questionnaire that covered history and symptoms of cardiovascular disease, ethnicity, physical activity, and smoking habits. The questionnaire was to be completed at home and brought to the examination site, where it was checked for inconsistencies.

The physical examination included measurement of weight, height, and blood pressure, and collection of a nonfasting blood sample. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice after 4 minutes’ rest and with the patient sitting, and were read to the nearest even values in millimeters of mercury. The lower values were used in this analysis.

Potential risk factors in the whole cohort. In the latter study, which included 7735 middle-aged men, physical inactivity and increased heart rate, arrhythmias, and antihypertensive treatment emerged as significant predictors, while blood pressure and smoking were not related to the case fatality rate. In contrast, pre-event blood pressure was related to survival after first MI among men in the Framingham study. Neither of the studies included women.

The aim of this population-based prospective study was to investigate cardiovascular risk factors that may influence survival in subjects with coronary heart disease (MI and sudden death). Included were 13,315 middle-aged men and women free from previous MI and stroke. The subjects were followed up for 14 years with regard to MI incidence and mortality. Potential risk factors for a fatal outcome of MI were examined.

RESULTS

During 186,643 person-years of follow-up, 635 events of first MI and sudden death among men and 125 events among women were registered. Mean follow-up was 14 years. The age-adjusted incidence rate of MI was 6.6 and 1.4 per 1000 person-years in men and women, respectively. The distribution of case categories did not differ between the sexes (Table 1), although men had a 4.7-fold higher incidence of MI.

Subjects who had an MI during follow-up were significantly older at study entry than those who did not. Mean age at time of event was similar between the sexes (fatal MI: 53.5 years in men, 54.9 years in women; nonfatal MI: 52.6 years in men, 53.7 years in women). In Table 2, age-adjusted baseline variables are shown for subjects without MI, and for those who had either a nonfatal or a fatal MI during follow-up. The SBP and DBP were significantly higher in those who died of a heart attack than in those who survived. Angina pectoris was more common in women who died after an MI (P = .03). No significant difference was observed in the age-adjusted frequency of smoking between survivors and those who died (men, P = .21; women, P = .91).

In the Figure, 1-year survival curves are shown for the 760 men and women who had a first MI or sudden death. Overall, there was no sex difference in the case fatality.
 alive by June 1, 1991. Fifteen percent of the study population had moved from Finnmark, but the Central Population Registry of Norway provided updated addresses regardless of present area of residency. The response rate was 81% in those who stayed and those who had moved from Finnmark. When a questionnaire reply indicated cardiovascular disease, medical information was obtained from the relevant hospital or attending physician, with the respondent’s written consent. In all, 97% of the participants were followed up by means of the postal survey and/or diagnosis registers and hospital record surveys. The linkage to the Causes of Death Registry ensured a 100% follow-up on vital status.

The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. The State Health Directorate permitted access to medical record files.

**DATA ANALYSIS**

Incidence rates were based on the number of person-years from date of first examination until first event of MI or sudden death, with date of death from other reasons, emigration, or December 31, 1989, as the censoring date. The case fatality rate was calculated as death from any cause within 28 days after date of first MI (including sudden death). All 232 subjects who died within 28 days died of cardiovascular disease. Among the 116 subjects who died later during follow-up, 103 (89%) had been assigned a cardiovascular diagnosis (International Classification of Diseases, Eighth Revision [ICD-8] 13 or International Classification of Diseases, Ninth Revision [ICD-9] codes 395-438) 13 as the underlying cause of death, and only 3 had no such diagnosis mentioned on the death certificate.

In 26 cases there was a discrepancy between date of onset of symptoms and hospital admission, with the latter registered by us as time of event. All those subjects survived for more than 28 days after onset of symptoms. One subject died on the 28th day after hospital admission and was assigned as having a nonfatal MI in the present analysis.

Analysis of covariation was used for age-adjusted between-group comparisons of baseline variables. Cox proportional hazards analysis was used for multivariate analysis of predictors of survival after a first MI. Of the 88 subjects who experienced a first MI during the last year and survived until the end of follow-up, all but 3 were alive by June 1, 1991, 1/2 years after the end of follow-up. One-year survival curves were estimated using the Kaplan-Meier method.

Due to a high intercorrelation (Pearson r = 0.6), either SBP or DBP was used in the multivariate modeling. Blood pressure, serum lipid levels, and body mass index, which is a measure of weight in kilograms divided by the square of the height in meters, were entered as continuous variables, while smoking and diabetes, angina pectoris, and antihypertensive treatment were entered as binary variables in the regression analysis. Leisure-time physical activity was self-reported into 1 of 4 categories that best described the usual activity level: L1, reading, watching television, or other sedentary activities; L2, walking, bicycling, or light physical activity for at least 4 hours per week; L3, exercise to keep fit, heavy gardening for at least 4 hours per week; and L4, regular hard training. For this study, leisure-time activity was dichotomized into low (L1 and L2) and high (L3 and L4) activity. Probability values less than .05 were regarded as statistically significant, and 2-tailed significance tests were used. All statistical modeling was performed with SAS statistical software Version 6.09 (SAS Institute Inc, Cary, NC).

In 2 analyses, SBP and DBP were categorized according to criteria of the Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V) 14 of normal pressure (SBP <140 mm Hg; DBP <90 mm Hg), mild hypertension (SBP, 140-159 mm Hg; DBP, 90-99 mm Hg), and moderate or severe hypertension (SBP ≥160 mm Hg; DBP ≥100 mm Hg).

### Table 1. Twenty-eight-Day Case Fatality Rate in First Myocardial Infarction (MI) in Men and Women by Case Category: The Finnmark Study 1974-1989

<table>
<thead>
<tr>
<th>Case Category</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died Within 28 d, No. (%)</td>
<td>Died Within 28 d, No. (%)</td>
<td></td>
</tr>
<tr>
<td><strong>All Cases, No.</strong></td>
<td><strong>All Cases, No.</strong></td>
<td></td>
</tr>
<tr>
<td>Definite MI</td>
<td>362</td>
<td>32 (8.8)</td>
</tr>
<tr>
<td>Probable MI</td>
<td>189</td>
<td>81 (42.9)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>84</td>
<td>84 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>635</td>
<td>197 (31.0)</td>
</tr>
</tbody>
</table>

... Continued
1.07-1.85) and age at time of event (RR per 5 years, 1.12; 95% CI, 1.01-1.24) were also significant predictors in the multivariate model. The relative risks associated with angina pectoris and diabetes mellitus were increased but there were few subjects with these conditions at baseline and the 95% CI ranges did not preclude unity. Leisure-time physical activity, body mass index, and serum triglyceride and total cholesterol levels did not predict a fatal outcome of MI. Ethnic origin was unrelated to the case fatality rate (risk estimates not shown). Similar results were obtained when DBP replaced SBP in the model. The RR of dying associated with a 10-mm Hg increase in DBP was 1.20 (95% CI, 1.10-1.32). To examine the role of HDL cholesterol level, a separate analysis was performed with the 1977 survey as baseline and with 686 cases (255 fatal) included in the Cox model. Adjusted for the same variables as those in Table 5 except triglycerides, the RR per millimole per liter increase in HDL cholesterol level was 1.03 (95% CI, 0.71-1.47).

A previous analysis showed that smoking, total serum and HDL cholesterol levels, and blood pressure were significant risk factors for MI incidence in both sexes in the Finnmark Study. Our analysis demonstrates that blood pressure was a highly significant predictor of a fatal outcome of MI. In the multivariate model, daily smoking and age were also significant determinants, while total se-
ies, 2, 7, 12, 36 depending heavily on diagnostic criteria, previous MI or stroke 1, 10, 12, 14 are major predictors, the case community-based study 2 among subjects aged 30 to 64 in this study was lower than in a 1967 to 1969 population. The case fatality rate will depend on the composition of the study population. The case fatality rate of 31% among men in our study was somewhat lower than the 36% case fatality rate in first events in the British Regional Heart Study. 12 However, that study included men who were up to 7 years older at study entry. The case fatality rate in this study was lower than in a 1967 to 1969 community-based study 2 among subjects aged 30 to 64 years in Oslo, which included first MIs and sudden, out-of-hospital deaths. The case fatality rate was also lower than in other community-based studies 35, 36 consisting of similar age groups, but those studies included first and recurrent heart attacks. A great effort was made to detect nonfatal events among the participants in our study. From the responses to the postal survey we estimated less than 20 nonfatal cases were missed, while the linkage to the official Registry of Deaths ensured that all deaths in the cohort were registered.

Blood pressure, measured according to standardized procedures in a population survey setting, was the most important predictor of a fatal outcome of MI. Our finding supports the early study by Weinblatt et al, 1 in which men with pre-event SBP higher than 140 mm Hg had a 1-month case fatality rate of 43%, while normotensive men had a case fatality rate of 21% after a first MI. Our finding contrasts with that of the British Regional Heart Study, in which no relationship was seen between blood pressure and the case fatality rate. The case fatality rate increased steadily with SBP categories in all age strata. The case fatality rate increased with higher DBP, but an apparent threshold was observed with no further increase in the case fatality rate between a DBP of 90 to 99 mm Hg and a DBP of 100 mm Hg or higher. Treatment of high blood pressure in clinical settings has mainly been directed at DBP. In the current study, subjects with untreated high blood pressure were referred back to general practitioners who generally used a DBP of 100 mm Hg as a cutoff point for treatment in the 1970s. 37 This raises the possibility that the apparent threshold effect may be attributable to treatment started after the screening. Interestingly, antihypertensive treatment was associated with an increased risk of MI in the Finnmark study, especially among men, 32 while our analysis shows that antihypertensive treatment was associated with a non-significantly lower risk of death during follow-up after MI (RR, 0.76; 95% CI, 0.50-1.14), adjusted for several risk factors including blood pressure. In analyses stratified by blood pressure level, the case fatality rate was non-significantly lower in those treated for hypertension in all SBP and DBP categories. In contrast, the British Re-

### Table 4. Twenty-eight-Day Case Fatality Rate (CFR) in First Myocardial Infarction (MI) by Systolic Blood Pressure and Age in Men and Women: The Finnmark Study 1974-1989

<table>
<thead>
<tr>
<th>Systolic Blood Pressure, mm Hg</th>
<th>Age at First MI, y</th>
<th>Men</th>
<th>CFR, No. (%)</th>
<th>Women</th>
<th>CFR, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>CFR, No. (%)</td>
<td>No.</td>
<td>CFR, No. (%)</td>
<td>No.</td>
</tr>
<tr>
<td></td>
<td>140-159 ≤139</td>
<td>140-159 ≥160</td>
<td>140-159 ≤139</td>
<td>140-159 ≥160</td>
<td>140-159 ≤139</td>
</tr>
<tr>
<td>35-44</td>
<td>41</td>
<td>12 (29.3)</td>
<td>21</td>
<td>6 (28.6)</td>
<td>6</td>
</tr>
<tr>
<td>45-54</td>
<td>171</td>
<td>36 (21.1)</td>
<td>102</td>
<td>33 (32.4)</td>
<td>43</td>
</tr>
<tr>
<td>55-64</td>
<td>136</td>
<td>37 (27.2)</td>
<td>79</td>
<td>32 (40.5)</td>
<td>36</td>
</tr>
<tr>
<td>Total</td>
<td>348</td>
<td>85 (24.4)</td>
<td>202</td>
<td>71 (35.1)</td>
<td>85</td>
</tr>
</tbody>
</table>

*P value for trend, age adjusted.
†P value for trend, age adjusted.

### Table 5. Predictors of Death After First Myocardial Infarction (MI): The Finnmark Study 1974-1989

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>1.08</td>
<td>0.79-1.44</td>
</tr>
<tr>
<td>Age at MI, 5 y</td>
<td>1.12</td>
<td>1.01-1.24</td>
</tr>
<tr>
<td>Systolic blood pressure, 15 mm Hg</td>
<td>1.22</td>
<td>1.13-1.31</td>
</tr>
<tr>
<td>Total cholesterol, 1 mmol/L</td>
<td>1.02</td>
<td>0.95-1.11</td>
</tr>
<tr>
<td>Triglycerides, log</td>
<td>0.94</td>
<td>0.74-1.18</td>
</tr>
<tr>
<td>Body mass index, 1 kg/m²</td>
<td>0.98</td>
<td>0.96-1.01</td>
</tr>
<tr>
<td>Daily smoking, yes/no</td>
<td>1.40</td>
<td>1.07-1.85</td>
</tr>
<tr>
<td>Physical activity, low/high</td>
<td>1.01</td>
<td>0.72-1.42</td>
</tr>
<tr>
<td>Treated hypertension, yes/no</td>
<td>0.76</td>
<td>0.50-1.14</td>
</tr>
<tr>
<td>Angina pectoris, yes/no</td>
<td>1.43</td>
<td>0.90-2.27</td>
</tr>
<tr>
<td>Diabetes mellitus, yes/no</td>
<td>1.97</td>
<td>0.86-4.49</td>
</tr>
</tbody>
</table>

* Seven hundred fifty-four cases (346 fatal) with data on all variables, adjusted for variables shown and ethnicity.
gional Heart Study reports that antihypertensive treatment carried an increased risk of dying within 28 days after a heart attack (odds ratio, 1.97; 95% CI, 1.06-3.67). Arrhythmias and heart rate could have been confounders, but were probably not the reason for the discrepant findings given the lack of association between age-adjusted blood pressure and the case fatality rate in the British study. The difference in statistical methods (proportional hazards vs logistic regression analysis) had little influence since most subjects (67%) in our study died within 28 days, and our results did not change materially when we used the logistic regression analysis method.

The mechanisms that link an increased blood pressure to MI and sudden death are incompletely understood, but may involve endothelial damage, atherosclerosis, insulin resistance and left ventricular hypertrophy, and ventricular arrhythmias. Blood pressure is the most important risk factor for left ventricular hypertrophy, which in turn increases the risk for and worsens the prognosis after MI. An inconsistent effect on left ventricular hypertrophy reversal may possibly explain why common antihypertensive drugs have not reduced coronary heart disease as expected. In the Multiple Risk Factor Intervention Trial (MRFIT), an excess coronary mortality, mainly sudden deaths that occurred during the first 2 to 3 years while receiving drug therapy, was observed among men with hypertension in the special intervention group treated with diuretics, while diuretic treatment apparently reduced the case fatality rate in the European Working Party on High Blood Pressure in the Elderly Trial. β-Blockers protect against sudden death and reinfarctions after an initial MI, but their ability to reduce first MI and sudden death in individuals with hypertension is unsettled and may possibly depend on whether the subject smokes. In the Framingham study, antihypertensive treatment contributed independently to the risk of sudden death in men and women with or without prior coronary heart disease and with or without abnormalities shown on the electrocardiogram. Our data were insufficient to examine whether exposure to antihypertensive treatment at time of the event may have influenced survival. No data on drug types used at study entry were available, but diuretics and β-blocking agents were the most common antihypertensives used in a Finmark subsample in 1977. One may speculate, but cannot conclude, whether differences in drug therapy may be a reason for discrepant findings between the population studies.

In this study, the risk of dying after an MI was significantly 40% higher in daily smokers after adjustment for other variables. In the British Regional Heart Study, the odds ratio was 1.64 (P = .09) in current smokers vs nonsmokers. The frequency of daily smoking differed between the studies (41% in Britain, 57% in Finmark). Our finding apparently contradicts a pooled analysis of 6 recent MI trials (of thrombolytic treatment), which demonstrated a more favorable prognosis after MI among smokers. The authors ascribe the improved survival among smokers to younger age and less severe coronary vessel disease. A cohort selection bias may be added: those who smoke may be more likely to die suddenly and never make it into the trials, while inclusion of out-of-hospital coronary deaths will allow detection of the impact of smoking in the general population. On the other hand, changes in exposure (smoking cessation) during follow-up but before the event may blur the associations between risk factor and outcome in a prospective cohort analysis.

Serum cholesterol level did not influence the case fatality rate in our study, consistent with studies in the general population and among subjects with hypertension. Leisure-time physical activity level did not influence survival, in contrast to the British Regional Heart Study, in which high physical activity was associated with lower case fatality rate (odds ratio, 0.53; P < .05). A broader range of activity categories in the latter study may have detected real contrasts between groups better.

Since the late 1980s thrombolytic therapy has become common in hospital treatment of MI. Seven percent of the present cohort may have received streptokinase, but some of those subjects were included in the Second International Study of Infarct Survival trial, and the actual treatment given is not known to us.

In conclusion, pre-event blood pressure measured up to 14 years before the event was strongly associated with case fatality in MI, while age and daily smoking were additional significant predictors in this population-based study. The results emphasize the role of the classic coronary risk factors and point to the possibility of preventing coronary deaths by avoiding cigarette smoking. A better understanding of the pathophysiological links between blood pressure, coronary heart disease, and drug effects is needed before it can be determined whether antihypertensive treatment improves or worsens the outcome of MI.

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Reprints: Inger Njølstad, MD, Institute of Community Medicine, University of Tromsø, N-9037 Tromsø, Norway (e-mail: inge.njolstad@ism.uit.no).

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