Hypertension and ST Segment Depression During Ambulatory Electrocardiographic Recording
Results From the Prospective Population Study ‘Men Born in 1914’ From Malmö, Sweden

Bo Hedblad and Lars Janzon

The aim of this study in 341 men (aged 68 years) without history of ischemic heart disease was to study the relation between hypertension and silent ischemic-type ST segment depression during ambulatory long-term electrocardiographic recording and to assess the influence between these two variables on cardiovascular morbidity and mortality rates. Seventy-nine men (23%) demonstrated one or more episodes of silent ischemic ST segment depression. One hundred and sixty-seven men (49%) were considered to have hypertension (i.e., they had a diastolic blood pressure of 95 mm Hg or greater or were treated with antihypertensive therapy). Forty-nine (72%) of the 68 treated hypertensive subjects were classified as uncontrolled (i.e., their diastolic blood pressure was 95 mm Hg or greater). The occurrence of ischemic ST depression was higher in hypertensive men (28%) than in normotensive men (19%). The highest incidence of ischemic ST depression (41%) was observed in treated hypertensive men with inadequate blood pressure control. Cardiac event rate during a 53-month follow-up was 6.6% in hypertensive men and 4.6% in normotensive men. Uncontrolled treated hypertensive men had a higher event rate (14%) than hypertensive men overall. Hypertensive men with inadequate blood pressure control and who demonstrated ST segment depression had the highest event rate (25%).

Hypertension is a common and serious medical problem, especially in elderly people living in industrialized countries. The prevalence of hypertension in a population depends on its definition, however. With a cut-off point equal to or exceeding 160/95 mm Hg, it has been estimated that almost 50% of an elderly population will be classified as hypertensive. Today it is well documented that high blood pressure is a risk factor for cardiovascular and cerebrovascular disease. Many studies have shown that treatment of high blood pressure leads to reduced cerebrovascular morbidity and mortality rate. It is still controversial, however, whether blood pressure–lowering treatment is associated with a reduced cardiac event rate. The apparent lack of effect in some studies might reflect the lack of a true treatment effect, but it is also possible that some studies had inadequate power to document an effect or that achieved blood pressure control was inadequate in too many patients. Several authors have questioned reported benefits of blood pressure treatment in the elderly. We have previously reported a high cardiac event rate in 68-year-old men with asymptomatic ischemic-type ST segment depression during ambulatory long-term electrocardiographic (ECG) recording (LTER). The mean systolic and diastolic blood pressure among men treated for hypertension in that study cohort was, in spite of treatment, 20 and 12 mm Hg, respectively, higher than it was among normotensive men, indicating lack of blood pressure control in a certain number of cases. The aim of the present 5-year follow-up study was to evaluate the occurrence of ischemic-type ST segment depression during LTER in relation to degree of blood pressure control and to assess the influence of blood pressure and ischemic-type ST segment depression on cardiovascular morbidity and mortality rates.

Methods

Study Population

The prospective population study “Men Born in 1914” is a cohort study that includes all men who were born in the even months in 1914 and who, in 1982 at the age of 68 years, were residents in the city of Malmö, Sweden. All 621 men were invited to a health examina-
tion. Five hundred agreed to participate. Characteristics of the nonparticipants have been discussed in a previous article. 20

The health examination program included an ambulatory 24-hour LTER. Four hundred and fifty-six of the invited men (73.4%) agreed to participate in the LTER part of the program. Sixty-two LTER recordings were excluded from ST segment analysis. Reasons for exclusion were active treatment with digitalis, atrial fibrillation, conduction disturbances, or technical problems. The study population included in the ST segment analysis part of the LTER program consisted of 394 men; 53 of these had ischemic heart disease (i.e., a previous myocardial infarction [MI] or present angina pectoris, or both 18). These men were not included in the analysis of possible relation between hypertension and ST segment depression.

Baseline Data

Long-term electrocardiographic recording. A conventional ECG tape recorder (Oxford Medilog II FM type, Oxford Electronics, Oxford, England) with a frequency response of 0.05-100 Hz was used with two pair of bipolar electrodes in the V 2 and V 6 location for continuous 24-hour two-channel ECG registrations during daily life activities. 18 The monitor units were calibrated before and after each recording. An Oxford MA 14/20 scanner (Oxford Electronics) was used for the analysis together with a visual interpretation by one well-trained laboratory technician. Evaluation included an assessment of frequency and total duration of ST segment depression of all the recording tapes. ECG areas of interest were printed out at 25 mm/sec. Significant ST segment of ischemic type was defined as planar or downsloping shift of the ST segment of 1 mm (0.1 mV) or more from baseline level, occurring 0.08 second after the J point, with a duration of at least 30 seconds. The intervals between episodes were at least 1 minute. The mean LTER time was 23.4 hours.

Cardiovascular Risk Factors

A single blood pressure was recorded in the morning after 15 minutes of seated rest. All subjects were told to abstain from breakfast and to abstain from smoking. Blood pressure was measured in the right arm using a mercury manometer (Trimline TS, LIC, Solna, Sweden) and a standard rubber cuff (12 x 35 cm). Blood pressure was recorded to the nearest 5 mm Hg.

Drug treatment, including blood pressure medication, was recorded at an interview. All drugs used were recorded together with indication for use. Drug compliance was not assessed.

Hypertension was defined as diastolic blood pressure 95 mm Hg or greater or medication for hypertension. 1, 21

Height was measured to the nearest centimeter. Body weight was measured to the nearest 0.5 kg, with the men wearing indoor clothing without shoes. Body mass index (BMI) was calculated as weight (in kilograms) and height (in square meters). Overweight was defined as BMI 25.1-30.0 and obesity as BMI above 30. 22

Blood samples were drawn after a minimum fasting period of 8 hours for determination of plasma cholesterol, plasma triglycerides, 23 and glucose. 24 Hypercholesterolemia was defined as cholesterol level equal to or above 6.5 mmol/l (252 mg/dl) and hypertriglyceridemia was defined as triglyceride level equal to or above 2.5 mmol/l (221 mg/dl). Hyperlipidemia was defined as a cholesterol level 6.5 mmol/l or above or triglyceride level 2.5 mmol/l or above. Diabetes mellitus was defined as fasting blood glucose 7.0 mmol/l (126 mg/dl) or above or medication for diabetes mellitus.

The following smoking categories were used: those who had never smoked, ex-smokers (those who had stopped smoking and maintained cessation for more than 1 month before the examination), and current smokers (those smoking at least 1 g tobacco per day or who had quit smoking within the last month). The validity of smoking data was analyzed by comparison with blood concentrations of carbon monoxide. 25

Average alcohol consumption during the year preceding the health examination was recorded with respect to different beverages, using a method described earlier. 26 High alcohol consumption was defined as consumption of more than 250 g alcohol per week.

Follow-up Data

All probands were followed from August 1982 until December 31, 1987. The 17 men who moved out of Malmö during the follow-up period were contacted by letter to find out if they had been hospitalized for a MI.

Definition of myocardial infarction. The diagnosis of MI was based on accepted criteria: central chest pain, shock, or syncope suggesting infarction, together with typical serum transaminase pattern, pathological Q wave, or localized ST changes on the electrocardiogram.

Mortality and causes of death. Mortality and causes of death were obtained from the Mortality Register at the Swedish National Bureau of Statistics. 27 Causes of death were coded in accordance with the international classification of diseases, injuries, and cause of death (ICD), eighth revised version. 28 Cases coded 410.0-412.9 were counted unquestionably as deaths from ischemic heart disease. The autopsy rate was 82%. Autopsy criteria for MI were fresh myocardial necrosis or, in the absence of a necrosis, a total or almost total occlusion of a coronary artery together with a medical history compatible with acute MI.

Definition of cardiac event. The definition of a cardiac event was fatal or nonfatal MI, ICD code 410.0-410.9, or death classified as due to chronic ischemic heart disease, ICD code 412.0-412.9. 28 In men with more than one event the first event was used for the analysis.

Statistical Analysis

Analysis of variance, Student's t test, and χ 2 test were used to compare mean values and frequencies. All statistical tests were two-tailed. Cox's proportional hazards model 29 was used to study cardiac event rate and all-cause mortality in relation to hypertension, occurrence of ischemic type ST depression, blood lipids, smoking habits, and alcohol consumption. Relative risks (RR) were computed as antilog of the risk coefficient. A probability (p) value below 0.05 was considered statistically significant.

Results

Hypertension was more common among men with than without history of ischemic heart disease (Table 1). Sixty-eight of 341 men without a history of ischemic heart disease were treated with antihypertensive mono-
therapy; 19 with a β-blocker, 21 with a diuretic, two with a vasodilator, and two with other antihypertensive drugs. The rest (n=24) were treated with a combination of different antihypertensive drugs.

The distribution of blood pressure in men with and men without treatment for hypertension is shown in Figure 1. A diastolic blood pressure equal to or exceeding 95 mm Hg in men with antihypertensive treatment was considered to be inadequate blood pressure control. Forty-nine (72%) of the 68 men with blood pressure treatment and no history of ischemic heart disease had a diastolic blood pressure above this level (upper diastolic blood pressure range, 120 mm Hg). Among the 273 men who were not treated for high blood pressure, 99 (36%) had a diastolic blood pressure equal to or exceeding 95 mm Hg (upper diastolic blood pressure range, 130 mm Hg).

The percentage of men with present or previous exposure to tobacco smoking was greater among men with than it was among men without history of ischemic heart disease. Diabetes was less common in men with than in those without ischemic heart disease.

Thirty-six percent of the men with ischemic heart disease and 23% of the men without ischemic heart disease at baseline had ischemic-type ST segment depression during ambulatory LTER. Both the cardiac event rate and the mortality rate were higher in men with than in men without history of ischemic heart disease at baseline (Table 1).

Table 2 illustrates the distribution of cardiovascular risk factors in relation to blood pressure treatment and degree of blood pressure control in men without history of ischemic heart disease (n=341). No less than 167 men, i.e., 49%, were classified as having hypertension, and 68 men (20%) were being treated for hypertension. The percentage of smokers was smaller among men with than without treatment for high blood pressure. Men with blood pressure treatment had a higher BMI and lower alcohol consumption than men without corresponding treatment.

Table 1. Blood Pressure Distribution, Prevalence of Cardiovascular Risk Factors, and Cardiac Event Rate Among Men With and Without History of Ischemic Heart Disease

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>History of IHD at baseline</th>
<th>No (n=341)</th>
<th>Yes (n=53)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td></td>
<td>153±21</td>
<td>155±24</td>
<td>0.407</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td></td>
<td>93±11</td>
<td>93±10</td>
<td>0.729</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td></td>
<td>49.0</td>
<td>69.8</td>
<td>0.007</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>(≥6.5 mmol/l)</td>
<td>31.9</td>
<td>28.3</td>
<td>0.719</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td></td>
<td>3.8</td>
<td>1.9</td>
<td>0.752</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td></td>
<td>35.0</td>
<td>28.3</td>
<td>0.431</td>
</tr>
<tr>
<td>Former smoker (%)</td>
<td></td>
<td>43.7</td>
<td>60.4</td>
<td>0.034</td>
</tr>
<tr>
<td>Ischemic ST depression (%)</td>
<td></td>
<td>23.2</td>
<td>35.9</td>
<td>0.069</td>
</tr>
</tbody>
</table>

Follow-up

| Cardiac event n (%)         | 19 (5.6)                  | 11 (20.8)  | <0.001 |
| Total mortality n (%)       | 36 (10.6)                 | 9 (16.7)   | 0.256   |

IHD, ischemic heart disease; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Ischemic-type ST segment depression during ambulatory LTER was more common among men with hypertension (28%) than it was among men with normal blood pressure (19%), p=0.080, Table 3. The highest frequency of ischemic ST depression and the longest ischemic ST depression duration was observed in treated hypertensive men with inadequate blood pressure control, i.e., men with diastolic blood pressure 95 mm Hg or greater. Men with hypertension had a slightly higher mortality rate (21 of 167 men, 12.6%) than men with normal blood pressure (8 of 174 men, 4.6%, p=0.424 and 15 of 174 men, 8.6%, p=0.233). The highest cardiac event rate (14.3%) was observed in treated hypertensive men with inadequate blood pressure control (p=0.016, Table 3). The cardiac event rate in treated hypertensive men with inadequate blood pressure control and who demonstrated ST segment depression was 25% (p<0.001).

The relative risk of a cardiac event in men with antihypertensive treatment and adequately controlled blood pressure was 1.4 (95% confidence interval [CI], 0.2–13.0) in comparison with normotensive men without history of ischemic heart disease. The risk remained when controlling for smoking habits, blood lipids, and high alcohol consumption. Men with antihypertensive
Table 2. Distribution of Risk Factors for Ischemic Heart Disease in Relation to Blood Pressure Treatment and Degree of Blood Pressure Control

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Normotension* (n=174)</th>
<th>Untreated hypertension† (n=99)</th>
<th>Treated and controlled hypertension‡ (n=19)</th>
<th>Treated and uncontrolled hypertension§ (n=49)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>140</td>
<td>170</td>
<td>150</td>
<td>165</td>
<td></td>
</tr>
<tr>
<td>Range (mm Hg)</td>
<td>(105–205)</td>
<td>(130–225)</td>
<td>(120–185)</td>
<td>(130–215)</td>
<td></td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>90</td>
<td>100</td>
<td>90</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Range (mm Hg)</td>
<td>(65–90)</td>
<td>(95–130)</td>
<td>(80–90)</td>
<td>(95–120)</td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.9±1.0</td>
<td>6.2±1.1</td>
<td>6.1±1.2</td>
<td>6.2±1.0</td>
<td>0.112</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.4±0.8</td>
<td>1.5±0.7</td>
<td>1.3±0.4</td>
<td>1.7±0.7</td>
<td>0.025</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>42</td>
<td>29</td>
<td>21</td>
<td>26</td>
<td>0.040</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>4</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>0.956</td>
</tr>
<tr>
<td>High alcohol consumers &gt;250 g/wk (%)</td>
<td>9</td>
<td>12</td>
<td>11</td>
<td>4</td>
<td>0.443</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.5±3.2</td>
<td>25.2±3.2</td>
<td>24.3±2.7</td>
<td>25.9±3.0</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Values are mean±SD unless otherwise stated. Men with ischemic heart disease at baseline not included. SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

*No medication and DBP <95 mm Hg.
†No medication and DBP £95 mm Hg.
‡Medication and DBP <95 mm Hg.
§Medication and DBP ≥95 mm Hg.

About one of seven men in this population-based cohort had ischemic heart disease. During the 53-month-long follow-up period, 21% of the men with history of ischemic heart disease suffered a cardiac event compared with 6% among men without such a history. The high morbidity and mortality rates in the former group emphasize the need for preventive measures.

The overrepresentation of ex-smokers and the overrepresentation of men taking antihypertensive treatment in the group with history of ischemic heart disease illustrate the well-known relation between ischemic heart disease, hypertension, and smoking but also

Table 3. Occurrence of Ischemic-Type ST Segment Depression During Ambulatory Long-Term Electrocardiographic Recording, Cardiac Event Rate, and All-Cause Mortality in Relation to Blood Pressure Treatment and Degree of Blood Pressure Control

<table>
<thead>
<tr>
<th>LTER results and follow-up</th>
<th>Normotension* (n=174)</th>
<th>Untreated hypertension† (n=99)</th>
<th>Treated and controlled hypertension‡ (n=19)</th>
<th>Treated and uncontrolled hypertension§ (n=49)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>STD (% of subjects)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodes/subject with STD/24 hr (No.)</td>
<td>33 (19)</td>
<td>22 (22)</td>
<td>4 (21)</td>
<td>20 (41)</td>
<td>0.016</td>
</tr>
<tr>
<td>Median</td>
<td>5</td>
<td>4.5</td>
<td>3</td>
<td>9</td>
<td>0.089</td>
</tr>
<tr>
<td>Range</td>
<td>1–21</td>
<td>1–22</td>
<td>2–5</td>
<td>1–19</td>
<td></td>
</tr>
<tr>
<td>Duration (min) of STD/subject with STD/24 hr</td>
<td>80</td>
<td>77</td>
<td>32</td>
<td>182</td>
<td>0.489</td>
</tr>
<tr>
<td>Median</td>
<td>1–1,440</td>
<td>0.5–1,440</td>
<td>3–128</td>
<td>3–1,202</td>
<td></td>
</tr>
<tr>
<td>Cardiac event (%)</td>
<td>8 (5)</td>
<td>3 (3)</td>
<td>1 (5)</td>
<td>7 (14)</td>
<td>0.035</td>
</tr>
<tr>
<td>Total mortality (%)</td>
<td>15 (9)</td>
<td>11 (11)</td>
<td>4 (21)</td>
<td>6 (13)</td>
<td>0.378</td>
</tr>
</tbody>
</table>

Values are mean±SD unless otherwise stated. Men with ischemic heart disease at baseline not included. LTER, long-term electrocardiographic recording; STD, one or more episodes of ischemic ST depression (≥0.1 mV) during ambulatory LTER.

*No medication and diastolic blood pressure (DBP) <95 mm Hg.
†No medication and DBP ≥95 mm Hg.
‡Medication and DBP <95 mm Hg.
§Medication and DBP ≥95 mm Hg.
by guest on November 12, 2017

The lower frequency of ischemic-type ST segment depression and occurrence of ischemic ST segment depression is the lack of resting electrocardiogram or echocardiogram in the present study. Without these tests we cannot determine how many subjects there were with ECG or echocardiographic signs indicating left ventricular hypertrophy. An enlarged left ventricular mass, detected by resting ECG or by echocardiography has been found to be associated with an increased mortality from cardiovascular disease.4142 With the well-established relation between hypertension and left ventricular hypertrophy43 it might be that in some cases, ST segment depression is a sign of left ventricular hypertrophy rather than of transient myocardial ischemia. Considering the high prevalence of treated hypertension in this cohort (20%, i.e., 68 of 341 men), it is reasonable to assume that part of the increased cardiac event rate in men with ischemic-type ST segment depression is explained by hypertension. However, the increased cardiac event rate among men with ischemic ST segment depression was independent of high blood pressure in the analysis (RR, 4.2; 95% CI, 1.3-13.2). Hence, it seems reasonable to conclude that ST segment depression in this study is an expression of myocardial ischemia with or without left ventricular hypertrophy. With new technical achievements it should now be possible to clarify, in a control trial, if blood pressure treatment reduces the occurrence of ischemic-type ST segment depression during ambulatory LTER and if this is followed by a reduced cardiac event rate. It is our conclusion that hypertension in the elderly is associated with an increased occurrence of ischemic-type ST segment depression and an increased cardiac event rate. The incidence of ischemic-type ST segment depression and the rate of cardiac events seems in

### Table 4. Multivariate Analysis of Cardiac Event Rate in Relation to Treatment for Hypertension and Degree of Blood Pressure Control

<table>
<thead>
<tr>
<th>Risk variable</th>
<th>Relative risk (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotension</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Untreated hypertension</td>
<td>0.8 (0.2-3.1)</td>
<td>1.264</td>
</tr>
<tr>
<td>Treated and controlled hypertension</td>
<td>1.4 (0.2-13.0)</td>
<td>0.772</td>
</tr>
<tr>
<td>Treated uncontrolled hypertension</td>
<td>4.2 (1.3-13.2)</td>
<td>0.015</td>
</tr>
<tr>
<td>Treatment for hypertension and ischemic ST depression on LTER</td>
<td>9.8 (2.6-36.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are risk estimates when controlling for following variables: cholesterol, triglycerides, smoking, and alcohol. Relative risk assessment based on comparison with normotensive men without history of ischemic heart disease. CI, confidence interval; DBP, diastolic blood pressure; LTER, long-term electrocardiographic monitoring. Men with ischemic heart disease at baseline not included.

We have in a previous study concluded that ischemic-type ST segment depression during ambulatory LTER should be considered a sign of coronary artery disease.1819 Of course, there are certain scientific limitations in the present type of study. There is the question of the validity of a single blood pressure recording3738; a certain degree of misclassification of normotensive and hypertensive subjects can be expected with only one measurement. The occurrence of ischemic ST segment depression has been found to be associated with transient blood pressure peaks3940. Judging from these studies, one would expect more than 20% with ischemic ST segment depression in the group with no antihypertensive treatment and a diastolic blood pressure equal to or exceeding 95 mm Hg. It is possible that these men have a less than average cardiac event rate because of a less severe blood pressure elevation than the ones put on medication. Another problem associated with the evaluation of blood pressure influence on the occurrence of ischemic ST segment depression is the lack of resting electrocardiogram or echocardiogram in the present study. Without these tests we cannot determine how many subjects there were with ECG or echocardiographic signs indicating left ventricular hypertrophy.

The high incidence of ischemic-type ST segment depression during ambulatory LTER is associated with an increased cardiovascular morbidity and mortality rate.3334 In the present study, 35% (i.e., 25 of the 68 men taking antihypertensive medication and without a history of ischemic heart disease) had one or more episodes of ischemic ST segment depression. The high incidence of ischemic-type ST segment depression (41%) and associated high cardiac event rate (14%) in hypertensive elderly men with adequate blood pressure control (i.e., men with diastolic blood pressure of 95 mm Hg or greater) emphasizes that this is a high risk group for cardiovascular disease. The increased risk of a cardiac event (RR, 9.8; 95% CI, 2.6-36.9) in treated hypertensive subjects with uncontrolled blood pressure and occurrence of ischemic ST segment depression remained when controlling for smoking habits, blood lipids, and high alcohol consumption.

The lower frequency of ischemic-type ST segment depression and the lower cardiac event rate in normotensive subjects and in treated hypertensive men with adequate blood pressure control is compatible with the view that antihypertensive treatment leads to reduced cardiac event rate. The high cardiac event rate in uncontrolled treated hypertensive subjects lends support to the hypothesis that the seeming lack of treatment effects that has been reported in some studies of older patients with hypertension1617 may be, at least partly, explained by an inadequate blood pressure control. In the recently published Systolic Hypertension in the Elderly Program, where the aim was to assess if adequate antihypertensive treatment of isolated systolic blood pressure (160 mm Hg or greater) in older hypertensive subjects (aged 60 years or greater) reduces the incidence of cardiac events, there was a 25% reduction in the drug-treated group in comparison with the placebo-treated group.36

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hypertensive patients, at least partly, to be related to the degree of blood pressure control.

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