Prognosis After the Onset of Coronary Heart Disease

An Investigation of Differences in Outcome Between the Sexes According to Initial Coronary Disease Presentation

Joanne M. Murabito, MD, MSc; Jane C. Evans, MPH; Martin G. Larson, ScD; Daniel Levy, MD

Background. Differences exist between men and women in prognosis after the onset of coronary heart disease (CHD).

Methods and Results. All Framingham Heart Study subjects with the onset of clinically apparent coronary disease from 1951 through 1986 were studied to compare prognosis in men and women according to CHD presentation. Coronary disease presentations included angina, coronary insufficiency (unstable angina), recognized myocardial infarction, unrecognized myocardial infarction, and coronary death. Less than 1% of subjects were lost to follow-up for overall mortality. Cox modeling was used to examine the sex differences in outcome for each coronary presentation. New nonfatal coronary disease developed in 750 men (mean age, 63 years) and 583 women (mean age, 67 years). After onset of angina, men were at greater risk than women for myocardial infarction (hazards ratio [HR], 2.20; 95% confidence interval [CI], 1.45 to 3.34) and coronary death (HR, 2.11; 95% CI, 1.32 to 3.36) after adjustment for age and coronary disease risk factors. After a recognized myocardial infarction, there was a trend toward greater risk for overall mortality in women than men after adjustment for age and risk factors (HR, 0.75; 95% CI, 0.53 to 1.08). In contrast, after an unrecognized myocardial infarction, men were at increased risk for death compared with women (HR, 2.01; 95% CI, 1.28 to 3.15).

Conclusions. Women fare at least as poorly as men after recognized myocardial infarction, whereas women have a more favorable outlook than men after the onset of angina or unrecognized myocardial infarction. The favorable outcome in women after angina and unrecognized myocardial infarction is due, in part, to greater misclassification of these coronary events in women than in men. (Circulation. 1993;88:2548-2555.)

Key Words • angina • myocardial infarction • epidemiology

Whereas differences exist between men and women in the incidence of coronary disease and its initial clinical presentation, it is unclear to what extent prognosis differs between the sexes once the disease becomes manifest.1-3 Although women with angina have a favorable prognosis compared with men,1,6,5 it remains uncertain whether sex differences in prognosis are present after myocardial infarction.5-14 Several reports have shown women to fare substantially worse than men after myocardial infarction,6,9 others have found no sex differences in postinfarction outcome,4,5,10-13 and one report demonstrated a survival advantage in women compared with men.14

Sex differences in the use of invasive diagnostic and therapeutic measures in patients with coronary heart disease have also been demonstrated.15-18 Even in the presence of greater cardiac disability, women are less likely than men to undergo potentially beneficial procedures.15 Sex differences in the rates of surgical revascularization have been observed even in the early postinfarction period.17 However, one recent study reported no sex difference in referral for coronary artery bypass in a high-risk subgroup, raising the possibility that surgical referral may be more appropriate in women.18 The reasons for the differences in management of coronary disease between men and women remain unknown but may be due in part to the perception that chest pain is a benign complaint in women.

The Framingham Study offers an opportunity to examine sex differences in coronary disease presentation and prognosis in a carefully monitored general population sample. The goals of this study were to describe the distribution of initial clinical coronary disease events in men and women, to examine the sex-specific differences in incidence of adverse outcomes after each coronary disease presentation, and to compare outcomes between men and women according to initial presentation.

Methods

Study Sample

The Framingham Heart Study began in 1948, when 2336 men and 2873 women between the ages of 28 and
62 years were enrolled in a prospective study of determinants of cardiovascular disease. The study design and selection criteria have been reported previously.\(^{19,20}\) Subjects with coronary heart disease present at examination 1 were excluded from the present study. Subjects in whom clinically overt coronary heart disease (angina, coronary insufficiency, or myocardial infarction) developed during biennial examinations 2 through 18 (1951 through 1986) were followed through examination 19 (1986 through 1988) for the incidence of myocardial infarction or reinfarction, coronary death, and all-cause mortality.

**Diagnostic Criteria**

Each biennial examination included a physician-administered medical history, physical exam, and 12-lead ECG. A second physician independently evaluated all subjects with a possible coronary disease event. All suspected events were subsequently reviewed and adjudicated by a committee of three physicians who examined all available records, including private physician records, hospital records, autopsy data, and next-of-kin interviews. If more than one event occurred on the same day, the most serious event was considered as the presenting manifestation (coronary death most serious, angina least serious).

Angina was diagnosed when a subject experienced recurrent chest discomfort that was brief in duration (≤15 minutes), precipitated by exertion or emotion, and relieved by rest or nitroglycerin. When the subject had a hospitalization or had personal physician records precisely documenting the onset of angina, the exact date was used; otherwise, the onset of angina was dated as the midpoint between the follow-up examination at which angina was detected and the last angina-free examination the subject attended.

Coronary insufficiency ("unstable angina") was diagnosed when a subject had a history of prolonged (>15 minutes) chest discomfort accompanied by transient ischemic ST-segment and T-wave abnormalities in the absence of elevation of cardiac enzymes or development of Q waves on the ECG. The hospitalization date was used as the date of onset of coronary insufficiency. If a subject developed a myocardial infarction during the hospitalization (within 15 days) for coronary insufficiency, only the myocardial infarction was recorded as a discrete event. Thus, the category of coronary insufficiency includes only subjects with unstable angina uncomplicated by acute myocardial infarction.

A recognized myocardial infarction was present when an episode of prolonged chest discomfort was accompanied by either serial ECG changes of infarction or elevation of cardiac enzymes. A recognized myocardial infarction was assigned the date of hospitalization. An unrecognized myocardial infarction was present when the ECG obtained at a follow-up examination or an interim hospitalization revealed new pathological Q waves or loss of R-wave potentials consistent with a myocardial infarction in the absence of symptoms precipitating a medical evaluation for the presence of coronary disease. An unrecognized myocardial infarction was assigned the midpoint date between the ECG on which the myocardial infarction was first detected and the subject's last available tracing free of evidence of the infarction.

Death from coronary disease (sudden or nonsudden) was recorded when available information clearly indicated that the cause of death was coronary disease and the death could not be attributed to another cause.

**Risk Factor Assessment**

Risk factor measurements were taken from the examination before the presenting coronary disease event and included age, resting blood pressure, smoking status, urine sample for glycosuria, and random serum glucose and lipid analysis. When risk factor data were missing from that examination, information from preceding examinations (up to two prior examinations and not more than 6 years before the coronary event) was used. Definite hypertension was diagnosed when the systolic blood pressure was ≥160 mm Hg or the diastolic blood pressure was ≥95 mm Hg on each of two readings taken by the examining physician or if the subject was receiving antihypertensive drug therapy. A subject was considered a current smoker if he or she regularly smoked any cigarettes in the year preceding the examination. A subject was diagnosed with diabetes when a random blood glucose level ≥8.33 mmol/L (150 mg/dL) was noted at two or more examinations; or if the subject was under treatment with insulin or an oral hypoglycemic agent; or if the subject had an abnormal glucose tolerance test.

**Outcome Events**

Subjects were followed for the occurrence of myocardial infarction or reinfarction (either recognized or unrecognized), coronary disease death, or death from any cause. In subjects with a recognized myocardial infarction, an infarct extension or reinfarction that occurred during the same hospitalization was not considered a separate event from the primary myocardial infarction.

Less than 1% of the study population was lost to follow-up for overall mortality.

**Statistical Analysis**

*Sex-specific differences among coronary presentations.* Direct age-adjusted prevalences of the dichotomous risk factors were computed within sex for each clinical presentation group, and the Cochran-Mantel-Haenszel statistic\(^{21}\) (SAS procedure `FREQ`) was used to test for overall statistical differences. Linear regression analyses\(^ {22}\) (SAS procedure `GLM`) were performed to compute age-adjusted means within sex for the continuous risk factors and to test for differences between groups. Sex-specific age-adjusted survival analyses were used to compute the incidence rates of subsequent myocardial infarction, coronary death, and overall mortality according to the initial clinical presentation. The logrank test\(^ {23}\) (SAS procedure `LIFETEST`) was used to test for differences in event rates among the four coronary disease presentation groups. The mean duration of follow-up from onset of coronary disease in the Kaplan-Meier analyses was 10.35 years ± 7.8 years. Statistical significance was assessed as \(P < 0.05\) per comparison.

* Differences between the sexes by coronary presentation.* Kaplan-Meier survival analyses, age-adjusted within coronary presentation type, were used to plot survival free of myocardial infarction in subjects with angina and to plot survival in subjects with recognized or unrecog-
nized myocardial infarction. Cox proportional hazards modeling \(^{22}\) (SAS procedure \texttt{PHREG}) was used to examine sex differences in time to onset of each end point. All analyses were carried out separately for each coronary disease presentation using a follow-up period of up to 10 years. The initial Cox model used sex as the only covariate; subsequent models incorporated age and then age plus traditional coronary disease risk factors (including cholesterol, diabetes, hypertension, and smoking status). Hazard ratios (HR) and 95% confidence intervals (CI) for outcome events in men versus women were generated. Complete risk factor data were available for 89% of subjects.

Results

Distribution of Initial Coronary Events

Sixty-five subjects (46 men and 19 women) in whom coronary disease was detected at examination 1 were excluded. Of the 5144 remaining subjects, 1569 (895 men, 674 women) developed a new coronary heart disease event. The mean age at onset of coronary disease was 63 years (range, 32 to 89) in men and 67 years (range, 43 to 90) in women. The initial presenting manifestation of coronary disease was angina in 610 subjects (39%), coronary insufficiency in 102 (6%), recognized myocardial infarction in 385 (25%), unrecognized myocardial infarction in 236 (15%), and coronary death in 240 (15%) (Table 1). Sudden death accounted for nearly two thirds of the coronary deaths and was the initial manifestation of coronary disease in 10.8% of men and 8.3% of women. Myocardial infarction (recognized or unrecognized) was the most frequent coronary disease presentation in men, whereas angina was the most frequent in women. Unrecognized myocardial infarctions accounted for one third of the infarctions in men and nearly half (45%) of the infarctions in women. Coronary insufficiency was an uncommon presenting manifestation of coronary disease.

Risk Factor Profile Within Sex According to Coronary Presentation

Differences in coronary disease risk factor profiles between groups were observed (Table 2). Men presenting with coronary death or unrecognized myocardial infarction were older than those with other presentations, and men with coronary insufficiency had a particularly adverse risk factor profile, with high prevalences of diabetes and hypertension. In women, diabetes was

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
\textbf{Risk Factor} & \textbf{Angina} & \textbf{Cl} & \textbf{Rec MI} & \textbf{Unrec MI} & \textbf{CHD Death} & \textbf{Overall P*} \\
\hline
\textbf{Men} & & & & & & \\
\hline
\textbf{Age, y} & 61 & 59 & 62 & 66 & 64 & <.001 \\
\textbf{Cholesterol, mmol/L} & 6.19 & 6.19 & 6.07 & 6.00 & 6.14 & .53 \\
\textbf{Diabetes, %} & 10 & 22 & 8 & 18 & 10 & .002 \\
\textbf{Hypertension, %} & 35 & 54 & 34 & 41 & 44 & .064 \\
\textbf{Smokers, %} & 57 & 67 & 58 & 62 & 67 & .21 \\
\hline
\textbf{Women} & & & & & & \\
\hline
\textbf{Age, y} & 64 & 67 & 69 & 68 & 70 & <.001 \\
\textbf{Cholesterol, mmol/L} & 6.71 & 6.91 & 7.01 & 6.35 & 6.98 & .01 \\
\textbf{Diabetes, %} & 12 & 10 & 22 & 16 & 25 & .004 \\
\textbf{Hypertension, %} & 49 & 43 & 51 & 63 & 46 & .21 \\
\textbf{Smokers, %} & 22 & 41 & 45 & 25 & 29 & <.001 \\
\hline
\end{tabular}
\caption{Age-Adjusted Coronary Disease Risk Factors by CHD Presentation}
\end{table}

CHD indicates coronary heart disease; Cl, coronary insufficiency; Rec MI, recognized myocardial infarction; and Unrec MI, unrecognized myocardial infarction.

*Comparisons among CHD presentations, separately for men and women, were as follows: linear regression was used to compare mean ages and to compare age-adjusted mean cholesterol levels; the Cochran-Mantel-Haenszel test was used to compare age-adjusted prevalences for diabetes, hypertension, and smoking.
most prevalent in those with a recognized myocardial infarction or coronary death. Women presenting with angina or unrecognized myocardial infarction had more favorable risk factor profiles than women with other coronary disease presentations: they were less likely to be smokers. Women with angina were younger, and those with an unrecognized myocardial infarction had lower cholesterol levels than other women.

**Sex-Specific Incidence of Adverse Events by Coronary Presentation**

Important differences in the rates of subsequent myocardial infarction according to the initial coronary disease presentation were noted in women but not in men (Table 3, A). In men, there were no significant differences in the incidence of subsequent myocardial infarction at 2 or 10 years between presentation groups. After 10 years of follow-up, the rates of myocardial infarction in women differed significantly among presentation groups ($P=0.02$), with the highest rates in the recognized myocardial infarction group (34.8%) and the unrecognized myocardial infarction group (24.9%) and lower rates in women presenting with angina (17.8%) or coronary insufficiency (13.0%).

Coronary death rates differed significantly by initial coronary presentation ($P<0.001$) in both sexes (Table 3, B). The 2-year rates of coronary death in the recognized infarction group greatly exceeded those of other coronary disease presentations. At 10 years, coronary death rates continued to be highest in the recognized myocardial infarction group, whereas coronary death rates for those with angina and coronary insufficiency were lower, particularly so in women.

Overall mortality rates were significantly different across coronary disease presentations both at 2 ($P<0.001$) and at 10 ($P<0.001$) years (Table 3, C). Early mortality rates for men and women were highest in those presenting with a recognized myocardial infarction, reflecting the high coronary death rate in this group. In contrast, late mortality in men was highest in the unrecognized myocardial infarction group, whereas in women it was highest in the recognized myocardial infarction group.

With regard to nearly all outcomes, subjects with coronary insufficiency (unstable angina uncomplicated by acute myocardial infarction during the first 15 days of hospitalization) had a prognosis similar to that of subjects with angina.

**Differences in Outcome Between the Sexes**

**Angina.** In subjects presenting with angina, men experienced a higher myocardial infarction rate than women throughout the follow-up period (Fig 1). Men with angina were at greater risk for all outcomes than women (Table 4, A). This persisted after adjustment for age and risk factors. The male-to-female HR for myocardial infarction after the onset of angina was 2.20 (95% CI 1.45, 3.34), for coronary death it was 2.11 (95% CI 1.32, 3.36), and for total mortality it was 1.59 (95% CI 1.14, 2.24).

**Coronary insufficiency.** Sex differences in risk after the onset of coronary insufficiency were not significant (Table 4, B), even though a 40% increased risk for both

---

**TABLE 3. Age-Adjusted 2- and 10-Year Incidence of Outcome Events According to CHD Presentation**

<table>
<thead>
<tr>
<th>CHD Presentation</th>
<th>2-Year</th>
<th>10-Year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Myocardial infarction rates by Initial CHD presentation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>14.3</td>
<td>33.4</td>
</tr>
<tr>
<td>Coronary insuff</td>
<td>7.7</td>
<td>23.1</td>
</tr>
<tr>
<td>Recognized MI</td>
<td>9.1</td>
<td>28.4</td>
</tr>
<tr>
<td>Unrecognized MI</td>
<td>8.1</td>
<td>20.6</td>
</tr>
<tr>
<td>$P^*$</td>
<td>.12</td>
<td>.15</td>
</tr>
<tr>
<td><strong>B. Coronary heart disease death rates by Initial CHD presentation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>5.5</td>
<td>28.2</td>
</tr>
<tr>
<td>Coronary insuff</td>
<td>3.4</td>
<td>27.5</td>
</tr>
<tr>
<td>Recognized MI</td>
<td>20.1</td>
<td>40.8</td>
</tr>
<tr>
<td>Unrecognized MI</td>
<td>5.5</td>
<td>34.0</td>
</tr>
<tr>
<td>$P^*$</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>C. Overall mortality rates by initial CHD presentation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>6.8</td>
<td>41.5</td>
</tr>
<tr>
<td>Coronary insuff</td>
<td>5.8</td>
<td>47.5</td>
</tr>
<tr>
<td>Recognized MI</td>
<td>23.6</td>
<td>52.8</td>
</tr>
<tr>
<td>Unrecognized MI</td>
<td>13.1</td>
<td>58.0</td>
</tr>
<tr>
<td>$P^*$</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Insuff indicates insufficiency and MI, myocardial infarction.

*Incidence rates over 2 years of follow-up and also over 10 years of follow-up were compared among CHD presentation types using age-stratified logrank tests separately for men and women.
subsequent myocardial infarction and total mortality was noted in men compared with women after adjustment for age and risk factors. Moderate sex differentials would not be statistically significant given the small samples and numbers of events observed. With a true hazard differential of 40%, power is only 11% to 17%, depending on outcome type.

**Recognized myocardial infarction.** After a recognized myocardial infarction, the unadjusted models revealed a worse prognosis in women than in men for all outcomes, significantly so for coronary death (HR, 0.57; 95% CI, 0.41, 0.80) and total mortality (HR, 0.55; 95% CI, 0.42, 0.73) (Table 4, C). The sex differences diminished but did not disappear with age and risk-factor adjustments. The age-adjusted models for coronary death gave a HR of 0.84 (95% CI, 0.59, 1.19); additional adjustment for cardiac risk factors made little difference (HR, 0.88; 95% CI, 0.57, 1.37). Nevertheless, the age-adjusted and risk-factor–adjusted model for overall mortality demonstrates an increased risk in women compared with men. Men experienced only 75% of the overall mortality observed in women after a recognized myocardial infarction; however, this finding was not statistically significant (HR, 0.75; 95% CI, 0.53, 1.08) because of limited power (44% if the true HR is 0.75). Women fared worse than men after a recognized myocardial infarction with respect to overall mortality throughout the entire study period (Fig 2).

**Unrecognized myocardial infarction.** There were no significant sex differences in risk of recurrent infarction after an unrecognized myocardial infarction. In contrast to outcomes after a recognized myocardial infarction, men fared worse than women with respect to coronary death and overall mortality after an unrecognized myocardial infarction (Table 4, D). Compared with women, men had nearly twice the risk for coronary death after

### TABLE 4. Sex Differences in Risk for Outcome Events According to Initial CHD Presentation: 10-Year Follow-up, Hazard Ratio* (95% Confidence Interval) Men Versus Women

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unadjusted</th>
<th>Age-Adjusted</th>
<th>Age- and RF-Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Angina as the Initial CHD presentation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>2.05 (1.44, 2.93)</td>
<td>2.10 (1.47, 3.01)</td>
<td>2.20 (1.45, 3.34)</td>
</tr>
<tr>
<td>CHD death</td>
<td>1.89 (1.28, 2.79)</td>
<td>2.20 (1.48, 3.25)</td>
<td>2.11 (1.32, 3.36)</td>
</tr>
<tr>
<td>Total mortality</td>
<td>1.49 (1.12, 1.99)</td>
<td>1.74 (1.30, 2.33)</td>
<td>1.59 (1.14, 2.24)</td>
</tr>
<tr>
<td><strong>B. Coronary Insufficiency as the Initial CHD presentation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>2.16 (0.82, 5.69)</td>
<td>2.15 (0.78, 5.89)</td>
<td>1.43 (0.45, 4.52)</td>
</tr>
<tr>
<td>CHD death</td>
<td>1.02 (0.40, 2.66)</td>
<td>1.43 (0.54, 3.76)</td>
<td>1.05 (0.32, 3.46)</td>
</tr>
<tr>
<td>Total mortality</td>
<td>1.07 (0.56, 2.04)</td>
<td>1.40 (0.72, 2.72)</td>
<td>1.35 (0.60, 3.02)</td>
</tr>
<tr>
<td><strong>C. Recognized myocardial infarction as the Initial CHD presentation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>0.71 (0.43, 1.18)</td>
<td>0.77 (0.45, 1.30)</td>
<td>0.80 (0.43, 1.51)</td>
</tr>
<tr>
<td>CHD death</td>
<td>0.57 (0.41, 0.80)</td>
<td>0.84 (0.59, 1.19)</td>
<td>0.86 (0.57, 1.37)</td>
</tr>
<tr>
<td>Total mortality</td>
<td>0.55 (0.42, 0.73)</td>
<td>0.83 (0.62, 1.11)</td>
<td>0.75 (0.53, 1.08)</td>
</tr>
<tr>
<td><strong>D. Unrecognized myocardial infarction as the Initial CHD presentation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>0.89 (0.47, 1.67)</td>
<td>0.89 (0.47, 1.67)</td>
<td>1.28 (0.61, 2.68)</td>
</tr>
<tr>
<td>CHD death</td>
<td>1.26 (0.73, 2.17)</td>
<td>1.29 (0.75, 2.22)</td>
<td>1.75 (0.92, 3.31)</td>
</tr>
<tr>
<td>Total mortality</td>
<td>1.32 (0.93, 1.90)</td>
<td>1.47 (1.02, 2.11)</td>
<td>2.01 (1.28, 3.15)</td>
</tr>
</tbody>
</table>

RF indicates risk factors: cholesterol, diabetes, hypertension, smoking; CHD, coronary heart disease; and MI, myocardial infarction.

A. Angina: In men there were 80 Mls, 67 CHD deaths, and 106 total deaths. In women there were 49 Mls, 41 CHD deaths, 83 total deaths. Risk factor data were complete for 268 men and 296 women.

B. Coronary insufficiency: In men there were 13 Mls, 9 CHD deaths, and 20 total deaths. In women there were 6 Mls, 8 CHD deaths, 17 total deaths. Risk factor data were complete for 48 men and 47 women.

C. Recognized myocardial infarction: In men there were 50 Mls, 93 CHD deaths, and 131 total deaths. In women there were 22 Mls, 57 CHD deaths, 80 total deaths. Risk factor data were complete for 233 men and 100 women.

D. Unrecognized myocardial infarction: In men there were 21 Mls, 35 CHD deaths, and 83 total deaths. In women there were 18 Mls, 21 CHD deaths, 47 total deaths. Risk factor data were complete for 121 men and 80 women.

*Experiences of men and women were compared by use of proportional hazards models for each outcome, by presentation type, unadjusted for age and risk factors, age-adjusted only, and age-adjusted plus risk-factor–adjusted.
correction for age and coronary disease risk factors (HR, 1.75; 95% CI, 0.92, 3.31), and they had twice the risk for total mortality (HR, 2.01; 95% CI, 1.28, 3.15) compared with women (Fig 3; Table 4, D).

Discussion

This study documents important sex differences in prognosis after the onset of coronary disease. Our analyses reveal that prognosis is worse in men than in women after the onset of angina and unrecognized myocardial infarction, whereas women fare at least as poorly as men after a recognized myocardial infarction. The better prognosis in women with angina must be regarded with caution, since many women presenting with chest pain, even those with symptoms typical of angina, do not have true coronary artery disease.27-30 Similarly, the favorable prognosis of women with unrecognized myocardial infarction may also be due to diagnostic misclassification. The difference in prognosis for men and women after an initial manifestation of coronary disease appears to depend largely on the likelihood of the presence of coronary disease. When the diagnosis is very likely to be correct, such as in recognized myocardial infarction, women do less well than men. When the diagnosis is less certain for women than men, such as for angina, women have a more favorable outlook than men.

Sex Differences in Prognosis After Recognized Myocardial Infarction

In accord with other studies, our initial analyses revealed that women fared worse than men with respect to coronary mortality and overall mortality after a recognized myocardial infarction.6-9 On average, however, women were 7 years older than men at the time of recognized myocardial infarction. Adjustment for age reduced the postinfarction coronary survival disadvantage in women, yet a trend toward excess overall mortality in women persisted after adjustment for age and risk factors. The higher mortality rates in women than in men after recognized myocardial infarction, therefore, appear to be only partly due to differences in age at onset of the disease.

Our study is consistent with two prior reports that documented a worse postinfarction prognosis in women than men.8,9 The Multicenter Investigation of the Limitation of Infarct Size (MILIS) study reported an adverse postinfarction prognosis for women compared with men, especially for black women.8 As in our study, women in the MILIS study were older than the men and had higher prevalence of hypertension and diabetes. MILIS reported cumulative 48-month postinfarction mortality rates of 36% in women and 21% in men, very similar to our 2-year mortality rates in the recognized myocardial infarction group of 35% and 24%, respectively (Table 3, C).

The Secondary Prevention Reinfarction Israeli Nitrendipine Trial (SPRINT) likewise found women to fare worse than men after an infarction.9 Unlike our study sample, 50% of SPRINT patients had prior angina, and 19% of women and 27% of men had a previous myocardial infarction. Two-year postinfarction mortality rates in our study sample are remarkably similar to the 1-year mortality rates in the SPRINT study (23.6% versus 23.1% for men, 35.2% versus 31.8% for women). Furthermore, among hospital survivors in the SPRINT study, the relative odds of mortality at 1 year in women versus men were 1.32, which is nearly identical to our age- and risk-factor-adjusted HR for 10-year mortality in women versus men of 1.33 (Table 4, C, inversion of the HR for total mortality in men versus women of 0.75). Our risk estimate did not achieve statistical significance because of the relatively small number of subjects, which limited our study power.

Other investigators have reported no prognostic differences between men and women after myocardial infarction once the contributions of age alone11,12 or age and clinical risk factors10,13 are taken into account. Differences in study populations and study size (and thus, power to detect a sex difference in prognosis after infarction) may be responsible for the varying conclusions between investigations.

Sex Differences in Prognosis After Angina

Favorable prognosis after the onset of angina in women compared with men has been reported previously in clinical studies with respect to both coronary attacks1 and mortality.5,31,32 Weinblatt et al3 reported that the observed survival advantage in women with angina was diminished when the female group of the Health Insurance Plan of Greater New York was limited to those with frequent exertional chest discomfort, reflecting the concern that women reporting anginal symptoms were more likely not to have true underlying coronary disease than men. Similarly, studies correlating chest pain symptoms with coronary angiography have demonstrated a higher prevalence of coronary disease in men than in women with clinically diagnosed angina.27,28 This finding is especially true in younger groups, in which only half the women with angina or suspected coronary disease had significant disease on
coronary angiography, in contrast to 90% of men with similar symptoms. Thus, the prognosis after the onset of angina would be expected to be better in women than in men because fewer women than men with clinically diagnosed angina actually have coronary disease.

Despite the better prognosis in women compared with men after angina onset, their prognosis compared with women free of clinically overt coronary disease is not benign. A prior report from the Framingham Study has shown that women with angina have five times the risk for a subsequent coronary event (coronary insufficiency, myocardial infarction, or coronary death) compared with women free of chest discomfort symptoms, a risk gradient just as high as that observed for men with angina.

Comparison With Prior Framingham Study Reports

Our results are consistent with an earlier report from the Framingham Study by Lerner and Kannel, who reported that women fared worse than men after a "coronary attack" (myocardial infarction or coronary insufficiency), with case fatality rates of 32% and 27% for women versus men. These estimates of case fatality are very similar to our 2-year death rates (35% and 24% in women and men, respectively) after a recognized myocardial infarction (Table 3, C). This report extends the prior study by using methodology that includes age and risk factor status into the assessment of differences in outcome between women and men. In the present study, the unadjusted model did reveal a significantly worse prognosis in women than men after a recognized infarction, with a persistent trend toward excess mortality in women compared with men after age and risk factors were accounted for.

Another Framingham Study investigation demonstrated a coronary survival advantage in women compared with men after a myocardial infarction. That report, by Wong et al, included survivors of a first myocardial infarction (either a recognized or unrecognized myocardial infarction) who attended their next follow-up examination, on average, 1 year later. This may have led to some selection biases, since subjects who failed to attend the follow-up examination were more likely to be women, to have suffered a recognized myocardial infarction, and to have a greater likelihood of a Q-wave event. Therefore, the most unstable women suffering a recognized infarction were likely to be excluded. Additionally, in that study, subjects with recognized and unrecognized myocardial infarctions were pooled, whereas in our study, subjects with recognized and unrecognized myocardial infarctions were analyzed separately and were found to have different prognoses.

Study Strengths

The Framingham Heart Study provides a unique opportunity to study prognosis after the onset of coronary heart disease and to compare prognosis in men and women. The study is population-based and includes comparable numbers of men and women. Prospectively obtained coronary disease risk factor data were available in 89% of subjects, and ascertainment of subsequent outcome events was nearly complete, with <1% of the study population lost to follow-up for mortality.

Finally, standardized definitions of coronary disease events were used. A review panel determines these events blinded to subject's sex, reducing sex-related biases in diagnostic thresholds for coronary disease. In contrast, most previous investigations used select clinical populations composed primarily of men, and they did not focus on the presenting manifestation of coronary disease. With ECGs obtained routinely every 2 years, our study was uniquely qualified to investigate unrecognized myocardial infarction, which was the initial coronary disease manifestation in 15% of subjects.

Study Limitations

Our study used a clinical diagnosis of coronary disease; hence, there are misclassifications. This is most problematic for the diagnoses of angina and unrecognized myocardial infarction. Women with chest pain have a lower prevalence of angiographically proven coronary disease than men, leading to a higher false-positive diagnosis of true coronary disease in women with angina. Additionally, ECG interpretation may have been more difficult in women because of lead placement issues arising from breast tissue. A greater misclassification of the diagnoses of angina and unrecognized myocardial infarction in women in this study is supported to some degree by their more favorable risk factor profile compared with women with other coronary disease presentations. This finding was not observed in men presenting with angina or unrecognized myocardial infarction.

Our study had modest sample sizes for some coronary presentations (in particular, coronary insufficiency) and some outcome events (especially myocardial infarction after any presentation except angina). This limited the power to detect sex differences. Even if the true HR were on the order of 1.50, there would be <25% power for all outcomes after coronary insufficiency and <35% power to detect sex differences in myocardial infarction and coronary death after an unrecognized myocardial infarction. Thus, some of our results may represent real sex differences but of a magnitude that did not reach statistical significance because of sample size limitations.

This study spans more than 35 years, during which time there have been changes in the incidence of coronary disease as well as a decline in the death rate from the disease. Advances in medical and surgical treatment of coronary disease may have enhanced overall survival and survival free of subsequent coronary events in recent years. Future studies are needed to determine the impact of changes in the incidence of coronary disease and improvements in diagnosis and treatment of the disease.

Conclusions

Coronary disease presentation differed between men and women. Men were most likely to present with myocardial infarction, whereas angina was the most common presentation in women. In addition, one third of infarctions were unrecognized in men, whereas nearly one half were unrecognized among women. Women fared at least as poorly as men after a recognized myocardial infarction; however, women had a more favorable prognosis than men after angina or unrecognized myocardial infarction. The sex differences in prognosis after an initial coronary presentation ap-
pear to depend partly on the likelihood of the presence of coronary disease. When the diagnosis is very certain, such as in recognized myocardial infarction, women do as poorly as men, whereas when the diagnosis is less certain in women, such as in angina, women do better than men. Since outcome after recognized myocardial infarction is at least as poor in women as in men, potentially beneficial diagnostic and therapeutic modalities should be equally available to both sexes.

Acknowledgments

This study was supported in part by National Institutes of Health grant N01-HC-38038. The authors wish to thank Sharon Rich for technical assistance in preparing the tables for the manuscript.

References

Prognosis after the onset of coronary heart disease. An investigation of differences in outcome between the sexes according to initial coronary disease presentation.

J M Murabito, J C Evans, M G Larson and D Levy

_Circulation_. 1993;88:2548-2555
doi: 10.1161/01.CIR.88.6.2548

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/88/6/2548

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/