Clinical research

Sex, age, and clinical presentation of acute coronary syndromes

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Received 28 October 2003; revised 15 February 2004; accepted 19 February 2004

Aim To investigate sex differences in clinical presentation in younger and older patients hospitalised with a wide spectrum of acute coronary syndromes (ACS).

Methods and results We analysed 10 253 patients with a discharge diagnosis of ACS in the Euro Heart Survey of patients with Acute Coronary Syndromes. There were 1010 women and 3709 men <65 years. Among patients <65 years, fewer women than men presented with ST elevation, (OR [odds ratio]: 0.62 [0.53–0.71]) and developed Q-wave myocardial infarction (OR 0.58 [0.50–0.67]), whereas in patients ≥65 years there was no significant sex difference. Women <65 years were more likely than men of the same age to be discharged with a diagnosis of unstable angina (OR 1.56 [1.35–1.79]), but there was no sex difference in older patients; the p for interaction between sex and age for both was <0.0001. Among patients who underwent coronary angiography, both younger and older women were less likely than men to have 3-vessel or main stem disease. In a logistic regression analysis stratified for age, female sex was a significant negative determinant of presenting with ST elevation in patients <65 years (OR 0.68 [0.58–0.79]), whereas there was no effect of sex in patients ≥65 years.

Conclusion In younger patients with ACS, women were less likely than men to present with ST elevation and more likely to be discharged with a diagnosis of unstable angina. In older patients there were no differences in clinical presentation. Both older and younger women had less extensive atherosclerosis. The findings suggest a different pathophysiology of ACS in younger, but not older, women.

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KEYWORDS
Myocardial infarction; Women; Sex; Age; Thrombolytic therapy; Coronary angiography

Introduction

Coronary heart disease is the single most common cause of death in both women and men in large parts of the industrialised world, but there are several clinically important differences between men and women. Although the incidence of acute myocardial infarction (AMI) increases sharply with age, women are less prone to develop AMI than men at any given age, with a lag of approximately 9–10 years between the sexes.1–3 The difference in mortality and morbidity diminishes with
age, but even between the ages of 75 and 85 years the incidence is almost twofold greater in men than in women. The difference in age seems to be less pronounced for non-Q-wave AMI and non-ST-elevation AMI, and may be still smaller for unstable angina.

Women and men with acute coronary syndromes (ACS) have been found to have different clinical profiles and presentation, with a smaller percentage of women than men presenting with ST-elevation AMI, but more presenting with unstable angina. We have previously shown, in a large population of unselected patients with ACS in Europe and the Mediterranean basin, that women have worse baseline clinical characteristics, undergo fewer revascularisation procedures, and have a higher mortality. However, after adjusting for baseline differences, sex had no impact on mortality. Although studies addressing differences in aspects of coronary heart disease between men and women routinely adjust for age differences, few have examined whether the effects of sex differ according to age. Because age and sex both influence clinical presentation in ACS, it may be important to investigate age-specific sex differences. The present analysis was undertaken with the aim of investigating possible age-specific sex differences with respect to clinical presentation in a large population of patients with AMI and unstable angina.

Methods

Euro heart survey of patients with acute coronary syndromes

The details of the Euro Heart Survey ACS have been described in detail elsewhere. The survey was performed in clusters composed of academic and non-academic hospitals and hospitals with and without cardiac catheterisation laboratories and cardiac surgery facilities. During the enrolment period from September 4, 2000 to May 15, 2001, 14,271 patients in 25 countries with suspected acute coronary syndrome were screened, of whom 10,484 were finally diagnosed with either AMI or unstable angina. Data on either age or sex were missing for 231 patients, leaving 10,253 who form the study population of the present analysis.

For all patients, the tentative initial diagnosis made by the attending physicians was recorded based on the initial electrocardiographic pattern: ACS with ST elevation, ACS without ST elevation, and ACS with an undetermined electrocardiographic pattern. The full case report form was filled out for patients with a confirmed diagnosis of unstable angina or AMI, who were categorised according to the discharge diagnosis as either unstable angina, non-Q-wave AMI, or Q-wave AMI.

The case report form included details of the demographic, clinical, and electrocardiographic characteristics of the patient, diagnostic and treatment modalities, in-hospital complications, and discharge status. Hyperlipidaemia was defined as a previous diagnosis by a physician, receiving lipid-lowering therapy, or either total cholesterol over 5 mmol/l or serum triglycerides over 2 mmol/l. Hypertension was defined as a previous diagnosis by a physician, receiving medication to lower blood pressure, or known blood pressure values of ≥140 mm Hg systolic or ≥90 mm Hg diastolic on two or more occasions. Diabetes was defined as a previous diagnosis by a physician. Current smoking was defined as smoking up to 1 month before admission. Chronic angina was defined as having had angina before at least 30 days before admission.

Coronary angiography was done in 5437 patients. The presence of ≥50% stenosis in any of the three main vessels or the left coronary main stem was recorded.

Analysis

Patients were divided into subgroups based on sex and age (<55, 55–64, 65–74, and ≥75 years). To facilitate comparisons between men and women while striving to retain sufficient statistical power in each age group, we arbitrarily selected a cutoff point of 65 years to differentiate between younger and older patients in most analyses. We analysed the age and sex-specific clinical characteristics, reperfusion therapy (in patients with ST-elevation ACS only), and angiographic findings.

Statistical methods

All analyses were performed using SAS software, version 8e. All tests were two-sided and P-values below 0.05 were considered significant. Differences in proportions were tested with Mantel–Haenszel tests, with stratification into two age categories (<65 years, and ≥65 years). The associations between ST-elevation AMI, Q-wave AMI, or 3-vessel or left main disease and age as a continuous variable were tested separately for men and women with simple Pearson correlation tests. Odds ratios with 95% confidence intervals for differences in proportions between women and men were calculated by logistic regression. We did not adjust for multiple statistical testing because many of the variables that were tested were intercorrelated and to do so would have increased the likelihood of type II error. However, confidence intervals are presented for all main findings.

To determine whether the differences in clinical presentation between men and women at different ages, as defined by the proportion of ST-elevation ACSs, were due to differences between the sexes in baseline clinical and demographic characteristics, we adjusted for these variables by logistic regression models. Independent variables that were significantly different between men and women in univariate analysis were entered, including age, smoking, hypertension, diabetes, prior AMI, chronic angina, and prior revascularisation. Because body mass index (BMI) was missing in 14% of the subjects, we included this variable in a second logistic analysis. A possible interaction between sex and age was tested in logistic regression with an interaction term (age × sex) created with age as a continuous variable and introduced in the logistic regression model with the relevant presenting diagnosis as the dependent variable. We also included, alone or separately, interaction terms for other variables, where a possible interaction could be detected with respect to age and other clinical variables.

Results

Coronary risk factors and prior disease

Obesity (body mass index [BMI] greater than 30 kg/m²) was present in 31% of women <65 years, but only in 23%
of men of the same age, and in 24% and 16%, respectively, in women and men ≥65 years (Table 1). Diabetes and hypertension were more common in women than men, irrespective of age. Over half (52%) of the younger men were current smokers, compared to 35% among the younger women but only 19% and 9%, respectively, among the older men and women. Relatively more men than women had a prior AMI, regardless of age. However, after stratification for age there were no major differences between men and women with respect to prior heart failure, prior cerebrovascular events, or prior medication with aspirin, β-blockers, or statins.

Clinical presentation

The highest proportion of ST-elevation ACS was found among young men <55 years (Fig. 1). With age, the proportion of ST-elevation ACS decreased in men (p < 0.0001). Among women there was a much weaker association overall between ST-elevation ACS and age (p = 0.06 with age as a continuous variable). Of men <65 years, over half (51%) presented with ST elevation, compared to 39% of women of the same age, yielding an OR (odds ratio) for women compared to men of 0.62 (95% confidence interval 0.53 to 0.71) (Table 2). Among men and women ≥65 years, 36% and 38%, respectively, presented with ST elevation (OR 0.92 [0.83–1.03]). There was a highly significant interaction between age and sex (p < 0.0001). Conversely, presentation with non-ST-elevation ACS was more common in younger women than in younger men, with a much less marked sex difference among older patients. Presentation with an undetermined electrocardiogram was slightly less common in older women than in older men, with no sex difference in the younger age group.

There was a strong association between age and Q-wave AMI among men (p < 0.0001), but no relation in women (p = 0.67; Fig. 2). The most common discharge diagnosis among the younger women with ACS was unstable angina (47%), followed by Q-wave AMI (27%) and non-Q-wave AMI (25%). Among younger men, Q-wave AMI was the most common diagnosis (40%), followed by unstable angina (37%) and non-Q-wave AMI (23%), with highly significant interaction effects.

**Table 1** Baseline risk factors and prior disease by sex and age in the Euro Heart Survey of Acute Coronary Syndromes

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Women</th>
<th>Men</th>
<th>Odds ratio (95% CI)</th>
<th>Women</th>
<th>Men</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese (BMI &gt; 30 kg m⁻²)</td>
<td>31 (281)</td>
<td>23 (768)</td>
<td>1.53 (1.10–1.98)</td>
<td>24 (443)</td>
<td>16 (423)</td>
<td>1.71 (1.47–1.99)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>23 (237)</td>
<td>18 (656)</td>
<td>1.43 (1.21–1.69)</td>
<td>30 (702)</td>
<td>24 (757)</td>
<td>1.41 (1.25–1.59)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>53 (531)</td>
<td>52 (1931)</td>
<td>1.02 (0.89–1.17)</td>
<td>45 (1047)</td>
<td>42 (1347)</td>
<td>1.14 (1.03–1.27)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>64 (645)</td>
<td>48 (1786)</td>
<td>1.90 (1.65–2.20)</td>
<td>70 (1612)</td>
<td>59 (1882)</td>
<td>1.62 (1.44–1.81)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>35 (349)</td>
<td>52 (1913)</td>
<td>0.50 (0.43–0.57)</td>
<td>9 (209)</td>
<td>19 (622)</td>
<td>0.41 (0.35–0.49)</td>
</tr>
</tbody>
</table>

All figures are percentages (number), unless stated otherwise.
Missing data for body mass index in 1398 subjects (327 men, 103 women below 65 years, 497 men and 471 women 65 years and older).

*P < 0.0001 for women compared to men, both age groups.

**Fig. 1** Acute coronary syndrome with ST elevation by age and sex in 10,253 patients in the Euro Heart Survey of patients with Acute Coronary Syndromes. P-value for association with age in women, 0.06, and in men, <0.0001.
between age and sex for Q-wave AMI and unstable angina ($p < 0.0001$ for both; Table 2). The presenting symptoms did not differ much by sex when stratified for age. In the younger age group, there was no difference with respect to Killip class on arrival, whereas older women presented with a higher Killip class than men of the same age (Mantel–Haenzsel test across the four Killip categories: $p = 0.009$; age–sex interaction: $p = 0.012$).

Among patients $<65$ years with ST-elevation ACS, 65% of the men and 62% of the women received some form of reperfusion therapy. In about one third of the cases primary percutaneous coronary interventions were performed and in two thirds, fibrinolytic therapy was given (Table 3). In older patients, 53% of the men but only 43% of the women received reperfusion therapy (OR 0.66 [0.55–0.78]; age–sex interaction $p < 0.0001$).

Among patients $<65$ years, coronary angiography was performed in 65% of the men and 57% of the women (Table 4), with corresponding figures of 49% and 38% in men and women $\geq 65$ years, respectively. Overall, more than 90% had at least one significant stenosis. Of the

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Clinical presentation by age group in women and men in the Euro Heart Survey of Acute Coronary Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td>Women $&lt;65$</td>
</tr>
<tr>
<td>Number</td>
<td>1010</td>
</tr>
<tr>
<td><strong>Initial diagnosis, % (n)</strong></td>
<td></td>
</tr>
<tr>
<td>ACS with ST elevation</td>
<td>39 (393)</td>
</tr>
<tr>
<td>ACS, no ST elevation</td>
<td>57 (579)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>4 (38)</td>
</tr>
<tr>
<td><strong>Discharge diagnosis, % (n)</strong></td>
<td></td>
</tr>
<tr>
<td>Q-wave myocardial infarction</td>
<td>28 (280)</td>
</tr>
<tr>
<td>Non-Q-wave myocardial infarction</td>
<td>25 (251)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>47 (479)</td>
</tr>
<tr>
<td>Any infarction</td>
<td>53 (531)</td>
</tr>
<tr>
<td><strong>Symptoms, % (n)</strong></td>
<td></td>
</tr>
<tr>
<td>Typical angina</td>
<td>87 (879)</td>
</tr>
<tr>
<td>Atypical chest pain</td>
<td>7 (69)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Normal ECG on arrival</td>
<td>21 (209)</td>
</tr>
<tr>
<td>SBP on arrival, mm Hg, mean</td>
<td>142 (29)</td>
</tr>
<tr>
<td>Heart rate, beats per minute, mean</td>
<td>80 (18)</td>
</tr>
<tr>
<td><strong>Killip class</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>86 (855)</td>
</tr>
<tr>
<td>II</td>
<td>11 (106)</td>
</tr>
<tr>
<td>III</td>
<td>3 (25)</td>
</tr>
<tr>
<td>IV</td>
<td>1 (11)</td>
</tr>
</tbody>
</table>

All figures are percentages (number).

* Missing data for SBP in 70 subjects, for HR in 39 subjects, and for Killip class in 92 subjects.

* $P$-values across the whole distribution.

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Fig. 2 Q-wave myocardial infarction by age and sex in 10,253 patients in the Euro Heart Survey of patients with acute coronary syndromes. $P$-value for association with age in women, 0.67, and in men, $<0.0001$. 
younger women, 13% had an angiogram without any stenosis \( \geq 50\% \), compared to 5% of the younger men (OR 2.52 [1.86–3.41]). Among the older women and men, 7% and 4%, respectively, had an angiogram without significant stenoses. The proportion with 3-vessel disease or left main stem disease increased with age in both men and women, but was lower in women, irrespective of age (Fig. 3). The odds ratio for women compared to men of having 3-vessel disease or left main stem disease was 0.74 (0.60–0.90) in patients <65 years, and 0.78 (0.66–0.92) among patients \( \geq 65 \) years, with no significant interaction effect.

In a logistic regression analysis, female sex was a significant negative determinant of presenting with ST elevation after adjustment for differences in age, smoking, history of hypertension, diabetes, prior AMI, prior revascularisation, and chronic angina (OR 0.83 [0.75–0.91]). BMI was missing in 14% of the subjects and was included in a second step, with only a marginal effect on the OR (OR 0.85 [0.77–0.94]). The inclusion of significant interaction terms between age and hypertension, or age and prior revascularisation, separately or jointly, did not change the odds ratio associated with female sex. After stratification for age, there was no significant effect of sex in the older patient group after adjustment for differences in smoking, history of hypertension, or age and prior revascularisation, separately or jointly, did not change the odds ratio associated with female sex. After stratification for age, there was no significant effect of sex in the older patient group after adjustment for differences in smoking, history of hypertension, diabetes, prior AMI, prior revascularisation, and chronic angina (OR 0.92 [0.82–1.04]). However, among the younger patients there was still a significantly lower likelihood in women of presenting with ST elevation after adjusting for differences in other factors (OR 0.68 [0.58–0.79]). This was true even if the analysis was restricted to patients discharged with a diagnosis of AMI, with an OR of 0.81 (0.66–0.99) among patients <65 years.

**Discussion**

In one randomised clinical trial, women were found to present with ST elevation less often than men, but more
often with unstable angina.\textsuperscript{8} This finding may reflect different pathophysiological processes, with ST elevation being secondary to occlusive thrombus and unstable angina reflecting subtotal occlusion. This study in a large, comparatively unselected, sample of patients from Europe and the Mediterranean basin expands on these prior findings, demonstrating that this difference seems to be confined to younger patients, with a significant interaction between age and sex.

**Differences in clinical presentation**

The interpretation of the available data with respect to clinical characteristics in ACS is complicated because the study populations involved have varied substantially in inclusion criteria. Some studies have included patients with a broader range of ACS\textsuperscript{5,11} but most have investigated only AMIs.\textsuperscript{12–15} Of these, some only included first AMIs\textsuperscript{15,16} and some only included AMIs in patients below 65 years of age\textsuperscript{17,18} or only in older patients.\textsuperscript{16} Several clinical studies investigated only patients eligible for certain treatments, i.e., thrombolysis,\textsuperscript{19,21} which excludes a large proportion of women because, as the present study shows, many of them are not candidates for acute reperfusion therapy. It is obvious that the selection criteria used are critical to any analysis of sex differences. The present study included patients irrespective of eligibility for any specific treatment and included patients with unstable angina who form an important subset of patients with ACS.

Outcome after hospitalisation for AMI has been demonstrated to be worse in women,\textsuperscript{22–24} particularly at younger ages.\textsuperscript{25} In an analysis based on the same registry as in the present study, there was no difference in inhospital mortality after adjustment for age and comorbidity.\textsuperscript{6} An interaction between age and sex has been demonstrated with respect to outcome after AMI, with younger, but not older, women having higher in-hospital mortality.\textsuperscript{26} To a great extent, however, this is explained by differences in baseline clinical characteristics.\textsuperscript{26} However, the high in-hospital mortality in younger women is counterbalanced by a higher mortality outside the hospital among men,\textsuperscript{3,16,28,27} This could possibly reflect more ST-elevation AMI among men, with a high early mortality.

Infarct size has been demonstrated to be smaller in women than in men.\textsuperscript{12,22,24,28} A systematic investigation of the consequences of including milder cases revealed that the increase in event rates and the decrease in case-fatality due to the inclusion of non-fatal, probable AMIs were larger for women than for men.\textsuperscript{29} In a validation study, a diagnosis of AMI was found not to be supported in a higher proportion of women (9\%) than in men (5\%).\textsuperscript{13} It is probable that the pattern of more unstable angina and less ST elevation in younger patients that we observed reflects the same phenomenon.

The incidence and presentation of cardiovascular disease differ between men and women, possibly because of the protective effect of oestrogen. The direct actions of oestrogen on blood vessels may contribute substantially to this cardiovascular protective effect, but a lipid-lowering effect may also be involved.\textsuperscript{30} Rupture of an atherosclerotic plaque is the most common type of plaque complication, but in some cases the thrombus appears to be superimposed on a de-endothelialised, but otherwise intact, plaque (“plaque erosion”). This is more often seen in younger individuals and women.\textsuperscript{31} In an autopsy study of women who had died suddenly from coronary heart disease or who had died from non-coronary causes, women >50 years were much more likely to have a ruptured plaque than were younger, premenopausal women, suggesting that oestrogen affects plaque stabilisation. Plaque erosion, which is possibly the major substrate for thrombosis in premenopausal women, may not be inhibited by oestrogen.\textsuperscript{32} It is likely that the variations in clinical presentation that we observed reflect, to some extent, a different and possibly less severe disease in younger women.

**Differences in investigations and treatment**

Women with AMI have been found to be less aggressively treated,\textsuperscript{20} partly because of their older age at presentation.\textsuperscript{33,34} In the present study, there was no difference in acute reperfusion therapy between younger men and women, whereas older women were less likely to be treated than men of the same age. It is not clear to what extent the high mortality in older patients is amenable to improvement, but studies suggest that older, as well as younger, patients benefit from thrombolysis\textsuperscript{35} and from treatment with β-blockers and aspirin.

Only half of the patients in the study underwent coronary angiography, with a smaller proportion among the women. Overall, the proportion of patients with a normal angiogram among both women and men was very low. Even among women <65 years, only 13\% had no significant stenosis. About one third of the patients with no significant stenosis were diagnosed with AMI, regardless of age or sex. In other studies the proportion with significant stenoses has been lower.\textsuperscript{7,8,36} This probably reflects a relatively more selective strategy with respect to coronary intervention in this study population, in contrast to North American populations. An absence of significant stenoses may be found in a proportion of patients even with documented AMI, more commonly among women.\textsuperscript{7,8} In a series of 8 women with documented AMI and normal, or not significantly stenosed, arteries that were investigated with intravascular ultrasound, atherosclerosis was found in all infarct-related arteries.\textsuperscript{37} Vulnerable plaques may be relatively non-stenotic and such lesions may undergo "outward" remodelling before impinging significantly on the vascular lumen.\textsuperscript{38}

**Limitations**

There was no strict validation of the diagnoses of AMI or unstable angina. Even though atherosclerosis is probably the main aetiological factor for ACS, even in cases without an angiographically obvious coronary stenosis, it is
possible that a proportion of the younger women diagnosed with ACS may have had chest pain of non-cardiac origin. Reanalysing the data only including patients with diagnosed AMI still demonstrated that younger women were at lower risk of developing ST-elevation ACS, but with a slightly less decreased odds ratio. In routine clinical practice, there is no optimal way of validating unstable angina and excluding patients with unstable angina will result in underestimation of an important subset of the ACS population, particularly women. The proportion of patients with significant coronary artery stenoses may be different in other regions of the world, based on local practices and the thresholds for referring patients to coronary angiography. Likewise, the use of invasive strategies may be different in other regions of the world.

Conclusions
The main finding of this large survey of ACS patients from 25 countries in Europe and the Mediterranean basin was the interaction between age and sex with respect to clinical presentation, with younger women presenting with less ST elevation and more unstable angina. Among those who underwent angiography, less extensive atherosclerosis was found in women compared to men, irrespective of age. These differences suggest variations in pathophysiology, with later onset of atherosclerosis in women but different pathophysiology with respect to ACS in younger, but not in older, women. These differences may be due to the influence of sex hormones and should be further explored in order to provide better insights into the atherosclerotic process.

Acknowledgements
The European Heart Survey of Acute Coronary Syndromes was sponsored by Schering-Plough and Centocor. The Swedish participation was supported by the Swedish Heart and Lung Foundation.

References
25. White HD, Barbash GJ, Mohan M et al. After correcting for worse baseline characteristics, women treated with thrombolytic therapy for acute myocardial infarction have the same mortality and ...


