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Gender differences in clinical trials in coronary heart disease: response to drug therapy

Introduction

Clinical experience supported by an abundance of trial data indicate that the presentation, management, response to treatment and prognosis of coronary heart disease, differs in several important aspects between men and women. The large-scale clinical trials of the last decade present unique insights into these differences.

Outcome after myocardial infarction

As long as 9 years ago, the MILIS study group found that women, and in particular black women, had an adverse prognosis after myocardial infarction in comparison with their male counterparts, even after adjustment for risk score[1]; women were found to have a greater risk of subsequent stroke, early reinfarction, and cardiac rupture.

These observations were confirmed by the large-scale trials of therapy in acute myocardial infarction. In the early ISIS-1, placebo-controlled trial of atenolol, the 7-day mortality in the control group was much greater in women than in men (7.5% vs 3.7%)[2]. Similar gender differences were seen in the trials of thrombolysis. In the meta-analysis of nine large thrombolytic trials by the Fibrinolytic Therapy Trialists (FTT) collaborative group, women were shown to have a 60% greater mortality than men 35 days after presentation to hospital with acute myocardial infarction[3].

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In the GUSTO-I study of streptokinase and tissue type plasminogen activator, for example, the mortality rate at 30 days in women was double that in men[4]. An increased risk of short- and long-term mortality, in the order of 50%, after myocardial infarction in women was also observed in the ISIS-4 study, which compared captopril with placebo in patients suffering from acute myocardial infarction and otherwise receiving optimal therapy with thrombolytics and aspirin[5]. Women were more likely to develop heart failure, cardiogenic shock and cardiac rupture.

There also appeared to be a gender-based susceptibility to cerebral haemorrhage after thrombolytic therapy, with recombinant tissue type plasminogen activator, a complication which was more frequent in female than in male patients (3% vs 1.3%)[6].

Ischaemic cardiomyopathy and heart failure

Data from several large-scale clinical trials of therapy in patients with heart failure and coronary heart disease-related left ventricular dysfunction, indicate that women are again at higher risk than men. In the SOLVD study of enalapril in patients with reduced left ventricular function and congestive heart failure[7], 22% of women compared with 17% of men had died after one year, a difference primarily attributable to a higher rate of cardiac mortality among the female subjects. Death caused by pump failure was also higher in women than in men, and the hospitalization rate for congestive heart failure greater (11.9% vs 8.8%). Thirty-three percent of women and 25% of men died or were hospitalized.

Many of these observed gender differences could, however, be explained by a higher prevalence of diabetes, pulmonary oedema and atrial fibrillation among the women. Gender had no influence on mortality in the SAVE study of captopril after myocardial infarction in patients with left ventricular dysfunction[8]. In the AIRE study, however, cumulative event-free survival was significantly higher in men than in women, irrespective of treatment with ramipril or placebo[9].

Angina and non-Q wave infarction

In contrast to the findings in patients suffering from acute myocardial infarction, women with stable angina tend to have a better prognosis than men[10], while recent studies have shown that the sexes experience similar outcomes after an episode of unstable coronary heart disease[11,12]. In the recently published FRISC trial[11] and the FRIC study[12], two large trials of low molecular weight heparin in addition to aspirin and conventional antianginal therapy, in patients with unstable angina or non-Q wave infarction, the frequency of the composite outcome of death, myocardial infarction or recurrence of angina during the first 6 days was similar in the two sexes, although fewer women underwent revascularization procedures (Table 1).

Explanations for gender differences in coronary heart disease

Several observations may explain these differences in coronary heart disease between men and women.

Pathophysiology and presentation

As coronary heart disease presents more commonly as acute myocardial infarction in men, and as angina in women, it is possible that the pathophysiology of the underlying disease differs in the sexes. This might be explained by women having smaller chests, hearts and coronary arteries than men; small plaques in women might be more likely to compromise coronary blood flow and cause angina in women than in men. Similar plaques in men, in contrast, may go unnoticed until they rupture and cause myocardial infarction. Once they do rupture, it is reasonable to hypothesize that the smaller calibre of the coronary arteries in women, might contribute to the worse outcome after myocardial infarction.

Against this suggestion, however, is the evidence that angiographically determined disease severity does not differ between men and women suffering from acute myocardial infarction[13].

Several other features of the presentation of coronary heart disease in women contribute to the adverse outcome after myocardial infarction. The most striking of these is age. The results of numerous studies demonstrate that morbidity and mortality

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Response to heparin and dalteparin in unstable angina and non-Q wave myocardial infarction in the FRIC study[12]</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Females Heparin Dalteparin Males Heparin Dalteparin</td>
</tr>
<tr>
<td>Angina (%)</td>
<td>8.1 9.0 7.6 9.5</td>
</tr>
<tr>
<td>Revascularization (%)</td>
<td>4.9 4.8 6.3 5.4</td>
</tr>
</tbody>
</table>
from coronary heart disease occurs about 10 years later in women than in men. This has led to the notion of female protection from coronary heart disease, and hypotheses examining the issue have been extensively researched. Any such protection, however, appears to be diminished after menopause, and the proportion of cardiac events, including myocardial infarction and sudden death, increases more sharply with age in women than in men: sudden coronary death increases from 5% from a first event in women aged 35–54 years to 17% of those aged 75–94 years. The corresponding risk of sudden death in men in these age groups were 9% and 14% respectively. The increased risk after menopause may be explained by elevations in total cholesterol, and an increased risk of diabetes and left ventricular hypertrophy.

As age is itself a major independent risk factor for poor outcome after acute myocardial infarction, it confounds the apparent influence of gender in clinical trials. The same problem arises with diabetes, hypertension and heart failure, all of which are important predictors of adverse outcome after myocardial infarction, and also occur more frequently in women than in men at presentation. Indeed, most studies have found that after adjustment for baseline factors, the impact of sex on outcome is weakened, though not eliminated. Logistic regression analyses of the GUSTO data, for example, revealed that female gender was only a marginal independent risk factor for outcome after myocardial infarction, when all prognostic variables were combined.

As in the studies of myocardial infarction, in studies of unstable angina female patients tended to be older than male patients and had more hypertension, diabetes and heart failure (Table 2). Somewhat surprising therefore was that the outcome in these studies was similar in the two sexes. It is possible that some of the women in the study had unstable angina without extensive underlying coronary heart disease and this might have improved the overall survival in the female subjects in comparison with the male subjects.

Similarly, the favourable outcome in women with stable angina and unrecognised myocardial infarction is due, in part, to greater misclassification of these coronary events in women than in men.

### Diagnosis and management

Women are also more likely than men to present with atypical symptoms in acute myocardial infarction, such as dyspnoea, nausea and fatigue, and to have less pronounced ST-segment changes on the ECG—a significant disadvantage as far as early reperfusion is concerned. Once in hospital women wait longer for an ECG evaluation and a physician’s evaluation than men, and once seen, the diagnosis of myocardial infarction is less likely to be made; only one third of infarctions go unrecognised in men, compared with nearly half in women.

These differences in presentation, together with other social and cultural factors, go some way to explaining some apparent discrepancies in the diagnosis and management of coronary heart disease in men and women.

Several studies have shown that women with myocardial infarction are under-treated. Women are also less likely to receive aggressive pharmacological treatment than men, partly because the decision to initiate such therapy is often based on ischaemic changes on the ECG. Late arrival at hospital, older age, pregnancy and menstruation, might also contribute to the lower rate of thrombolysis in women than in men, although the primary factor underlying this difference is the likelihood of admission to a coronary care unit; this is less for women with acute myocardial ischaemia than men. Once in the CCU, women and men are equally likely to receive thrombolytic therapy.

In addition to thrombolytic therapy, beta-blockers are prescribed less commonly for women than for men, and this again may be explained by the higher prevalence of ineligibility criteria, including congestive heart failure and diabetes. In a study of 3361 men and 2119 women hospitalized with acute myocardial infarction between 1975 and 1990, the only gender differences in therapy were that diuretics were more commonly prescribed to women than men, and the reverse was true for antiplatelet and antiarrhythmic agents. The investigators concluded that gender per se did not influence the routine pharmacological management of myocardial infarction.

Some investigators have observed that fewer women than men suffering an acute myocardial

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**Table 2 Baseline characteristics in unstable angina and non-Q wave infarction in the FRIC study**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Females (n = 530)</th>
<th>Males (n = 950)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66</td>
<td>63</td>
</tr>
<tr>
<td>Body mass index (kg.m⁻¹)</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>48</td>
<td>34</td>
</tr>
<tr>
<td>Non-insulin dependent diabetes (%)</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Insulin-dependent diabetes (%)</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>15</td>
<td>34</td>
</tr>
</tbody>
</table>

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infarction undergone angiography, angioplasty and coronary artery bypass surgery[24]. In the SAVE study[8], half as many women as men had angiography, angioplasty and bypass grafting, even though the incidence of angina was the same in both sexes. Other studies have shown that women with abnormal thallium scans are ten times less likely than men to have angiography, and four times less likely to undergo CABG for a given coronary lesion[24]. However, these findings were not confirmed in a recent retrospective analysis[25], in which no gender differences were found in the overall utilization of revascularization procedures after diagnostic coronary angiography, although women were more likely to undergo PTCA and less likely to undergo CABG than men.

### Table 3  Response to drug therapy in acute myocardial infarction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Risk reduction</th>
<th>Males</th>
<th>Females</th>
<th>Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>-5%</td>
<td>-31%</td>
<td>ISIS-1[28]</td>
<td></td>
</tr>
<tr>
<td>Mononitrate</td>
<td>-2%</td>
<td>-10%</td>
<td>ISIS-4[19]</td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>-22%</td>
<td>-2%</td>
<td>SAVE[14]</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>-8%</td>
<td>-4%</td>
<td>ISIS-4[19]</td>
<td></td>
</tr>
<tr>
<td>Streptokinase</td>
<td>-25%</td>
<td>-20%</td>
<td>ISIS-2[28]</td>
<td></td>
</tr>
</tbody>
</table>

Comparably, in earlier series, the outcome after PTCA was worse in women than men, results which might be explained by smaller coronary arteries in women. However, newer data indicate that, with improvements in PTCA technology, the gender difference has been eliminated[26]. In contrast, the early mortality rate after CABG in women remains twice that in men, although 5 and 10 years' survival rates are similar between the sexes[27].

### Conclusion

Data from large-scale clinical trials of the last ten years support the notion of gender differences in the presentation, management, response to treatment and prognosis of coronary heart disease. Many, though not all, of these differences can be explained by disparities between men and women in baseline risk factors for adverse outcome.

Differences in response to treatment can be explained, at least in part, by the underrepresentation of females in clinical trials.

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### References


