

# Sex differences in risk factors, treatment and mortality after acute myocardial infarction: an observational study

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## Abstract

**Background**—Coronary heart disease is the major cause of death of postmenopausal women in industrialised countries. Although acute myocardial infarction (AMI) affects men in greater numbers, the short-term outcomes for women are worse. In the longer term, studies suggest that mortality risk for women is lower or similar to that of men. However, length of follow up and adjustment for confounding factors have varied and more importantly, the association between treatment and outcomes has not been examined.

**Study objective**—To investigate the association between sex differences in risk factors and hospital treatment and mortality after AMI.

**Design**—A prospective observational study collecting demographic and clinical data on cases of AMI admitted to hospitals in Yorkshire. The main outcome measures were mortality status at discharge from hospital and two years later.

**Setting**—All district and university hospitals accepting emergency admissions in the former Yorkshire National Health Service (NHS) region of northern England.

**Participants**—3684 consecutive patients with a possible diagnosis of AMI admitted to hospitals in Yorkshire between 1 September and 30 November 1995.

**Main results**—AMI was confirmed by the attending consultant for 2196 admissions (2153 people, 850 women and 1303 men). Women were older and less likely than men to be smokers or have a history of ischaemic heart disease. Crude in-hospital mortality was higher for women (30% versus 19% for men, crude odds ratio of death before discharge for women 1.78, 95% confidence intervals 1.46, 2.18,  $p=0.00$ ). This difference persisted after adjustment for age, risk factors and comorbidities (adjusted OR 1.29, 95% CI 1.04, 1.63,  $p=0.02$ ), but was not significant when treatment was taken into account. Women were less likely to be given thrombolysis (37% versus 46%,  $p<0.01$ ) and aspirin (83% versus 90%,  $p<0.01$ ), discharged with  $\beta$  blockers (33% versus 47%,  $p<0.01$ ) and aspirin (82% versus 88%  $p<0.01$ ) or be scheduled for angiography, exercise testing or revascularisation. Adjustment for age removed much of the disparity in

treatment. Crude mortality rate at two years was higher for women (OR 1.81, 95%CI 1.41, 2.31,  $p=0.00$ ). Age, existing risk factors and acute treatment accounted for most of this difference, with treatment on discharge having little additional influence.

**Conclusions**—Patients admitted to hospital with AMI should be offered optimal treatment irrespective of age or sex. Women have a worse prognosis after AMI and under-treatment of older people with aspirin and thrombolysis may be contributing to this.

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Coronary heart disease is the major cause of death of postmenopausal women in industrialised countries.<sup>1</sup> Although men are affected in greater numbers, women have been shown repeatedly to have worse short-term outcomes after acute myocardial infarction (AMI).<sup>2-19</sup> Women tend to be older than men when they experience AMI, and more of them have a history of hypertension, impaired left ventricular function or diabetes. Over the past three decades, the influence of sex on outcome after AMI has been studied using varying methods and patient groups. Most authors agree that risk factor profiles may account for much of the sex difference in mortality.<sup>20</sup> Recent large studies in the USA have confirmed this, though Vaccarino and colleagues found that the higher in-hospital mortality was confined to younger women.<sup>21</sup> Hochman *et al* suggested that women may present a different clinical picture to men; less likely to have ST segment elevation on the electrocardiogram, but experiencing more complications.<sup>22</sup> Long term survival has been investigated by studies of patients admitted consecutively to hospital and those on community registers. Length of follow up and adjustment for confounding factors have varied, but all studies that report results beyond one year have shown mortality risk for women to be lower, or similar to that of men.<sup>23-27</sup> However, adjustment for age and comorbidities may not have been adequate and management of AMI may have changed since some of these were published. None of the studies with follow up beyond six months considered the impact of treatment on outcomes. This is important, as aspirin,<sup>28</sup> thrombolysis,<sup>29</sup>  $\beta$  blockers<sup>30</sup> and ACE inhibitors<sup>31</sup> have a significant impact on survival, and sex differences in treatment with thrombolysis and  $\beta$  blockers have been shown

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to exist.<sup>18</sup> Work on single sites in the UK has described higher short-term mortality for women, and found that they are less likely to receive all appropriate treatments.<sup>17, 18</sup> The Scottish MONICA study produced similar findings in the under 65 years age group, but identified a higher pre-hospital fatality rate among men.<sup>32</sup>

Our work builds on previous research by reporting treatment, and mortality at two years, in an unselected population across all hospitals in one region. Our hypothesis is that inequities in treatment of men and women contribute to sex differences in short and long term outcome after myocardial infarction. The overall aim is to investigate sex differences in risk factors and treatment, and their association with mortality after AMI.

## Methods

### SUBJECTS

All possible cases of AMI admitted to 18 district and two teaching hospitals in the former NHS region of Yorkshire were identified between 1 September and 30 November 1995. Study inclusion criteria were: (one of the following) chest pain or suspected AMI recorded as reason for admission in the ward registers, at least one cardiac enzyme assay result above twice the limit of normal, or code 410 for principal diagnosis in the hospital patient administration systems. For patients who fulfilled the criteria, demographic and clinical data were extracted from the hospital notes (table 1). AMI was confirmed if the discharge summary or clinical notes stated this as the final diagnosis. Date of death was established by flagging study patients at the NHS central registry, and examining certificates relating to deaths outside of the index admission.

### EXPLANATORY VARIABLE DEFINITIONS

Risk factors such as hyperlipidaemia, hypertension and diabetes were recorded as present if mentioned in the medical notes relating to the index admission. If the notes were unavailable or incomplete, the nursing chart for the index admission, letters relating to outpatient attendance and discharge summaries were searched. A single historic total serum cholesterol measurement of >5.2 mmol/l was sufficient for the recording of hyperlipidaemia. If no

relevant data were available, the risk factor was recorded as absent.

### STATISTICAL ANALYSIS

Patient characteristics and in-hospital treatments for men and women were compared using  $\chi^2$  and unpaired Student's *t* test. Influence of various factors on mortality at discharge were investigated using multiple logistic regression. The factors considered were sex, age, history of myocardial infarction, cardiac failure, hypertension, angina, hyperlipidaemia, coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA), smoking status, diabetes, stroke, chronic obstructive pulmonary disease (COPD), admission to coronary care units, in-hospital treatment with thrombolysis and ACE inhibitors and aspirin on the day of infarction. (Smoking status and age were entered as categorical variables, current and former smoker, or never smoked, age in 10 year bands between 35 and 85 years). Smoking status was defined on the basis of the history in the notes, with former smoker indicating any record of smoking. A history of left ventricular failure (LVF) complicating the admission was used as a proxy measure for the severity or size of infarct.

For patients discharged from hospital, multiple logistic regression analysis was used to assess the influence on mortality at two years of known risk factors, LVF during admission and treatment on discharge (ACE inhibitors, aspirin, diuretics,  $\beta$  blockers, anticoagulants, calcium antagonists, antiarrhythmics). All statistical analyses were performed using Statistical Package for the Social Sciences version 9.0.<sup>33</sup>

## Results

### PATIENT CHARACTERISTICS

AMI was confirmed in 850 women and 1303 men. Patient characteristics are shown in table 1. Men were younger than women, and significantly more of them had had previous AMI or re-vascularisation and were current or former smokers. Women were more likely to have given a history of hypertension, diabetes or valvular heart disease.

### MANAGEMENT IN HOSPITAL

Treatment and procedures received in hospital are shown in table 2. Fewer women received aspirin, thrombolysis or had inpatient exercise testing or radionuclide scans. There were no statistically significant differences in use of intravenous  $\beta$  blockers, angiography or echocardiography between men and women. More women than men had AMI complicated by left ventricular dysfunction (476 (57%) *v* 588 (45%) *p*=0.00). After adjustment for age, only the differences in exercise testing remained clearly significant.

Proportionately more men than women were admitted to coronary care units (959 (74%) *v* 507 (61%) *p*=0.00), the age distribution of patients admitted to CCU is shown in figure 1. There were no sex differences in treatments administered in CCU.

Table 1 Characteristics of patients admitted to Yorkshire hospitals with AMI

	Men (n=1303)	Women (n=850)	Total (n=2153)	<i>p</i> Value
Mean age (y) (SD)	68.0 (11.9)	74.9 (10.9)		0.00
Smokers (current or former)	946 (73%)	479 (56%)	1453 (66%)	0.00
<i>History of</i>				
Myocardial infarction	377 (29%)	180 (21%)	557 (26%)	0.00
Angina	483 (37%)	320 (37%)	803 (37%)	0.82
Hypertension	324 (25%)	302 (36%)	626 (29%)	0.00
Cardiac failure	111 (9%)	92 (11%)	203 (10%)	0.08
Arrhythmia	89 (7%)	75 (9%)	164 (8%)	0.10
Valvular heart disease	19 (2%)	37 (4%)	56 (3%)	0.00
CABG/PTCA	56 (4%)	13 (2%)	69 (3%)	0.00
Stroke	123 (10%)	86 (10%)	209 (10%)	0.66
Diabetes	146 (11%)	132 (16%)	278 (13%)	0.00
COPD	19 (15%)	121 (14%)	312 (15%)	0.80
Liver disease, alcohol or drug abuse	20 (1%)	8 (1%)	28 (1%)	0.20
Hyperlipidaemia	94 (7%)	52 (6%)	140 (7%)	0.34

Table 2 Management of acute myocardial infarction in hospital

Treatment/investigation	Men (%)	Women (%)	OR for treatment of women (95% confidence intervals)	Age adjusted OR for treatment of women (95% confidence intervals)
Early aspirin	1070 (90)	597 (83)	0.55 (0.42, 0.72, p=0.00)	0.78 (0.59, 1.04, p=0.09)
Thrombolysis	593 (66)	311 (37)	0.69 (0.58, 0.82, p=0.00)	0.89 (0.74, 1.08, p=0.25)
Angiography	60 (5)	33 (4)	0.84 (0.54, 1.29, p=0.42)	1.41 (0.90, 2.22, p=0.13)
Echocardiography	328 (25)	192 (23)	0.87 (0.71, 1.06, p=0.17)	0.93 (0.75, 1.15, p=0.52)
Exercise test/radionucleide scan	68 (5)	5 (1)	0.11 (0.04, 0.27, p=0.00)	0.16 (0.06, 0.41, p=0.00)

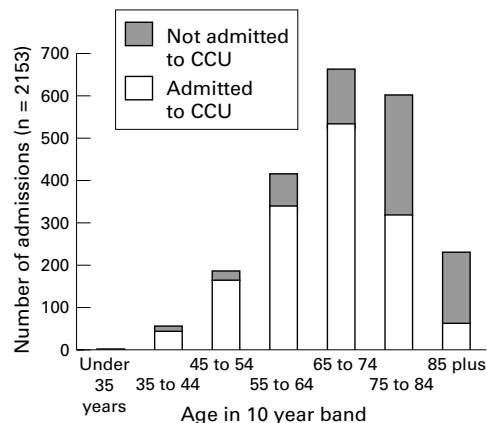


Figure 1 Admissions to CCU by age.

## INHOSPITAL MORTALITY

Women had a higher inhospital mortality compared with men (30% v 19%, crude odds ratio (OR) 1.78, 95% confidence intervals 1.46, 2.18, p=0.00). After adjustment for age, history of AMI, cardiac failure, hypertension, angina, hyperlipidaemia, CABG/PTCA, smoking status, diabetes, stroke, COPD, women were still slightly more likely to die (adjusted OR 1.29, 95% CI 1.04, 1.63, p=0.02). When treatment in coronary care units, aspirin (on day of infarct), thrombolysis and ACE inhibitors (within 48 hours of admission) were added into the model, the influence of sex was not statistically significant (adjusted OR 0.83, 95% CI 0.61, 1.13, p=0.24).

## TREATMENT ON DISCHARGE

Drugs and planned investigations on discharge are shown in table 3. Women were less likely to be discharged taking aspirin and  $\beta$  blockers, or with planned angiography or exercise testing. Both sexes were equally likely to receive ACE inhibitors, antiarrhythmics, anticoagulants, calcium antagonists, nitrates, statins and echocardiography. After adjustment for age, only differences in planned investigations remained significant.

Table 3 Drugs and investigations planned on discharge after AMI

Treatment	OR for treatment of women (95% confidence intervals)	Age adjusted OR for treatment of women (95% confidence intervals)
Aspirin	0.64 (0.48, 0.85, p=0.00)	0.91 (0.68, 1.23, p=0.55)
$\beta$ blockers	0.54 (0.44, 0.66, p=0.00)	0.84 (0.67, 1.07, p=0.15)
ACE inhibitors	1.09 (0.88, 1.34, p=0.44)	1.01 (0.81, 1.26, p=0.91)
Antiarrhythmics	1.22 (0.89, 1.68, p=0.22)	0.84 (0.60, 1.18, p=0.32)
Anticoagulants	1.22 (0.85, 1.73, p=0.28)	1.40 (0.97, 2.03, p=0.07)
Calcium antagonists	1.28 (1.00, 1.65, p=0.05)	1.25 (0.96, 1.63, p=0.09)
Nitrates	0.95 (0.78, 1.17, p=0.63)	0.85 (0.69, 1.06, p=0.15)
Statins	0.88 (0.60, 1.27, p=0.48)	1.37 (0.92, 2.03, p=0.12)
Angiography	0.29 (0.14, 0.62, p=0.00)	0.48 (0.22, 1.02, p=0.06)
Exercise testing	0.43 (0.33, 0.55, p=0.00)	0.69 (0.53, 0.92, p=0.01)
CABG/PTCA	0.35 (0.12, 1.04, p=0.06)	0.58 (0.19, 1.73, p=0.33)

## MORTALITY AT TWO YEARS

Altogether 1683 (77%) patients were discharged from hospital. Of these, 164 (27%) women and 183 (17%) men were dead at two years (crude OR 1.81, 95% CI 1.41, 2.31, p=0.00). Adjustment for age and risk factors removed this sex difference (OR 1.22, 95% CI 0.95, 1.67, p=0.18). When treatment in hospital was added into the model, the OR was reduced further (OR 0.91, 95% CI 0.67, 1.25, p=0.70). Treatment on discharge had little additional effect (OR 1.11, 95% CI 0.81, 1.54, p=0.60).

## Discussion

This study has shown that although men and women admitted to hospital with AMI are treated differently, much of the disparity is attributable to less intensive management of older people.

Women in our study had worse short-term prognosis, which could be explained by their age, risk factors, place and content of treatment. At two years, a higher proportion of women had died, and age was responsible for much of this difference. Despite accounting for a wide range of risk factors and treatments, our results concur with other studies that have shown that beyond one year, mortality risk for women is lower or similar to men, after adjustment for risk factors.<sup>6 8 24-28</sup>

Women with AMI in Yorkshire were less likely to receive thrombolysis, aspirin,  $\beta$  blockers and revascularisation, all of which are known to influence outcomes. The tendency for a smaller proportion of women to receive thrombolysis has been described elsewhere,<sup>34-38</sup> and it is recognised that some of the differences may be explained by patient characteristics.<sup>38</sup> Our observations that fewer women were treated with aspirin on the day of infarction, or discharged home with aspirin or  $\beta$  blockers, are also not new.<sup>11 20</sup> For all investigations and treatments except exercise testing, the greater age of women admitted to Yorkshire hospitals seemed to account for the disparities in treatment. Age also influences admission to CCU, but delay in presenting to hospital and lower female case fatality before admission<sup>39</sup> may contribute to the variation. Treatment on discharge did not seem to influence mortality at two years. We do not have data from this study on sustained compliance with discharge treatment, which is clearly relevant here. Similarly, we have no information on smoking cessation after discharge. Women in this study were older, had more comorbidity, and were more likely to have left ventricular dysfunction associated with their AMI. It is possible, therefore, that treatments were contraindicated



more often. However, similar proportions of men and women received treatment with ACE inhibitors, which does not reflect the higher incidence of left ventricular dysfunction among women in hospital.

The problem of agism within the health service has been recently highlighted by the charity Age Concern England.<sup>40–41</sup> Agism in cardiology is particularly well identified,<sup>42</sup> although it has also been demonstrated in other specialties.<sup>43</sup> It is not clear whether under-treating in the elderly results from implicit rationing decisions, prejudice, or ignorance of the evidence base for treatment in this group.<sup>42</sup> On the basis of ethics and clinical knowledge, age should not be used as a determining factor in treatment decisions, yet this continues to be the case.<sup>42–44</sup>

Other research highlights the importance of treatment, thereby underlining the importance of our findings. Modelling of Scottish mortality data suggests that inhospital and secondary prevention treatments may prevent or postpone up to 16% of coronary heart disease deaths in both sexes.<sup>45</sup> The MONICA study also found that changes in treatment were inversely correlated with coronary end points in men and women under 65 years.<sup>46</sup> The implication for physicians in Yorkshire is that significant improvement in outcomes for women may lie in equitable treatment of people of all ages.

Although our study was conducted in one region, the results should be generalisable to other areas. Patients were unselected, from an area of mixed ethnic origin and social status, and admitted to all hospitals. We collected a broad range of data prospectively and followed up patients for more than two years after their AMI. The physicians treating the patients were not aware that we would be examining treatment differences by sex.

The study has a number of possible limitations. The sample size was relatively modest, and our results are consistent with two year mortality rate for women, adjusted for age, risk factors and treatment, of between 20% lower and 50% higher than men. Although measures of patients' delay in seeking treatment, such as "call to needle" time were collected, the data were too incomplete for analysis. This means that the possibility that men with worse prognosis died before admission cannot be excluded. A further limitation of our study, and other research, is the choice of mortality status as the main outcome measure. Three quarters of patients were alive at two years, and for them, the impact of inequalities in treatment on quality of life is also important.

This study has described less intensive treatment and higher mortality for women at discharge and two years. Age accounts for most, but not all of these differences. Women are older at presentation and therefore are liable to discrimination on the grounds of both sex and age. We echo Wilkinson's conclusion from 1994; sex cannot be considered as an independent determinant of risk for AMI until treatment is equitable,<sup>18</sup> where equity encompasses age as well as sex.

#### KEY POINTS

- Differences in age, risk factors and treatment account for much of the higher short-term and long term mortality in women after acute myocardial infarction.
- Fewer women were treated with aspirin and thrombolysis but this sex difference was not significant after adjustment for age.
- Under-treatment of the elderly may contribute to worse outcomes for women after acute myocardial infarction.

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