likely to be afforded admission to the coronary care unit than a woman of the same age.

There is already enough evidence to suggest that women with chronic angina are less likely to receive surgical treatment,¹⁹ and we now have evidence that they are less likely to receive the best available treatment after acute myocardial infarction. Overall, women with ischaemic heart disease seem to be receiving a less than fair deal.

We acknowledge the contributions of Dr John Rowley, Pat Mounser, and the late Jennifer Murdock, all of whom collected data for the Nottingham Heart Attack Register. KWC is the Proffit-Rosser fellow of the Royal College of Physicians.

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(Accepted 12 July 1994)

Acute myocardial infarction in women: survival analysis in first six months

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Abstract

Objective—To examine the influence that being female has on the outcome of acute myocardial infarction.

Design—Observational follow up study.

Setting—London district general hospital.

Patients—216 women and 607 men with acute myocardial infarction admitted to a coronary care unit from 1 January 1988 to 31 December 1992.

Main outcome measures—All cause mortality and recurrent ischaemic events in the first six months.

Results—Event free survival (95% confidence interval) at six months was 63.3% (56.3% to 69.4%) in women and 76.1% (72.4% to 79.4%) in men, $P < 0.001$. The difference was confined to the first 30 days but thereafter the hazard plots for women and men converged, with reduction of the hazard ratio from 2.36 (1.70 to 3.27) to 0.81 (0.44 to 1.48). Women were older, but their excess risk persisted after adjustment for age, other baseline variables, and indices of severity of infarction (hazard ratio 1.53 (1.09 to 2.15), $P = 0.015$). Women tended to be treated with thrombolysis less commonly than men but the difference was small. Substantially fewer women than men, however, were discharged taking β blockers (23.3% v 41.4%, $P < 0.001$), and although additional adjustment for discharge treatment did not further reduce the point estimate of the hazard ratio (1.84 (0.89-3.83)), the 95% confidence interval was wide and statistical significance was lost.

Conclusions—Women with acute myocardial infarction have a worse prognosis than men but the excess risk is confined to the first 30 days and is only

partly explained by age and other baseline variables. The tendency for women to receive less vigorous treatment than men must be remedied before gender can be considered to be an independent determinant of risk.

Introduction

It is well established that women with myocardial infarction have a worse prognosis than men, but disagreement persists about whether this reflects differences in age, risk profiles, or treatment given.¹⁻⁷ Women with myocardial infarction are typically older than men, and some investigators have found the difference in age sufficient to account for all their excess risk.^{4,6} Also, hypertension and diabetes may be more common in women, and this factor too may contribute to the prognostic imbalance between the sexes.^{1,2,4,5} More recently, evidence has shown that women with coronary heart disease tend to be treated less intensively than men.⁸⁻¹² If this applies to use of thrombolysis and drugs such as aspirin and β blockers, it may not only help explain women's less favourable outcome but also provide a relatively simple remedy for correcting it.

Although women with myocardial infarction have a worse prognosis than men, it is not known for how long after the acute phase the excess risk persists. Certainly, the survival curves for women and men presented by previous investigators are in most cases approximately parallel after initially diverging,^{1,5} which implies that the excess risk in women is a temporary phenomenon that eventually disappears. It is important, however, that the time it takes to disappear is defined if specific

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BMJ 1994;309:566-9

strategies are to be developed to protect women with acute myocardial infarction during the period of heightened risk.

We examined the influence that being female has on the outcome of acute myocardial infarction in consecutive patients admitted to our coronary care unit. We paid particular attention to evaluating the confounding effects of baseline risk factors and treatment strategies and to identifying how long after the acute event women remain at greater risk than men.

See papers on p 563 and 573 and editorial by Jackson

Patients and methods

STUDY GROUP

The study group comprised 823 consecutive patients with acute myocardial infarction admitted for the first time to the coronary care unit of Newham General Hospital from 1 January 1988 to 31 December 1992. During the study the hospital's policy was to admit all patients with suspected acute myocardial infarction to the coronary care unit. Myocardial infarction was diagnosed on the basis of any two of the following three criteria: typical chest pain; ≥ 0.1 mV ST segment elevation in at least one standard or two precordial leads; rise in the serum concentration of creatine kinase to > 400 IU/l (upper limit of reference range is 200 IU/l).

DATA COLLECTION

Baseline clinical data were collected prospectively and stored electronically as previously described.¹³ Information recorded included details of clinical history, examination findings, electrocardiographic

TABLE I—Characteristics of 823 patients admitted to coronary care unit with acute myocardial infarction. Values are numbers (percentages) of patients unless stated otherwise

	Women (n=216)	Men (n=607)	Significance		
			χ^2	df	P value
Age (years)*:					
<50	9 (4.2)	111 (18.3)	70.0	3	<0.001
50–	34 (15.7)	187 (30.8)			
60–	74 (34.3)	178 (29.3)			
≥ 70	99 (45.8)	131 (21.6)			
Ethnic group:					
White	188 (87.0)	442 (72.8)	19.2	2	<0.001
Indian,					
Pakistani,					
Bangladeshi	24 (11.1)	154 (25.4)			
Others	4 (1.9)	11 (1.8)			
Smoking:					
Non-smoker	78 (36.1)	128 (21.1)	24.7	2	<0.001
Former-smoker	48 (22.2)	116 (19.1)			
Smoker	90 (41.7)	363 (59.8)			
Diabetes	53 (24.5)	110 (18.1)	4.1	1	0.04
Hypertension	90 (41.7)	166 (27.3)	15.5	1	<0.001
Previous infarction	60 (27.8)	150 (24.7)	0.79	1	0.38

*Test for trend, $\chi^2=69.0$, $P<0.001$.

TABLE II—Characteristics and management of acute myocardial infarction in 823 patients admitted to coronary care unit. Values are numbers (percentages) of patients unless stated otherwise

	Women (n=216)	Men (n=607)	Significance		
			χ^2	df	P value
Duration of symptoms before presentation (hours)*:					
<2	95 (47.5)	290 (50.8)	1.47	3	0.69
2–	52 (26.0)	147 (25.7)			
≥ 4	53 (26.5)	134 (23.5)			
Regional ST elevation	199 (92.1)	548 (90.3)	0.47	1	0.49
Development of Q wave	172 (79.6)	478 (78.8)	0.08	1	0.79
Primary ventricular fibrillation	28 (13.0)	49 (8.1)	4.58	1	0.03
Left ventricular failure	86 (39.8)	152 (25.0)	16.9	1	<0.001
Treatment with thrombolysis or aspirin:					
Neither	25 (11.6)	51 (8.4)	5.49	3	0.14
Aspirin only	47 (21.8)	108 (17.8)			
Thrombolysis only	18 (8.3)	41 (6.8)			
Both	126 (58.3)	407 (67.1)			
Drug treatment on discharge†:					
Aspirin	134 (84.3)	458 (88.6)	1.70	1	0.19
β Blocker	37 (23.3)	214 (41.4)	16.3	1	<0.001

*Information not available for 52 patients. Test for trend, $\chi^2=0.87$, $P=0.35$.

†Data for patients discharged taking aspirin and β blockers exclude the 112 patients who died in hospital and 35 patients for whom information was not available.

data, results of cardiac enzyme tests, and details of treatment in hospital and after discharge. A diagnosis of diabetes was recorded if a patient required insulin, oral hypoglycaemic drugs, or a restriction in dietary sugar. A diagnosis of left ventricular failure was recorded for patients requiring treatment with diuretic drugs whose x ray films showed interstitial or alveolar pulmonary oedema or who were breathless and had basal crepitations or a third heart sound, or both.

FOLLOW UP

The purpose of the follow up was to define the all cause mortality and recurrent ischaemic events (readmission with unstable angina or acute myocardial infarction) in the first six months after acute myocardial infarction. Survival until discharge (or death) was recorded for all 823 patients. Follow up was continued until June 1993, and additional data were obtained on 675 (95%) of the 711 patients discharged. Death during the initial admission was recorded prospectively. We obtained data on patients' experiences after discharge by postal questionnaire in those patients for whom data on follow up in the outpatient department or on readmission to the coronary care unit were not available. We telephoned, whenever possible, the patients who did not respond to the questionnaire. We obtained details of deaths after discharge from general practitioners.

STATISTICAL ANALYSIS

Survival was calculated with the Kaplan-Meier method,¹⁴ and survival probabilities were expressed as percentages with 95% confidence intervals. Univariate comparison of survival in women and men was done with the log rank test. Multivariate predictors of survival were based on a proportional hazard model,¹⁵ with improvements in model fit based on the likelihood ratio. Hazard functions were generated by locally weighted smoothing of daily event rates (death, myocardial infarction, unstable angina) with the Stata 3.1 statistical package.^{15a} We used the χ^2 test to compare the distribution of discrete variables in women and men.

Results

Table I shows the characteristics of the patients before myocardial infarction. Of the 823 patients, 216 were women. Comparison of patients' characteristics by sex showed important differences: the women were significantly older, and, although fewer smoked, they were more commonly hypertensive or diabetic. The incidence of previous myocardial infarction was not significantly different between the women and the men.

Table II shows the characteristics of the patients' myocardial infarction and how the patients were managed. The duration of symptoms before presentation to hospital was similar in women and in men. Although change in ST segment and development of Q wave did not differ between the sexes, heart failure occurred in a greater proportion of women. Women tended to receive thrombolytic drugs less commonly than men, but this was not significant. The proportion of patients discharged taking aspirin was similar in both sexes, but significantly fewer women were discharged taking β blockers.

Survival probability throughout follow up was consistently lower for women than for men (table III). At six months the estimated survival was only 70.0% (95% confidence interval 63.3% to 75.8%) for women compared with 84.7% (81.5% to 87.4%) for men. Figure 1 shows that the pattern was the same when all deaths, second infarctions, and readmissions with unstable angina were considered, with the event free

survival at six months being 63.3% (56.3% to 69.4%) for women compared with 76.1% (72.4% to 79.4%) for men (log rank $\chi^2=16.3$, $P<0.001$).

When hazard was plotted against time, differences in the risk of recurrent ischaemic events between women and men were confined to the first 30 days after myocardial infarction, during which the crude hazard ratio was 2.36 (1.70 to 3.27) (fig 2). Thereafter, the hazard plots converged, with a reduced ratio of 0.81 (0.44 to 1.48) at six months.

INDEPENDENT EFFECT OF BEING FEMALE ON PROGNOSIS

Table IV shows the crude and adjusted hazard ratios for women compared with men for recurrent ischaemia within 30 days of myocardial infarction. The characteristics of patients before infarction that might have contributed to the excess of recurrent ischaemic events in women during the first 30 days included age, smoking, diabetes, hypertension, and previous infarction. Adjustment for age reduced the hazard ratio to 1.84 (1.29 to 2.54) but the lower limit of confidence remained above 1.0. Additional adjustment for the other risk factors before infarction and for the severity of infarction (judged by electrocardiographic changes and complications) did not reduce the hazard ratio any further.

Additional adjustment for treatment with thrombolytic drugs and aspirin did not affect the excess hazard for women during the first 30 days. Most men and most women were discharged taking aspirin, but a smaller proportion of women than men was discharged taking β blockers. Nevertheless, inclusion of these treatments given on discharge did not further reduce the hazard ratio (1.84 (0.89-3.83)), although the 95% confidence interval was wide and significance was lost. This may reflect the reduced number of patients who could be included in the analysis—112 had died in hospital, and information on drugs to be taken after discharge was not recorded for 35 patients.

Discussion

In common with previous studies, our study showed that women admitted to a coronary care unit with acute myocardial infarction had a worse prognosis than men.^{1,7} Women also tended to be older, diabetic, and hypertensive. The adverse effect that these variables may have on prognosis is well established,¹³ and some investigators have found that, once these variables

FIG 1—Kaplan-Meier event free survival curves in women and in men with acute myocardial infarction during first six months after infarction ($P<0.001$)

FIG 2—Smoothed curves for women and men illustrating hazard of death or recurrent ischaemic events (myocardial infarction, readmission with unstable angina) during first six months after infarction

have been adjusted for, women with acute myocardial infarction fare no worse than men.^{4,7} Our analysis, however, is consistent with at least three other reports in which the adverse prognosis in women persisted after adjustment for age and other clinical risk factors.^{1,3} Even after adjustment for the severity of infarction, as reflected by electrocardiographic criteria and left ventricular failure, women remained at significantly greater risk than men.

CHARACTERISTICS OF STUDY POPULATIONS

The reasons for the discordant findings of different studies are not clear, but, as the Framingham study's investigators suggested, differences in the characteristics of the study populations are probably important.³ Our study, for example, is the first from Britain, and because it was conducted in east London a large proportion (>21%) of the patients were of Indian, Pakistani, or Bangladeshi origin.¹⁶ The potential importance of ethnic group was emphasised by Tefler *et al* in their conclusion that the poorer prognosis for the American population of women with acute myocardial infarction was influenced by particularly high mortality among black women.¹ In our study population, however, most of the Indians, Pakistanis, and Bangladeshis were men, and the few women from south Asia could not have contributed significantly to the poor outcome among women.

Other differences in study populations are reflected in the methods of recruiting patients. Thus in contrast to some previous studies, we included consecutive admissions (to a coronary care unit) rather than selected patients who fulfilled age criteria⁶ or other criteria demanded by a concurrent clinical trial.^{1,2,7}

TABLE III—Event free survival analysis for all cause mortality and for all cause mortality and recurrent ischaemic events* in women and in men. Survival probabilities are expressed as percentages (95% confidence intervals)

	Survival		
	At 10 days	At 30 days	At six months
All cause mortality:			
Women (n=216)	80.5 (74.6 to 85.2)	74.7 (68.3 to 80.0)	70.0 (63.3 to 75.8)
Men (n=607)	90.7 (88.1 to 92.8)	88.7 (85.9 to 91.0)	84.7 (81.5 to 87.4)
All cause mortality and recurrent ischaemic events:			
Women (n=216)	78.2 (72.0 to 83.1)	69.9 (63.2 to 75.6)	63.3 (56.3 to 69.4)
Men (n=604)	89.5 (86.8 to 91.7)	86.2 (83.2 to 88.7)	76.1 (72.4 to 79.4)

*Recurrent ischaemic events are readmission with unstable angina or readmission with acute myocardial infarction.

TABLE IV—Crude and adjusted hazard ratios for women compared with men for recurrent ischaemia within 30 days of infarction

	Hazard ratio (95% confidence interval)	Likelihood ratio	df	P value
Crude	2.36 (1.70 to 3.27)	24.8	1	<0.001
Adjustment for age	1.84 (1.29 to 2.54)	11.39	1	<0.001
Adjustment for age, smoking, diabetes, hypertension, previous infarction, ST elevation, Q waves, primary ventricular fibrillation, and left ventricular fibrillation	1.53 (1.09 to 2.15)	5.87	1	0.015
Adjustment for age, smoking, diabetes, hypertension, previous infarction, ST elevation, Q waves, primary ventricular fibrillation, left ventricular failure, thrombolysis, and aspirin	1.43 (1.02 to 3.83)	4.11	1	0.04

Selection bias was therefore reduced, although by no means eliminated. Admission to our coronary care unit depends on multiple factors such as availability of beds and the correct diagnosis during triage in the accident and emergency department. The lower prevalence of coronary artery disease in women seems to be matched by a lower level of diagnostic suspicion not only in hospitals but also in the community, with the result that women are less likely than men to receive non-invasive and invasive investigations and treatment for their symptoms.⁸⁻¹² This could potentially introduce important selection bias in a study of this type, not only because of delays in diagnosis but also, no doubt, because of failure to diagnose correctly when symptoms are atypical and complications have not developed. Nevertheless, the extent to which a bias of this type might select a population of women at higher risk than men is impossible to quantify.

TREATMENT GIVEN ON DISCHARGE

In previous studies, all but one of which were conducted before the widespread use of thrombolysis and aspirin,⁷ the effects of treatment variables on differences related to sex in the prognosis of myocardial infarction have received little attention. Preliminary evidence suggests, however, that the treatment bias against women with coronary artery disease discussed previously may extend to the use of thrombolytic agents.^{17,18} In the present study rates of treatment with thrombolytic agents and aspirin were high regardless of the patients' sex, and the trend towards underuse of such drugs in women was not significant. Similarly, most men and most women were discharged taking aspirin for secondary prevention, with no significant difference between the sexes. The data for β blockers were different, however, in that these drugs were given to only a few patients on discharge and to a significantly smaller proportion of women than men. The high prevalence of chronic lung disease in this inner city population may account partly for the small proportion of patients discharged taking β blockers, but the undertreatment of women cannot be explained clearly, although the women tended to be older and a greater proportion developed heart failure. The value of β blockers for secondary prevention after acute myocardial infarction is well established¹⁹ so the finding of a lower rate of treatment in women gives cause for concern. Although adjustment for drug treatment given on discharge did not affect the hazard ratio, the reduced number of patients included in this analysis ensured a wide 95% confidence interval, and the possibility that undertreatment with β blockers adversely affected the outcome in women cannot be discounted.

INCREASED RISK IN WOMEN IN FIRST 30 DAYS

An important finding of this study was that the increased risk of recurrent ischaemic events in women with myocardial infarction was restricted to the first 30 days after infarction, after which the continuing risk was no greater in women than in men. Effective strategies must be developed to protect women during this early period, but this may not be possible until all the factors that account for the increased risk are defined. Clearly, the tendency for women with myocardial infarction to be older than men cannot readily be reduced, but the potentially adverse effects of other factors—such as diabetes and differences in hormonal profiles—require further investigation because a more practical choice of treatment may then be available. Meanwhile, any tendency for women with acute myocardial infarction to receive less vigorous treatment than men must be remedied.

In conclusion, our finding that women with acute myocardial infarction have a worse prognosis than men

Clinical implications

- Women have a poorer outcome than men after myocardial infarction
- Reports also suggest that treatment for myocardial infarction is less vigorous in women than in men
- Disagreement persists, however, about the influence of sex on outcome
- This study of 823 patients admitted with myocardial infarction found that the difference in survival between the sexes was confined to the first 30 days after infarction and that β blockers were given less commonly to women than men at discharge
- Sex should not be considered to be an independent predictor of outcome until women are treated as vigorously as men

is only partially explained by differences in age, risk profiles and treatment variables. Nevertheless, while it is plausible to suggest that there are biological differences between men and women in the natural course of myocardial infarction, sex should not be accepted as an independent predictor of outcome until the debate about equity in the provision of coronary care of women is resolved.

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(Accepted 29 July 1994)