

## A COMPARISON OF THE EARLY OUTCOME OF ACUTE MYOCARDIAL INFARCTION IN WOMEN AND MEN

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### ABSTRACT

**Background** In previous studies, unadjusted comparisons of mortality and major morbidity after acute myocardial infarction have generally indicated that women have a poorer outcome than men. Much larger studies are needed, with more complete adjustment for coexisting conditions, to determine whether this difference is explained by the older age of the women studied or by the presence of other unfavorable prognostic factors, or both.

**Methods** As part of the Third International Study of Infarct Survival (ISIS-3), information was collected on deaths during days 0 to 35 and on major clinical events during hospitalization up to day 35 for 9600 women and 26,480 men with suspected acute myocardial infarction who were considered to have a clear indication for fibrinolytic therapy. We compared the outcome among women and men, first without adjustment, then with adjustment for age, and finally with adjustment for other recorded baseline characteristics by means of multiple logistic regression.

**Results** The unadjusted odds ratio for death among women as compared with men was 1.73 (95 percent confidence interval, 1.61 to 1.86). The women were significantly older than the men, and after adjustment for age the odds ratio was reduced markedly to 1.20 (95 percent confidence interval, 1.11 to 1.29). Adjustment for other differences in base-line clinical features further reduced the odds ratio to 1.14 (95 percent confidence interval, 1.05 to 1.23). Excesses in other major clinical events among women were generally reduced to a similar extent by adjustment.

**Conclusions** It seems likely that there is at most only a small independent association between female sex and early mortality and morbidity after suspected acute myocardial infarction. (N Engl J Med 1998;338:8-14.)

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studies, the unadjusted death rates were higher among the women than among the men. Eleven of the studies reported age-adjusted analyses, and in all but two, such adjustment reduced the relative risk of death for women as compared with men to less than 1.2. Only six studies provided estimates of relative risk after adjustment for additional variables, and the relative risk was greater than 1.0 in all six studies and greater than 1.2 in four. The review concluded that much, though perhaps not all, of the higher mortality rate among women was explained by their older age and the presence of more unfavorable prognostic factors.

Many of the individual studies included in the previous review were too small to detect or refute reliably the sort of moderate associations of sex with mortality that appeared to be plausible. A meta-analysis of the individual studies, to increase statistical power, was not considered to be appropriate because of differences between the studies in their design and the extent of adjustment. Instead, it was suggested that larger studies were needed, with more complete adjustment for important base-line characteristics, to allow firm conclusions to be drawn about any differences between the sexes in outcome after myocardial infarction.<sup>1</sup>

The Third International Study of Infarct Survival (ISIS-3) involved a large number of men and women with suspected acute myocardial infarction who were considered to have a clear indication for fibrinolytic therapy.<sup>2</sup> Sex and various prognostic factors were recorded on admission to the hospital, and clinical outcomes in the hospital and mortality during and after hospitalization were recorded. Along with a few other, more recently reported studies,<sup>3-9</sup> the ISIS-3 trial provides an opportunity to help resolve some of the uncertainties remaining<sup>1</sup> about the relevance of sex to early mortality and morbidity.

**T**HE prognosis after myocardial infarction in women as compared with men remains uncertain, but it is commonly held that women have a worse prognosis. A recent systematic review identified 17 studies published before June 1994 that compared in-hospital or one-month mortality rates after myocardial infarction between women and men.<sup>1</sup> In all but one of these

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\*The Steering Committee is listed in the Appendix.

## METHODS

### Study Design and Patient Population

Details of the design and main results of the ISIS-3 trial have been described previously.<sup>2</sup> Patients were eligible if they were seen within 24 hours after the onset of symptoms of suspected acute myocardial infarction, with no definite contraindications for fibrinolytic therapy. Electrocardiographic abnormalities were not a requirement, and no age restriction was imposed by the protocol. Patients for whom their physicians thought there was a clear indication for fibrinolytic therapy were randomly assigned with equal frequency to receive streptokinase, tissue plasminogen activator, or anistreplase, whereas those for whom the indication was considered uncertain were randomly assigned with equal frequency to fibrinolytic therapy or an open-label control. Using a factorial design, we randomly assigned half of all patients to receive aspirin plus a high-dose subcutaneous heparin regimen and half to receive aspirin alone. Patients were eligible for the ISIS-3 trial even if aspirin or heparin was thought to be clearly indicated, or if it was thought that aspirin alone was not enough. In such cases, the assigned antithrombotic regimen was to be modified as considered appropriate for the particular patient.

### Base-Line Data

Patients were enrolled in the study by means of telephone calls to central 24-hour answering services. A limited amount of base-line information on each patient was recorded, either directly onto a computer or first on computer-generated randomization lists, before a specific study treatment was assigned. The information to be recorded included patient identifiers; sex; date of birth; the number of hours since the onset of pain; the number of hours since pain ended; systolic blood pressure; heart rate; history of myocardial infarction, stroke, or gastrointestinal bleeding or ulcer; presence or absence of diabetes mellitus; smoking status; and country of origin. In addition, the patient's physician classified the findings on the most recent electrocardiogram into one of nine groups: bundle-branch block; ST elevation that was anterior, lateral, or anterolateral alone; inferior ST elevation alone; ST elevation that was anterior and inferior (or any other type); ST depression without ST elevation; Q waves; T-wave inversion; no abnormalities; or other findings.

Between September 1989 and January 1991, a total of 45,856 patients at 914 hospitals in 20 countries underwent randomization. Of these, 36,381 men and women were considered by their clinicians to have a clear indication for fibrinolytic therapy. Two hundred sixty-nine of these patients had one of the base-line data items missing, and 32 had more than one item missing. The 36,080 patients with complete base-line information were the subject of the present analysis.

### Follow-up Data

At discharge, a simple one-page form was to be completed, and this was obtained for 35,625 of the 36,080 patients. The form provided brief details regarding the study treatments actually given, investigations and procedures, possible side effects of the study treatments, and major clinical events and mortality in the hospital. Confirmation or refutation of any reported stroke and its probable cause was based on a blinded central review of any available relevant information (such as computed tomographic scans and autopsy reports). Mortality was also monitored by searches of government records (wherever possible) or by direct contact with the patients and their relatives and was continued after discharge.

### Statistical Analysis

We compared mortality during days 0 to 35 between women and men first without adjustment for any base-line characteristics, then with adjustment for age alone, and finally with adjustment for age and other base-line characteristics by means of multiple

logistic regression.<sup>10</sup> All characteristics recorded at study entry were considered in the model, with a step-up logistic regression in which a P value of less than 0.05 was used as the criterion for inclusion in the model.

Age was considered a quantitative variable, along with age-squared and age-cubed terms, as was the number of hours between the onset of pain and randomization. Systolic blood pressure (<100, 100 to 124, 125 to 149, 150 to 174, and  $\geq$ 175 mm Hg) and heart rate (<60, 60 to 79, 80 to 99, and  $\geq$ 100 beats per minute) were considered categorical variables, since their relation with prognosis was not considered to be monotonic. More than two thirds of the patients were still in pain at study entry, and so the number of hours since pain ended was considered as a dichotomous (two-group) variable. Findings on the electrocardiogram at presentation (nine categories, as described above) and nation of origin (16 groups) were considered categorical variables, and all the other base-line characteristics included were dichotomous. (Since randomization was balanced with respect to sex, it was not necessary to consider the assigned study treatment in the model.) The step-up logistic-regression procedure resulted in a model that included all these base-line features, except for a history of gastrointestinal bleeding or ulcer and the age-squared and age-cubed terms.

Adjusted comparisons of mortality from day 0 to day 1 and from day 2 to day 35 and the rates of major clinical events in the hospital up to day 35 were performed by fitting models involving the same covariates selected by the step-up logistic-regression analysis of mortality from day 0 to day 35. All comparisons are presented in terms of odds ratios for mortality or morbidity among women as compared with that among men, along with 95 percent confidence intervals.

## RESULTS

### Base-Line Characteristics

Of the 36,080 patients in the ISIS-3 trial who were considered to have a clear indication for fibrinolytic therapy and had complete base-line data, 9600 were women and 26,480 were men. As expected, the women were significantly older than the men (Table 1). Even when the women and men were compared within three similar-sized age groups (<60, 60 to 69, and  $\geq$ 70 years), there were significant tendencies for the women to present later after the onset of symptoms, to have higher heart rates, and to be more likely to have diabetes (Table 2). Men,

TABLE 1. AGE DISTRIBUTION OF THE WOMEN AND MEN.\*

AGE	WOMEN	MEN
	(N=9600)	(N=26,480)
	percent	
yr		
<50	7.1	18.4
50-59	16.9	26.9
60-69	36.3	34.5
70-79	31.5	17.5
$\geq$ 80	8.3	2.6

\*Because of rounding, percentages do not total 100. P<0.001 for the comparison of age distributions in women and men.

**TABLE 2. BASE-LINE CHARACTERISTICS OF THE WOMEN AND MEN ACCORDING TO AGE.**

CHARACTERISTIC	<60 yr		60-69 yr		≥70 yr	
	WOMEN (N=2303)	MEN (N=12,009)	WOMEN (N=3480)	MEN (N=9128)	WOMEN (N=3817)	MEN (N=5343)
	percent					
Hours between onset of pain and randomization						
0-3	52	58	48	53	43	48
4-6	29	26*	32	29*	33	32*
7-24	18	16	21	18	24	20
Systolic blood pressure (mm Hg)						
<100	8	5	8	6	8	8
100-174	86	89*	84	86†	82	84
≥175	6	6	8	8	10	9
Heart rate (beats/min)						
<60	11	12	12	14	10	12
60-79	41	45	40	43	38	41
80-99	35	31*	33	29*	33	30*
≥100	13	12	15	14	20	17
Previous myocardial infarction	14	16†	18	24*	21	26*
Previous stroke	2.3	1.5‡	4.1	4.1	4.5	5.9†
Diabetes	14	7*	15	10*	18	12*
Current smoker	62	61	39	37	16	22*
Previous gastrointestinal bleeding or ulcer	6	9*	6	10*	6	10*
Electrocardiographic findings at presentation						
Bundle-branch block	2	2	3	4	5	7
Anterior ST elevation	35	37	36	38	38	39
Inferior ST elevation	38	39	38	37	33	33
Other type of ST elevation	8	9*	10	9	10	9†
ST depression	6	4	6	6	7	7
Other findings	10	8	7	7	6	6

\*P<0.001 for the comparison of the distributions in women and men.

†P<0.01 for the comparison of the distributions in women and men.

‡P<0.05 for the comparison of the distributions in women and men.

on the other hand, were more likely to have a history of myocardial infarction or gastrointestinal bleeding or ulcer.

### 35-Day Mortality

Overall mortality at 35 days was 14.8 percent among the women and 9.1 percent among the men (Table 3 and Fig. 1), and the unadjusted odds ratio for death among women as compared with that among men was 1.73 (95 percent confidence interval, 1.61 to 1.86) (Table 4). Crude comparisons of mortality among women and men in broad age groupings suggested that much of the difference in mortality may reflect differences in age distribution between the women and men (Table 3 and Fig. 2). Adjustment for age as a continuous variable reduced the odds ratio markedly, to 1.20 (95 percent confidence interval, 1.11 to 1.29) (Table 4). Adjustment for other differences in the base-line features in the logistic-regression model produced a further moderate reduction in the odds ratio, to 1.14 (95 percent confidence interval, 1.05 to 1.23). Similar excesses in mortality during days 0 to 1 and days 2 to 35 were reduced to a similar extent by adjustment for age and for other covariates.

### Major Clinical Events during Hospitalization

In the unadjusted comparisons of the major clinical events that were recorded during hospitalization up to day 35, the odds ratio for each was greater than 1.0 (Table 5). As with mortality, however, adjustment for age alone moved each of these odds ratios markedly toward 1.0. For example, the unadjusted odds ratio for stroke of 1.66 (95 percent confidence interval, 1.36 to 2.02) was reduced by adjustment for age alone to 1.21 (95 percent confidence interval, 0.98 to 1.48) and by further adjustment for other covariates to 1.16 (95 percent confidence interval, 0.94 to 1.43). Even so, all these odds ratios for major events during hospitalization remained greater than 1.0 after adjustment for age and other base-line characteristics.

### Treatment and Investigations during Hospitalization

All the patients in this part of the ISIS-3 trial were assigned to receive some type of fibrinolytic therapy, and 96.9 percent of the women and 97.1 percent of the men did receive fibrinolytic therapy. Similarly, all patients were assigned to receive aspirin, and some form of antiplatelet therapy (predominantly aspirin) was received in the hospital by 97.2 percent of the

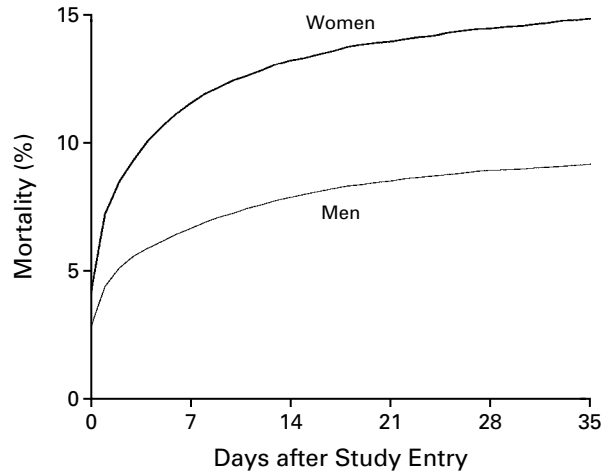
**TABLE 3.** COMPARISON OF 35-DAY MORTALITY AMONG THE WOMEN AND MEN ACCORDING TO AGE.

AGE	WOMEN	MEN
yr	no. of deaths/no. of patients (%)	
<60	124/2303 (5.4)	496/12,009 (4.1)
60-69	415/3480 (11.9)	900/9128 (9.9)
≥70	882/3817 (23.1)	1021/5343 (19.1)
Any age	1421/9600 (14.8)	2417/26,480 (9.1)

women and 97.8 percent of the men. Half the patients were assigned to receive high-dose subcutaneous heparin, and 54.3 percent of the women and 54.8 percent of the men received high-dose subcutaneous or intravenous heparin. The infarction was confirmed in 90.6 percent of the women and 91.1 percent of the men; coronary angioplasty was performed in 3.6 percent and 4.5 percent, respectively; and coronary-artery bypass grafting was performed in 1.8 percent and 2.4 percent. Owing to the large numbers studied, these differences in management between women and men were statistically significant, but they were too small to be of much relevance to any differences in outcome.

**DISCUSSION**

Early mortality after myocardial infarction was at least 40 percent higher among women than among men in most of the studies included in the previous review.<sup>1</sup> Adjustment for differences in the age distributions of the women and men studied generally reduced the excess mortality to less than 20 percent, but it was uncertain whether any residual excess was merely due to differences in other presenting char-



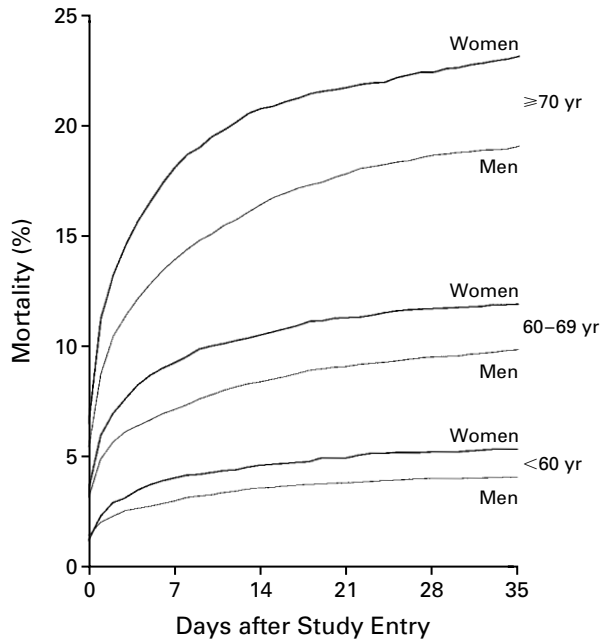
**Figure 1.** Cumulative Mortality from Day 0 to Day 35, According to Sex.

acteristics or whether, other things being equal, early mortality was really higher among women. That review identified the paucity of large studies with adequate adjustment for age and other important prognostic factors as the main reason for such uncertainty. Among more than 36,000 patients considered to have a clear indication for fibrinolytic therapy in the ISIS-3 trial, the unadjusted odds ratio for mortality among women during the first 35 days after myocardial infarction was 1.73 (95 percent confidence interval, 1.61 to 1.86). Adjustment for age alone eliminated more than two thirds of this excess mortality (odds ratio, 1.20; 95 percent confidence interval, 1.11 to 1.29), and further adjustment for the restricted set of presenting characteristics that had been recorded in this streamlined trial eliminated about one third of the remaining excess (odds ratio, 1.14; 95 percent confidence interval,

**TABLE 4.** COMPARISON OF 35-DAY MORTALITY AMONG THE WOMEN AND MEN, BEFORE AND AFTER ADJUSTMENT FOR AGE AND OTHER COVARIATES.\*

FOLLOW-UP PERIOD	WOMEN (N=9600)	MEN (N=26,480)	UNADJUSTED ODDS RATIO (95% CI)	ODDS RATIO ADJUSTED FOR AGE (95% CI)	ODDS RATIO ADJUSTED FOR AGE AND OTHER COVARIATES (95% CI)
	no. (%)				
Days 0-1	686 (7.1)	1141 (4.3)	1.71 (1.55-1.88)	1.21 (1.10-1.34)	1.15 (1.03-1.28)
Days 2-35	735 (7.7)	1276 (4.8)	1.64 (1.49-1.80)	1.14 (1.04-1.26)	1.10 (0.99-1.21)
Days 0-35	1421 (14.8)	2417 (9.1)	1.73 (1.61-1.86)	1.20 (1.11-1.29)	1.14 (1.05-1.23)

\*CI denotes confidence interval.



**Figure 2.** Cumulative Mortality from Day 0 to Day 35, According to Age and Sex.

1.05 to 1.23). The findings were similar for clinical events during hospitalization.

Given the substantial extent to which the excess risk in the unadjusted ISIS-3 comparison could be attributed to a limited number of rather crudely measured determinants of prognosis, it is quite plausible that much of the residual 14 percent excess mortality (as well as the residual excess morbidity) among women could be due to residual differences

between the characteristics of the women and men studied. First, random errors in the measurement of the presenting characteristics included in the adjusted analyses may have led to systematic underadjustment for differences in those characteristics (i.e., regression-dilution bias).<sup>11</sup> Second, crude categorization of the findings on the presenting electrocardiogram into a small number of groups is also likely to have led to insufficient adjustment for all the electrocardiographic differences between the women and men studied. Third, no adjustment at all could be made for any differences in the many other important determinants of prognosis that had not been or could not be recorded. For example, although the probable site of infarction was included at least partially in the adjustment, the extent of the electrocardiographic changes — which is strongly associated with prognosis<sup>12</sup> — was not. Similarly, there was no record in the ISIS-3 trial of many other adverse prognostic features, including congestive heart failure, preexisting hypertension, obesity, abnormal lipid profile or hemostatic function, and noncardiac coexisting conditions (e.g., renal failure and pulmonary disorders), and hence, no adjustment for any differences between the women and men could be made.

The present analyses are based not on a consecutive series of patients presenting with myocardial infarction, but on a very large cohort of patients in whom fibrinolytic therapy was considered to be clearly indicated. There is evidence that women are less likely to receive fibrinolytic therapy, at least in part because women are more likely than men to be considered ineligible for such therapy since they tend to be older, present later after the onset of symptoms, and have more coexisting conditions.<sup>13,14</sup>

**TABLE 5.** COMPARISONS OF MAJOR CLINICAL EVENTS DURING HOSPITALIZATION UP TO DAY 35 AMONG THE WOMEN AND MEN, BEFORE AND AFTER ADJUSTMENT FOR AGE AND OTHER COVARIATES.\*

CLINICAL EVENT	WOMEN	MEN	UNADJUSTED ODDS RATIO (95% CI)	ODDS RATIO ADJUSTED FOR AGE (95% CI)	ODDS RATIO ADJUSTED FOR AGE AND OTHER COVARIATES (95% CI)
	(N=9478)	(N=26,147)			
	no. (%)				
Cardiogenic shock	979 (10.3)	1592 (6.1)	1.78 (1.63–1.93)	1.33 (1.22–1.45)	1.29 (1.17–1.42)
Heart failure	2050 (21.6)	4196 (16.0)	1.44 (1.36–1.53)	1.12 (1.05–1.19)	1.08 (1.02–1.16)
Cardiac rupture	229 (2.4)	266 (1.0)	2.41 (2.02–2.88)	1.70 (1.41–2.04)	1.62 (1.34–1.96)
Cardiac arrest	1137 (12.0)	2505 (9.6)	1.29 (1.19–1.39)	1.07 (0.99–1.16)	1.03 (0.95–1.11)
Reinfarction	433 (4.6)	777 (3.0)	1.56 (1.39–1.76)	1.34 (1.19–1.52)	1.35 (1.19–1.53)
Any stroke	157 (1.7)	263 (1.0)	1.66 (1.36–2.02)	1.21 (0.98–1.48)	1.16 (0.94–1.43)
Cerebral hemorrhage	57 (0.6)	101 (0.4)	1.56 (1.13–2.16)	1.19 (0.85–1.66)	1.12 (0.80–1.58)
Major bleeding	140 (1.5)	181 (0.7)	2.15 (1.72–2.69)	1.74 (1.38–2.19)	1.68 (1.33–2.12)

\*Information on clinical events in the hospital was not available for all patients. CI denotes confidence interval.

Consequently, the requirement that patients have a clear indication for fibrinolytic therapy to enter this study may have reduced to some extent differences between the women and men in coexisting conditions that were not recorded or formally adjusted for. It has previously been suggested that a tendency toward less aggressive management of myocardial infarction in women may be an explanation for some of the excess mortality observed among women.<sup>3,5,15</sup> A further advantage of the present study is that certain treatments known to be particularly effective in reducing mortality in the short term in this setting (i.e., aspirin and fibrinolytic therapy<sup>16</sup>) were assigned to all the patients, and there was very little difference between the women and men in the use of these treatments or in the use of heparin. Moreover, the study was conducted in a predominantly non-U.S. population, in which angiographic investigation and revascularization procedures were rarely performed during the index hospitalization. Again, this is likely to have helped to reduce or avert any material differences in outcome between the women and men due to the very small differences in these procedures.

Only a few other studies whose magnitude is similar to that of the ISIS-3 trial have reported on outcome after myocardial infarction among women as compared with men with adjustment for age and other prognostic factors. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) trial<sup>17,18</sup> and the International Tissue Plasminogen Activator/Streptokinase Mortality Study<sup>19</sup> were two parts of the same clinical trial, and they were included in the previous review.<sup>1</sup> Overall, in the GISSI-2 and International trials,<sup>17-19</sup> there were approximately 4000 women and 14,000 men (about half in each part), and the unadjusted odds ratios for in-hospital mortality among women were 3.6 (95 percent confidence interval, 3.0 to 4.3) and 1.9 (95 percent confidence interval, 1.6 to 2.3), respectively. These results are more extreme in general than the results of other studies included in the previous review.<sup>1</sup> Even so, most if not all the excess mortality was eliminated by adjustments for age and other recorded base-line variables: the adjusted odds ratio was 1.8 (95 percent confidence interval, 1.4 to 2.2) in the GISSI-2 trial (unpublished data) and 1.1 (95 percent confidence interval, 0.9 to 1.4) in the International trial.<sup>19</sup>

More recently, the large Myocardial Infarction Data Acquisition System (MIDAS) study<sup>3</sup> reported the relative risks of death during the index hospitalization after adjustment for age and several other covariates (including left ventricular dysfunction and cardiac catheterization) in three age strata. Overall, the unadjusted in-hospital mortality was about 40 percent higher in women than in men (23.8 percent vs. 17.0 percent). For patients who were 30 to 49

years of age (715 women and 3149 men), the adjusted relative risk was 1.36 (95 percent confidence interval, 1.06 to 1.73); for those 50 to 59 years of age (5432 women and 11,736 men), it was 1.06 (95 percent confidence interval, 0.99 to 1.13); and for those 70 to 89 years of age (8964 women and 7928 men), it was 0.93 (95 percent confidence interval, 0.89 to 0.97). That study had the advantage of having included all patients who had a myocardial infarction within a given geographic area. Women were less likely to undergo invasive interventions than men, and it was thought that this might explain the slightly less favorable outcome in younger women. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial,<sup>6-8</sup> 10,315 women and 30,706 men with acute myocardial infarction were treated with fibrinolytic therapy, aspirin, and heparin. The unadjusted mortality rate at 30 days was about twice as high in women as in men (11.3 percent vs. 5.5 percent). But after adjustment for age and all the other important presenting prognostic factors that had been recorded, only a slight excess remained (relative risk, 1.15; 95 percent confidence interval, 1.0 to 1.3).

In conclusion, the results of this analysis of the large ISIS-3 data base are generally consistent with those of the smaller studies reviewed previously<sup>1</sup> and of more recent large studies.<sup>3-9</sup> Among a population of patients with suspected acute myocardial infarction who were considered to have a clear indication for fibrinolytic therapy, it seems likely that there is at most only a small independent effect of sex on early mortality and morbidity.

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## APPENDIX

The Steering Committee of ISIS-3 included E. Paolasso, R. Diaz (Argentina); D. Hunt, J. Varigos (Australia); F. Dienstl, P. Leichleitner (Austria); G. De Backer, M. Kornitzer (Belgium); J. Cairns, A. Turpie (Canada); P. Fritz-Hansen, K. Skagen (Denmark); R. Kala, J. Heikkilä (Finland); J.-P. Boissel, A. Leizorovicz (France); R. Schröder (Germany); N. Karatzas (Greece); J. Horgan, D. O'Callaghan (Ireland); G. Tognoni, M.-G. Franzosi, A. Maggioni (Italy); A. Cohen, R. Koster (the Netherlands); H. White, S. MacMahon (New Zealand); J. Kjekshus, A. Reikvam (Norway); L. Ceremuzynski (Poland); V. Valentin (Spain); L. Wilhelmsen, L. Lundkvist (Sweden); T. Moccetti, R. Malacrida, M. Genoni (Switzerland); R. Collins (coordinator), P. Sleight (chairman), R. Peto, S. Parish (statisticians), S. Cederholm-Williams, D. Chamberlain, M. Conway, P. Dove, M. Flather, D. Julian, J. Marshall, L. Youngman (United Kingdom); C. Hennekens, S. Goldhaber, G. Timmis, S. Yusuf (United States). A list of the participating centers and investigators has been published previously.<sup>2</sup>

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