Role of age and sex in short-term and long term mortality after a first Q wave myocardial infarction

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Abstract

***Study objective*—The objective of this study was to analyse whether the risk of death within 28 days and three years after a first Q wave myocardial infarction was higher in hospitalised women than in men.**

***Design*—Follow up study.**

***Patients and setting*—All consecutive first Q wave myocardial infarction patients aged 25 to 74 years (447 women and 2322 men) admitted to a tertiary hospital in Gerona, Spain, from 1978 to 1997 were registered and followed up for three years.**

***Main results*—Women were older, presented more comorbidity and developed more severe myocardial infarctions than men. A significant interaction was found between sex and age. Women aged 65–74 had higher early mortality risk than men of the same age (OR 1.62; 95% CI 1.01, 2.66) after adjusting for age, comorbidity and acute complications including heart failure. Women under 65 tended to be at lower risk of early mortality than men (0.45 (95% CI 0.19, 1.04). Three year mortality of 28 day survivors did not differ between sexes.**

***Conclusions*—These data support the idea that the higher 28 day mortality in hospitalised women with a first Q wave myocardial infarction is mainly attributable to the large number of patients aged 65 to 74 years in whom the risk is higher than that in men. Women under 65 with myocardial infarction do not seem to be a special group of risk.**

(*J Epidemiol Community Health* 2001;**55**:487–493)

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Accepted for publication 21 February 2001

Women hospitalised with an acute myocardial infarction (AMI) have higher short-term mortality rates than men.[1] Such a difference is mostly explained by the greater age of women at the time of myocardial infarction.[2] Other contributing factors are the increased prevalence of cardiovascular risk factors or comorbidity in women, a tendency toward the underuse of diagnostic procedures or therapeutic interventions in women compared with men.[2] Some studies have, however, reported a significantly higher mortality in women after adjustment for some or all of these factors.[3–8] Suggestions as to mechanisms that may be implicated in this excess risk for women have been speculative and remain unclear.[9 10] A candidate factor is the higher frequency in women of clinical manifestations of left ventricular dysfunction (acute pulmonary oedema or cardiogenic shock) during the acute phase.[2 6] Nevertheless, some studies have reported an increased risk of death or complications in women even after adjusting for such dissimilarities in heart failure variables.[3 11–14]

An interaction between sex and age group has also been described that suggests that the effect of sex on coronary artery disease prognosis may be different according to the age group analysed.[7 14–17]

On the other hand, few studies have investigated long term mortality differences between sexes in myocardial infarction with varying results.[18–27] In general, women have worse prognosis when follow up is less than one year.[2]

This study was aimed at analysing whether the risk of death within 28 days after a myocardial infarction, and during the following three years in 28 day survivors, is higher in women than men and, if so, to assess the role of age, comorbidity and severity of myocardial infarction in this excess of risk.

Methods

Since 1978, REGICOR (*REgistre GIroní del COR*; Gerona Heart Registry) has been registering all first myocardial infarction patients arriving alive at the only reference hospital in Gerona with a coronary care unit[27 28] where most of the myocardial infarction patients in this area are admitted. There are also six community hospitals that refer 70% of these patients to the reference hospital after emergency treatment. This setting provides the population-based registry of hospitalised myocardial infarction patients in a north eastern region of Spain that covers 591 060 km^2 and has 509 628 inhabitants according to the 1996 census.

PATIENTS

All patients aged 25 to 74 years, residents in Gerona and admitted to the reference hospital between 1978 and 1997 with a definite diagnosis of first Q wave myocardial infarction, were included in the study. Diagnosis of Q wave myocardial infarction was based on a definite electrocardiogram—that is, new Q or QS waves—and at least one of the following: increased AMI enzymes (at least twice the upper normal value) and typical pain—that is, located in the anterior chest wall—lasting 20 minutes or more and for which no cause other than coronary heart disease was found.

VARIABLES MEASURED

The following data were prospectively collected: age, sex, smoking status, hypertension and diabetes, history of angina and electrocardiographic myocardial infarction location. Disease severity was established by the clinical

degree of ventricular dysfunction (acute pulmonary oedema or cardiogenic shock) and the presence of ventricular arrhythmias (fibrillation or tachycardia) requiring immediate treatment. Management variables including thrombolysis, antiplatelet drugs, coronary angiogram, percutaneous transluminal coronary angioplasty and coronary artery bypass surgery were also recorded.

FOLLOW UP

Vital status at 28 days was verified in patients admitted between 1978 and 1997 (n=2606). Long term follow up of patients admitted between 1978 and 1993 who survived the first 28 days (n=1790) was completed in 1996 by personal or telephone contact and by linkage with the Catalonia Mortality Registry, which collects all death certificates. Thus, patients were followed up for a minimum of three years or until a fatal event occurred.

END POINTS

All cause 28 day mortality was considered as the end point to analyse short-term mortality. To analyse three year mortality, all cause mortality was considered as the end point, although the cause of death was recorded.

STATISTICAL ANALYSIS

Differences between men and women and between deceased and surviving patients were assessed by χ^2 test for categorical variables and by Student's *t* test for continuous variables.

The adjusted odds ratios (OR) of 28 day mortality for women were estimated by a logistic model and the adjusted OR of three year mortality in 28 day survivors for women were estimated using a Cox model. Demographic, comorbidity, clinical and severity variables that showed at least marginally significant differences ($p \leq 0.15$) in bivariate analysis between men and women and between survivors and non-survivors at 28 days or three years and those important variables based on clinical judgement were included as potential confounders. Severity variables (that is, acute pulmonary oedema or cardiogenic shock) that may be interpreted as intermediate mechanisms of death were also included in separated models along with the former variables.

All possible two way biologically plausible interactions were tested in a model that included all main variable effects.

Survival curves were estimated with the Kaplan-Meier method and compared by Mantel-Cox statistics. Calculations were made with the SPSS statistical package.

Results

Between 1978 and 1997, 2159 men and 447 women aged 25 to 74 admitted consecutively with a first Q wave myocardial infarction were registered. Overall mean age was 59.9 (SD 9.8).

28 DAY FOLLOW UP

Among the 2606 patients admitted between 1978 and 1997, 284 (10.9%) died in the first 28 days. Only two cases died from non-cardiovascular causes. Within the same period, women presented greater mortality and more frequent severe clinical heart failure than men (table 1). Compared with men, women were older, had more comorbidity (hypertension, diabetes), a greater proportion had an anterior myocardial infarction, there were fewer smokers and they received less thrombolysis. Antiplatelet therapy, coronary angiograms and revascularisation procedures were used similarly in men and women in the first 28 days (table 1).

Older age, female gender, history of hypertension, diabetes, non-smoking status, presence of severe arrhythmias or severe clinical heart failure during the acute phase, anterior myocardial infarction and non-use of thrombolysis and antiplatelet drugs were associated with greater 28 day mortality (table 1).

Crude OR of dying within 28 days was 2.27 (95% confidence intervals: 1.72, 2.99) in women. In a fully adjusted model, an interaction between sex and age was found. Mortality risk increased with age but was not linear. Therefore, a cut off at 65 years was established

Table 1 Characteristics of 2606 patients with first acute myocardial infarction in Gerona, Spain (1978–1997) by sex and vital status at day 28

	Sex differences			*28 day survival differences*		
	Men (n=2159)	*Women (n=447)*	*p*	*Deceased (n=284)*	*Survivors (n=2322)*	*p*
Age:mean (SD)	59.4 (10.1)	65.0 (8.2)	<0.001	65.4 (7.7)	59.7 (10.1)	<0.001
Sex (% women)	—	—	—	29.6	15.6	<0.001
Hypertension (%)	40.3	61.2	<0.001	54.2	42.7	<0.001
Diabetes (%)	18.4	45.9	<0.001	30.3	22.3	0.04
Current smokers (%)	66.2	7.5	<0.001	41.6	58.4	<0.001
Angina (%)	46.8	51.3	0.09	50.2	47.2	0.48
History of cardiac failure (%)†	8.0	19.4	<0.001	27.0	8.4	<0.001
Clinical characteristics of acute event and interventions						
Anterior myocardial infarction (%)	45.8	53.0	0.008	65.2	44.9	<0.001
APE/cardiogenic shock (%)	10.8	25.4	<0.001	61.8	7.5	<0.001
Severe arrhythmia (%)*	15.3	14.4	0.69	36.3	12.5	<0.001
Thrombolysis (%)‡	42.2	23.9	<0.001	15.9	41.1	<0.001
Antiplatelet drugs (%)‡	86.9	85.8	0.39	66.9	88.6	<0.001
28 day coronary angiograms (%)	6.6	7.2	0.70	3.5	7.1	0.03
28 day revascularisation (%)§	2.1	2.7	0.54	2.7	2.1	0.7
28 day mortality (%)	9.3	18.8	<0.001	—	—	—

APE = acute pulmonary oedema. *Ventricular fibrillation or tachycardia requiring immediate medical intervention. †Only 1988–1997. ‡In patients admitted from 1988 to 1997 after introduction of routine antiplatelet drugs and thrombolysis. §Percutaneous transluminal coronary angioplasty or coronary artery bypass surgery.

Table 2 Characteristics of men and women with first acute myocardial infarction by age group

	<65 y (n=1561)			65–74 y (n=1045)		
	Men (n=1386)	*Women (n=175)*	*p*	*Men (n=773)*	*Women (n=272)*	*p*
Hypertension (%)	37.7	52.9	<0.001	44.9	66.4	<0.001
Diabetes (%)	16.1	43.0	<0.001	22.6	47.8	<0.001
Current smokers (%)	74.6	14.0	<0.001	50.9	3.4	<0.001
Angina (%)	45.8	51.5	0.2	48.4	51.1	0.49
History of cardiac failure (%)†	6.1	14.0	0.01	10.9	22.5	<0.001
Clinical characteristics of acute event and interventions						
Anterior myocardial infarction (%)	43.2	57.0	0.001	50.6	50.4	1
APE/cardiogenic shock (%)	8.7	16.0	0.03	14.8	33.3	<0.001
Severe arrhythmia (%)	15.6	9.8	0.06	14.8	17.5	0.34
Thrombolysis (%)‡	46.6	31.2	0.007	35.3	19.8	<0.001
Antiplatelet drugs (%)‡	88.4	93.5	0.2	84.7	81.5	0.4
28 day coronary angiograms (%)	5.0	5.7	0.81	9.4	8.1	0.62
28 day revascularisation (%)§	1.4	1.3	1	3.4	3.7	1
28 day mortality (%)	6.9	6.9	0.91	13.6	26.5	<0.001

APE = acute pulmonary oedema. *Ventricular fibrillation or tachycardia requiring immediate medical intervention. †Only 1988–1997. ‡In patients admitted from 1988 to 1997 after introduction of routine antiplatelet drugs and thrombolysis. §Percutaneous transluminal coronary angioplasty or coronary artery bypass surgery.

that defined two groups according to, on the one hand, statistical and, on the other, demographic criteria.

Unadjusted 28 day case fatality in patients under 65 was similar in men and women (6.9% and 6.9%, respectively). In women aged 65 to 74, case fatality was twice that of men (26.5% and 13.6%, respectively). Differences in comorbidity and clinical characteristics in each age stratum between men and women are shown in table 2.

Adjusted logistic regression models showed opposing results in patients over and under 65 (fig 1): women aged 65 to 74 years had a higher risk of dying within 28 days than men of the same age, but women younger than 65 had lower mortality risk than their male counterparts. These findings were consistently significant regardless of the adjustment for confounding factors (model 1, fig 1) and even if we add the severity of myocardial infarction (pulmonary oedema, cardiogenic shock) to the model 1 (model 2, fig 1).

THREE YEAR FOLLOW UP

Overall three year survival curves, (that is, including first 28 days) are presented by sex and age group in figure 2 for the 2053 patients admitted from 1978 to 1993. Altogether 263 of these patients died within 28 days after onset of myocardial infarction symptoms. Differences between age and gender groups in survival curves were mainly attributable to differences in early mortality (28 days).

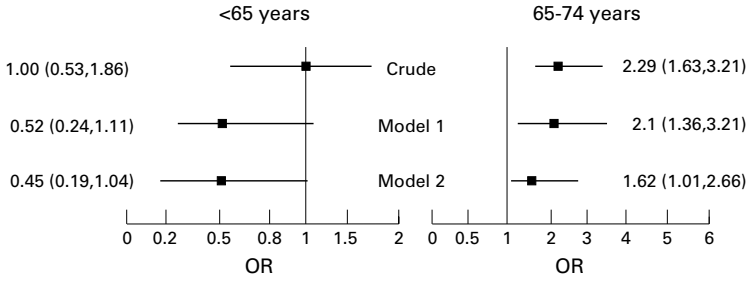

Figure 1 Adjusted odds ratio and 95% confidence intervals of 28 day mortality for women after a first myocardial infarction by age group (over and under 65). Model 1 adjusted for smoking, anterior location of myocardial infarction, diabetes, hypertension, and thrombolysis. Model 2 as model 1 plus acute pulmonary oedema or cardiogenic shock. Further adjustment for age (as a continuous variable) or period of inclusion did not significantly change the odds ratio in any model.

Only 10 patients (0.5%) were lost to the three year follow up among the 1790 28 day survivors of the 1978–1993 cohort. Among these 28 day survivors, three year mortality was 12.0% and women showed worse total three year mortality than men (21.8% versus 10.3%, p<0.0001). Causes of death during long term follow up were coronary in 73.7% of men and 83.1% of women, other cardiac 3.8% and 5.1%, cerebrovascular 2.6% and 1.7% and other causes 16.4% and 10.2%, respectively.

Twenty eight day survivors' characteristics related to three year total mortality are shown in table 3. Baseline differences between sexes in 28 day survivors were very similar to those observed for the whole cohort and, during the first three years of follow up, women and men presented similar non-fatal Q wave reinfarction rates and showed no significant differences in the use rates of coronary angiograms and revascularisation procedure (table 3).

Crude risk of three year total mortality for 28 day survivors was higher in women than men (OR=2.3, 95% confidence intervals: 1.7, 3.1). Adjustment for confounding variables (that is, age, smoking, diabetes, hypertension, thrombolysis, and acute pulmonary oedema or cardiogenic shock during the acute phase) led to non-statistically significant OR for gender (OR=1.3, 95% confidence intervals: 0.9, 1.9). No interaction was found to be statistically significant.

Discussion

This study shows that women aged 65 to 74 have more than twofold the risk of 28 day mortality after a first Q wave myocardial infarction than men, regardless of any clinical or severity characteristic. In contrast, female patients younger than 65 showed similar crude risk of dying compared with men of the same age group, and there were no statistically significant differences between sexes after adjustment for potential confounders. No independent sex effect on three year mortality risk was observed in 28 day survivors.

Though crude early mortality is higher in hospitalised women than in men in most studies, adjusted results differ.[2 9 29] Comparability of adjusted results is difficult because of the

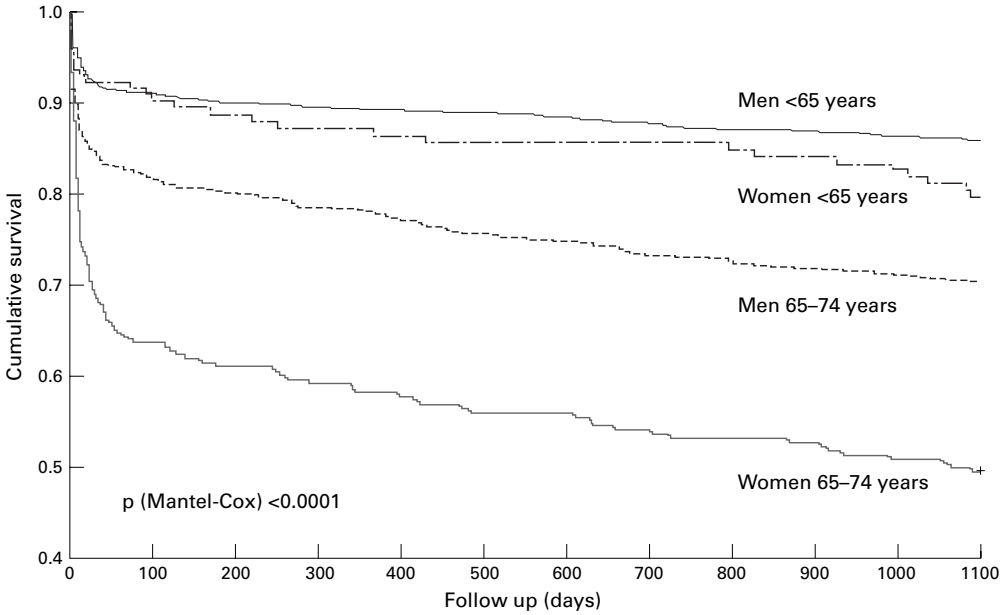

Figure 2 Survival curves by sex and age group in 2053 patients (351 women and 1702 men) with a first myocardial infarction in Gerona, Spain 1978–1993.

great heterogeneity in methodology, either in study design, inclusion criteria of the patients or in controlling for confounding factors.[2 9 30]

Age has been recognised to be a major independent risk factor of mortality after myocardial infarction.[2 9] In many studies the excess risk in women disappeared after adjusting for differences in age distribution or other confounding variables.[2 9] In our study, a differential risk in women was observed according to age strata (younger and older than 65), even after adjusting for other potentially confounding variables (fig 1). Few works have suggested a diverging effect of female sex on myocardial infarction survival in different age groups.[7 14–17] All found a significant interaction between age and sex, but in the opposite direction to ours. However, it is difficult to compare our results because of considerable differences in the study designs: studies differed in age range; some included patients enrolled in clinical trials (non-consecutive),[7 17] or only patients admitted to coronary units[17] and some included a large proportion of patients with non-Q wave myocardial infarction or with previous history of myocardial infarction.[7 14 15] Particularly striking are the differences between our results and those from Vaccarino in her large cohort study of more than 380 000 patients after excluding 21% of candidates because of transfer to another hospital.[16] This may have introduced a selection bias because it is probable that transferred patients were more severely diseased. In fact, the mortality observed could be considered low taking into account that patients up to 89 years of age were included. Furthermore, no information is provided as to which proportion of races are

Table 3 Baseline patient demographic, clinical and management characteristics associated with three year total mortality in 28 day survivors

	Sex differences			*Three year survival differences*		
	Men (n=1519)	*Women (n=271)*	*p*	*Deceased (n=215)*	*Survivors (n=1575)*	*p*
Age:mean (SD)	58.9 (10.1)	64.0 (8.1)	<0.001	65.4 (7.7)	59.7 (10.1)	<0.001
Sex (% women)	—	—	—	27.4	13.5	<0.001
Hypertension (%)	39.0	59.1	<0.001	50.5	41.1	0.01
Diabetes (%)	16.7	48.0	<0.001	30.2	20.4	0.001
Current smokers (%)	68.9	7.8	<0.001	46.2	61.6	<0.001
Angina (%)	46.7	51.7	0.15	52.4	46.8	0.15
History of cardiac failure (%)†	7.1	14.9	0.008	18.4	7.2	0.002
Clinical characteristics of acute event and interventions						
Anterior myocardial infarction (%)	44.1	53.5	0.005	48.1	45.2	0.48
APE/cardiogenic shock (%)	5.4	15.8	<0.001	19.2	5.3	<0.001
Severe arrhythmia (%)*	10.8	9.8	0.7	15.0	10.0	0.03
Thrombolysis (%)‡	37.2	14.9	<0.001	17.7	35.4	0.002
Antiplatelet drugs (%)‡	81.6	85.1	0.43	75.9	82.8	0.17
28 day coronary angiograms (%)	4.1	5.5	0.4	3.8	4.5	0.78
28 day revascularisation (%)§	1.1	1.8	0.5	1.0	1.3	1
Events during three year follow up (after day 28)						
Three year mortality (%)	21.8	10.3	<0.001	—	—	—
Three year coronary angiograms (%)	13.6	12.8	0.8	9.2	14.0	0.09
Three year revascularisation (%)§	7.0	7.9	0.74	5.5	7.4	0.42
Three year non-fatal Q wave reinfarction (%)	5.1	4.2	0.63	6.1	4.8	0.50

APE = acute pulmonary oedema during acute phase. *Ventricular fibrillation or tachycardia requiring immediate medical intervention during acute phase. †Only after 1988. ‡In patients admitted after introduction of routine antiplatelet drugs and thrombolysis (1988). §Percutaneous transluminal coronary angioplasty or coronary bypass surgery.

present in the cohort, which may be important according to recent findings suggesting that black patients were less likely to receive lifesaving treatment.[31] The low mortality observed in Vaccarino's cohort may also be related to the high proportion of non-Q wave AMI (50%), which is known to have lower early mortality, and they were excluded in our study. Non-Q wave myocardial infarction cases may range 7% to 50% in several published studies.[16 32]

Moreover, these studies were conducted in countries with a high incidence of myocardial infarction.[7 14–17] Other studies have described a strong inverse correlation between population event rate and female/male case-fatality ratio.[33] Thus, southern European countries are an example of this phenomenon: low myocardial infarction incidence rates are observed together with high female:male case fatality ratios.

Myocardial infarction incidence among Spanish women is approximately one fifth that of the USA, which leads to a low number of female cases below 65 years in our region and around one third in men. All these factors may play a part in the fact that we found lower mortality in women younger than 65 years, in discrepancy with other authors. Interestingly, myocardial infarction case-fatality is also lower in both sexes in Spain.[34] In this respect, we might hypothesise that young women develop AMI not only with less frequency but also with less severe characteristics in southern Europe than in the USA. This idea is in accordance with lower absolute risk associated to particular risk factor values found in southern Europe by other authors in this region.[35 36] Maybe the necessity of longer exposure to risk factors exists in this area to develop coronary heart disease.

To assess whether worse prognosis in women is related to greater severity of myocardial infarction (pulmonary oedema, cardiogenic shock), adjustment for these mechanisms of death, even if they fail to meet confounding criteria, would be useful.[8] Some studies reflect a worse prognosis in hospitalised women after adjusting for heart failure and other dissimilarities between sexes,[3 11–14] others do not find these differences after adjustment.[8 15]

In this study, women had more frequent severe heart failure during the acute phase than men for both age groups. However, the adjusted decreased mortality risk in women under 65 and the increased risk in women aged 65 to 74 were not modified by the inclusion of variables that measured heart failure during the acute phase (fig 1, model 1 and 2 respectively). This suggests that some unknown factor would contribute to the different prognosis in women before and after 65 years independently of the development of heart failure. Given that differences in heart failure between men and women do not seem to explain the early mortality risk differences, alternative possibilities should be sought.

In relation to other factors influencing mortality, some studies reflected gender differences either in the efficacy of medications used to treat myocardial infarction (particularly, thrombolysis, β blockers and aspirin) or in the use of effective treatments.[29] Moreover, some studies suggest a gender gap in the likelihood of women receiving less acute cardiovascular diagnostic procedures (coronary angiogram) or interventions (revascularisation procedures).[37 38] In our study, as in others,[39] invasive procedures and aspirin treatment did not differ between sexes. Women received less thrombolysis, which was probably related to longer delay in reaching hospital (4.7 hours in women and 2.3 hours in men, p=0.02, data not shown, period 1992–94). However, the results held after adjusting for this treatment.

The high prevalence of diabetes in our population of myocardial infarction patients, particularly in women, is similar to that found in other Spanish registries.[8 40]

KEY POINTS

- Mortality risk in men and women hospitalised after a myocardial infarction differ according to age.
- Women aged 65–74 had higher early mortality risk than men of the same age after adjusting for age, comorbidity and acute complications including heart failure. Conversely, women under 65 tended to be at lower risk of early mortality than men.
- Three year mortality of 28 day survivors did not differ between sexes.

THREE YEAR MORTALITY OF FIRST MYOCARDIAL INFARCTION SURVIVORS

As in short-term mortality, there is great heterogeneity in the methodology across the different studies that assess long term prognosis after a myocardial infarction.[30]

Higher risk of death in women, even after adjustment for age and comorbidity, was observed in studies analysing periods of one year or less.[3 8] Conversely, those analysing longer periods observed no differences,[6 18–22 34] increased risk in women[26] or a statistically significant benefit in women.[23–25] In our study, no statistically significant differences were found between sexes in three year 28 day survivors' mortality when adjusting for all confounding variables.

STUDY CHARACTERISTICS AND CLINICAL IMPLICATIONS

For patients older and younger than 65, the need for age adjustment could also be postulated as age, even within each of the two age subgroups, may continue to influence early mortality. Over the long inclusion period of this study (1978 to 1997), a decreasing mortality risk was reported, although no differences in gender distribution were observed among time periods.[28] Adjustment for the period of inclusion and age within each age group yielded ORs for sex that did not change significantly in any model (results not shown).

Considering previous heart failure—which is more frequent among women—in the multivariate analysis implies excluding 1194 cases admitted before 1988 because of the lack of

information on this variable before that year, but yielded similar results to those presented with no modification of the risk estimates for sex.

In our study, only first Q wave definite myocardial infarction patients aged 25–74 years admitted to a reference hospital were included. The use of some restrictive criteria, such as upper age limit at 74 years and first myocardial infarction, may help to improve the accuracy of excess risk estimates and prevent complex model adjustment (that is, time since last event, number of previous events, or left ventricular ejection fraction after these events). Moreover, patients are homogeneous in diagnostic criteria as we excluded non-Q wave myocardial infarction cases that may range 6.6 to 42.6% in several published studies.[32] In our study non-Q wave myocardial infarction represents a 16.7% of total myocardial infarction admitted after 1990.

It is possible that case fatality differences during hospitalisation according to age and sex were attributable to sex and age differences in the mortality before hospitalisation. According to 1990–97 data of our REGICOR population MI registry, overall 28 day case fatality in women was significantly higher than in men (47.2% versus 39.6%, p=0.005). Furthermore, we did not find any substantial differences between the proportion of prehospital deaths between men and women in each age strata (proportion of prehospital deaths: 69.5% and 71.3% in men and women under 65 respectively, and 61.8% and 59.8% in men and women of 65 and older). From a public health point of view, the large prehospital case fatality is a major issue. None the less, the health care system is concerned with the fate of AMI patients who reach hospitals alive, as clinicians need to orientate their efforts towards reducing inhospital case fatality. In our study only patients admitted in a tertiary hospital are included and the results are adjusted for the possible confounding factors (that is, age, comorbidity, severity) that would be difficult in prehospital deaths because of the large proportion of missing comorbidity data.

Our data support the idea that the higher 28 day mortality in women with Q wave myocardial infarction is mainly attributable to the large number of patients aged 65 to 74 years in whom the risk is at least twice that in men. This difference is not explained by the greater frequency of severe heart failure after myocardial infarction. Young women with myocardial infarction do not seem to be a special group of risk. In 28 day survivors, total mortality at three years is similar in both sexes.

Persons and institutions colaborating in REGICOR: X Albert, (Clinica Girona); M Saguer, M Vicente, F Monzón (Hospital Comarcal de Figueres); J Bisbe, P Cortés, A Agustí, M Barcons (Hospital Comarcal Sant Jaume d'Olot); N Constans, R Massa (Hospital Comarcal de La Selva); F Bassó, A Masabeu, J Inoriza (Hospital Comarcal de Palamós); C Martinez, (Servei d'Emergencies Mèdiques); J C Guerra (Hospital Provincial de Santa Caterina, Gerona); X Albert, R Masiá, J Sala (Hospital Universitari Dr Josep Trueta, Gerona); C Aubó, M Bosch, M Cardona, M I Covas, R Elosua, M Gil, J Marrugat, S Martín, A Pena, G Pérez, P Roset, M Sentí M (Institut Municipal d'Investigació Mèdica, Barcelona). We appreciate the English revision of the manuscript made by Christine O'Hara.

Funding: this project was supported by grants FIS-90/0672 and FIS-93/0568 from the *Fondo de Investigación Sanitaria* and received partial support through grant CIRIT/1999 SGR 00423 of the Generalitat de Catalunya.
Conflicts of interest: none.

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