Both mortality due to cerebrovascular disease in individuals aged under 85 years and mortality due to acute myocardial infarction (AMI) are lower in women than men. In contrast, the age-adjusted 28-day case fatality rate after a first AMI is 20% higher in women, particularly in countries where the incidence of AMI is low. In Spain, the case fatality rate is elevated in women hospitalized for a first AMI, but not in those with other forms of coronary heart disease. The pattern of mortality observed after symptom onset, which shows that death is delayed in women, suggests that the mechanism of death is different in the 2 sexes. The substantial variation that exists in the way results are adjusted and presented makes it very difficult to compare the findings of different studies. Relative to men, women with AMI are 10 years older, reach hospital 1 hour later on average, more frequently have a comorbid condition (mainly diabetes and hypertension), progress to a more serious clinical state, and have a higher adjusted 28-day mortality risk. Moreover, the treatment given to women during the acute phase is less aggressive. A change in healthcare workers’ attitudes is needed so that women with acute coronary syndromes can be identified earlier, thereby increasing the use of diagnostic and therapeutic procedures to a level that corresponds to the greater severity of AMI observed in women at presentation.

**Key words:** Sex. Coronary disease. Cerebrovascular disease. Incidence. Mortality

---

**INTRODUCTION**

The incidence and mortality rates of acute myocardial infarction (AMI) are greater in males than in females in all the population registries for this disease (Figure 1). The AMI mortality ratio between males and females depends on age and varies between countries with a magnitude of 2 to almost 6 in the 35- to 64-year-old age group (Figure 2). On average, females who develop AMI do so 7 to 10 years later than males.
these differences, it is believed that coronary heart disease will continue to be the leading individual cause of death in developed countries and, probably, in developing ones.\textsuperscript{9}

The advantage of females regarding incidence and mortality is lost when presenting AMI, since population mortality at 28 days is greater in females, especially in hospitalized patients.\textsuperscript{10-36}

**ABBREVIATIONS**

CVD: cerebrovascular disease.
AMI: acute myocardial infarction.
MONICA: Monitoring Trends and Determinants of Cardiovascular Diseases.
REGICOR: Registre Gironí del Cor.

**Figure 1.** Age-adjusted rates per 1 000 000 population in males and females at death due to ischemic heart disease in several developed countries in 2002.

**Figure 2.** Male/female ratio regarding death rate in 38 MONICA-WHO centers ordered by increasing population mortality rate in 35- to 64-year-old males. Adapted from Chambless et al.\textsuperscript{6}
Older age and the prevalence of comorbidity (in particular diabetes, hypertension and heart failure) in females explains some of these differences and have been cited as among the causes leading to this unfavorable situation. Nevertheless, the differences are maintained in many studies despite adjusting for these factors.10,11,14,15,19,30,32,33,36 Prognosis in the medium- and long-term is, however, similar in both sexes among survivors at 28 days from symptom onset when differences regarding the characteristics of both sexes are taken into account.35-46

The problem of cerebrovascular disease (CVD) in Catalonia and Spain has continued to decrease in magnitude since the 1950s in terms of population mortality, and has done so faster than in ischemic heart disease. This fast reduction in CVD mortality means that Spain is among the countries with the lowest rates in the developed world (Figure 3). The standardized cumulative incidence rate in the 45- to 84-year-old age range in Catalonia only (268/100 000) (unpublished data) is slightly higher than that observed in the mid-1980s in France (238/100 000), and much lower than that in some developed countries.47 The incidence and mortality (unpublished data) rates of CVD also are higher in males than in females48 (Figure 4).

Differences between sexes in the prognosis of AMI have been analyzed in observational studies and as a secondary endpoint in clinical trials as well as in other research that had not initially been designed to address this issue. All the approaches have advantages and
within 28 days after symptom onset with most fatal cases tending to occur in hospitalized patients and 24 h after admission.

This distribution indicates that females die more often from heart failure than from acute complications due to myocardial ischemia, such as ventricular arrhythmias. Overall, age-adjusted mortality in females aged 35 to 64 years old is only slightly greater than in males (51.3 and 49.4%, respectively),

although there is considerable geographical variability: in 13 of the 29 centers included in the MONICA study (Monitoring Trends and Determinants of Cardiovascular Diseases), the female/male ratio was significantly >1 but, surprisingly, in the remaining ones, no significant differences were found which were unfavorable to males (Table 1). In Spain, an interaction between sex and age regarding 28-day mortality has been described, such that females <64 years old do not have a worse prognosis than males of the same age, although those between 65 to 74 years old do.

Most fatal events (median, 70% in males and 64% in females) occur before the patients manage to get to hospital.

After admission, age-adjusted mortality is greater among females (26.9 and 21.8%, respectively; ratio, 1.24).

There is a strong inverse correlation between the population event rate and the mortality ratio between

**MORTALITY FROM ACUTE MYOCARDIAL INFARCTION**

**Population Mortality**

Population registries have the advantage of including patients who die from AMI before being admitted to hospital and, thus, they offer the opportunity to analyze mortality occurring before and after hospitalization in this population.

It has been found that fatal cases are distributed differently by sex: whereas sudden death more frequently occurs in males, females have a worse overall prognosis within 28 days after symptom onset with most fatal cases tending to occur in hospitalized patients and 24 h after admission.6,22,24

This distribution indicates that females die more often from heart failure than from acute complications due to myocardial ischemia, such as ventricular arrhythmias. Overall, age-adjusted mortality in females aged 35 to 64 years old is only slightly greater than in males (51.3 and 49.4%, respectively),6 although there is considerable geographical variability: in 13 of the 29 centers included in the MONICA study (Monitoring Trends and Determinants of Cardiovascular Diseases), the female/male ratio was significantly >1 but, surprisingly, in the remaining ones, no significant differences were found which were unfavorable to males (Table 1). In Spain, an interaction between sex and age regarding 28-day mortality has been described, such that females <64 years old do not have a worse prognosis than males of the same age, although those between 65 to 74 years old do.6,24

Most fatal events (median, 70% in males and 64% in females) occur before the patients manage to get to hospital.6,13,49-51 After admission, age-adjusted mortality is greater among females (26.9 and 21.8%, respectively; ratio, 1.24).6,24

There is a strong inverse correlation between the population event rate and the mortality ratio between

**Figure 4.** Specific (A) and standardized (B) death rates by age and sex per 100,000 inhabitants, due to cerebrovascular disease in those more than 24 years old by decade in Catalonia 2002.

**Figure 5.** Female/male mortality odds ratio in 38 MONICA/World Health Organization centers, ordered by population incidence of myocardial infarction in males from 35 to 64 years (A), and by the population incidence in females of the same age (B).
TABLE 1. Results and Characteristics of Studies on Differences Between Sexes in Early Mortality After Myocardial Infarction in Which the Type of Adjustment Could Be Determined*

<table>
<thead>
<tr>
<th>Reference</th>
<th>Author and Year of Sampling Design</th>
<th>No. Females/ Males</th>
<th>Age Range</th>
<th>Mortality Adjustment Factors and Results</th>
<th>Age Comorbidity</th>
<th>Severity</th>
<th>Treatment in Adjusted OR/RR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Puletti et al 18</td>
<td>1984 C/R HR/S 106/535 All</td>
<td>42.4%/16.6%</td>
<td>Yes</td>
<td>DH/H/K/E</td>
<td>1.4 (1.05-1.88)</td>
<td></td>
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<tr>
<td>Fiebach et al 30</td>
<td>1990 C/R HR/S 332/790 30-74</td>
<td>14.2%/9.9%</td>
<td>Yes</td>
<td>DH/H/K/E</td>
<td>1.28 (NS)</td>
<td></td>
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<tr>
<td>Greenland et al 18</td>
<td>1991 C/R HR/M 152/4310 All</td>
<td>36.5%/14.6%</td>
<td>Yes</td>
<td>DH/H/K/E</td>
<td>1.16 (1.34-1.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fieritz et al 25</td>
<td>1992 C/R HR/S 348/1060 All</td>
<td>25.6%/12.8%</td>
<td>Yes</td>
<td>K/L/R/E</td>
<td>1.72 (1.45-2.04)</td>
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<tr>
<td>Goldberg et al 25</td>
<td>1993 C/R HR/M 1320/1196 All</td>
<td>21.7%/12.7%</td>
<td>Yes</td>
<td>K/L/R/E</td>
<td>1.18 (0.86-1.65)</td>
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<tr>
<td>White et al 18</td>
<td>1993 NCR CT/M 1944/5317 All</td>
<td>12.1%/7.2%</td>
<td>Yes</td>
<td>H/K/L/E</td>
<td>1.11 (0.86-1.43)</td>
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<tr>
<td>Beden et al 1 9</td>
<td>1994 NCR CT/M 972/742 &lt;76</td>
<td>98%</td>
<td>Yes</td>
<td>DH/H/K/A/P</td>
<td>1.54 (0.94-2.54)</td>
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<tr>
<td>Jenkins et al 7</td>
<td>1991 C/R HR/S 155/355 All</td>
<td>21.4%/12.1%</td>
<td>Yes</td>
<td>K/L/R</td>
<td>1.63 (1.45-2.04)</td>
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<tr>
<td>He et al 25</td>
<td>1994 C/I HR/S 294/601 All</td>
<td>23.5%/12.0%</td>
<td>Yes</td>
<td>K/L/R</td>
<td>1.74 (1.17-2.60)</td>
<td></td>
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<tr>
<td>Marugat et al 13</td>
<td>1995 C/R HR/M 193/1023 0-74</td>
<td>20.2%/11.3%</td>
<td>Yes</td>
<td>D/H/Q/K/L/R</td>
<td>1.11 (0.86-1.43)</td>
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<tr>
<td>He et al 25</td>
<td>1994 C/I HR/S 105/99 &gt;75</td>
<td>40%/32.0%</td>
<td>Yes</td>
<td>K/L/R</td>
<td>0.75 (0.25-2.21)</td>
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<tr>
<td>Demirovic et al 13</td>
<td>1995 NCR HR/M 198/113 30-65</td>
<td>12.5%/8.5%</td>
<td>Yes</td>
<td>No</td>
<td>2.0 (1.2-3.3)</td>
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<tr>
<td>Kober et al 26</td>
<td>1996 C/R CT/M 2170/4501 All</td>
<td>19.5%/21.6%</td>
<td>Yes</td>
<td>K/L/R</td>
<td>0.9 (0.5-1.6)</td>
<td></td>
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<tr>
<td>Weaver et al 18</td>
<td>1996 NCR CT/M 10315/3076 All</td>
<td>11.3%/5.5%</td>
<td>Yes</td>
<td>D/H/A/P</td>
<td>1.16 (0.93-1.41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canessa et al 10</td>
<td>1997 C/I HR/S 253/623 All</td>
<td>27.2%/13.5%</td>
<td>Yes</td>
<td>D/H/L</td>
<td>1.25 (1.01-1.54)</td>
<td></td>
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<tr>
<td>Coronado et al 18</td>
<td>1997 C/R HR/M 325/757 &gt;60</td>
<td>10.3%/4.7%</td>
<td>Yes</td>
<td>D/H/A/P</td>
<td>1.16 (1.05-1.33)</td>
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<tr>
<td>Mayard et al 13</td>
<td>1997 C/R HR/M 425/907 All</td>
<td>13.7%/8.4%</td>
<td>Yes</td>
<td>D/H/A/P</td>
<td>1.22 (1.08-1.4)</td>
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<tr>
<td>Marugat et al 13</td>
<td>1998 C/R HR/M 330/117 All</td>
<td>18.9%/8.3%</td>
<td>Yes</td>
<td>D/H/A/P</td>
<td>1.16 (1.04-1.32)</td>
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<tr>
<td>Maldare et al 13</td>
<td>1998 C/R HR/M 300/918 All</td>
<td>14.8%/9.1%</td>
<td>Yes</td>
<td>D/H/A/P</td>
<td>1.26 (1.06-1.51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marugat et al 13</td>
<td>2001 C/I HR/M 175/1876 20-64</td>
<td>6.9%/4.9%</td>
<td>Yes</td>
<td>D/H/A/P</td>
<td>1.27 (1.06-1.52)</td>
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<td></td>
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<tr>
<td>Marugat et al 24</td>
<td>2004 C/I HR/M 272/773 65-74</td>
<td>26.5%/13.6%</td>
<td>Yes</td>
<td>D/H/A/P</td>
<td>1.19 (1.01-1.46)</td>
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<tr>
<td>Chambless et al 10</td>
<td>1997 C/I HR/S 294/9710 All</td>
<td>24.3%/10.9%</td>
<td>Yes</td>
<td>D/H/A/P</td>
<td>1.16 (1.07-1.26)</td>
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<tr>
<td>Herman et al 27</td>
<td>1997 C/I PR NA 25-69</td>
<td>36.8%/30.0%</td>
<td>Yes</td>
<td>D/H/A/P</td>
<td>1.19 (1.06-1.33)</td>
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<tr>
<td>Chatless et al 10</td>
<td>1997 C/I HR/M 16250/3274 35-64</td>
<td>35.2%/22.2%</td>
<td>Yes</td>
<td>D/H/A/P</td>
<td>1.19 (1.06-1.33)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Table continued on the next page.*
males and females (Figure 5). Southern European countries constitute an example of this phenomenon: there is a low incidence of AMI together with a high ratio of female/male mortality. The reasons for this considerable geographical variability in population mortality can clearly be found in cultural differences, health systems and, no doubt, the actual differences in the incidence and severity of AMI. Despite all this, none of these hypotheses have been deeply explored up to the present, and should be an area of interest for future research.

Observations in Hospitalized Patients

The high prehospital mortality in both sexes is a serious challenge to public health and if this can be reduced it would have a greater impact on total mortality at 28 days due to AMI than any other therapeutic advance to date. This stated, it has to be admitted that the health system also needs to direct its efforts toward the patients who manage to get to hospital and, thus, decrease hospital mortality due to AMI.

There is a lack of detailed information on the clinical picture and medical history of a substantial number of patients who die before arriving at hospital, thus making it difficult to accurately determine the etiology of coronary death, and who are later included in the population registries (1%-51%). However, this information is available regarding the patients included in hospital registries, which are, therefore, the only ones in which it is possible to determine whether the greater mortality in females after AMI is related to greater comorbidity or severity of the disease.

Table 1 presents the characteristics and basic results of the studies published to date where it was possible to estimate the relative risk of death after an AMI for females and to determine for which variables risk was adjusted. In 10 of 14 of the 19 registries which included patients consecutively, the relative risk (RR) for females was >1.20, and in 9 this was >1.39. In 10 of these studies, the RR was statistically significant. It needs to be emphasized that RR was 1.50 in all the studies on the Mediterranean area—mainly Spanish—and which included a broad age range. Only 3 of the studies reported RR less than 1; in 2 of them patients were >64 years old, but risk did not reach statistical significance.

In the MONICA-WHO study, a similar pattern was found in the relationship between the male/female 28-day mortality ratio and the incidence of AMI among hospitalized patients. The female/male mortality ratio was also higher in the areas with lower AMI incidence rates.

LONG-TERM MORTALITY

Few studies have compared male and female mortality beyond 6 months. Table 2 presents a selection of articles that described patient evolution between 6 months and 14 years.
If we consider the average age at the time of AMI symptom onset, a follow-up of more than 15 years would give similar results in both sexes. A greater risk of mortality in females was found in follow-ups <1 year, even after adjusting for age and comorbidity.\textsuperscript{13,16,21} In contrast, in studies which analyzed longer periods, no differences were observed between males and females.\textsuperscript{13,16,21,23,28,34,41,42,44} greater risk of death in females\textsuperscript{28} or statistically significant lower mortality among females.\textsuperscript{31,36,38,41,42,44}

**SOURCES OF VARIATION THAT AFFECT COMPARABILITY OF RESULTS**

Selection criteria vary from one study to another. The population basis can change how the findings are viewed.\textsuperscript{13} The upper age limit is one of the crucial factors for the assessment of population differences between sexes; however, the inclusion of incident cases or incident cases plus recurrent ones, non-Q wave AMI or patients with unstable angina in the hospital registries can also limit comparability between them. Many studies that have addressed the role played by sex in AMI survival were not originally designed with this aim, such as the clinical trials or AMI registries which included non-consecutive patients.\textsuperscript{13,19,20,27,28}

There are a large number of follow-up times used to establish mortality: at 28 days at the population scale or in hospitalized patients, at 28 days among 24-h survivors, and prehospital mortality or mortality at 24 h, are all examples of the variability that can be found in the literature, together with other less precise ones, such as the period of hospitalization. Another source of variation and uncertainty is related to some studies which excluded patients who died in the emergency ward. This bias is particularly important, since most deaths occur in the first 24 h.\textsuperscript{21}

Tables 1 and 2 include the adjusted RR or odds ratio (OR). However, there is great heterogeneity in the number and type of variables included in this adjustment. Apart from age, which is clearly a confounding factor related both to mortality and sex, other variables related to previous risk in each patient also require adjustment in order to take into account their capacity to respond to the disease. Furthermore, the revascularization procedures used soon after symptom onset can radically change prognosis and should also be included in the models. Finally, to determine if the higher risk in females is attributable to greater severity, models can be included with variables such as cardiogenic shock, pulmonary edema or serious ventricular arrhythmias that could help to evaluate this situation of increased serious risk. Unfortunately, the multivariate analyses carried out in many of the studies listed in Tables 1 and 2 consist in step-by-step logistical regressions only. This fact hinders the comparability of results.

**POSSIBLE EXPLANATIONS OF WORSE SHORT-TERM PROGNOSIS IN FEMALES AFTER A FIRST MYOCARDIAL INFARCTION**

Killip class measures the presence and severity of left ventricular dysfunction and is one of the most powerful predictors of mortality after an AMI.\textsuperscript{14} Females who present this have a more frequent background of heart failure than males and usually receive more diuretic and inotropic medication.\textsuperscript{29} However, overall, females receive less treatment than males (see below).\textsuperscript{30-32} Diastolic function during myocardial ischemia is probably related to the greater frequency of Killip class III-IV found in females in the acute phase of AMI. However, this is not necessarily accompanied by a worse ejection fraction (in fact, the opposite has been observed) or by more extensive necrotic lesions than in males.\textsuperscript{30,31,32} As mentioned, females present worse Killip class than males during the acute phase of AMI.\textsuperscript{14,16,21} Regardless of age at presentation, females develop more serious complications than males in terms of heart failure and reinfection, even when ventricular function is similar at admission. This could indicate that there is a smaller cardiac reserve in females leading to worse diastolic function.\textsuperscript{21} These possible differences between sexes regarding diastolic function probably require in-depth study.

Surprisingly, females also seem to develop mitral regurgitation more frequently, septal rupture, free-wall rupture, ventricular aneurysms, asystole and advanced atrioventricular block than males after AMI.\textsuperscript{14,15,30} but less fibrillation or ventricular tachycardia.\textsuperscript{14}

The possibility that females have smaller caliber coronary arteries, fewer collateral vessels or longer-lasting ischemia have also been suggested as explaining these differences.\textsuperscript{21,25,28}

Some theories are based on physiopathology. These include the existence of hypercoagulability states\textsuperscript{22} and coronary arterial spasm,\textsuperscript{24} which are mechanisms described in young females that could explain greater mortality after AMI compared to males, both in the short- and long-term; such differences were not found when ages were >75.\textsuperscript{22,24,25}

A possible genetic mechanism has also been described, whereby females would be more susceptible to presenting ischemic events compared to males when there is a family history of ischemic heart disease.\textsuperscript{25}

**PRESENTATION OF INFARCTION SYMPTOMS IN FEMALES**

Some studies have shown that females present silent heart attacks more frequently than males after 55 years of age,\textsuperscript{23} which could be easily explained by the greater prevalence of diabetes among AMI patients. This would also explain the fact that females present signs of serious heart failure as a first symptom of AMI more frequently than males.\textsuperscript{13,16,21} It seems that females not only present...
<table>
<thead>
<tr>
<th>Author and Bibliographic Reference</th>
<th>Year of Publication</th>
<th>Sampling Method</th>
<th>Design</th>
<th>Follow-Up, No.</th>
<th>Age</th>
<th>Raw Mortality (Females/Males)</th>
<th>OR/RR for Females Adjusted for Confounding Factors</th>
<th>Age</th>
<th>Concomitancy</th>
<th>Severity of on Admission</th>
<th>Treatment in Acute Phase</th>
<th>OR/RR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Weinblatt et al (a) (\ddagger)</td>
<td>1973</td>
<td>NC/I</td>
<td>O</td>
<td>5</td>
<td>120/604</td>
<td>25-64</td>
<td>16.3%/21.3%</td>
<td>Yes</td>
<td>0.69 (0.44-1.08)</td>
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<tr>
<td>Pohjola et al (a) (\ddagger)</td>
<td>1980</td>
<td>C/R</td>
<td>HR/M</td>
<td>5</td>
<td>219/959</td>
<td>&lt;66</td>
<td>35.5%/31.6%</td>
<td>Yes</td>
<td>0.64 (P=0.02)</td>
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<tr>
<td>Martín et al (a) (\ddagger)</td>
<td>1983</td>
<td>C/R</td>
<td>HR/M</td>
<td>9</td>
<td>167/699</td>
<td>30-69</td>
<td>OR=0.91 (NS)</td>
<td>Yes</td>
<td>0.73 (0.54-0.98)</td>
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<td>C/I</td>
<td>HR/S</td>
<td>1</td>
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<td>&lt;66</td>
<td>7.2%/16.4%</td>
<td>Yes</td>
<td>1.09 (0.67-1.77)</td>
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<tr>
<td>Wang et al (a) (\ddagger)</td>
<td>1989</td>
<td>C/I</td>
<td>CS</td>
<td>9.7</td>
<td>1092/236</td>
<td>All</td>
<td>39.4%/30.5%</td>
<td>Yes</td>
<td>0.78 (0.55-1.08)</td>
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<td>1990</td>
<td>C/R</td>
<td>HR/S</td>
<td>3</td>
<td>2857/320</td>
<td>30-74</td>
<td>16.8%/15.8%</td>
<td>Yes</td>
<td>0.49 (0.31-0.77)</td>
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<td>Greenland et al (a) (\ddagger)</td>
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<td>C/R</td>
<td>HR/M</td>
<td>1</td>
<td>524/1435</td>
<td>All</td>
<td>13.1%/8.2%</td>
<td>Yes</td>
<td>1.27 (P=0.03)</td>
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<td>HR/M</td>
<td>14</td>
<td>965/1673</td>
<td>All</td>
<td>NA</td>
<td>Yes</td>
<td>1.32 (1.05-1.66)</td>
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<td>Galáut-Wassén et al (a)</td>
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<td>C/R</td>
<td>CT/M</td>
<td>10</td>
<td>621/1974</td>
<td>&lt;76</td>
<td>60.9%/58.7%</td>
<td>Yes</td>
<td>0.9 (0.8-1.01)</td>
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<td>Gottlieb et al (a) (\ddagger)</td>
<td>1994</td>
<td>C/R</td>
<td>CT/M</td>
<td>2</td>
<td>451/1650</td>
<td>&lt;75</td>
<td>12.6%/11.1%</td>
<td>Yes</td>
<td>1.04 (0.67-1.52)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kostis et al (a) (\ddagger)</td>
<td>1994</td>
<td>C/R</td>
<td>HR/M</td>
<td>3</td>
<td>715/3149</td>
<td>30-49</td>
<td>13%/8%</td>
<td>Yes</td>
<td>1.06 (0.54-1.09)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hu et al (a) (\ddagger)</td>
<td>1994</td>
<td>C/R</td>
<td>HR/S</td>
<td>10</td>
<td>694/4732</td>
<td>70-89</td>
<td>52%/52%</td>
<td>Yes</td>
<td>0.83 (1.03-1.12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marmugat et al (a) (\ddagger)</td>
<td>1994</td>
<td>C/O</td>
<td>HR/S</td>
<td>5</td>
<td>1549/87</td>
<td>25-74</td>
<td>33.7%/19.2%</td>
<td>Yes</td>
<td>1.17 (0.88-1.56)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brett et al (a) (\ddagger)</td>
<td>1995</td>
<td>R</td>
<td>CS/M</td>
<td>12</td>
<td>353 (total)</td>
<td>&gt;35</td>
<td>OR=1.85</td>
<td>Yes</td>
<td>1.9 (0.75-5.76)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kobar et al (a) (\ddagger)</td>
<td>1996</td>
<td>C/R</td>
<td>CT/M</td>
<td>3</td>
<td>9A/1122</td>
<td>All</td>
<td>NA</td>
<td>Yes</td>
<td>0.83 (0.77-0.91)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benderly et al (a) (\ddagger)</td>
<td>1997</td>
<td>C/R</td>
<td>CT/M</td>
<td>12</td>
<td>112/2936</td>
<td>0.6%</td>
<td>0.5%</td>
<td>Yes</td>
<td>1.08 (1.02-1.33)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maynard et al (a) (\ddagger)</td>
<td>1997</td>
<td>C/R</td>
<td>HR/M</td>
<td>2</td>
<td>744/3672</td>
<td>All</td>
<td>18%/13%</td>
<td>Yes</td>
<td>0.87 (0.79-0.96)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marmugat et al (a) (\ddagger)</td>
<td>2001</td>
<td>C/I</td>
<td>HR/S</td>
<td>3</td>
<td>271/1519</td>
<td>25-74</td>
<td>21.8%/10.3%</td>
<td>Yes</td>
<td>1.23 (0.89-1.71)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marmugat et al (a) (\ddagger)</td>
<td>1998</td>
<td>C/I</td>
<td>HR/M</td>
<td>1/2</td>
<td>207/1250</td>
<td>&lt;80</td>
<td>25.8%/10.8%</td>
<td>Yes</td>
<td>1.73 (1.18-2.52)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*NA indicates not available; OR, odds ratio; CI, confidence interval; RR, relative risk; AMI, acute myocardial infarction.
Sampling Method: C, case-control; NC, non-consecutive; I, incident cases; R, incident and recurrent cases of AMI; O, only includes Q-wave AMI; RO, only recurrent cases.
Design: C indicates clinical trial; P, population registry; N, mortality at 60 days in excluding patients with AMI at the index hospitalization; P, mortality at 30 days in excluding patients with AMI at the index hospitalization; CT, mortality at 60 days in excluding patients with AMI at the index hospitalization; CS, mortality at 60 days in excluding patients with AMI at the index hospitalization.
Follow-Up, No.: The number of patients or cases at follow-up.
Age: The age range of the patients or cases at follow-up.
Raw Mortality (Females/Males): The raw mortality rate of females divided by the raw mortality rate of males.
OR/RR for Females Adjusted for Confounding Factors: The odds ratio or relative risk for females adjusted for confounding factors.
Age: The age range of the patients or cases at follow-up.
Concomitancy: The presence of comorbidities.
Severity of on Admission: The severity of admission.
Treatment in Acute Phase: The treatment received in the acute phase of AMI.
OR/RR (95% CI): The odds ratio or relative risk with 95% confidence interval.

\(\ddagger\)Women received thrombolysis; \(\ddagger\)Women received revascularization procedures; \(\ddagger\)Women received coronary angiography; \(\ddagger\)Women received all procedures; \(\ddagger\)Women received other procedures.
more moderate symptoms of AMI, but more frequently develop atypical symptoms, such as abdominal discomfort and dyspnea.14 Between 13 and 25% of myocardial ischemic episodes lack symptoms due to the presence of diabetes and older age.15

**DELAYED HOSPITALIZATION**

On average, hospital admissions are delayed by 1 h compared to males, probably due to the atypical symptoms.16,17 This factor, together with those described above and older age, would explain the lower use of thrombolyis, and, partly, the worse short-term prognosis.18,19,20,32

**USE OF DIAGNOSTIC AND THERAPEUTIC PROCEDURES**

Females also receive less aggressive drug treatment, with less aspirin, beta-blockers (both in the acute phase and at discharge) and angiotensin-converting enzyme inhibitors.20,21,22 Such differences are probably explained by older age, comorbidity and Killip class at admission. Furthermore, females undergo fewer diagnostic procedures (coronary angiography) and therapeutic ones (such as coronary artery bypass graft surgery and angioplasty) and these are done later than in males, even after adjusting for age and AMI location.11,12,25,26,33 In some studies it seems that the percentage of coronary angiographies and percutaneous interventions is lower among females, but this difference disappears after adjusting for comorbidity and age,27 and only persists in cases where the indications are more uncertain.27 A recent substudy in patients with non-ST elevation acute coronary syndrome highlights the underuse of angiography in females, especially in high-risk groups, as well as a short-term increase in refractory angina and readmissions due to angina.28 If it is taken into account that females with AMI present more serious symptoms than males, it is reasonable to assume that even the absence of differences in the use of diagnostic procedures and invasive treatments can be interpreted as their underuse in patients who would benefit from a more aggressive approach.29 In the countries with a low incidence there are no observed differences in the use of these procedures.13,14

Given the difficulties encountered when comparing the results of published studies, it seems advisable to find a way to analyze and present standardized results, which could consist of including consecutive cases of Q-wave AMI admitted to hospital (not only those with a coronary care unit). Neither is it necessary to impose age limits, but it is advisable to carry out subanalyses in the 25- to 74-year-old subgroup. Standard follow-up at 28 to 30 days and adjusting for risk of death in females by age, diabetes, hypertension, and smoking are equally recommended to facilitate comparability between studies.

Overall, mortality due to CVD is lower in females up to 84 years old, and population mortality due to AMI is from two to seven times less than in 25- to 64-year-old males. This advantage is lost once a first AMI has occurred: mortality at 28 days in females tends to be around 20% greater when adjusted for age, especially among those from areas with a low incidence of this disease. In hospitalized patients, mortality is greater in females, but exclusively among patients with a first Q-wave AMI: this difference has not been found in Spain for the remaining acute coronary syndromes.30 There is a perceived difference in the distribution of deaths between males and females during the 28 days from symptom onset that indicates different death mechanisms: ventricular fibrillation in males and ventricular failure in females. The treatments used are proportionally less aggressive in females. All this indicates that a change of attitude is needed in all health contexts so that it is possible to more promptly identify females who have begun to show symptoms of an acute coronary syndrome in order to accelerate diagnosis and increase the use of diagnostic and therapeutic procedures, such that they are proportional to the severity of the picture presented.31

**REFERENCES**

23. Bueno H, Vidán T, Almazán A, López-Sendón JL, Delcán JL. In-
20. White HD, Barbash GI, Modam M, Simes J, Díaz R, Hampton
19. Malacrida R, Genoni M, Maggioni AP, Spataro V, Parich S, Pal-
18. Puletti M, Sunseri L, Curione M, Erba SM, Borgia C. Acute myo-
17. Tofler GH, Stone PH, Muller JE, Willich SN, Davis VG, Poo-
7. Lourie G, Stinson MB, Van de Water B, et al, for the Third Inte-
5. Brett KM, Madans JH. Long-term survival after coronary heart
term mortality in women and men with acute cardiac ischemia: a
prospective multicenter study. J Am Coll Cardiol. 1997;29:
1940-6.
Acute myocardial infarction in women; influence of gender on
generator Activator/Streptokinase Mortality Study. After correcting
for baseline characteristics, women treated with throm-
bolysis therapy for acute myocardial infarction have the same
mortality and morbidity as men except for a higher incidence of
Dennovitch J, Blackburn H, McGovern PG, Larcker SN, Sprafka
JMB, Gibbison D. Sex differences in early mortality after acute
Sonke GS, Deegelholt J, Steward AW, Jackson R, Steward FM.
Sex differences in case fatality and after admission to hospital af-
ter acute cardiac events: analysis of community-based coronary
Buero H, Vidan T, Almazán A, López-Sendón JL, Delcán JL. In-
fluence of sex on the short-term outcome of elderly patients with
Tunstall-Pedoe H, Morrison C, Woodward M, Fitzpatrick R, Watt
G. Sex differences in myocardial infarction and coronary deaths
in the Scottish MONICA population of Glasgow 1985-91: pre-
sentation, diagnosis, treatment, and 28-day case fatality of 3,991
Berman H, Greiser E, Polabuh I. A sex difference in short-term
survival after initial myocardial infarction: the MONICA-Bremen
Coronado BE, Griffith JL, Beshansky JR, Selker HT. Hospital
mortality in women and men with acute cardiac ischemia: a
prospective multicenter study. J Am Coll Cardiol. 1997;29:
1940-6.
Fletcher RH, Vossol CM, Horwitz RJ. Differences between wo-
men and men in survival after myocardial infarction. Biology or
He J, Klag MJ, Whelton PK, Yushak Z, Xinhui W. Short- and
long-term prognosis after acute myocardial infarction in Chinese
Goldberg RJ, Gerson EJ, Yarzabski J, Honser DW, Dalen P, Gore
JM, et al. A community wide perspective of sex differences and
temporal trends in the incidence and survival rates after acute
myocardial infarction and out-of-hospital deaths caused by coro-
Kober L, Torg-Pedersen C, Ottesen M, Rasmussen S, Leswing M,
Skagen K on behalf of the TRACE Study Group. Influence of
gender on short- and long-term mortality after acute myocardial
Maynard C, Every NR, Martin JS, Kudenchuk PJ, Weaver D. As-
sociation of gender and survival in patients with acute myocardial
Galatius-Jensen S, Launbjerg J, Spange Mortensen LS, Hansen
JF. Sex-related differences in short- and long-term prognosis after
acute myocardial infarction: 10-year follow-up of 3,073 patients
in database of first Danish verapamil infarction trial. BMJ.
1996;313;137-40.
Acute myocardial infarction in women: influence of gender on
Marrugat J, Gil M, Masri S, Sala J, Elorriaga R, Amo JM, et al, and
the REGICOR Investigators. Role of age and sex in short-term
and long term mortality after a first Q wave myocardial in-
Bendoly E, Behar S, Reicher-Reiss H, Broks V, Goldbourt U, for
the SPRENT Investigators. Long-term prognosis of women af-
Wong DN, Cutles LA, Orfield AM, Levy D, Kannel WB. Risk fac-
tors for long-term coronary prognosis after initial myocardial in-
farction: the Framingham Study. Am J Epidemiol. 1989;130:
460-81.
Brett KM, Madans JH. Long-term survival after coronary heart
disease. Comparisons between men and women in a national
Martin CA, Thompson PL, Armstrong BK, Hobbs MST, De
Clerck N. Long-term prognosis after recovery from myocardial in-
farction: a nine-year follow-up of the Perth Coronary Register.
Johansson S, Bergstrand R, Ulfenstam G, Yedin A, Wilhemsson
C, Widel H, et al. Sex differences in preinfarction characteristics
and long-term survival among patients with myocardial infarc-
Robinson K, Conroy RM, Maley T, Hickey N. The 15-year
prognosis of a first acute coronary episode in women. Eur Heart
Weisblat E, Shapiro S, Frank CW. Prognosis of women with
newly diagnosed coronary disease: a comparison with causes of
Pohlby S, Siljander P, Romeo M. Five-year survival of 728 pa-
tients after myocardial infarction: a community study. Br Heart J.
1980;43:176-83.
Gottlieb S, Moss A, McDermott M, Eberly S. Comparison of
posthospital survival after acute myocardial infarction in women
N, et al for the MIDAS study group. Sex differences in the mana-

Rev Esp Cardiol. 2006;59(3):264-74

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