Cardiovascular Diseases in Women (I)

Epidemiology of Cardiovascular Disease in Women

Jaume Marrugat,[a] Joan Sala,[b] and Jaime Aboal[b]

[a]Unitat de Lípids i Epidemiologia Cardiovascular, Institut Municipal d'Investigació Mèdica, Barcelona, Spain.
[b]Servei de Cardiologia i Unitat Coronària, Hospital Josep Trueta, Girona, Spain.

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 make 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*

Epidemiología de las enfermedades cardiovasculares en la mujer

Tanto la mortalidad poblacional por enfermedad cerebrovascular hasta los 84 años como por infarto agudo de miocardio (IAM) es menor en mujeres que en varones. En cambio, la mortalidad a 28 días ajustada por edad tras un primer IAM es un 20% mayor en las mujeres, especialmente en países de baja incidencia de esta enfermedad. En España, la mortalidad es mayor en las mujeres hospitalizadas por un primer IAM, pero no en el resto de formas de presentación de la cardiopatía isquémica. La distribución de las muertes, más retrasada en mujeres, desde el inicio de los síntomas indica distintos mecanismos de fallecimiento en ambos sexos. Hay diferencias en la presentación de resultados que dificultan mucho la comparabilidad de los estudios publicados. Las mujeres con IAM son unos 10 años mayores, llegan a los hospitales 1 h más tarde de promedio, presentan mayor comorbilidad (diabetes e hipertensión, principalmente), desarrollan cuadros clínicos más graves y tienen mayor riesgo de muerte a 28 días, ajustado por varios de los factores anteriores, que los varones. La intensidad de los tratamientos empleados es proporcionalmente inferior en las mujeres. Es necesario un cambio de actitud en todos los ámbitos asistenciales que permita identificar precozmente a las mujeres con síntomas de un síndrome coronario agudo, para acelerar el diagnóstico y aumentar el uso de procedimientos diagnósticos y terapéuticos de forma proporcional a la mayor gravedad que presenta el IAM en la mujer.

Palabras clave: *Sexo. Cardiopatía isquémica. Enfermedad cerebrovascular. Incidencia. Mortalidad.*

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[1-4] (Figure 1). The AMI mortality ratio between males and females depends on age[5] and varies between countries with a magnitude of 2 to almost 6 in the 35- to 64-year-old age group[6] (Figure 2). On average, females who develop AMI do so 7 to 10 years later than males.[7,8] Despite

Correspondence: Dr. J. Marrugat.
Unitat de Lípids i Epidemiologia Cardiovascular. Institut Municipal d'Investigació Mèdica.
Dr. Aiguader, 80. 08003 Barcelona. España.
E-mail: jmarrugat@imim.es

ABBREVIATIONS

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

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.[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.[10-36]

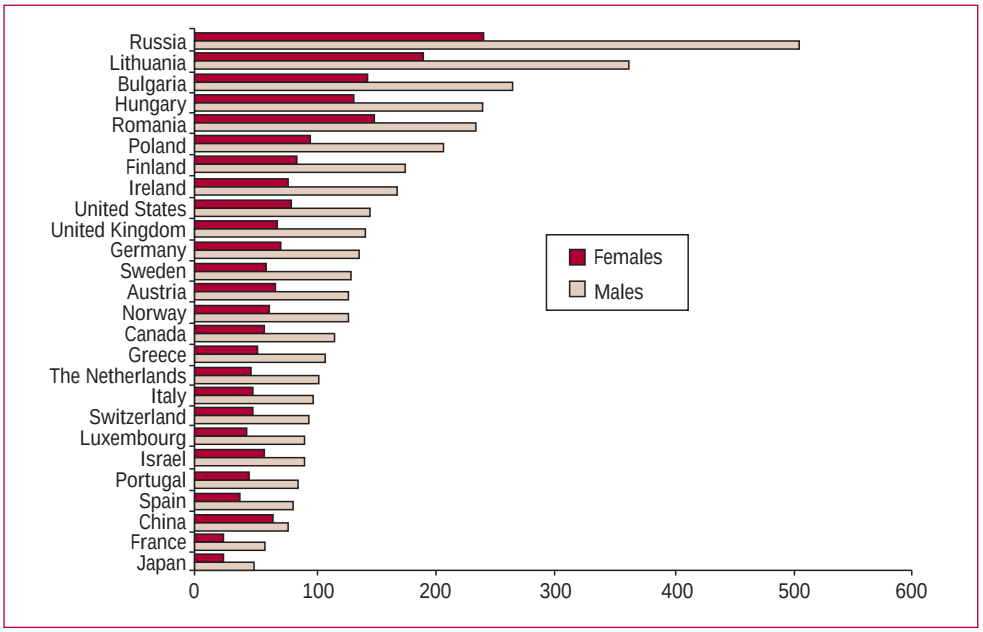

Figure 1. Age-adjusted rates per 1 000 000 population in males and females at death due to ischemic heart disease in several developed countries in 2002.

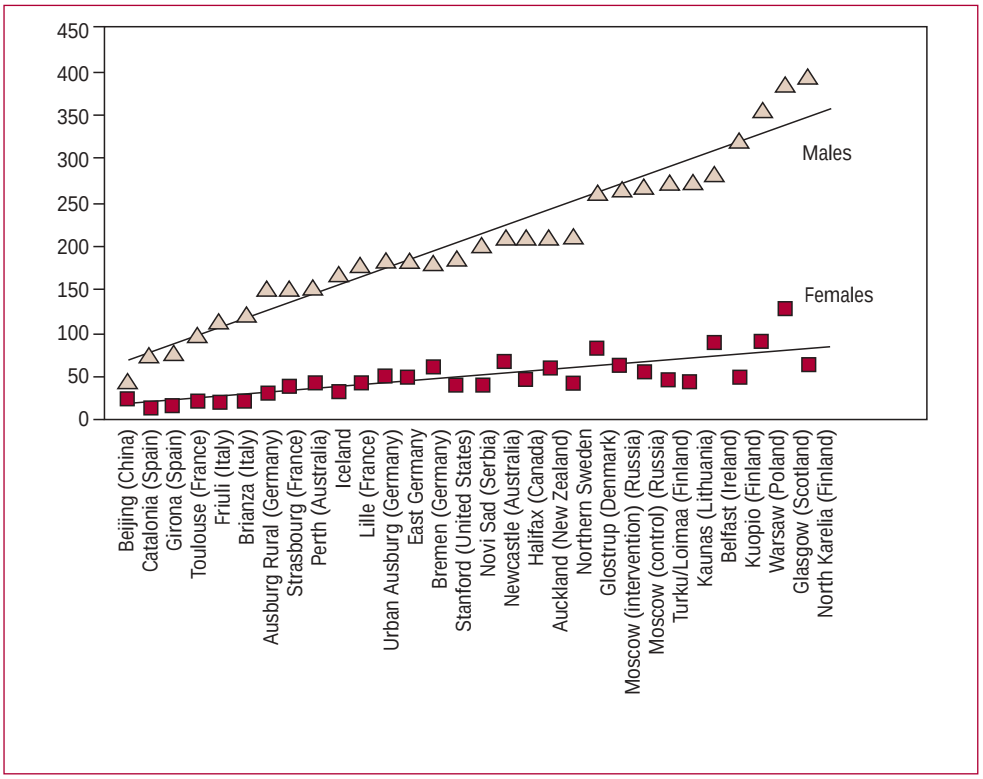

Figure 2. Male/female ratio regarding death rate in 38 MONICA-WHO centers ordered by increasing population mortality rate in 35- to 64-year-old males. Adapted from Chambless et al.[6]

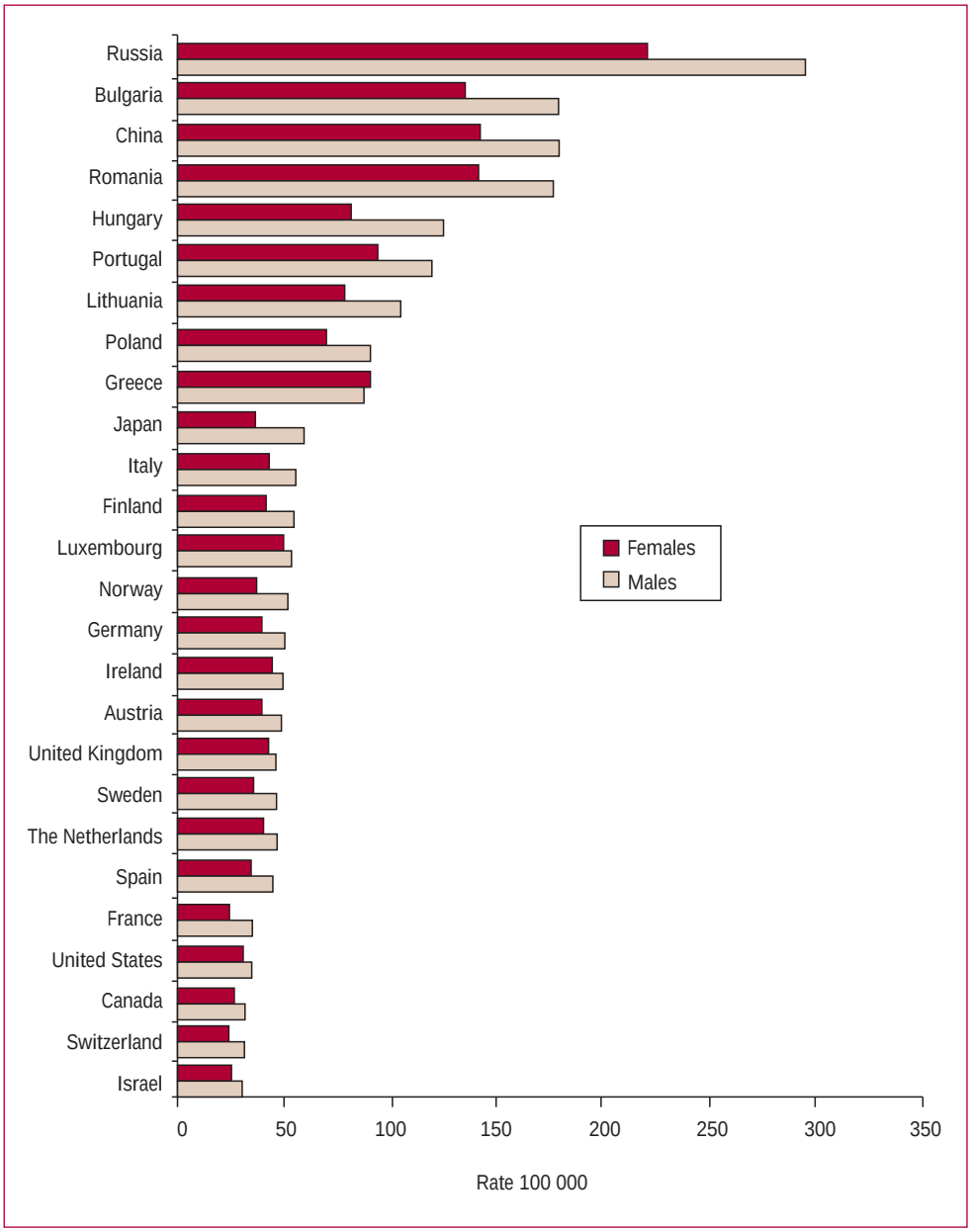

Figure 3. Rates per 100 000 inhabitants adjusted by age at mortality due to cerebrovascular disease in several industrialized countries in males and females, in 2002.

Older age and the prevalence of comorbidity (in particular diabetes, hypertension and heart failure) in females explains some of these differences[7] 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 factores.[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.[32-46]

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 for 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 females[48] (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

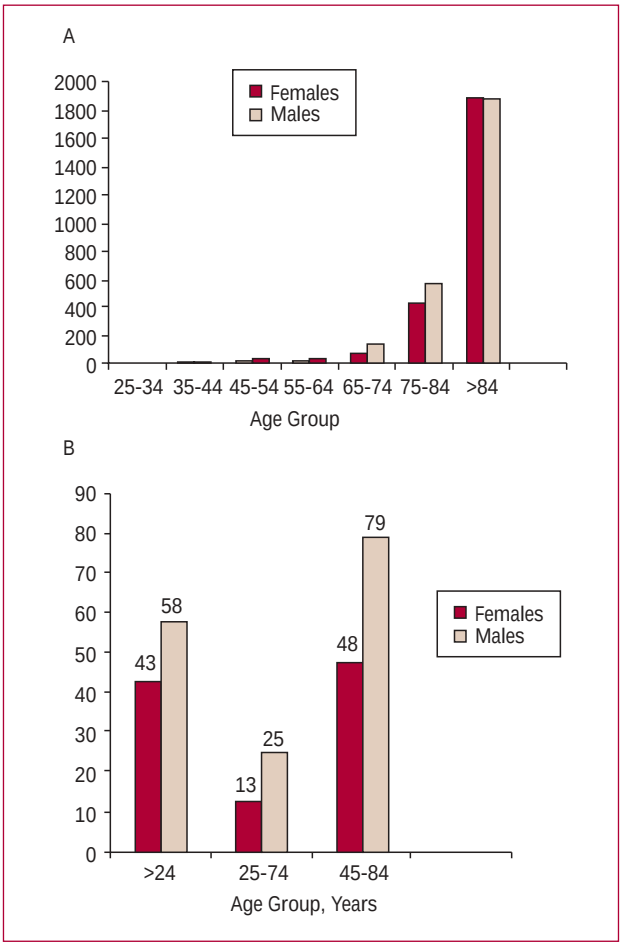

Figure 4. Specific (A) and standardized (B) death rates by age and sex per 100 000 inhabitants, due to cerebrovascular disease in those more than 24 years old by decade in Catalonia 2002.

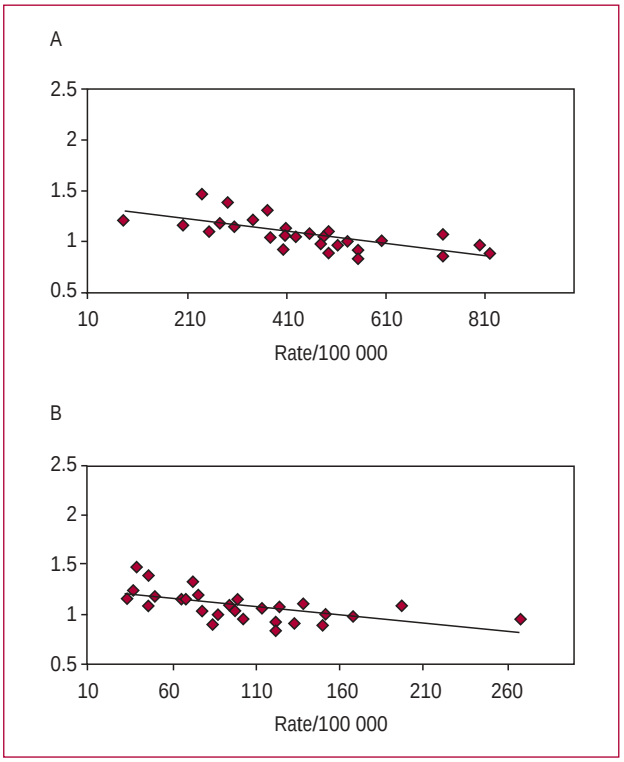

Figure 5. Female/male mortality odds ratio in 38 MONICA/World Health Organization centers, ordered by population incidence of myocardial infarction in males from 35 to 64 years (A), and by the population incidence in females of the same age (B).

drawbacks: whereas the population studies offer a broader vision that includes prehospital deaths due to these causes, hospital registries offer the opportunity to analyze in greater detail the clinical characteristics of the patients and comorbidity. A serious limitation that makes it difficult to compare the results of different studies lies in the fact of using different criteria to select patients.

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.[49]

Most fatal events (median, 70% in males and 64% in females) occur before the patients manage to get to hospital.[4,6,13,49-51] After admission, age-adjusted mortality is greater among females (26.9 and 21.8%, respectively; ratio, 1.24).[4,6]

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

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*

Author and Reference	Year of Publication	Sampling Method	Design$	No. Females/ Males	Age Range	Raw Mortality (Female/Male)	Adjustment Factors and Results				
							Age	Comorbidity	Severity	Treatment in Acute Phase	Adjusted OR/RR (95% CI) for Females
Puletti et al[18]	1984	C/R	HR/S	106/535	All	42.4%/16.6%	Yes				1.4 (1.05-1.88)
Fiebach et al[30]	1990	C/R	HR/S	332/790	30-74	14.2%/8.9%	Yes	D/H/HF/S	K/L/E		1.28 (NS)
Greenland et al[10]	1991	C/R	HR/M	1524/4315	All	26.5%/14.6%	Yes				1.56 (1.34-1.84)
							Yes	P	K/L/R/E		1.72(1.45-2.04)
Ferriz et al[16]	1992	C/R	HR/S	348/1603	All	25.6%/12.8%	Yes	A	K/L		1.63 (*P*<.005)
Goldberg et al[31]	1993	C/R	HR/M	1232/1916	All	21.7%/12.7%	Yes				1.18 (0.95-1.45)
							Yes	D/H/A	K/L/E	PA/T/RV/O	1.11 (0.86-1.43)
White et al[20]	1993	NC/R	CT/M	1944/6317	All	12.1%/7.2%	Yes	D/H/A/S/P	K	To	1.11 (0.89-1.39)
Becker et al[11]	1994	NC/R	CT/M	597/2742	<76	9%/4%	Yes	D/H/HF/A/P	L	To	1.54 (99% CI, 0.98-2.43)
Jenkins et al[12]	1994	C/R	HR/S	155/355	All	21.4%/12.1%	Yes	D	K	RV	1.7 (0.96-3.2)
He et al[30]	1994	C/I	HR/S	294/601	All	23.5%/12.0%	Yes	H	K/L/R		1.74 (1.17-2.60)†
Marrugat et al[13]	1994	C/R/Q	HR/S	193/1023	25-74	20.2%/11.3%	Yes	D/H/Q	L/R		1.56 (0.99-2.48)
Bueno et al[23]	1995	C/I	HR/S	105/99	>75	40%/23.2%	Yes	S	K/R/E		0.75 (0.25-2.21)
Demirovic et al[21]	1995	NC/R	HR/M	198/813	30-65	12.5%/6.5%	No	HF/P	K		2.0 (1.2-3.5)†
				234/355	≥65	19.5%/21.6%	Yes		K		0.9 (0.6-1.5)†
Kober et al[32]	1996	C/R	CT/M	2170/4501	All	Gross OR:	Yes				1.16 (0.99-1.35)
						1.61 (1.38-1.85)	Yes	D/H/A/P	K/E	T	1.25 (1.01-1.54)
Weaver et al[25]	1996	NC/R	CT/M	10 315/30 706	All	11.3%/5.5%	Yes	D	K/L	To	1.15 (1.01-2.26)
Ceniceros et al[15]	1997	C/I	HR/S	253/623	All	27.2%/13.5%	Yes	D/H	L	T	1.51 (1.01-1.39)
Coronado et al[27]	1997	C/R	HR/M	322/572	>30	10.3%/7.4%	Yes	D	K	T/RV	0.8 (0.5-1.2)
Maynard et al[33]	1997	C/R	HR/M	4255/8076	All	13.7%/7.8%	Yes	HF/P			1.22 (1.06-1.39)
Marrugat et al[14]	1998	C/I	HR/M	330/1127	<80	18.5%/8.3%	Yes	D/H/S	L	T	1.64 (1.06-2.54)
Malacrida et al[19]	1998	NC/R	CT/M	9600/26 480	All	14.8%/9.1%	Yes	D/S/P	K/L	To	1.20 (1.11-1.29)
Marrugat et al[36]	2001	C/I		175/1876	25-64	6.9%/6.9%	Yes	D/H/A/S	K/L/R	T	1.62 (1.01-2.66)
				272/773	65-74	26.5%/13.6%	Yes	D/H/A/S	K/L/R	T	0.45 (0.19-1.04)
Marrugat et al[50]	2004	C/I	HR/S	2942/9571	All	24.3/10.9	Yes	D/H/A/S	K/L/R	T	1.27 (1.06-1.52)
		C/Q/RO	HR/S	402/1784	All	32.8/22.5	Yes	D/H/A/S	K/L/R	T	0.97 (0.68-1.40)
		C/NQ	HR/S	862/2410	All	15.8/10.1	Yes	D/H/A/S	K/L/R	T	1.25 (0.74-2.12)
		UA	HR/S	855/1826	All	3.5/2.2	Yes	D/H/A/S	K/L/R	T	1.53 (0.84-2.77)
Herman et al[26,27]	1997	C/I	PR	NA	25-69	36.8%/30.9%	Yes				1.19 (*P*=.006)
			HR/M	563/1710	25-69	23.1%/16.1%	Yes				1.31 (1.02-1.68)
							Yes	HF		T/A	1.13 (0.86-1.50)
Chambless et al[6]	1997	C/R	PR	NA	35-64	Gross OR: 1.09	Yes				1.07‡
			HR/M	16 365/63 574	35-64	Gross OR: 1.32	Yes				1.24‡

continue in the next page

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* *(Continuation)*

Author and Reference	Year of Publication	Sampling Method	Design$	No. Females/ Males	Age Range	Raw Mortality (Female/Male)	Adjustment Factors and Results				
							Age	Comorbidity	Severity	Treatment in Acute Phase	Adjusted OR/RR (95% CI) for Females
Tunstall-Pedoe et al[24]	1996	C/R	PR	1551/3991	25-64	49.6%/49.8%	Yes				0.97 (NS)
			HR/M	1043/2525	25-64	24.1%/21%	Yes				1.06 (*P*=.07)
Sonke et al[22]	1996	C/R	PR	1078/4028	25-64	51.4%/48.3%	Yes	A/S/P		T/A/O	0.85 (0.72-1.01)
		HR/M		686/2446	25-64	22.5%/14.9%	Yes	A/S/P		T/A/O	1.16 (0.88-1.53)
Pérez et al[4]	1998	C/R	PR	257/960	25-74	52.9%/40.3%	Yes				1.26 (0.94-1.69)

*AMI indicates acute myocardial infarction; CI, confidence interval; NA, not available; OR, odds ratio; RR, relative risk.
Sampling Method. C indicates consecutive; NC, non-consecutive; I, only incident cases; R, incident and recurrent cases of AMI; Q, only includes Q-wave AMI; RO, only recurrent cases; NQ, only non-Q wave infarction; UA, only unstable angina.
Design. CT indicates clinical trial; PR, population registry (mortality at 28 days, including prehospital deaths); includes the following definitions of AMI from the MONICA/WHO study: definite AMI, fatal or not; death due to possible or non-classifiable AMI; HR, hospital registry (only includes patients arriving at hospital alive); CS, population sample; S, single center; M, multicenter.
Comorbidity. D indicates diabetes; H, hypertension; HF, previous heart attack; A, previous angina; S, smoking; P, Previous AMI.
Severity. K indicates heart failure in the acute phase of AMI; L, ECG location of AMI; R, arrhythmias; E, enzymatic values.
Treatment. PA indicates platelet antiaggregation; T, thrombolysis; To, all the patients received thrombolysis; RV, revascularization procedures; O, other.
†Interaction between age and sex.
‡Mean of 29 centers collaborating in the MONICA/WHO study.
$Follow-up: all the studies describe hospital mortality except for 6, 11, 13, 14, 21, 22, 24, 26, 30 (28 days), 25, 32 (30 days), 19 (35 days), and 11 (42 days).

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.[2,6] 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.[51]

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,[1,5] and who are later included in the population registries (1%-51%). However, this information is available regarding the patients included in hospital registries,[6,12,21,49,52] 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.[22]

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 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.[5] The female/male mortality ratio was also higher in the areas with lower AMI incidence rates.[13-16]

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.[13,30,31,34,36-38,41,42]

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.[10,14,39] In contrast, in studies which analyzed longer periods, no differences were observed between males and females,[13,29,30,32-34,37,43,44] greater risk of death in females[35] or statistically significant lower mortality among females.[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.[53] 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.[11,19,20,25,32]

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.[6]

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.[54] Females who present this have a more frequent background of heart failure than males and usually receive more diuretic and inotropic medication.[26] However, overall, females receive less treatment than males (see below).[55-59] 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.[28,29,35] As mentioned, females present worse Killip class than males during the acute phase of AMI.[13,28,59] Regardless of age at presentation, females develop more serious complications than males in terms of heart failure and reinfarction, 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.[25] 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,[14,31,59] but less fibrillation or ventricular tachycardia.[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.[21,25,28]

Some theories are based on physiopathology. These include the existence of hypercoagulability states[60] and coronary arterial spasm,[61] 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.[62,63]

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.[64]

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,[24] 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.[13,16,21] It seems that females not only present

TABLE 2. Results and Characteristics of Studies on the Differences Between Sexes Regarding Long-Term Mortality in Myocardial Infarction Survivors*

Author and Bibliographic Reference	Year of Publication	Sampling Method	Design	Follow-Up, Years	No. Females/Males	Age	Raw Mortality (Females/Males)	OR/RR for Females Adjusted for Confounding Factors				
								Age	Comorbidity	Severity of on Admission	Treatment in Acute Phase	OR/RR (95% CI)
Weinblatt et al[43]	1973	NC/I	O	5	120/604	25-64	16.3%/21.5%	Yes				0.69 (0.44-1.08)
Pohjola et al[44]	1980	C/R	HR/M	5	219/509	<66	26.5%/31.6%	Yes				0.64 (P=.002)
Martín et al[40]	1983	C/R	HR/M	9	167/499	30-69	OR=0.91 (NS)	Yes	D/H/P/O	K/R		0.73 (0.54-0.98)
Johansson et al[41]	1984	C/I	HR/S	1	262/1259	<66	7.2%/6.4%	Yes				1.09 (0.67-1.77)
Wong et al[38]	1989	O/I	CS	9.7	108/236	All	39.4%/30.5%†	Yes				0.78 (0.55-1.08)
								Yes	D/O			0.49 (0.31-0.77)
Fiebach et al[29]	1990	C/R	HR/S	3	285/720	30-74	16.8%/15.6%	Yes	D/H/HF/A/S/P/O	K	O	0.69 (P=.06)
Greenland et al[10]	1991	C/R	HR/M	1	1524/4315	All	13.1%/8.2%	Yes				1.27 (P<.03)
								Yes	A/P/O	K/L/E		1.32 (1.05-1.66)
Golberg et al[31]	1993	C/R	HR/M	14	965/1673	All	NA	Yes				0.91 (0.79-1.05)
								Yes	D/H/A	K/L/E	PA/T/RV/O	0.83 (0.72-0.97)
Galatius-Jensen et al[34]	1994	C/R	CT/M	10	612/1974	<76	60.9%/58.7%	Yes				0.9 (0.8-1.01)
Gottlieb et al[45]	1994	NC/R	CTb/M	2	451/1650	<75	12.6%/11.1%	Yes				1.04
								Yes	D/H	K/R		1.06 (0.74-1.52)
Kostis et al[46]	1994	C/R	HR/M	3	715/3149	30-49	13%/8%	No	D/H/O	K/R	O	0.74 (0.58-0.94)
					5432/11 736	50-69	27%/23%	No	D/H/O	K/R	O	0.94 (0.88-1.01)
					8.964/7928	70-89	52%/52%	No	D/H/O	K/R	O	1.08 (1.03-1.12)
Hu et al[30]	1994	C/I	HR/S	10	222/523	All	35.1%/24.3%	Yes				1.17 (0.88-1.56)
								Yes	O	K		1.15 (0.86-1.54)
Marrugat et al[13]	1994	C/I/Q	HR/S	5	154/907	25-74	35.7%/19.2%	Yes	D/H	K/L/R		1.27 (0.90-1.78)
Brett et al[39]	1995	R	CS/M	12	353 (total)	>25	OR=1.3	Yes				1.10 (0.77-1.57)
							(0.92-1.85)	Yes	D/H/S/P/O			1.01 (0.76-1.48)
Kober et al[32]	1996	C/R	CT/M	3	NA	All	OR=1.19	Yes				0.83 (0.77-0.91)
							(1.08-1.33)		Yes	D/H/A/P	K/E	0.86 (0.76-0.97)
Benderly et al[37]	1997	C/R	CT/M	12	1120/3688	All	65%/52%	Yes	D/H/HF/A/S/P	K/L/E		1.20 (1.08-1.33)
	C/I	CT/M	12	900/2795	All	NA		Yes	D/H/HF/A/S/P	K/L/E		1.15 (1.02-1.29)
Maynard et al[33]	1997	C/R	HR/M	2	744/3672	All	18%/13%	Yes				0.87 (0.79-0.96)
Marrugat et al[36]	2001	C/I	HR/S	3	271/1519	25-74	21.8%/10.3%	Yes	D/H/A/S	K/L/R	T	2.3 (0.9-1.9)
Marrugat et al[13]	1998	C/I	HR/M	1/2	207/1250	<80	25.8%/10.8%	Yes	D/H/A/S			1.73 (1.18-2.52)
								Yes	D/H/A/S		T	1.64 (1.06-2.54)
								Yes	D/H/A/S	K/R	T	1.31 (0.77-2.51)

*NA indicates not available; OR, odds ratio; CI, confidence interval; RR, relative risk; AMI, acute myocardial infarction.
Sampling Method. C indicates consecutive; NC, non-consecutive; I, only incident cases; R, incident and recurrent cases of AMI; Q, only includes Q-wave AMI; RO, only recurrent cases.
Design. CT indicates clinical trial; PR, population registry (mortality at 28 days, including prehospital deaths); it includes the following definitions of AMI from the MONICA/WHO study: definite AMI, fatal or not; death due to possible or non-classifiable AMI; HR, hospital registry (only includes patients who arrive at hospital alive); CS, population sample; S, single center; M, multicenter.
Comorbidity. D indicates diabetes; H, hypertension; HF, previous heart failure; A, previous angina; S, smoking; P, previous AMI.
Severity. K indicates heart failure in the acute phase of AMI; L, ECG location of AMI; R, arrhythmias; E, enzymatic values.
Treatment. PA indicates platelet antiaggregation; T, thrombolysis; To, all the patients received thrombolysis; RV, revascularization procedures; O, other.
†Coronary death.
‡Two clinical trials.

more moderate symptoms of AMI, but more frequently develop atypical symptoms, such as abdominal discomfort and dyspnea.[54] Between 13 and 25% of myocardial ischemic episodes lack symptoms due to the presence of diabetes and older age.[28]

DELAYED HOSPITALIZATION

On average, hospital admissions are delayed by 1 h compared to males, probably due to the atypical symptoms.[56,59] This factor, together with those described above and older age, would explain the lower use of thrombolysis, and, partly, the worse short-term prognosis.[14,25,28,29,52]

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.[56,58,59] 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.[11,12,25,54,55] 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,[59] and only persists in cases where the indications are more uncertain.[57] 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.[58] 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.[58] 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.[52] 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.[65]

REFERENCES

1. World Health Statistics. World Health Organization. Geneve, 2000. Disponible en: http://www.who.int/ncd_surveillance/infobase/web/InfoBasePolicyMaker/Reports/
2. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. WHO MONICA. Project. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. Circulation. 1994;90:583-612.
3. McGovern PG, Pankow JS, Shahar E, Doliszny KM, Folsom AR, Blackburn H, et al, for the Minnesota Heart Survey Investigators. Recent trends in acute coronary heart disease. N Engl J Med. 1996;334:884-90.
4. Pérez G, Pena A, Sala J, Roset P, Masiá R, Marrugat J and the REGICOR Investigators. Acute myocardial infarction case-fatality, incidence and mortality rates in a population registry in the province of Gerona, Spain 1990 to 1992. Int J Epidemiol. 1998;27:599-604.
5. Kannel WB, Abbot RD. Incidence and prognosis of myocardial infarction in women: The Framingham Study. En: Eaker ED, Packard B, et al, editors. Coronary heart disease in women: Proc NIH Workshop. New York: Haymarket-Doyma; 1987. p. 208-14.
6. Chambless L, Keil U, Dobson A, Mähonen M, Kuulasma K, Rajakangas AM, et al, for the MONICA Project. Population versus clinical view of case fatality from acute coronary heart disease. Results from the WHO MONICA Project 1985-1990. Circulation. 1997; 96:3849-59.
7. Vaccarino V, Krumholz HM, Berkman LF, Horwitz RI. Sex differences in mortality after myocardial infarction. Is there evidence for an increased risk for women? Circulation. 1995:91:1861-71.
8. Eaker ED, Chesebro JH, Sacks FM, Wenger NK, Whisnant, Winston M. Cardiovascular disease in women. Circulation. 1993;88:1999-2009.
9. Murray CJL, López AD. Alternative projections of mortality and disability by cause 1990-2020: global burden of disease study. Lancet. 1997;349:1498-504.

10. Greenland P, Reicher-Reiss H, Goldbourt U, Behar S, and the Israeli SPRINT Investigators. In-hospital and 1-year mortality in 1,524 women after myocardial infarction. Comparison with 4,315 men. Circulation. 1991;83:484-91.
11. Becker RC, Terrin M, Ross R, Knatterud GL, Desvigne-Nickens P, Gore JM, et al. Comparison of clinical outcomes for men and women after acute myocardial infarction. Ann Intern Med. 1994;120:638-45.
12. Jenkins JS, Flaker GC, Nolte B, Prince LA, Morris D, Kurz J, et al. Causes of higher in-hospital mortality in women than in men after acute myocardial infarction: the Framingham study. Am J Cardiol. 1994;73:319-22.
13. Marrugat J, Antó JM, Sala J, Masiá R, and the REGICOR Investigators. Influence of gender in acute and long-term cardiac mortality after a first myocardial infarction. J Clin Epidemiol. 1994;47:111-8.
14. Marrugat J, Sala J, Masiá R, Pavesi M, Sanz G, Valle V, et al, and the RESCATE Investigators. Differences in acute and six-month mortality between men and women hospitalized for a first myocardial infarction. JAMA. 1998;280:1405-9.
15. Ceniceros Rozalén I, Gastaldo Simeón R, Cabadés O'Callaghan A, Cebrián Doménech J. El sexo femenino es un factor pronóstico independiente de mortalidad en la fase aguda del infarto de miocardio. Med Clin (Barc). 1997;109:171-4.
16. Ferriz JA, Vera A, Suárez G, Torrado E, Rodríguez JJ, Álvarez JM, et al. Sexo femenino y mortalidad tras infarto agudo de miocardio. Rev Esp Cardiol. 1993;46:796-801.
17. Tofler GH, Stone PH, Muller JE, Willich SN, Davis VG, PooleWK, et al and the MILIS Study Group. Effects of gender and race on prognosis after myocardial infarction: adverse prognosis for women, particularly black women. J Am Coll Cardiol. 1987;9:476-82.
18. Puletti M, Sunseri L, Curione M, Erba SM, Borgia C. Acute myocardial infarction: sex-related differences in prognosis. Am Heart J. 1984:108:63-6.
19. Malacrida R, Genoni M, Maggioni AP, Spataro V, Parich S, Palmer A, et al, for the Third International Study of Infarct Survival Collaborative Group. A comparison of the early outcome of acute myocardial infarction in women and men. N Engl J Med. 1998;338:8-13.
20. White HD, Barbash GI, Modam M, Simes J, Díaz R, Hampton JR, et al for the Investigators of the International Tissue Plasminogen Activator/Streptokinase Mortality Study. After correcting for worse baseline characteristics, women treated with thrombolytic therapy for acute myocardial infarction have the same mortality and morbidity as men except for a higher incidence of hemorrhagic stroke. Circulation. 1993;88:2097-3103.
21. Demirovic J, Blackburn H, McGovern PG, Luepker R, Sprafka JM, Gilbertson D. Sex differences in early mortality after acute myocardial infarction (The Minnesota Heart Survey). Am J Cardiol. 1995;75:1096-101.
22. Sonke GS, Beaglehole R, Steward AW, Jackson R, Steward FM. Sex differences in case fatality and after admission to hospital after acute cardiac events: analysis of community-based coronary heart disease register. BMJ. 1996;313:853-5.
23. Bueno H, Vidán T, Almazán A, López-Sendón JL, Delcán JL. Influence of sex on the short-term outcome of elderly patients with first acute myocardial infarction. Circulation. 1995;92:1133-40.
24. Tunstall-Pedoe H, Morrison C, Woodward M, Fitzpatrick B, Watt G. Sex differences in myocardial infarction and coronary deaths in the Scottish MONICA population of Glasgow 1985-91: presentation, diagnosis, treatment, and 28-day case fatality of 3,991 events in men and women. Circulation. 1996;93:1981-92.
25. Weaver WD, White HD, Wilcox RG, Aylward PE, Morris D, Guerci A, et al for the GUSTO-I Investigators. Comparisons of characteristics and outcomes among women and men with acute myocardial infarction treated with thrombolytic therapy. JAMA. 1996;275:777-82.
26. Herman B, Greiser E, Polabeln H. A sex difference in short-term survival after initial myocardial infarction: the MONICA-Bremen acute myocardial infarction register 1985-90. Eur Heart J. 1997;18:963-70.
27. Herman B, Greiser E, Polabeln H. A reply [letter]. Eur Heart J. 1998;19:354.
28. Coronado BE, Griffith JL, Beshansky JR, Selker JT. Hospital mortality in women and men with acute cardiac ischemia: a prospective multicenter study. J Am Coll Cardiol. 1997;29: 1490-6.
29. Fiebach NH, Viscoli CM, Horwitz RI. Differences between women and men in survival after myocardial infarction. Biology or methodology? JAMA. 1990;263:1092-6.
30. He J, Klag MJ, Whelthon PK, Yuchang Z, Xinzhi W. Short- and long-term prognosis after acute myocardial infarction in Chinese men and women. Am J Epidemiol. 1994;139:693-703.
31. Goldberg RJ, Gorak EJ, Yarzebski J, Hosmer 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 coronary heart disease. Circulation. 1993;87:1947-53.
32. Kober L, Torp-Pedersen C, Ottesen M, Rasmussen S, Lessing M, Skagen K on behalf of the TRACE Study Group. Influence of gender on short- and long-term mortality after acute myocardial infarction. Am J Cardiol. 1996;77:1052-6.
33. Maynard C, Every NR, Martin JS, Kudenchuk PJ, Weaver D. Association of gender and survival in patients with acute myocardial infarction. Arch Intern Med. 1997;157:1379-84.
34. 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.
35. Dittrich H, Gilpin E, Nicod P, Cali G, Henning H, Ross JR Jr. Acute myocardial infarction in women: influence of gender on mortality and prognostic variables. Am J Cardiol. 1988;62:1-7.
36. Marrugat J, Gil M, Masiá R, Sala J, Elosua R, Antó 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 infarction. J Epidemiol Community Health. 2001;55:487-93.
37. Benderly M, Behar S, Reicher-Reiss H, Boyko V, Goldbourt U, for the SPRINT Investigators. Long-term prognosis of women after myocardial infarction. Am J Epidemiol. 1997;146:153-60.
38. Wong DN, Cupples LA, Ostfeld AM, Levy D, Kannel WB. Risk factors for long-term coronary prognosis after initial myocardial infarction: the Framingham Study. Am J Epidemiol. 1989;130: 469-80.
39. Brett KM, Madans JH. Long-term survival after coronary heart disease. Comparisons between men and women in a national sample. Ann Epidemiol. 1995;5:25-32.
40. Martin CA, Thompson PL, Armstrong BK, Hobbs MST, De Clerk N. Long-term prognosis after recovery from myocardial infarction: a nine-year follow-up of the Perth Coronary Register. Circulation. 1983;68:961-9.
41. Johansson S, Bergstrand R, Ulvenstam G, Vedin A, Wilhemsson C, Wedel H, et al. Sex differences in preinfarction characteristics and long-term survival among patients with myocardial infarction. Am J Epidemiol. 1984;119:610-23.
42. Robinson K, Conroy RM, Mulcahy R, Hickey N. The 15-year prognosis of a first acute coronary episode in women. Eur Heart J. 1992;13:67-9.
43. Weinblatt E, Shapiro S, Frank CW. Prognosis of women with newly diagnosed coronary disease: a comparison with causes of disease among men. Am J Public Health. 1973;63:577-93.
44. Pohjola S, Siltanen P, Romo M. Five-year survival of 728 patients after myocardial infarction: a community study. Br Heart J. 1980;43:176-83.
45. Gottlieb S, Moss A, McDermott M, Eberly S. Comparison of posthospital survival after acute myocardial infarction in women and men. Am J Cardiol. 1994;74:727-30.
46. Kostis J, Wilson A, O'Dowd K, Gregory P, Chelton S, Cosgrove N, et al for the MIDAS study group. Sex differences in the mana-

gement and long-term outcome of acute myocardial infarction. Circulation. 1994;90:1715-29.
47. Sudlow CL, Warlow CP. Comparable studies of the incidence of stroke and its pathological types: results from an international collaboration. International Stroke Incidence Collaboration. Stroke. 1997;28:491-9.
48. Centro Nacional de Epidemiología. Área de Epidemiología Aplicada del Servicio de Epidemiología de Enfermedades Cardiovasculares. Cited Nov 4 2005]. Available from: http://193.146.50.130/ htdocs/cardiov/cerebrovasc/grafica2CV1951.htm.
49. Marrugat J, Gil M, Sala J. Sex differences in survival rates after acute myocardial infarction. J Cardiovasc Risk. 1999;6:89-97.
50. Marrugat J, Elosua R, Aldasoro E, Tormo MJ, Vanaclocha H, Segura A, et al, and the IBERICA Investigators. Regional variability in population acute myocardial infarction cumulative incidence and mortality rates in Spain 1997 and 1998. Eur J Epidemiol. 2004;19:831-9.
51. Marrugat J, Elosua R, Martí H. Epidemiología de la cardiopatía isquémica en España: estimación del número de casos y de las tendencias entre 1997 y 2005. Rev Esp Cardiol. 2002;55:337-46.
52. Marrugat J, García M, Elosua E, Aldasoro E, Tormo MJ, Zurriaga O, et al for the IBERICA, PRIAMHO, RESCATE, PEPA, and REGICOR Investigators. Short-Term (28 Days) Prognosis Between Genders According to the Type of Coronary Event (Q-Wave Versus Non-Q-Wave Acute Myocardial Infarction Versus Unstable Angina Pectoris). Am J Cardiol. 2004;94:1161-5.
53. Luepker RV. Population versus clinical views in coronary disease: can epidemiological data be useful to clinicians? Circulation. 1997;96:3836-7.
54. Killip T, Kimball JT. Treatment of myocardial infarction in a coronary care unit; a two-year experience with 250 patients. Am J Cardiol. 1967;20:457-64.
55. Maynard C, Litwin PE, Martin JS, Weaver WD. Gender differences in the treatment and outcome of acute myocardial infarction. Results from the myocardial infarction triage and intervention registry. Arch Intern Med. 1992;152:972-6.
56. Barakat K, Wilikinson P, Suliman A. Acute myocardial infarction in women: Contribution of treatment variables to adverse outcome. Am Heart J. 2000;140;740-6.
57. Rathore S, Yongfei W, Radford M. Sex differences in cardiac catheteritzation after acute myocardial infarction: the role of procedure appropriateness. Ann Intern Med. 2000;137:487-93.
58. Anand S, Chun C, Mehta S. Differences in the management and prognosis of women and men who suffer from acute coronary syndromes. J Am Coll Cardiol. 2005;46:1845-51.
59. Gottlieb S, Harpaz D, Shotan A. Sex differences in management and outcome after acute myocardial infarction in the 1990s. Circulation. 2000;102:2484-98.
60. Berglund U, Wallentin L, von Schenk H. Platelet function and plasma fibrinogen and their relations to gender, smoking habits, obesity and beta-blocker treatment in young survivors of myocardial infarction. Thromb Haemost. 1988;60:21-4.
61. Heupler FA. Syndrome of symptomatic coronary arterial spasm with nearly normal coronary arteriograms. Am J Cardiol. 1980;45:873-81.
62. Vaccarino V, Parsons L, Every N. Sex based differences in early mortality after myocardial infarction. N Engl J Med. 1999;341:217-25.
63. Vaccarino V, Krumholz M, Yarzebski J. Sex differences in 2-year mortality after hospital discharge for myocardial infarction. Ann Intern Med. 2001;134:173-81.
64. Marenberg ME, Risch N, Berkman L. Genetic susceptibility to death from coronary heart disease in a study of twins. N Engl J Med. 1994;330:1041-6.
65. Lansky AJ, Hochman JS, Ward PA, Mintz GS, Fabunmi R, Berger PB, et al. Percutaneous coronary interventions and adjunctive pharmacotherapy in women. A statement for healthcare professionals from the American Heart Association. Circulation. 2005;111:940-53.