2.- OBJETIVOS

2. OBJETIVOS

- Evaluar si el pronóstico a corto plazo (letalidad a 28 días) de los pacientes ingresados en el Hospital Josep Trueta de Girona ha mejorado entre 1978 y 1993.
- Evaluar si los cambios en la letalidad en el período analizado se pueden explicar por cambios en la comorbilidad de los pacientes ingresados o por la gravedad de sus infartos agudos de miocardio.
- Analizar el papel de los cambios terapéuticos recientes, especialmente la aspirina y la trombólisis, en el pronóstico tras un infarto agudo de miocardio.

Capítulo 2: Gil M, Marrugat J, Sala J, Masià R, Elosua R, Albert X, Pena A, Vila J, Pavesi M, Pérez G, for the REGICOR Investigators. Relationship of therapeutic improvements and 28-day case fatality in patients hospitalized with acute myocardial infarction between 1978 and 1993 in the REGICOR study, Gerona, Spain. Circulation 1999;99:1767-1773.

- Analizar si el riesgo de morir a 28 días tras un infarto agudo de miocardio y durante los siguientes 3 años en los supervivientes a 28 días, es mayor en mujeres que en hombres y, en ese caso, evaluar el papel de la edad, comorbilidad y severidad del IAM.

Capítulo 3: Marrugat J, Gil M, Sala J, Elosua R, Antó JM 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;55:487-493 (en prensa).

3.- HIPÓTESIS DE TRABAJO

3. HIPÓTESIS DE TRABAJO

- El riesgo de morir a 28 días en los pacientes ingresados por un IAM en el Hospital Josep Trueta ha disminuido entre 1978 y 1993.
- Esta mejoría en el pronóstico se da aunque la gravedad de los pacientes ingresados ha aumentado por la mejora en el manejo del paciente previa a su ingreso en el hospital de referencia.
- La introducción de cambios terapéuticos a partir de 1986, fundamentalmente la trombólisis y el ácido acetilsalicílico, han contribuido a mejorar el pronóstico de los pacientes hospitalizados.
- Las mujeres que ingresan por un IAM tienen mayor edad, mayor comorbilidad y presentan unos IAM más severos que los hombres.
- El riesgo de morir a 28 días entre hombres y mujeres puede ser diferente según el grupo de edad que se analice.
- No hay diferencias entre sexos en la mortalidad a 3 años en los supervivientes a 28 días.

4.- RESULTADOS

4. RESULTADOS

4.1. CAPÍTULO 2: RELACIÓN DE LAS MEJORAS TERAPÉUTICAS Y LA LETALIDAD A 28 DÍAS EN PACIENTES HOSPITALIZADOS TRAS UN INFARTO AGUDO DE MIOCARDIO ENTRE 1978 Y 1993 EN GIRONA

Relationship of Therapeutic Improvements and 28-Day Case Fatality in Patients Hospitalized With Acute Myocardial Infarction Between 1978 and 1993 in the REGICOR Study, Gerona, Spain

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Background—The aim of this study was to analyze 28-day case fatality trends between 1978 and 1993 among hospitalized acute myocardial infarction (AMI) patients in the REGICOR registry, Gerona, Spain, and relate them to thrombolytic and antiplatelet drug use and changes in patient characteristics.

Methods and Results—A total of 2053 consecutive patients 25 to 74 years of age with a first Q-wave AMI admitted to the reference hospital between 1978 and 1993 were registered. Clinical characteristics and patient management were recorded. Four 4-year periods were considered: 1978 to 1981, 1982 to 1985 (prethrombolytic therapy), 1986 to 1989 (thrombolytic and antiplatelet drugs introduced), and 1990 to 1993 (thrombolytic and antiplatelet drugs used routinely). The end point was death at 28 days. Case fatality at 28 days decreased 6% per year between 1978 and 1993. A logistic model adjusted for comorbidity and severity showed the last 3 periods to present a steep decrease in the OR of death at 28 days: 0.86 (95% CI, 0.52 to 1.41), 0.59 (95% CI, 0.35 to 0.99), and 0.40 (95% CI, 0.24 to 0.69), respectively, compared with the first period. After 1986, 85.7% of the 112 lives saved could be attributed to the use of antiplatelet and thrombolytic drugs. Adjusted relative risk reduction was 56.0% for antiplatelet drugs, 34.1% for thrombolytic drugs, and 77.9% for the 2 combined.

Conclusions—Our results strongly suggest that new therapies introduced since 1986 have contributed to the decrease in 28-day case fatality of patients admitted with a first Q-wave AMI. This decrease could be attributable mainly to the use of antiplatelet and thrombolytic drugs. These findings should encourage the routine use of thrombolytic and antiplatelet drugs and particularly their combination in the acute phase of AMI. **(*Circulation*. 1999;99:1767-1773.)**

Key Words: myocardial infarction ■ mortality ■ platelet aggregation inhibitors ■ thrombolysis

Coronary heart disease (CHD) mortality has been declining since 1970 in most developed countries,[1] accounting for 10.7% of deaths in Spain in 1993.[2] This decline has been more evident in countries in which mortality was initially higher.[1] Primary prevention interventions, particularly reduction in mean population cholesterol levels, cigarette smoking, and arterial blood pressure levels, have been judged to be principally responsible for this decline before the mid-1980s.[3,4] Since then, improved medical care appears to have contributed greatly to the decrease in CHD mortality.[5,6] Furthermore, these improvements should result in lower short-term mortality in hospitalized acute myocardial infarction (AMI) patients. In fact, a decline in case fatality has been observed in recent decades.[7] The introduction of different pharmacological treatments and particularly thrombolytic therapy and the widespread use of antiplatelet drugs, anticoagulant drugs, β-blockers, and the advent of coronary angioplasty in the 1980s reduced in-hospital mortality to 13% to 16%.[8] Therapeutic improvements such as fibrinolytic and antiplatelet agents[9] have proved to reduce early mortality in clinical trial settings in selected groups of patients who do not necessarily reflect a real-life hospital patient case mix.[10,11]

More extensive evaluation of effectiveness in a general setting such as population-based registries is required to ascertain the effect of these therapeutic modalities on short-term AMI mortality.

The aim of this study was to analyze 28-day case fatality trends between 1978 and 1993 among hospitalized first Q-wave AMI patients in Gerona, Spain, and to relate them to the introduction and use of thrombolytic and antiplatelet drugs and to changes in patient characteristics (age, sex, AMI severity, or comorbidity).

Methods

The hospital under study is the only reference teaching center with a coronary care unit (CCU) in the area. There are 6 community hospitals that refer their AMI patients to that hospital after emergency treatment.

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See the "Appendix" for a list of REGICOR investigators.

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TABLE 1. Changes in AMI Patient Management From 1978 to 1993

	1978–1981 (n=333), %	1982–1985 (n=509), %	1986–1989 (n=615), %	1990–1993 (n=596), %
Thrombolytic drugs	0	0	14.0	33.7
Antiplatelet drugs	0	0	24.6	90.1
28-d Coronary angiograms	0	1.4	5.6	8.0
28-d Revascularizations	0	0.6	2.1	2.2

Most AMI patients initially admitted to community hospitals have been transferred to the reference center by medically attended ambulances since 1988. Since then, emergency treatment in community hospitals has been coordinated by CCU staff from the reference center using guidelines for early AMI management.

This setting provides the population-based Registre Gironí del COR[11] (REGICOR) registry of hospitalized AMI patients in a northeastern region of Spain that covers 591 060 km^2 and has 509 628 inhabitants (1991 census).

Patients

All patients 25 to 74 years of age who were residents of Gerona and were admitted to the reference hospital with a definite diagnosis of first Q-wave AMI between 1978 and 1993 were included in the study. Diagnosis of Q-wave AMI was based on a definite ECG, ie, new Q or QS waves, and at least 1 of the following: increased AMI enzymes (at least twice the upper normal value) and typical pain, ie, located in the anterior chest wall, lasting ≥20 minutes for which no cause other than CHD was found.

Measured Variables

The following data were recorded: age, sex, cardiovascular risk factors or comorbidity (smoking status, hypertension, and diabetes), history of angina, and ECG AMI location. Disease severity was established by the clinical degree of ventricular dysfunction (acute pulmonary edema or cardiogenic shock) and the presence of ventricular arrhythmias (fibrillation or tachycardia) requiring immediate treatment. Management variables, including thrombolytic and antiplatelet drugs, coronary angiogram, PTCA, and CABG surgery, were also recorded.

Follow-Up and End Points

Vital status at 28 days was verified by personal or telephone contact and by linkage of our database with the Catalonia Mortality Registry, which collects all death certificates (updated to December 1995).

AMI Management From 1978 to 1993

The 16-year study was divided into 4 inclusive 4-year periods. The first 4-year period was considered to be the CCU "running-in" period (1978 to 1981). The period from 1982 to 1985 may be considered prethrombolytic. In the next period, 1986 to 1989, thrombolytic and antiplatelet drugs were progressively introduced into clinical practice after the publication of trial results. In the last period, 1990–1993, these drugs were routinely used at the reference and community hospitals. The proportion of patients receiving each of the above-mentioned treatments in each period is shown in Table 1.

Statistical Analysis

The χ^2 test was used to assess the association between categorical variables. Trends among periods were analyzed with the Mantel-Haenszel χ^2 test for linear trends. Age-adjusted annual decrease in mortality was assessed by logistic regression.

For analysis purposes, a 4-category variable was created, with each category corresponding to the periods described above. Each patient was allocated to the category covering the date he or she entered the study. This permitted ecological analysis of the effect of entering the study in each period on 28-day mortality of hospitalized AMI patients.

Adjusted OR of 28-day mortality in the different study periods was estimated by including the period of enrollment variable in a logistic model, together with demographic, comorbidity, clinical, and severity factors that statistically differed with a $P<0.05$ in bivariate analysis among the 4 periods studied and were further associated with 28-day mortality as potential confounders. The influence of the 2 major therapeutic improvements (thrombolytic and antiplatelet drugs) on the effect of the periods studied was measured by adding the corresponding treatment variable to the former model.

Assessment of Relative Risk Reduction and Number of Lives Saved by New Treatments

In an observational cohort study such as that presented here, treatments are provided on a clinical indication basis according to current knowledge of their efficacy. Because randomization is not applied, a favorable outcome cannot be attributed solely to the beneficial effects of the drug. Thus, risk estimates require previous adjustment for the factors that may differ between treated and untreated patients (ie, age, smoking, comorbidity, and severity).

The crude odds of dying in patients receiving each treatment were calculated and divided by the adjusted OR of treated patients and thus gave the odds of death in the treated group if the treated patients' characteristics had been the same as among the untreated. Converting these odds to a probability resulted in an adjusted estimation of death probability if they had not received treatment (I_{OA}). The number of lives saved with each treatment was calculated as the difference between the expected number of deaths in each treatment group on the basis of the above probability minus the observed deaths in that treatment.[12] The same method was used to calculate the number of lives saved in each period. These results are presented with their 95% CIs.

An estimation of the adjusted relative risk reduction (ARRR) of the different treatments was then obtained with the following formula: $ARRR=(I_{OA}-I_t)/I_{OA}$, where I_t is the event incidence among treated patients.

Results

Between February 1978 and December 1993, 2053 consecutive patients (1702 men, 351 women) 25 to 74 years of age admitted with a first Q-wave AMI were prospectively registered. Overall mean age was 59.9±9.8 years (mean±SD): 65.1±7.9 years in women and 59.4±9.9 years in men. No patient was lost to follow-up.

Overall 28-day case fatality rate was 12.3%. Mortality decreased from 25.3% in 1978 to 11.6% in 1993. Age-adjusted mortality decreased 6% (95% CI, 3% to 9%) per year from 1978 to 1993: 7% (95% CI, 4% to 11%) in men and 3% (95% CI, −3.5% to 9%) in women. Four-year proportion of patients with clinically severe ventricular dysfunction (pulmonary edema or cardiogenic shock) decreased from the 1978 to 1981 period (16.8%) to the 1986 to 1989 period (9.9%) but increased thereafter up to 17.0% in 1990 to 1993. The proportion of patients with severe arrhythmias paralleled the ventricular dysfunction pattern. Despite these changes,

TABLE 2. Trends in Demographic, Comorbidity, and Clinical Characteristics and Complications of AMI Hospitalized Patients in Gerona, Spain, Between 1978 and 1993

	1978–1981 (n=333), %	1982–1985 (n=509), %	1986–1989 (n=615), %	1990–1993 (n=596), %	P (χ^2)
>65 y of age	39.3	33.2	39.2	45.0	<0.01*
Women	16.2	15.5	16.3	19.8	0.21
Hypertensive	48.3	46.4	38.4	45.0	<0.01
Diabetic	16.7	18.3	24.6	27.1	<0.001*
Current smokers	70.8	61.1	56.4	48.9	<0.001*
Previous angina	53.7	48.4	42.8	49.8	<0.001
Anterior AMI	55.6	47.0	50.7	40.8	<0.001*
Severe arrhythmias†	12.7	10.4	11.8	18.3	<0.001*
APE/CS	16.8	11.6	9.9	17.0	<0.001
28-d mortality	18.3	12.6	9.8	11.4	<0.001*

APE/CS indicates acute pulmonary edema or cardiogenic shock.
*Linear trend statistically significant (Mantel-Haensz test for trends).
†Ventricular tachycardia or ventricular fibrillation.

28-day mortality decreased until 1986 to 1989 to stabilize in the following years (Table 2).

Period Effect on 28-Day Mortality

Demographic, comorbidity, and clinical characteristics and 28-day mortality in the different periods are shown in Table 2. A statistically significant increase was observed in the proportion of older patients and diabetics and a decreasing proportion of smokers throughout the study periods. A marginally significant trend toward a higher proportion of women was observed ($P=0.06$). The proportion of severe arrhythmias significantly increased, whereas that of anterior AMI decreased. However, all variables but sex showed differences among periods in a χ^2 test (Table 2).

Regarding patient characteristics according to vital status, survivors were younger and predominantly men; there were a lower proportion of hypertensives and diabetics and a higher proportion of smokers. Fatal cases presented a higher proportion of severe ventricular dysfunction, severe arrhythmias, and anterior AMI location but a lower use rate of thrombolytic and antiplatelet drugs. Although the use rate of coronary angiograms was similar in both groups, that of revascularization procedures was higher among fatal cases (Table 3).

Crude and adjusted ORs for 28-day case fatality of the 4 study periods are shown in Table 4. The adjusted OR was higher than the crude OR in the 1990 to 1993 period but lower in the 1982 to 1985 and 1986 to 1989 periods. Compared with 1978 to 1981, a steep decrease in adjusted 28-day mortality risk was found throughout the study periods (see the Figure and period effect model in Table 4). Mortality risk reduction was statistically significant after 1986, when most management improvements were introduced, and the lowest risk corresponded to the more recent period, when the use of the new therapies had become routine.

Treatment Effectiveness

Thrombolytic and antiplatelet drugs were introduced in the 1986 to 1989 period and were routinely used in the last period analyzed (Table 1). Acetylsalicylic acid was used in 99.7% of cases, and streptokinase was the thrombolytic drug of choice in 95.5%. When these treatments were included in an adjusted logistic model (period effect model in Table 4), the 1986 to 1989 period effect was attenuated and became statistically non–significant, and the 1990 to 1993 period effect disappeared (therapeutic effect model in Table 4). Furthermore, 112 lives were saved in the last 2 periods when new treatments were used (35 in the 1986 to 1989 and 77 in the 1990 to 1993 periods) compared with the case fatality expected if patients had been treated in the 1978 to 1981 period (Table 5).

The number of lives saved by antiplatelet and thrombolytic drugs was 96 (63 by antiplatelet drugs, 2 by thrombolytic drugs, and 31 by both treatments combined, as shown in Table 6). This represents 85.7% of the 112 lives saved after 1986.

Compared with patients treated with neither antiplatelet nor thrombolytic drugs, adjusted relative risk reduction was 56.0% for patients treated with antiplatelet drugs, 34.1% with thrombolytic drugs, and 77.9% with both drugs administered together.

Discussion

In the present study, 28-day mortality significantly decreased from 1978 to 1993 despite dramatic increases in disease severity of patients admitted in the last 4 years studied. A risk reduction was conclusively established in appropriately adjusted logistic models. Most of the decrease in risk from 1986 to 1993 might be explained by thrombolytic and antiplatelet drug use. Their individual and combined effectiveness has also been established in terms of the number of lives saved in all consecutive patients registered for a first AMI from 1978 to 1993.

Decrease in Case Fatality at 28 Days

Crude case fatality rates declined from 1978 to 1989, which might be explained in part by the progressively increasing referral of patients with AMI to the new CCU that opened in

TABLE 3. Characteristics of 2053 Patients with First Q-wave AMI in Gerona, Spain (1978 to 1993), by 28-Day Vital Status

	Survivors (n=1798)	Deceased (n=255)	*P*
Age,* y	59.6 (9.9)	65.7 (7.3)	<0.0001
Women, %	15.2	30.4	<0.0001
Hypertension, %	42.2	56.0	<0.0001
Diabetes, %	21.5	30.0	0.003
Current smokers, %	59.7	42.8	<0.0001
Previous angina, %	47.4	52.0	0.15
Severe arrhythmias,† %	10.6	33.6	<0.0001
Anterior AMI,‡ %	45.4	64.1	<0.0001
APE/CS, %	7.0	60.4	<0.0001
Coronary angiogram, %	4.4	3.9	0.88
Treatments, %			
Neither antiplatelet nor thrombolytic drugs	62.5	75.3	<0.0001
Antiplatelet drugs alone	22.3	19.5	<0.0001
Thrombolysis alone	2.7	1.6	<0.0001
Antiplatelet+thrombolytic drugs	12.6	3.6	<0.0001
Revascularization§	1.2	2.8	0.08

APE/CS indicates acute pulmonary edema or cardiogenic shock.
*Mean SD.
†Ventricular fibrillation or tachycardia.
‡In 27 cases, ECG location was not possible.
§PTCA or CABG.

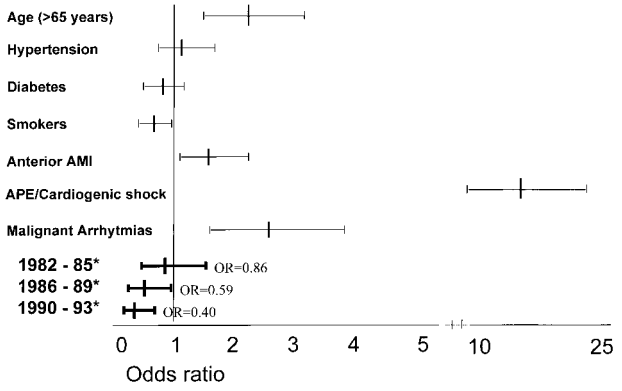
1978. It is reasonable to assume that more severe cases were referred to the CCU in the earlier period. Over the years, it is logical to suppose that fewer selected cases of AMI were sent to the reference CCU. The fact that the decline stopped after 1989 is surprising, considering that the use of improved therapies increased in the last 4 years (Table 1). This apparent paradox can be explained by the admission after 1989 of older patients and those with greater disease severity and comorbidity. In fact, the only crude OR that decreased after adjustment was that corresponding to the last period (Table 4). Moreover, the adjusted OR of the period variable was statistically significant in the last 2 periods, when most management improvements were introduced, and the lowest risk corresponded to the last period, when they were routinely used.

The increase in severity of AMI patients admitted to the reference hospital in the last period could be related to faster access to improved emergency management in community hospitals. In this period, emergency care for AMI patients in community hospitals was provided according to standard guidelines that were periodically updated and coordinated by the reference CCU medical staff. Furthermore, medically attended transportation began in 1988 and has been routinely used since 1990. These changes may have resulted in an

TABLE 4. Crude and Adjusted (Period Effect Model) OR and 95% CIs of 28-Day Mortality Associated With Periods Under Study: Effect of Including the Use of Thrombolytic and Antiplatelet Drugs in the Model Fit (Therapeutic Effect Model)

	Crude OR	Period Effect Model*	Therapeutic Effect Model*
Period			
1978–1981	1	1	1
1982–1985	0.64 (0.43–0.96)	0.86 (0.52–1.41)	0.86 (0.52–1.41)
1986–1989	0.48 (0.32–0.72)	0.59 (0.35–0.99)	0.77 (0.46–1.31)
1990–1993	0.57 (0.39–0.85)	0.40 (0.24–0.69)	1.07 (0.50–2.31)
Antiplatelet drugs alone			0.37 (0.18–0.72)
Thrombolytic drugs alone			0.63 (0.18–2.17)
Antiplatelet and thrombolytic drugs			0.19 (0.07–0.55)

Values in parentheses are 95% CIs.
*All models are adjusted for age, hypertension, diabetes, smoking, severe ventricular dysfunction, ventricular fibrillation or tachycardia, and myocardial infarction ECG location.



Declining OR of 28-day mortality after a first AMI in Gerona, Spain, through 4 periods: 1978 to 1981, 1982 to 1985, 1986 to 1989, and 1990 to 1993. APE indicates acute pulmonary edema.*Reference period was 1978 to 1981.

increasing admission of patients who, without the described facilities, might have died in the emergency departments of community hospitals. However, the impact of these factors on the increasing severity of AMI patients admitted to the reference hospital cannot be precisely measured. Some studies have reported an increasing trend of early care that may result in more severe AMI patients being admitted to hospitals.[12]

Our results concur with those of most studies analyzing trends in short-term case fatality in the 1980s and 1990s that found a decline in short-term mortality of hospitalized patients in most industrialized countries in the last few decades.[6–8,13,14,15] Only 1 study analyzing similar periods of time did not find a decrease in in-hospital case fatality.[16]

Interestingly, declining trends in early mortality did not appear to correlate with variations in disease severity or comorbidity of admitted patients in other studies as they did in ours.[17]

Despite this, results of different studies that examined changes over time in short-term case fatality must be compared with caution, given the potential differences in sociodemographic and clinical characteristics of patients, diagnostic criteria for AMI (especially non–Q-wave AMI), period of time studied (which determines the treatments available), follow-up considered (in-hospital versus 28-day or similar), and inclusion of recurrent AMIs.

Treatment Effectiveness

The introduction of new diagnostic procedures and new treatments appears to account for the decrease in in-hospital case fatality observed between 1979 and 1990[7,12]; in particular, 20% of the improvement between 1985 and 1990 could be related to the use of thrombolytic drugs.[14] Moreover, if the benefit of antiplatelet drugs is as described in ISIS 2,[9] it might explain as much as 50% of the decrease in early case fatality after AMI between 1985 and 1990.[6]

In our study, the fact that the 1986 to 1989 and 1990 to 1993 period protective effects disappeared with the inclusion of therapeutic variables in the logistic models suggests that thrombolytic and antiplatelet drugs were largely responsible for the decreasing adjusted mortality observed. In fact, 85.7% of lives saved from 1986 to 1993 can be attributed to these treatments. Similar results were obtained by other authors.[6]

Adjusted relative risk reduction with both types of treatments in this observational study is higher than that reported in clinical trials and highest when the drugs are administered together, which concurs with current knowledge.[18] Some studies have already highlighted the differences between AMI patients enrolled in clinical trials and an unselected general AMI population,[12,15,16] resulting in the exclusion of high-risk patients from clinical trials.[10] The explanation for the discrepancy could be related to these and other differences in case mix; ie, we included only first Q-wave AMIs and our age limit was set at 74 years, whereas in clinical trials, there is no upper limit. Other hypotheses that cannot be tested with our design refer to the effect of the lower population AMI case fatality in our region compared with that of other industrialized countries.[19,20] Although protective, the effect of thrombolytic therapy was not statistically significant owing to the low number of patients receiving this drug alone; most received it combined with antiplatelet drugs, as shown in Table 6.

Study Characteristics and Limitations

The large sample size provides this population-based hospital registry study with a highly representative, statistically powered group of myocardial infarction patients.

Less than 10% of the all-area patients hospitalized with a myocardial infarction were treated in community hospitals after 1988, which indicates that a selection bias is unlikely. Prehospital case fatality represented 62.4% of total 28-day case fatality in Gerona between 1988 and 1993.[19] This figure is similar to that reported in most community myocardial infarction registries in the world.[20] Incidence and mortality in Gerona are low and did not vary substantially between 1988 and 1993.[19]

TABLE 5. Observed Case Fatality, Expected Case Fatality, and Number of Lives Saved in the Different Periods in Gerona, Spain, From 1978 to 1993

	n	Adjusted OR	Observed Case Fatality, %	Expected Case Fatality* (95% CI), %	Lives Saved† (95% CI), n
1978–1981	333	1	18.3		
1982–1985	509	0.86 (0.52–1.41)	12.6	14.3 (9.3–21.7)	9 (−17–46)
1986–1989	615	0.59 (0.35–0.99)	9.6	15.5 (9.8–23.6)	35 (1–85)
1990–1993	596	0.40 (0.24–0.69)	11.4	24.4 (15.7–34.9)	77 (26–140)

*If patients had been treated in the 1978–1981 period.

†Number of lives saved=(n×expected case fatality)−(n×observed case fatality).

TABLE 6. Observed Case Fatality, Expected Case Fatality, and Number of Lives Saved Attributable to Thrombolytic and Antiplatelet Drug Use in Gerona, Spain, From 1978 to 1993

	n	Adjusted OR	Observed Case Fatality, %	Expected Case Fatality* (95% CI), %	Lives Saved (95% CI), n
Antiplatelet drugs	450	0.37 (0.18–0.72)	10.9	24.8 (14.5–40.4)	63 (16–133)
Thrombolytic drugs	52	0.63 (0.18–2.17)	7.7	11.7 (3.7–31.7)	2 (−2–13)
Both combined	235	0.19 (0.07–0.55)	3.8	17.2 (6.7–36.1)	31 (7–76)
None	1313	1	14.4	...	...

*If patients had not been treated.

†Number of lives saved=(n×expected case fatality)−(n×observed case fatality).

This is an observational study, and no cause-effect relationship should be drawn from our findings that, however, convincingly support the effectiveness of thrombolytic and antiplatelet drugs in daily clinical practice because (1) they are biologically plausible, (2) an increasing protective effect emerges in the last 2 periods studied (when the drugs were used), (3) they are consistent with those of other studies,[6,9,14] (4) the combination of both treatments has been found to provide an optimum additive benefit, and (5) the strength of the relationship between drug use and case fatality reduction is great in terms of OR magnitude. The effect of improvements in primary care and prehospital emergency care, changes in primary prevention, and better lifestyles cannot be readily ascertained. Nevertheless, the variable "period of inclusion" would contain the impact of all the unmeasurable effects described, and the models are properly adjusted to obtain the intrinsic effect of thrombolytic and antiplatelet drugs.

Characteristics of the study patients were homogeneous because patients with previous AMI and those ≥75 years of age, in whom prognosis is worse, were excluded. These differential characteristics may have been counteracted in part by the worse prognosis of Q-wave compared with non–Q-wave AMI that were also excluded from our study. This selection, however, provides homogeneity and requires less mathematical adjustment than when all cases are included.

β-Blocker use rate in our study was low (19.5% after 1988), as in the rest of Spain.[21] Their use was recorded only after 1988, whereas information on their administration route was not. Moreover, β-blockers were given on discharge in most cases. This use of β-blockers provides no benefit in 28-day case fatality, which is the end point of our study. Inclusion of this variable in our models would produce distortions in risk estimators, ie, a large, illusory protective effect. A model further adjusted for coronary angiography and revascularization use did not change the effect of periods or the drugs analyzed (results not shown).

Conclusions and Clinical Implications

Although patients with increasing disease severity were admitted during the last 4 years of the register, 28-day case fatality risk adjusted for age, disease severity, and comorbidity steadily decreased. Our results convincingly suggest that most of the case fatality reduction was related to thrombolytic and antiplatelet treatments, which contributed to counteracting the effect of the higher risk profile of the more recently admitted patients. These findings should encourage the routine use of thrombolytic and antiplatelet drugs and particularly their combination in the treatment of AMI patients.

Appendix

The REGICOR investigators were C. Aubó, M. Bosch, M. Cardona, M.I. Covas, R. Elosua, M. Gil, J.M. Manresa, J. Marrugat, S. Martín, M. Pavesi, A. Pena, G. Pérez, P. Roset, M. Sentí, J. Vila (Institut Municipal d'Investigació Mèdica), X. Albert, R. Masiá, and J. Sala (Hospital Universitari "Josep Trueta").

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4.2. CAPÍTULO 3: PAPEL DE LA EDAD Y EL SEXO EN LA MORTALIDAD A CORTO Y LARGO PLAZO TRAS UN PRIMER INFARTO AGUDO TRANSMURAL

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

J Marrugat, M Gil, R Masiá, J Sala, R Elosua, J M Antó, and the REGICOR Investigators

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.**

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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).

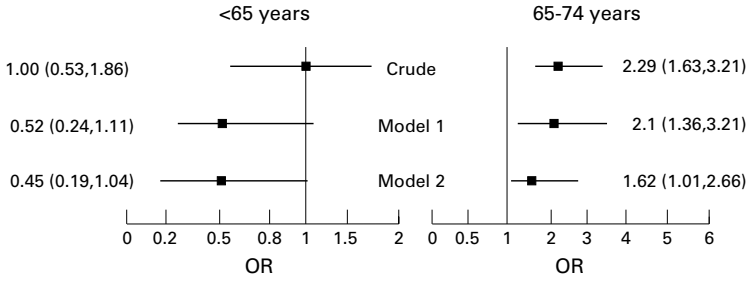

Figure 1 Adjusted odds ratio and 95% confidence intervals of 28 day mortality for women after a first myocardial infarction by age group (over and under 65). Model 1 adjusted for smoking, anterior location of myocardial infarction, diabetes, hypertension, and thrombolysis. Model 2 as model 1 plus acute 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

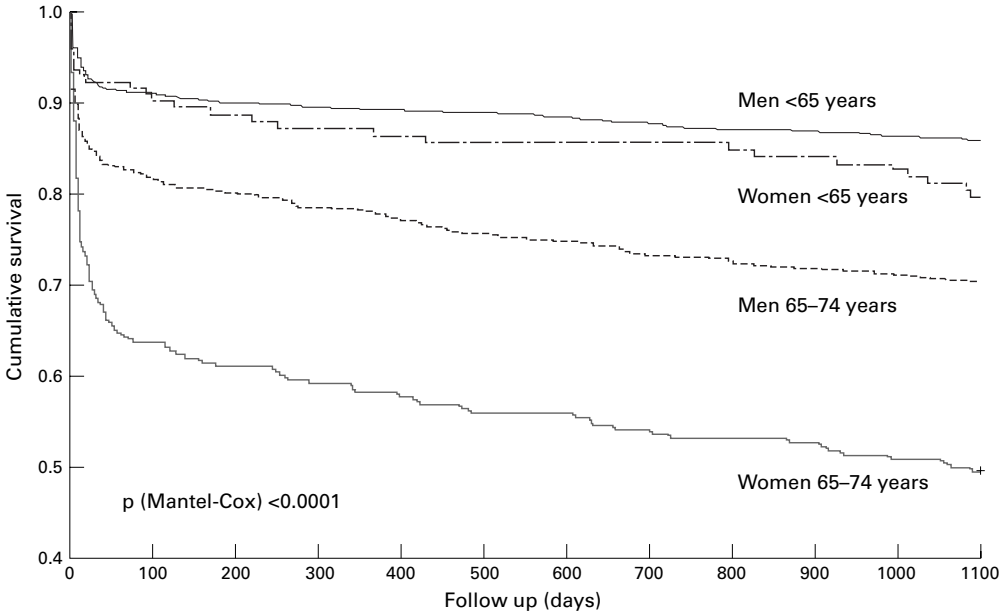

Figure 2 Survival curves by sex and age group in 2053 patients (351 women and 1702 men) with a first myocardial infarction in Gerona, Spain 1978–1993.

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.

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5.-DISCUSIÓN

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Diversos factores clínicos —la edad, el sexo, los factores de riesgo cardiovascular y los antecedentes cardiovasculares— se han relacionado con el pronóstico de los pacientes tras un IAM. De ellos, la edad es probablemente el que tiene más impacto sobre el pronóstico. Los posibles mecanismos a través de los cuales estos factores influyen en el pronóstico están relacionados con el tamaño del IAM, con la capacidad funcional del miocardio no infartado (reserva funcional) y con el desarrollo de complicaciones agudas.[145]

La presente tesis hace referencia al pronóstico tras un IAM en pacientes hospitalizados, analizando el papel del sexo y la influencia que ha tenido la introducción de nuevos tratamientos —especialmente el AAS y la trombólisis— en el manejo del paciente con IAM.

Ambos aspectos se abordan desde el punto de vista hospitalario, por cuanto se analizan todos los pacientes que llegan vivos al Hospital Josep Trueta de Girona. Éste es el hospital terciario de referencia de la Región Sanitaria dotado de unidad coronaria, donde se tratan la mayor parte de los residentes en Girona que padecen un IAM. Así, menos del 10% de los pacientes residentes en la Región se tratan en hospitales fuera de la Región Sanitaria.[222] El hecho de que no se incluyan para el estudio los IAM de no residentes tratados en el Hospital Josep Trueta confiere al registro hospitalario una base poblacional. El período de análisis para evaluar la influencia de los cambios en el tratamiento abarca desde 1978 a 1993; de 1978 a 1994 para analizar el papel del sexo en la mortalidad a largo plazo (3 años) y de 1978 a 1997 para la evaluación del papel del sexo en la supervivencia a corto plazo. Esta diferencia en el período de inclusión para ambos estudios es debida a que se utilizaron los datos disponibles en el momento de preparación de cada uno de los artículos. El período de análisis es amplio, y durante éste, se han introducido mejoras en el tratamiento del paciente con IAM (en particular a partir de 1986). Esto permite evaluar la tendencia en la utilización de los distintos tratamientos en el Hospital Josep Trueta y de qué manera se ha traducido en una mejoría del pronóstico

del paciente hospitalizado. Se ha focalizado el análisis en la trombólisis y el AAS por haber tenido ambos un gran impacto en el tratamiento del paciente con IAM.

Las características de los pacientes incluidos son homogéneas por cuanto: no se han incluido a los pacientes con antecedente de IAM, debido al diferente pronóstico en la supervivencia a corto plazo entre IAM incidentes y recurrentes; se han excluido para el análisis a los IAM no Q, por la existencia de una heterogeneidad manifiesta a la hora de su diagnóstico (que oscila entre el 6,6% y el 42,6% según las series[223,224]). Además, y siguiendo las recomendaciones de la Organización Mundial de la Salud, el período de seguimiento es a 28 días, independientemente que el paciente haya sido dado de alta del hospital o no. Con esto se evita el sesgo derivado de la consideración de la letalidad intrahospitalaria, ya que los cambios en la letalidad podrían estar relacionados con cambios en la estancia media de los pacientes hospitalizados durante el período analizado.[168]

A continuación, se comentan en detalle los aspectos relacionados con cada uno de los factores pronósticos estudiados incluyendo las evidencias aparecidas posteriormente a la redacción de los artículos que forman parte de la tesis.

5.1. El papel de los avances terapéuticos recientes y la letalidad a 28 días en los pacientes hospitalizados por infarto agudo de miocardio

La mortalidad por CI ha disminuido desde 1970 en los países industrializados. Esta tendencia es más patente en los países donde la incidencia de la enfermedad es más alta (USA, Finlandia, Nueva Zelanda, etc.). En los países donde la incidencia es más baja, como España o Japón, la disminución de la mortalidad es menos marcada.[37]

Como ya se ha comentado, diversos estudios reflejan que la disminución de los factores de riesgo clásicos (fundamentalmente colesterol, consumo de tabaco e hipertensión) fueron los principales responsables de la disminución en las tasas de mortalidad hasta mediados de los 1980.[53,57,59-63] Sin embargo, a partir de la segunda mitad de la década de los 80, el descenso de la mortalidad observado era superior al descenso predicho por los cambios en los factores de riesgo. Esto sugiere un aumento en la importancia relativa de la contribución de los cambios en la atención médica en la disminución de la mortalidad (ver punto1.2.4).

Los cambios en la atención médica que han contribuido a la disminución de la letalidad de los pacientes ingresados incluyen:

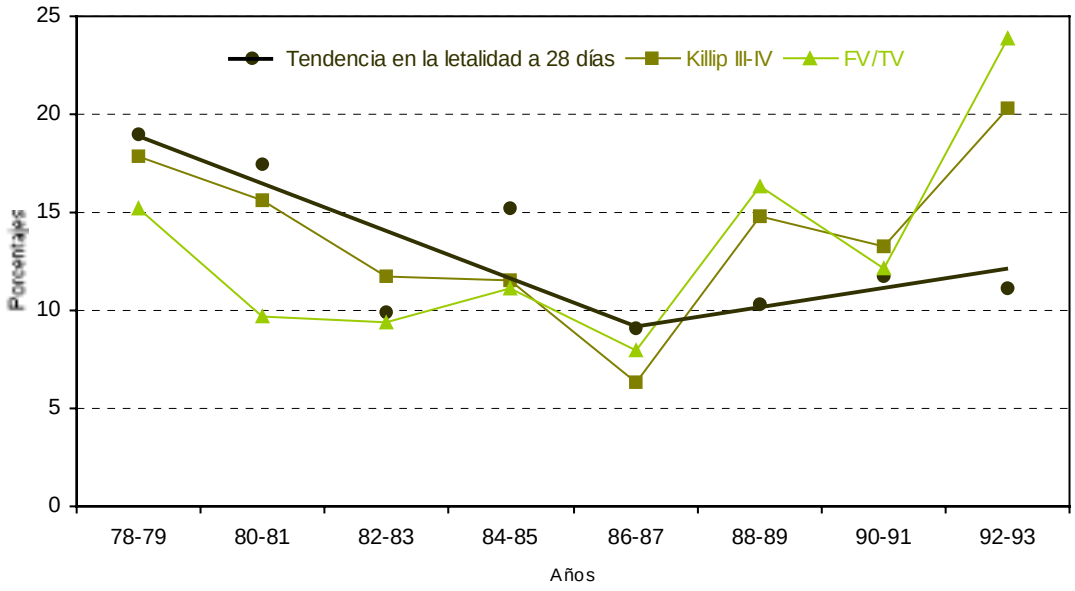
- La introducción de las Unidades Coronarias (a mediados de los 70).
- La mejora en el abordaje terapéutico (en particular la trombólisis, el AAS, los Betabloqueantes y los IECA).
- La generalización del uso de la coronariografía.
- El desarrollo de las técnicas de revascularización coronaria (ACTP y CABG).

5.1.1. Análisis de las tendencias en la letalidad

Cronológicamente, la UC del Hospital Josep Trueta se puso en funcionamiento en 1978. Aunque no se dispone de datos de letalidad intrahospitalaria por IAM previos a la introducción de la UC, diversos estudios han demostrado el mejor pronóstico de los pacientes tratados en las UC comparados con otras localizaciones (salas de medicina general, etc.)[190-194]

Los resultados de nuestro estudio reflejan una disminución de la letalidad a 28 días del 46,8% desde el período 1978-1979 (letalidad del 19,0%) al período 1992-1993 (11,1%). Sin embargo, se observan 2 fases en las tendencias: en una primera fase, la letalidad disminuye desde 1978 a 1986-87 para posteriormente aumentar ligeramente hasta 1993 (Figura 6).

Figura 6 Tendencias en la letalidad y gravedad de los pacientes con un infarto agudo de miocardio. Período 1978-1993

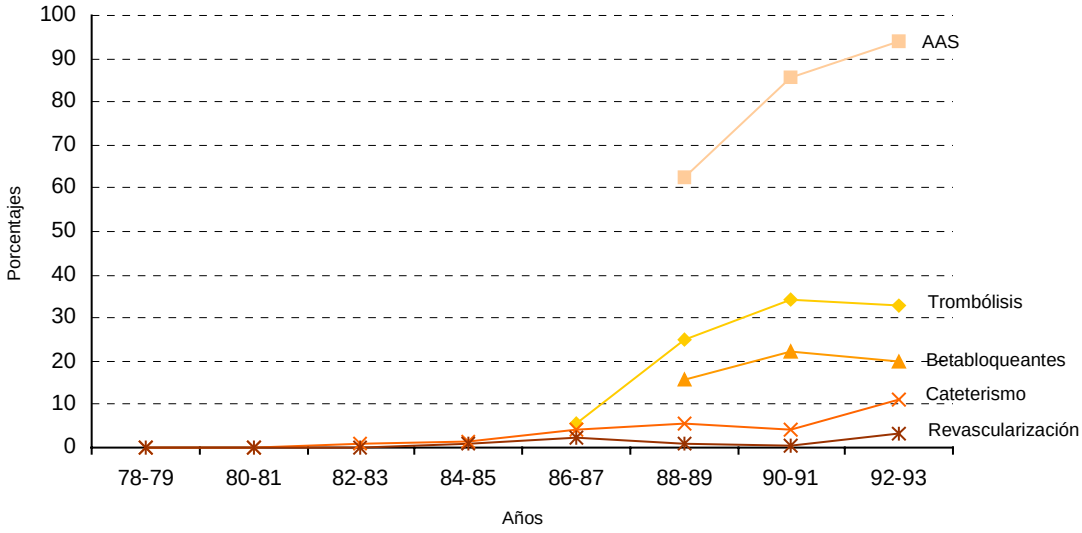


El descenso inicial hasta 1986-87 podría ser en parte explicado por un progresivo incremento de los pacientes referidos al Hospital Josep Trueta

desde 1978. Es razonable asumir que, inicialmente tras la apertura de la UC los casos más graves serían transferidos a la UC desde otros hospitales periféricos. Con el paso del tiempo es lógico suponer una menor selección en los casos que se derivan al igual que una mayor experiencia del centro, con lo que la letalidad podría disminuir.

Sin embargo, la estabilización de la letalidad a partir de 1986 es sorprendente sobre todo si se tiene en cuenta que es a partir de entonces cuando los principales cambios terapéuticos (trombólisis, AAS) se introdujeron en el Hospital Josep Trueta y su uso ha ido en aumento desde entonces. Asimismo, la proporción de cateterismos y revascularizaciones también aumentó considerablemente en este período (ver tabla 1 capítulo 2 y Figura 7).

Figura 7 Tendencias en el manejo del paciente coronario. Período 1978-1993



Todo esto implicaría que los cardiólogos disponían de mejores herramientas para el manejo del paciente coronario y, por tanto, esto debería reflejarse en una disminución de la letalidad cruda de los pacientes ingresados a partir de 1986. Esta aparente paradoja se puede explicar por la mayor comorbilidad y gravedad de los pacientes ingresados a partir de 1986-87 (Figura 6).

5.1.1.1 Tendencias en las características demográficas y clínicas de los pacientes ingresados

En nuestra cohorte hubo un incremento significativo de los mayores de 65 años, diabéticos y no fumadores a lo largo del período de estudio (tabla 2 capítulo 2). Aunque la proporción de mujeres aumentó a lo largo del período estudiado, la significación estadística de este incremento fue sólo marginal. En lo referente a la proporción de pacientes con angina previa e hipertensión arterial, su prevalencia disminuyó hasta 1989 para aumentar en el período 1990-1993 (tabla 2 capítulo 2).

Por todo esto, en lo referente a las características demográficas y de factores de riesgo, se observó una tendencia general al ingreso de pacientes con mayor comorbilidad o factores de riesgo en los últimos años del período estudiado. Otros estudios han descrito un incremento en la edad media y la prevalencia de diabetes e hipertensión entre 1975 y 1995, mientras que la proporción de mujeres y de antecedente de angina permanecía relativamente estable.[169]

5.1.1.2 Tendencias en la gravedad de los pacientes ingresados. Influencia de la accesibilidad de los servicios sanitarios

En lo referente a la gravedad, la proporción de pacientes ingresados con Edema agudo de pulmón (EAP) o shock cardiogénico, y de pacientes con arrítmias graves disminuyó hasta 1986-87 (6,3% y 8,0% respectivamente). A partir de entonces se incrementaron espectacularmente (20,3% y 23,9% respectivamente en 1992-93), siguiendo patrones muy similares. Este aumento de la gravedad de los pacientes ingresados a partir de 1986 coincidió temporalmente con la mejora en el manejo del paciente previo a su ingreso en el hospital de referencia debido a:

- La formación específica para el correcto manejo del paciente coronario del personal de urgencias de los hospitales comarcales. Esta formación fue

potenciada por el personal de la UC del Hospital Josep Trueta a partir de 1986 y se tradujo en la protocolización de las actuaciones. A partir de 1990 se protocolizó la administración precoz de la trombólisis en dichos hospitales.

- El transporte secundario monitorizado y medicalizado de los pacientes entre los hospitales comarcales y el Hospital Josep Trueta. El Servicio de Emergencias Médicas (SEM) fue el responsable, a partir de 1986, del traslado de los pacientes. Las ambulancias utilizadas permiten que el traslado sea medicalizado y monitorizado.

Ambos hechos aumentaron las probabilidades de supervivencia para los pacientes más graves, de forma que pudieran acceder a los cuidados terciarios del Hospital Josep Trueta. Esta tendencia a la hospitalización terciaria precoz, que implicaría la admisión de pacientes más graves, ya había sido descrita en varios estudios japoneses.[226,227]

A pesar de este aumento de la gravedad y comorbilidad de los pacientes ingresados, el incremento en el uso de las distintas terapias para el tratamiento del IAM y otros factores difícilmente medibles como la mayor experiencia del personal responsable de la atención en urgencias estabilizaron la letalidad en torno a un 11% en los últimos períodos del estudio en los pacientes analizados.

5.1.1.3 Resultados del análisis ajustado

Sin embargo, esta aproximación analítica, basada en la estadística descriptiva, sólo permite establecer conclusiones en cierto modo ecológicas. El hecho de disponer de información individual de los pacientes permite evaluar el riesgo de morir que presentaron los pacientes que ingresaron en los diferentes períodos, ajustados por otros factores que podrían actuar como potenciales confusores (comorbilidad, gravedad del IAM, edad y sexo). Para este análisis se definieron 4 períodos: 1978-1981 (puesta en marcha de la Unidad Coronaria), 1982-1985 (período pretrombolítico), 1986-1989 (inicio de los cambios terapéuticos) y 1990-1993 (utilización de las terapias plenamente consolidadas). El análisis de regresión logística refleja que hay un gradiente de

disminución de riesgo a lo largo de los 4 períodos definidos. En los períodos 1986-89 (donde se iniciaron los cambios terapéuticos) y 1990-93 (donde dichas terapias ya estaban plenamente consolidadas), esta disminución del riesgo fue estadísticamente significativa (figura 1 capítulo 2).

Así, tomando como referencia el período 1978-81 (de apertura de la UC), el período 1982-85 (previo a la introducción de cambios terapéuticos) tuvo un 19% menos de riesgo (aunque no fue estadísticamente significativo) probablemente relacionado con una mayor experiencia del personal sanitario en el manejo del paciente con IAM. Por el contrario en los períodos posteriores a la introducción de los cambios terapéuticos, las reducciones del riesgo fueron notables (-51% en 1986-89 y -142% en 1990-93). Al estar el modelo ajustado por variables individuales que miden la edad, sexo, comorbilidad de los pacientes y la gravedad de sus IAM, puede considerarse que el riesgo de morir a 28 días de los pacientes ingresados ha disminuido a lo largo de los períodos estudiados independientemente de las mismas.

5.1.1.4 Comparación con otros estudios

La comparación de los resultados de los distintos estudios que analizan la letalidad en pacientes hospitalizados resulta a veces difícil por varias razones ya comentadas: la falta de homogeneidad del tipo de IAM analizado (inclusión de IAM subendocárdicos o sólo IAM transmurales, IAM incidentes o incidentes y recurrentes, etc.), las diferencias en los períodos de seguimiento del paciente (intrahospitalario o a 28 días), las diferencias en las características de los pacientes incluidos (p.ej. sólo IAM incidentes o IAM incidentes y recurrentes) o la base del estudio (institucional o poblacional). Pero básicamente en todas ellas se comparan las defunciones que se producen en el ámbito hospitalario de los IAM que ingresan en el hospital. Además, los registros de larga duración tienen el inconveniente de que los resultados pueden estar influenciados por cambios en los criterios diagnósticos, en la política de admisiones del hospital, o en el desarrollo de nuevos métodos diagnósticos más sensibles.

Diversos estudios han analizado la evolución de las tendencias en la letalidad en la fase aguda de los pacientes hospitalizados en las últimas décadas.[163,164,168,169] En general, los países industrializados muestran una tendencia a la disminución de la letalidad en los distintos períodos analizados, sobre todo si son períodos amplios. Sin embargo, es importante establecer si las disminuciones de las tendencias en la letalidad reflejan una mejoría real en el manejo del paciente coronario o si, por el contrario, se pueden explicar por cambios en la severidad de los pacientes ingresados u otros factores. Diversos estudios hacen valoraciones ecológicas indirectas aludiendo a la estabilidad en el número de IAM ingresados a lo largo del período de estudio o mediante comparación de la comorbilidad y severidad entre períodos. De todas maneras, el manejo de información individual, mediante la inclusión de variables de comorbilidad o gravedad en un modelo multivariante para evaluar si son confusoras de la relación período-letalidad aporta una novedosa perspectiva al análisis.[157,169]

De hecho, la letalidad en pacientes hospitalizados por IAM ha sido uno de los indicadores que ha presentado una evolución más favorable en los últimos años. Así, la letalidad intrahospitalaria fue del 29% en los años 60, del 21% en los 70 y del 16% en los 80. Si se considera la letalidad al mes de seguimiento, estas tasas son del 31%, 25% y 18% respectivamente.[163]

El análisis de la información disponible a partir de 1987 es fundamental ya que éste es un período crucial en el cual diversos ensayos clínicos mostraron los beneficios de la trombólisis, los antiagregantes plaquetarios, los IECA y betabloqueantes en la supervivencia en la fase aguda de los pacientes con IAM. En general, los estudios que incluyen este período muestran una disminución en la letalidad cruda y un mejor pronóstico de los pacientes que ingresan tras ajustar por las características de los pacientes incluidos.[157,169,228]

5.1.2. Efectividad de los tratamientos en los períodos estudiados

La evaluación de la efectividad de los distintos tratamientos clásicamente se ha llevado a cabo en el contexto de los ensayos clínicos sobre poblaciones

seleccionadas. De todos modos, es importante conocer también si ha mejorado, y en qué medida, el pronóstico en poblaciones no seleccionadas (como los registros poblacionales o registros hospitalarios de base poblacional), ya que esta aproximación refleja más adecuadamente la efectividad global de los cambios en el tratamiento en la supervivencia en la fase aguda del IAM. El registro hospitalario de IAM del Hospital Josep Trueta puede considerarse como un registro hospitalario de base poblacional al incluir para su estudio únicamente a los residentes en Girona. Además, este hospital cuenta desde 1978 (año en que se inició el registro) con una UC.

En el presente estudio, la efectividad de los tratamientos se ha evaluado de 3 maneras diferentes: descriptivamente; mediante la evaluación del cambio de los OR de los períodos al introducir la variable tratamiento y mediante el cálculo de la reducción relativa del riesgo en los pacientes tratados y el de las vidas salvadas en los diferentes períodos atribuibles a los tratamientos.

En el análisis descriptivo, y al igual que en otros estudios,[54,164,169] se observa un incremento en la utilización de las distintas terapias y procedimientos (coronariografía, revascularización) a partir de la publicación de los ensayos clínicos en los que se demuestra su eficacia, habiéndose relacionado este hecho con una mejoría en el pronóstico de los pacientes ingresados.[169] La mayor utilización del AAS en el período 1990-93 respecto del 1986-89 (91,1% vs 24,6%), de la trombólisis (33,7% vs 14,0%) y demás tratamientos o procedimientos diagnósticos y terapéuticos (tabla 1, capítulo 2) podría contribuir a explicar que el riesgo de los pacientes ingresados en este último período sea menor de lo esperado por su gravedad (17% con Killip III/IV y 18,3% con FV/TV en 1990-93 vs 9,9% y 11,8% en 1986-89, respectivamente) (tabla 2 capítulo 2).

Como ya se ha mencionado, al disponer de la información individual de los tratamientos recibidos por los 2.053 pacientes estudiados, se puede evaluar el impacto de la introducción de los distintos tratamientos —en particular el AAS y la trombólisis— en la disminución del riesgo de los períodos. Partiendo del modelo ajustado por comorbilidad y gravedad, la introducción de la variable tratamiento (AAS o trombólisis) en el modelo, explica parte del efecto protector

del período 1986-1989 (OR 0,77; IC95% 0,46-1,31) y la totalidad del efecto protector de los pacientes ingresados entre 1990 y 1993 (OR 1,07; IC95% 0,5-2,31) (tabla 4, capítulo 2). Además, se observa que el riesgo de morir en las personas que recibieron la combinación de AAS y trombólisis era mucho menor que los que recibieron una terapia u otra, en la línea de las conclusiones del estudio ISIS-2[109] que demostró que los beneficios del AAS y la trombólisis eran aditivos.

Por último, al ser éste un estudio observacional, las características de los pacientes en los distintos períodos o en las distintas categorías según el tratamiento recibido pueden ser diferentes. El cálculo de la letalidad esperada —si las características de los pacientes fueran similares al del período de referencia (1978-1981) o a las de los no tratados— permite estimar el número de vidas salvadas en cada uno de los períodos y las atribuibles al uso de los tratamientos. Según esto, el 86% de las vidas salvadas después de 1986 pueden ser atribuidas al uso del AAS y la trombólisis.

Diversos estudios cuantifican la importancia que han tenido los avances terapéuticos en la disminución de la letalidad por IAM. Muchos de estos, para el cálculo, se basan fundamentalmente en la aplicación de las reducciones de riesgo observadas en los distintos tratamientos en los grandes ensayos clínicos randomizados.[61,165,229]

Así, Heidenreich[164] refleja que el AAS y la trombólisis son responsables del 51% de la reducción de la letalidad observada en EEUU entre 1975 y 1995. Este porcentaje aumenta al 71% (IC95% 37%-95%) si se incluye el resto de tratamientos que se han demostrado eficaces (betabloqueantes, IECA y angioplastia primaria). En este estudio, la mayor contribución al descenso fue del AAS (34%), cuyo uso se incrementó marcadamente en el período estudiado, seguido de la trombólisis (17%), la ACTP (10%), los betabloqueantes (7%) e IECA (3%). Por otro lado, McGovern[61] atribuye al más frecuente uso de la trombólisis un 25% del descenso de la letalidad observado entre 1985 y 1990 en Minnesota y, con respecto al AAS, el incremento en su uso podría ser responsable de hasta un 50% del descenso en la mortalidad

entre 1985 y 1990[61] si sus beneficios fueran los observados en el estudio ISIS-2.[109]

Por otro lado, en Suecia[165] el número de vidas salvadas por los tratamientos puede suponer 2/3 partes del descenso de la mortalidad observado entre 1979 y 1990. Finalmente, en Noruega[229] se calculó que, en 1993 el uso del AAS y la trombólisis redujo la letalidad intrahospitalaria en un 12% contribuyendo el AAS en 4/5 partes y la trombólisis en 1/5 parte.

Otra conclusión que se desprende de los resultados es que la reducción ajustada del riesgo por el AAS y la trombólisis es superior a la descrita en los ensayos clínicos, especialmente cuando ambos tratamientos se administran juntos. Diferentes estudios reflejan las diferencias entre los pacientes incluidos en los ensayos clínicos y la población general no seleccionada que se traduce en la exclusión de los pacientes de alto riesgo de los ensayos clínicos.[168,230,231] De hecho, en general la letalidad es mucho más alta en la práctica clínica habitual que la descrita en los ensayos clínicos.[228] Un estudio poblacional que comparaba los pacientes con IAM incluidos en dos grandes ensayos clínicos de evaluación de la terapia trombolítica, con los pacientes que no fueron incluidos, concluyó que aquellos eran significativamente más jóvenes, había una mayor proporción de hombres, presentaban una menor comorbilidad y presentaban una menor supervivencia incluso tras ajustar por esas diferencias clínicas.[230]

Además, el número absoluto de vidas salvadas por el AAS es superior al del AAS y trombólisis administrados simultáneamente aun cuando su reducción relativa del riesgo es menor. Esto se debe al mayor número de pacientes que han recibido AAS, sugiriendo que medidas menos efectivas aplicadas sobre una población más amplia se traducen en un mayor impacto de la intervención.

En lo referente a los tratamientos que se han demostrado eficaces, el resultado de los ensayos clínicos no se refleja a menudo en la práctica clínica diaria y varios estudios han demostrado una gran variabilidad en la utilización de las diferentes terapias.[54,206] Diversos estudios sugieren que el AAS permanece ampliamente infrautilizado en el tratamiento del IAM y más del 10% de los pacientes con IAM no lo reciben a pesar de no presentar contraindicaciones.[198] Esto se acentúa en las personas de edad avanzada.[199]

Esta infrautilización es mayor en el caso de los betabloqueantes que se utilizan en menos de la mitad de los pacientes elegibles tras un IAM[122] o en los IECA. En lo referente a la trombólisis, un estudio realizado en 11 países europeos mostró un amplio rango de utilización (entre un 13% y un 52%).[207] Esta variabilidad ha sido relacionada con diferencias en los sistemas sanitarios, en la práctica médica o en las características de los pacientes.[208] No se dispone de información suficiente para determinar la importancia de cada uno de los factores a la hora de explicar las variaciones regionales.

Una medida del impacto que supondría aplicar estas terapias a todos los pacientes sin contraindicaciones, es que si estos tratamientos se usaran en todos los posibles candidatos para cada terapia (80% en el caso de los betabloqueantes, 90% en el AAS; 40% en los IECA, 30% en la angioplastia primaria y 30% en la trombólisis) se calcula que en EEUU, se hubiera producido una reducción relativa de la letalidad a 30 días del 20% en 1995.[164] Esto implica que 24.800 pacientes que fallecieron por IAM en los EEUU habrían sobrevivido. Otros estudios demuestran que más de 10.000 muertes son atribuibles a la infrautilización de la terapia trombolítica en EEUU anualmente.[232]

5.2. El papel del sexo y la edad en el pronóstico a corto y largo plazo tras un primer IAM transmural

El análisis del papel del sexo en el pronóstico de los pacientes con un IAM debe diferenciarse de la distinta magnitud del problema o incidencia entre hombres y mujeres. Los registros poblacionales muestran clara e inequívocamente que las tasas de incidencia son entre 2 y 7 veces más altas en los hombres que en las mujeres en los diferentes países[5,233]. Además, en promedio, las mujeres desarrollan los IAM entre 7 y 10 años después que los hombres.[234] Sin embargo, una vez que se ha producido el IAM, el análisis de la influencia del sexo en el pronóstico debe tener en consideración otra serie de elementos.[233,235] El factor fundamental es si se incluyen en el análisis todos los pacientes que presentan un IAM en la población, o sólo los que ingresan en el hospital. Este hecho diferenciaría los estudios con una orientación de salud pública de aquellos más clínicos que tienen como referente el sistema sanitario, por cuanto analizan sólo los casos hospitalizados.

Los estudios que incluyen para el análisis a los pacientes que mueren extrahospitalariamente revelan que, en general, las mujeres tienen una letalidad global a 28 días ajustada por edad ligeramente superior a la de los hombres, aunque existe cierta variabilidad entre países.[5] También se observa que la distribución en el tiempo de las muertes es diferente: los hombres que mueren por IAM lo hacen generalmente más precozmente que las mujeres. Esto sugiere que las mujeres mueren fundamentalmente de fallo cardíaco, mientras que los hombres fallecerían por complicaciones más agudas como las arritmias ventriculares.[5,236,237] Esto se traduce en una mayor proporción de casos mortales extrahospitalarios en los hombres comparado con las mujeres.[5,236,237] Por otro lado, los estudios que incluyen únicamente a los casos hospitalizados abordan el problema desde el punto de vista asistencial, esto es, del clínico que tiene que tomar decisiones en base a las características de los pacientes que llegan al hospital y de la evidencia científica disponible. Este estudio aborda el problema desde esta perspectiva.

Los resultados del presente estudio muestran que, tras un primer IAM transmural, las mujeres de 65 a 74 años tienen 2 veces más riesgo de morir a 28 días que los hombres de la misma edad. Por contra, en los menores de 65 años y tras ajustar por los posibles factores confusores, el sexo femenino se comporta como factor de protección de muerte a 28 días, aunque las diferencias no fueron estadísticamente significativas.

En prácticamente todos los estudios, incluido el nuestro (tabla 1 capítulo 3), la mortalidad cruda es más alta en las mujeres que en los hombres. Sin embargo, los resultados ajustados difieren.[233,238,239] En la mayor parte de ellos, el exceso de riesgo de las mujeres desaparece tras ajustar por las diferencias en la edad y otras variables confusoras.[233,239] En otros estudios, generalmente localizados en el área mediterránea, este exceso de riesgo permanece tras dicho ajuste, e incluso cuando se incluyen variables que miden la severidad del IAM.[233,240-246] Por otro lado, diversos estudios sugieren un efecto diferencial del sexo en la supervivencia de los pacientes hospitalizados según la edad.[244,247-250]

Sin embargo, la comparabilidad entre los diferentes trabajos es difícil debido a la gran heterogeneidad en la metodología, tanto en lo referente al diseño del estudio, a los criterios de inclusión de los pacientes como al control de los factores confusores.[233,235]

Recientemente 2 estudios de grandes dimensiones han señalado un diferente riesgo de las mujeres con respecto de los hombres según la edad. [249,250] En ambos estudios las mujeres menores de 75 años (en el estudio de Vaccarino[249]) o 70 años (en el estudio de Rosengren[250]), presentaron un mayor riesgo de morir a 28 días que los hombres de su edad. Por encima de estas edades no se detectaron diferencias significativas entre hombres y mujeres. A diferencia de nuestro estudio, en el estudio de Vaccarino[249] se detectó un mayor riesgo de muerte en las mujeres por debajo de 65 años que en los hombres del mismo grupo de edad, mientras que, al igual que en nuestro estudio, las mujeres de entre 65 y 74 años presentan mayor riesgo de morir que los hombres. Por otro lado, en el estudio de Rosengren[250] las mujeres menores de 70 años hospitalizadas presentaban un mayor riesgo

estadísticamente significativo que los hombres y no se detectaban diferencias entre sexos en el grupo de edad de 70 a 74 años. En cuanto a la comparabilidad de ambos estudios con el nuestro, en el estudio de Vaccarino, se incluyeron también los pacientes con infarto no Q (que representaban el 50% del total de casos) y los infartos recurrentes. Además, no se incluyeron para el análisis los casos que se transfirieron a hospitales que no participaban en el registro (21% del total de casos), lo que podría implicar un sesgo diferencial en la selección. Por otro lado, en el estudio de Rosengren,[250] a diferencia del nuestro, se incluyeron los infartos no Q (se desconoce la proporción) y los resultados se ajustaron por la edad pero no por variables clínicas.

En nuestro medio, en el estudio RESCATE,[251] que incluyó 330 mujeres y 1127 hombres de 80 o menos años con un primer IAM (16,8% de los cuales eran IAM no Q), la mortalidad a 28 días en los pacientes hospitalizados era similar entre hombres y mujeres menores de 60 años (5,3% y 5,0% respectivamente), pero significativamente más alta en las mujeres de 60 a 69 años (14,3% y 7,2%) y en el grupo de edad de 70 a 80 (24,7% y 16%). Estos resultados son similares a los del registro poblacional del estudio REGICOR entre 1990 y 1997 (17,8% de IAM no Q) donde la mortalidad en los primeros IAM fue similar en mujeres y hombres menores de 65 años (7,2% y 7,5% respectivamente), pero más alta en las mujeres que en los hombres de 65 a 74 años (23,6% y 14,8%).

5.2.1. Posibles explicaciones

Los mecanismos y factores sugeridos por los distintos autores para explicar este riesgo diferencial de las mujeres respecto a los hombres según el grupo de edad no están claros y en algunos casos son especulativos.

✓ Diferencias fisiopatológicas

Desde el punto de vista fisiopatológico, se observa que la enfermedad coronaria difiere entre las mujeres fértiles y las menopáusicas. En las mujeres jóvenes, la causa más frecuente de acontecimientos coronarios agudos como la muerte súbita es la erosión de la placa, mientras que en las de edad avanzada y en los hombres es su ruptura.[252] Además, las mujeres jóvenes que tienen un IAM,[253] que mueren súbitamente por causas cardíacas[254] o que sobreviven a un paro cardíaco[253] tienen los vasos coronarios menos estenosados que las mujeres de edad avanzada y los hombres. También se ha observado que las mujeres jóvenes que sobreviven a un IAM tienen las plaquetas más reactivas que los hombres jóvenes.[254] Esto sugiere que el IAM se podría desencadenar por diferentes mecanismos en las mujeres jóvenes, quizás relacionados con un estado de hipercoagulabilidad o por un vasoespasmo que podrían influir en el pronóstico. Estos y otros mecanismos pueden tener su origen en una predisposición genética.[256]

✓ Estrógenos

Los estrógenos podrían tener un papel por cuanto se esperarían niveles más elevados en las mujeres menores de 65 años, pudiendo conferirles cierta protección al mantener una mayor capacidad de vasodilatación y, por tanto, de respuesta a la trombosis. Esto es debido a que los receptores para los estrógenos están presentes en el endotelio vascular, el músculo liso, las células miocárdicas y en otros muchos órganos de hombres y mujeres y su número aumenta proporcionalmente a la concentración plasmática de estrógenos. Su expresión afecta a numerosos procesos relevantes para la enfermedad cardiovascular como: la vasodilatación, el remodelado vascular, el crecimiento celular tras una agresión, la angiogénesis, la proliferación de las células endoteliales, las funciones hemostáticas y trombolíticas así como las funciones relacionadas con el metabolismo lipídico y antioxidante.[257]

✓ Manejo del paciente con IAM

Existe cierta heterogeneidad en los resultados de los diferentes estudios que analizan las diferencias en el manejo hospitalario del IAM entre hombres y mujeres. Diversos estudios han observado que las mujeres reciben intervenciones intrahospitalarias menos agresivas que los hombres.[200,239,249,251,258-260] Gran parte de estos estudios incluyen para el análisis a todos los pacientes, tanto si son elegibles para las terapias como si no lo son. Por tanto, las variaciones detectadas pueden ser debidas a diferencias en la indicación del tratamiento entre hombres y mujeres.[200] Los estudios que incluyen sólo a los pacientes sin contraindicaciones para las terapias también reflejan este infratratamiento, especialmente en la trombólisis y el AAS, aunque en general las diferencias son de poca magnitud y explican una pequeña proporción de las diferencias en el riesgo entre hombres y mujeres[200,202]

En lo referente a los procedimientos, diversos estudios encuentran una menor probabilidad de que a las mujeres se les lleve a cabo procedimientos diagnósticos (coronariografías),[258-260] especialmente en las edades avanzadas,[200] lo que se traduce en una menor número de revacularizaciones entre las mujeres. Aunque, una vez que la coronariografía se ha llevado a cabo, éstas tienen las mismas probabilidad de revascularización que los hombres.[200,261] Esto sugiere que, aunque la decisión de llevar a cabo la coronariografía puede estar influenciada por el sexo en algunos entornos, la decisión de llevar a cabo la revascularización no lo está. Por otro lado, la mayor mortalidad observada en las mujeres tras una cirugía de revascularización coronaria en algunos estudios, se debe probablemente a otras variables como la edad, el retardo en la operación, la diabetes u otras enfermedades concurrentes, el calibre de las arterias coronarias o la disminución de la superficie corporal.[262] Sin embargo, estas diferencias en el tratamiento entre hombres y mujeres generalmente no explican la totalidad de las diferencias en la mortalidad entre sexos.[200,249] A pesar de ello hay estudios que sugieren que

la mayor mortalidad en las mujeres puede ser el resultado de la menor utilización de las terapias de reperfusión.[202]

✓ Diferencias en la mortalidad prehospitalaria

También es posible que las diferencias en la mortalidad durante la hospitalización según los grupos de edad y sexo sean atribuibles a diferencias en la mortalidad prehospitalaria. Diversos estudios sugieren que la más alta mortalidad intrahospitalaria entre las mujeres se contrarresta por una mayor mortalidad extrahospitalaria en los hombres.[236,237,250] Los resultados de los diferentes registros incluidos en el proyecto MONICA sugieren que, como media, el 64% de las mujeres que mueren tras un IAM lo hacen antes de llegar al hospital y este porcentaje es más elevado en los hombres (70%),[5] aunque se observa mucha variabilidad entre los diferentes registros.

✓ Factor geográfico

Diversos hechos sugieren la posible influencia del factor geográfico en la diferencia en el pronóstico entre hombres y mujeres. Por un lado, aunque la variabilidad en la letalidad global entre los diferentes países no es muy elevada, ésta es más baja en España y otros países mediterráneos para ambos sexos.[22] Esto podría llevar a la hipótesis que no sólo los países mediterráneos presentan menos riesgo de padecer enfermedad coronaria, sino que ésta es, a su vez menos grave. Por otro lado, los países con menor incidencia de IAM presentan un mayor riesgo en las mujeres comparado con los hombres.[5] En la figura 2 del capítulo 1 se muestra la relación lineal que observaron los investigadores del estudio MONICA de la OMS entre ambas variables. Este hecho se ha relacionado con un menor reconocimiento de los casos no fatales en las mujeres de los países de baja incidencia.[5] Y por último, en los estudios que analizan los casos hospitalizados, los llevados a cabo en los países mediterráneos, generalmente presentan un mayor riesgo en las mujeres tras

ajustar por los factores confusores e incluso cuando se incluyen variables que miden la severidad del IAM.[157,233,240-246]

✓ Otros factores

No puede descartarse que existan otros factores ambientales y/o metabólicos desconocidos hasta ahora que expliquen parte de las diferencias entre hombres y mujeres o entre las mujeres jóvenes y de edad avanzada. Sin embargo, no existe ninguna evidencia científicamente contrastada al respecto.

Aunque nuestro estudio no está diseñado para verificar hipótesis acerca de mecanismos fisiopatológicos y hormonales, se pueden hacer consideraciones respecto a otros aspectos apuntados.

Respecto al manejo del paciente con IAM, en nuestro estudio, al igual que en otros,[237] el tratamiento con AAS y los procedimientos de revascularización no diferían entre sexos en cada uno de los grupos de edad (tablas 1 y 2, capítulo 2). Por otro lado, las mujeres —especialmente en el grupo de mayores de 65 años— recibieron menos trombólisis que los hombres. Esto puede estar relacionado con el mayor intervalo entre el inicio de los síntomas y la llegada al hospital de las mujeres respecto de los hombres secundario al menor reconocimiento del IAM en las mujeres en las fases iniciales del proceso diagnóstico. Entre las causas que justificarían este retraso están la mayor probabilidad de la presentación atípica de los síntomas en las mujeres, especialmente en las de edad avanzada, debido a la más alta prevalencia de diabetes en las mujeres. Sin embargo, y al igual que en otros estudios,[200,249] al estar los resultados ajustados, las diferencias en los tratamientos no explican la totalidad de la diferencia en el pronóstico entre hombres y mujeres en ambos grupos de edad.

En lo referente a la distribución de otros factores pronósticos conocidos, la edad de los pacientes ingresados fue 6 años superior en las mujeres que en los hombres, y la prevalencia de factores de riesgo (hipertensión, diabetes,

antecedentes de insuficiencia cardíaca), fue superior en las mujeres que en los hombres en global, y para cada uno de los grupos de edad definidos (tablas 1 y 2, capítulo 3). Por otro lado, no se detectaron diferencias en el antecedente de angina y la proporción de fumadores fue menor en las mujeres. El tabaquismo se ha asociado con un menor riesgo de morir en los pacientes hospitalizados tras un IAM en éste y otros estudios.[263] Sin embargo, este hecho parece estar relacionado con una mayor mortalidad extrahospitalaria en el grupo de fumadores.[263] De todas maneras, el ajuste por éstas y otras variables confusoras no explica la totalidad de las diferencias en el riesgo entre hombres y mujeres del grupo de edad de 65 a 74 años, siendo marginalmente significativo en los menores de 65 años.

En lo que respecta a la mortalidad prehospitalaria, no se puede descartar que ésta sea la causa de las diferencias observadas en la letalidad entre hombres y mujeres por grupo de edad -ya que no se dispone de esta información en toda la cohorte-. El análisis de los datos poblacionales entre 1990 y 1997 no refleja diferencias sustanciales entre la proporción de muertes prehospitalarias en hombres y mujeres para ambos grupos de edad.

6.- CONCLUSIONES

6. CONCLUSIONES

6.1 Capítulo 2: Relación de las mejoras terapéuticas y la letalidad a 28 días en pacientes hospitalizados tras un infarto agudo de miocardio entre 1978 y 1993 en Girona

1. El riesgo de morir a 28 días de los pacientes con un primer IAM transmural ingresados en el Hospital Josep Trueta de Girona ha disminuido entre 1978 y 1993, a pesar de que se observa un aumento de la gravedad de los pacientes ingresados a partir de 1986.
2. El aumento de gravedad de los pacientes ingresados a partir de 1986 coincide temporalmente con el desarrollo del transporte secundario y con las mejoras en el manejo del paciente, previos a su ingreso en el Hospital de referencia.
3. La introducción de nuevos avances terapéuticos y el incremento en su utilización, han contribuido a la disminución del riesgo de morir de los pacientes ingresados a partir de 1986, a pesar del incremento en la gravedad observado.
4. El 86% de las vidas salvadas a partir de 1986 es atribuible a la utilización del ácido acetilsalicílico y la trombólisis.

6.2 Capítulo 3: El papel del sexo y la edad en el pronóstico a corto y largo plazo tras un primer IAM transmural

5. Las mujeres que ingresan con un IAM son de mayor edad y presentan más comorbilidad e infartos más severos que los hombres.
6. Las mujeres de 65 a 74 años tienen un riesgo de morir a 28 días 62% mayor que los hombres del mismo grupo de edad.

7. Por el contrario, las mujeres menores de 65 años presentan un menor riesgo ajustado que los hombres de la misma edad, aunque esta diferencia es sólo marginalmente significativa.
8. No se ha observado diferencias entre hombres y mujeres en la mortalidad a 3 años en los supervivientes a 28 días.

7.- BIBLIOGRAFÍA

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