Original article

Reduction in 28 Days and 6 Months of Acute Myocardial Infarction Mortality From 1995 to 2005. Data From PRIAMHO I, II and MASCARA Registries

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A B S T R A C T

Introduction and objectives: To determine whether mortality from acute myocardial infarction has reduced in Spain and the possibly related therapeutic factors.
Methods: Nine thousand, nine hundred and forty-nine patients with ST-segment elevation myocardial infarction admitted to the Coronary Care Unit were identified from PRIAMHO I, II and MASCARA registries performed in 1995, 2000 and 2005, with a 6 month follow-up.
Results: From 1995 to 2005 patients were increasingly more likely to have hypertension, hyperlipidemia and anterior infarction, but age of onset and the proportion of females did not increase. Twenty-eight-day mortality rates were 12.6%, 12.3% and 6% in 1995, 2000 and 2005 respectively, and 15.3%, 14.6% and 9.4% at 6 months (both *P*-trend <.001). Multivariate analysis was performed and the adjusted odds ratio for 28-day mortality for an infarction occuring in 2005 (compared with 1995) was 0.62 (95% confidence interval: 0.44-0.88) whereas the adjusted hazard ratio for mortality at 6 months was 0.40 (95% confidence interval: 0.24-0.67). Other variables independently associated with lower mortality at 28 days were: reperfusion therapy, and the use of anti-thrombotic treatment, beta-blockers and angiotensin-converting enzyme inhibitors. The 28-day-6-month period had an independent protective effect on the following therapies: coronary reperfusion, and prescription of antiplatelet agents, beta-blockers and lipid lowering drugs upon discharge.
Conclusions: Twenty-eight-day and six-month mortality rates fell among patients with ST-elevation myocardial infarction in Spain from 1995 to 2005. The possibly related therapeutic factors were the following: more frequent reperfusion therapy and increased use of anti-thrombotic drugs, beta-blockers, angiotensin-converting enzyme inhibitors and lipid lowering drugs.

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Reducción de la mortalidad precoz y a 6 meses en pacientes con IAM en el periodo 1995-2005. Datos de los registros PRIAMHO I, II y MASCARA

R E S U M E N

Introducción y objetivos: Determinar el cambio en la mortalidad a corto y medio plazo por infarto agudo de miocardio en España y los factores terapéuticos relacionados.
Métodos: Se identificó y se siguió durante 6 meses a 9.949 pacientes con infarto agudo de miocardio con elevación del ST ingresados en la unidad coronaria en los registros PRIAMHO I, II y MASCARA realizados en 1995, 2000 y 2005.
Resultados: En el periodo 1995-2005 aumentó (p < 0,001) el porcentaje de pacientes con hipertensión, hiperlipemia e infarto anterior, pero no el de mujeres ni la edad. La mortalidad a los 28 días fue del 12,6, el 12,3 y el 6% en 1995, 2000 y 2005 respectivamente y del 15,3, el 14,6 y el 9,4% a los 6 meses (ambas p < 0,001 para tendencia). Los pacientes de 2005 presentaron menos mortalidad ajustada por confusores que los de 1995, tanto a los 28 días (*odds ratio* = 0,62; intervalo de confianza del 95%, 0,44-0,88) como a los 6 meses (*hazard ratio* = 0,4; intervalo de confianza del 95%, 0,24-0,67). Otras variables asociadas con menor mortalidad a los 28 días fueron: reperfusión coronaria y uso en la unidad coronaria de antitrombóticos, bloqueadores beta e inhibidores del sistema renina-angiotensina. En el periodo

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28 días-6 meses, la reperfusión coronaria y la prescripción al alta de antiagregantes bloqueadores beta e hipolipemiantes explicaron la menor mortalidad en 2005.
Conclusiones: La mortalidad precoz y a los 6 meses del infarto con elevación del ST disminuyó en 1995-2005. Los factores terapéuticos relacionados son: incremento de la reperfusión y mayor utilización de antitrombóticos, bloqueadores beta, inhibidores del sistema renina-angiotensina e hipolipemiantes.

Abbreviations

ACEI: angiotensin-converting enzyme inhibitor
ARB-II: angiotensin II receptor blockers
BB: betablockers
CICU: cardiac intensive care unit
GCP: guidelines on clinical practice
STEMI: ST-segment elevation acute myocardial infarction

INTRODUCTION

The health care provided to patients with acute myocardial infarction (AMI) has greatly changed during the past two decades, with the advent of new diagnostic and therapeutic procedures. As a result, mortality has decreased, as has been demonstrated in several international registries.[1–3] These advances endorsed by scientific evidence, have been incorporated by successive good practice guidelines (GPC)[4,5] implying that if the guidelines are closely followed, a lower mortality can be achieved.[6,7]

Mortality in patients with ST-segment elevation acute myocardial infarction (STEMI) very much depends on how early the ischemic myocardium is reperfused, and amongst the available options, primary angioplasty has proven to be better than fibrinolysis.[8] However, it is not as frequently used in Spain as in other western countries.[9] Furthermore, many other effective therapies recommended by guidelines could also be employed more.[1,7]

National registries enable us to monitor disease treatment changes and how they may affect mortality. In Spain, the PRIAMHO I, II and MASCARA registries collected AMI patient data for 1995, 2000 and 2005, respectively.[10–12]

The aims of this paper are: *a)* to analyze the changes in 28-day and 6-month mortality in patients with STEMI from 1995 to 2005, and *b)* to determine which therapeutic factors are associated with this variation.

METHODS

The methodology used by the PRIAMHO I, II and MASCARA registries has already been described in detail.[10–12] In summary, the PRIAMHO registries, designed by the *Sección de Cardiopatía Isquémica y Unidades Coronarias de la Sociedad Española de Cardiología* (Department of Ischaemic Heart Diseases and Coronary Care Units from the Spanish Society of Cardiology) registered all patients with and without STEMI admitted to the coronary care unit/cardiac intensive care unit (CICU) between October 1994 and September 1995 and from 15 May to 16 December 2000. Forty-seven hospitals participated in the PRIAMHO I and 81 in PRIAMHO II. All hospitals had to meet the following requirements: *a)* register at least 70% of AMI patients admitted to the hospital; *b)* register at least 75% of the AMI patients admitted to the CICU; *c)* reach a Kappa concordance index above 70% between the data registered

and data obtained by an external auditor from a random sample of 15% of the patients, and *d)* perform follow-up after one year for more than 90% of the registered patients.

The MASCARA study[12] broadened the patient type analyzed to all acute coronary syndromes with and without AMI, and also included patients that were not admitted to the CICU. The recruitment period was from September 2004 to June 2005. Sixty hospitals were chosen at random in accordance with the hospital's attendance. Between 2005 and 2006 an exhaustive inclusion control was performed. The study excluded hospitals whose inclusion rate was lower than 50% that expected in accordance with the health centre's attendance rate and whose 95% confidence interval (CI) for each acute coronary syndrome type mortality rate was not within the mean range of the reference centers. As such, 18 out of the 50 centers that had completed the recruitment were excluded.

For our study, we have chosen the STEMI patient subgroup admitted to the CICU from the PRIAMHO I, II and MASCARA study. Of those patients in the CICU, those with ST-segment elevation were identified among those who met the AMI criteria. AMI diagnosis was based on the definition that existed when the study took place.[13,14] Data was recorded for: demographics, clinical history, characteristics of the acute event and complications, diagnostic and therapeutic procedures used in the CICU and drug treatment upon discharge. Follow-up was performed in an outpatient clinic or by telephone. Mortality data was collected for any cause.

Statistical Analysis

Patient characteristics are expressed as mean ± standard deviation, or frequency and percentage. For the bivariate analysis, the χ^2 test, Student's-t test or Mann-Whitney U test were used, depending on the data distribution. When analyzing evolution over three periods, the *P* value is presented for linear tendency. To analyze the relationship between period and short-term mortality (28 days) logistic regression models have been used, expressing the results as odds ratio (OR), given that most deaths occur during the first 24 h and these data are better adjusted to a binomial distribution. To analyse the relationship between the period and time to long-term mortality (28 days-6 months) Cox's regression models have been used, expressing the results as hazard ratio (HR). The HR's linearity assumption for continuous variables is calculated using a smoothing spline regression, and the proportionality assumption is calculated by testing the interaction with time. None of these tests reached a statistical significance against these assumptions. The influential cases were analyzed using the delta-beta method, in which the variation of estimations was compared following the extraction of each of the patients.

In addition to the variable 'period', with 1995 as a reference, each of the models were including more and more variables regarding demographics, clinical history, acute events and lastly, diagnosis and therapeutic procedures. Variables that showed, at least, a significant marginal relationship of $P < .15$ were included as possible confounding factors in the bivariate analysis by comparing the surviving patients with those that died after 30 days or during the 28-day-6-month period.

Table 1

General Data for Patients With ST-Segment Elevation Acute Myocardial Infarction Admitted to the Cardiac Intensive Care Unit and Included in the PRIAMHO I, PRIAMHO II and MASCARA Registers in 1995, 2000 and 2005, Respectively

	1995 (n = 3516)	2000 (n = 4080)	2005 (n = 2353)	P-trend
Age, years	63.8 ± 12.3	64.4 ± 13.1	63.2 ± 13.2	.123
Female	735 (20.9)	1005 (24.6)	464 (19.8)	.703
Risk factors				
Diabetes	784 (22.3)	1133 (27.8)	512 (21.8)	.712
Tobacco use	1467 (41.7)	1928 (47.3)	987 (41.9)	.388
Hyperlipidemia	1002 (28.5)	1625 (39.9)	985 (41.9)	<.001
Hypertension	1398 (39.8)	1771 (43.5)	1134 (48.2)	<.001
Previous heart disease				
Previous heart attack	480 (13.7)	475 (11.7)	272 (11.6)	.010
Revascularization	101 (2.9)	239 (5.9)	118 (5.0)	<.001
ECG (anterior vs others)	1580 (44.9)	1867 (45.8)	1069 (57.7)	<.001
Catheterization laboratory	2135 (60.7)	2422 (59.4)	1625 (69.1)	<.001

ECG, electrocardiography.

Data are expressed as mean ± standard deviation or no. (%).

We used the R: A language and environment for statistical computing program (version 2.11.0). Foundation for Statistical Computing, Vienna, Austria.

RESULTS

The PRIAMHO I and II results included 3516 and 4080 STEMI patients, respectively. Two thousand three-hundred and fifty-three STEMI patients attended to in the CICU in the MASCARA study. Therefore, this paper includes 9949 STEMI patients admitted to the CICU in 1995, 2000 and 2005.

Clinical Characteristics

General patient data are shown in Table 1. During 1995-2005, there was a significant increase in patients with

Table 2

Treatment for Patients With ST-Segment Elevation Acute Myocardial Infarction Admitted to the Cardiac Intensive Care Unit and Included in 1995, 2000 and 2005 in the PRIAMHO I, PRAIMHO II and MASCARA Registers, Respectively

	1995 (n = 3516)	2000 (n = 4080)	2005 (n = 2353)	P-trend
Reperfusion				
Thrombolysis	2125 (60.4)	2429 (59.7)	1132 (48.1)	<.001
Primary PTCA	–	298 (7.3)	569 (24.2)	<.001
Rescue PTCA	–	166 (4.1)	180 (7.6)	<.001
Symptom-monitoring time	135 [60-300]	120 [60-265]	95 [45-202]	<.001
Symptom-thrombolysis time	180 (120-264)	170 (115-255)	164 (96-288)	.191
Door-to-needle time	60 [30-93]	47 [30-76]	43 [25-75]	.001
Door-to-balloon time	–	80 [50-127]	95 [60-179]	<.001
Drug treatment				
Antiplatelet agents	3190 (90.7)	3925 (96.5)	2266 (96.3)	<.001
Clopidogrel	–	296 (7.3)	1455 (61.8)	<.001
GPIIb-IIa antagonists	–	387 (9.5)	722 (30.7)	<.001
Unfractionated heparin	2274 (64.7)	2503 (62.1)	432 (18.4)	<.001
LMWH	–	1695 (42.4)	1664 (70.7)	<.001
Beta-blockers	1109 (31.5)	2078 (51.1)	1712 (82.1)	<.001
ACEI/ARB-II	893 (25.4)	1757 (43.2)	1522 (73)	<.001
Lipid lowering drugs	–	745 (18.3)	1682 (80.7)	<.001
Nitrates (taken orally or applied to skin)	1110 (31.6)	1217 (30.7)	1101 (52.8)	<.001
IV nitrates	2544 (72.4)	2782 (70.2)	1528 (73.3)	.749
Calcium channel blockers	389 (11.1)	250 (6.2)	246 (11.8)	.577
Procedures				
Coronary angiography	258 (7.3)	677 (16.8)	935 (39.9)	<.001
Echocardiography	1464 (41.6)	1405 (34.9)	2010 (85.4)	<.001
Swan-Ganz catheter	210 (6.0)	134 (3.3)	74 (3.2)	<.001

ACEI, angiotensin-converting enzyme inhibitors; ARB-II, angiotensin II receptor blockers; GPIIb-IIa, glycoprotein IIb/IIIa; IV, intravenous; LMWH, low molecular weight heparin; PTCA, percutaneous transluminal coronary angioplasty.

Data are expressed as no. (%) or median [interquartile range].

hypercholesterolemia (from 28.5% to 41.9%), hypertension (from 39.8% to 48.2%), and anterior infarction (from 44.9% to 57.7%). The percentage of patients with a history of revascularization and the percentage of patients provided health care in hospitals with a catheterization laboratory also increased.

Acute Phase Management in the Cardiac Intensive Care Unit

Reperfusion treatment use gradually rose from 1995 to 2005 (60.4%, 67.0% and 72.3%) due to the increase in using primary angioplasty (Table 2). Delay in administering anti-thrombotic drugs did not significantly decrease, although the Symptom-monitoring time went from 135 min in 1995 to 95 min in 2005 and the door-to-needle time dropped from 60 to 43 min. On the other hand, the median door-to-balloon time increased 15 min between 2000 and 2005.

Anti-thrombotic treatment used in the CICU changed greatly from 2000, when the double/triple antiplatelet therapy was introduced and low molecular weight heparin was used almost globally. Administration of beta-blockers (BB), angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptors blockers (ARB-II), lipid lowering drugs and nitrates also significantly increased.

The diagnostic and therapeutic procedures used in CICU are also shown in Table 2. Coronary angiography went from 7.3% in 1995 to 39.9% in 2005 and echocardiography from 41.6% to 85.4%. On the contrary, Swan-Ganz catheterization was used less frequently.

Clinical Evolution in the Cardiac Intensive Care Unit

Less patients developed severe heart failure (Killip class III/IV), which lowered in 2005 (11.3%), compared to 1995 and 2000 (13.5% and 16.1%) without reaching statistical significance (Table 3). The incidence of atrial fibrillation and mechanical complications significantly reduced, while AMI relapses did not increase despite there being more patients with post-infarction angina. Mortality in the CICU decreased from 9.5% in 1995 to 5.9% in 2005 (P < .001), as is shown in Table 3 and Figure 1.

Treatment Upon Discharge

Figure 2 shows the drugs with type I recommendations in the GPC. We have only provided data for 2000 and 2005 because data

on this matter was not collected in 1995. There was a significant increase in all of the therapies analyzed.

Twenty-Eigh-Day and Six-Month Mortality and Related Factors

Mortality significantly decreased between 1995 and 2005: at 28 days (12.6%, 12.3%, 6%) and at 6 months (15.3%, 14.6%, 9.4%) as shown in Figure 1.

Table 4 shows the 28-day mortality determinants. This is associated with age, female sex, diabetes mellitus, hypertension, previous heart attack, Q-wave heart attack, delay in monitoring, anterior infarction, reinfarction, and Killip class III/IV. Early reperfusion and reperfusion were significantly related to a decrease in mortality, as were tobacco use, hyperlipidemia, using anti-thrombotic drugs, BB, ACEI/ARB-II and lipid lowering drugs in the CICU, and coronary angiography.

Several logistic regression models were carried out (Table 5), and for each one we added more potential confounding variables. A significantly lower mortality was shown for all of them in 2005, compared with 1995, and this decrease was independent of the variables with most impact on mortality, such as age, sex, diabetes, reperfusion therapy, and Killip class III/IV. Other factors with a protective effect are: reperfusion therapy and anti-thrombotic drugs, BB, and ACEI/ARB-II administered in CICU. The risk of dying rose with age, female sex, anterior infarction and above all, the Killip class III/IV.

Table 5 shows that the lower mortality of 2000 (as compared to 1995) disappeared in model 4. This is because anti-thrombotic treatment, BB and ACEI/ARB-II were introduced to CICU. On the other hand, the protective effects of 2005 remained.

The 28-day-6-month mortality-related factors are shown in Table 6. The following factors had a significant relationship with risk of dying at 28-days: age, female sex, diabetes, hypertension, previous heart attack, maximum Killip class, AMI relapses and post-infarction angina. On the contrary, the following were related to lower mortality: tobacco use, hyperlipidemia, early reperfusion, administering antiplatelets agents, BB and lipid lowering drugs upon discharge, and performing a coronary angiography during the hospital stay.

The results from the Cox's regression models are shown on Table 7. The risk of dying during the 28-day-6-month period was significantly lower in 2005 than in 1995 (HR: 0.40; 95% CI: 0.24-0.67) after adjusting for confounding factors and severity. Model 4 shows that the HR for 2005 is 0.42 (95% CI: 0.25-0.68) compared with 2000 (there were no data for 1995). Model 5 proves
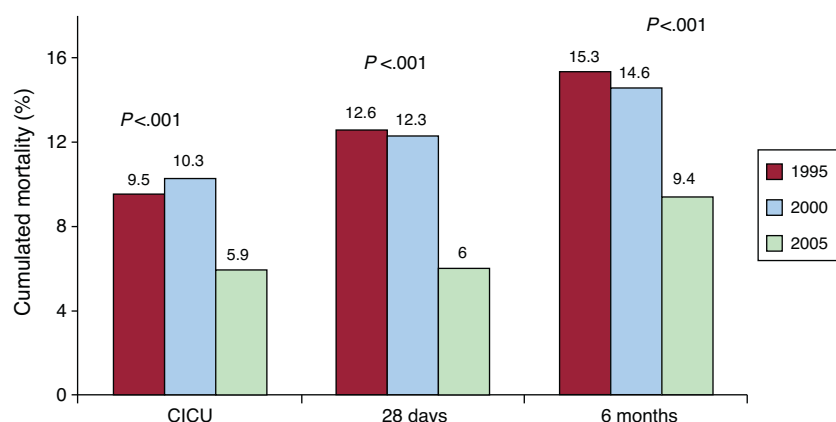

Figure 1. Cumulated mortality in the cardiac intensive care unit, at 28 days and at 6 months for patients with ST-segment elevation acute myocardial infarction, admitted to the cardiac intensive care unit, included in 1995, 2000 and 2005 in the PRIAMHO I, PRIAMHO II and MASCARA registers, respectively (P-trend). CICU, cardiac intensive care unit.

Table 3

Clinical Evolution for Patients With ST-Segment Elevation Acute Myocardial Infarction Admitted to the Cardiac Intensive Care Unit and Included in 1995, 2000 and 2005 in the PRIAMHO I, PRAIMHO II and MASCARA Registers, Respectively

	1995 (n=3516)	2000 (n=4080)	2005 (n=2353)	P-trend
Complications				
Maximum Killip class III/IV	475 (13.5)	654 (16.1)	265 (11.3)	.078
AMI relapse	118 (3.4)	97 (2.4)	66 (2.8)	.133
post-AMI angina	323 (9.2)	322 (8.0)	273 (11.6)	.008
Primary VF	191 (5.4)	259 (6.5)	147 (6.2)	.145
Sustained VT	322 (9.2)	133 (3.3)	171 (7.3)	<.001
Advanced AVB in CICU	207 (5.9)	295 (7.4)	150 (6.4)	.293
Atrial fibrillation	307 (8.7)	324 (8.1)	90 (3.8)	<.001
Mechanical complications	119 (3.4)	131 (3.3)	26 (1.1)	<.001
Mortality	333 (9.5)	419 (10.3)	139 (5.9)	<.001

AMI, acute myocardial infarction; AVB, atrioventricular block; CICU, cardiac intensive care unit VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 4

Determining Factors for 28-Day and 6-Month Mortality for Patients With ST-Segment Elevation Acute Myocardial Infarction, Admitted to the Cardiac Intensive Care Unit and Included in 1995, 2000 and 2005 in the PRIAMHO I, PRAIMHO II and MASCARA Registers, Respectively

	Survivors (n=8863)	Death within 28 days (n=1086)	P
Age, years	62.8 ± 12.7	72.7 ± 10.7	<.001
Female	1798 (20.3)	407 (37.5)	<.001
Risk factors			
Diabetes mellitus	2045 (23.1)	384 (35.4)	<.001
Tobacco use	4108 (46.4)	274 (25.3)	<.001
Hyperlipidemia	3320 (37.5)	292 (26.9)	<.001
Hypertension	3785 (42.7)	518 (47.7)	.002
Clinical characteristics			
Previous heart attack	1040 (11.7)	187 (17.2)	<.001
History of revascularization	403 (4.5)	55 (5.1)	.484
Q-wave heart attack	7572 (85.5)	966 (89.1)	.001
Anterior AMI vs others	3930 (46.7)	586 (56.6)	<.001
Symptom-monitoring time	120 [60-246]	164 [65-384]	<.001
Maximum Killip class III/IV	688 (7.8)	706 (65.4)	<.001
AMI relapse in CICU	202 (2.3)	79 (7.3)	<.001
Post-AMI angina in CICU	827 (9.4)	91 (8.4)	.318
Treatments and procedures			
Thrombolysis and/or PTCA	5961 (67.3)	567 (52.3)	<.001
Time to reperfusion			
<3 h	2387 (31.6)	171 (17.6)	<.001
3-6 h	1659 (22.0)	181 (18.6)	
>6 h-12 h	487 (6.4)	80 (8.2)	
No reperfusion or >12 h	3024 (40.0)	542 (55.6)	
Antiplatelet agents in CICU	8472 (95.7)	909 (83.8)	<.001
Clopidogrel in CICU	1674 (29.0)	77 (12.1)	<.001
GPIIb-IIIa antagonists in CICU	1047 (18.1)	62 (9.7)	<.001
UFH in CICU	4699 (53.3)	510 (47.1)	<.001
LMWH in CICU	3115 (54.5)	244 (38.6)	<.001
Betablockers in CICU	4715 (54.7)	184 (17.5)	<.001
ACEI/ARB-II in CICU	3874 (45.0)	298 (28.3)	<.001
Lipid lowering drugs in CICU	2353 (42.5)	74 (12.2)	<.001
Coronary angiography in CICU	1693 (19.2)	177 (16.4)	.025

ACEI, angiotensin-converting enzyme inhibitors; AMI, acute myocardial infarction; ARB-II, angiotensin II receptor blockers; CICU, cardiac intensive care unit; GPIIb/IIIa, glycoproteins IIb/IIIa; LMWH, low molecular weight heparin; PTCA, percutaneous transluminal coronary angioplasty; UFH, unfractionated heparin.
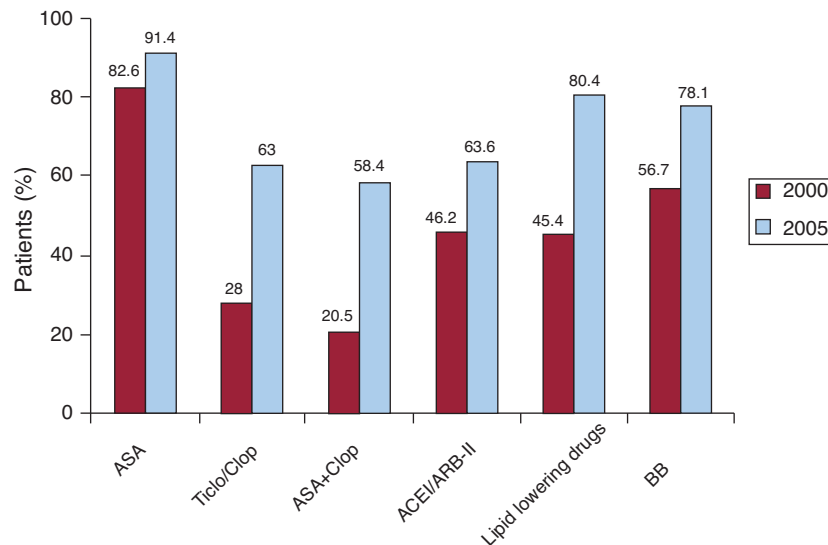Data are expressed as no. (%), mean ± standard deviation or median [interquartile range].

Figure 2. Treatment upon discharge from the hospital for patients with ST-segment elevation acute myocardial infarction, admitted to the cardiac intensive care unit, included in the PRIAMHO II and MASCARA registers respectively in 2000 and 2005 (this data was not included in 1995). All differences reached statistical significance ($P < .001$). ACEI/ARB-II, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; ASA, acetylsalicylic acid; BB, beta-blockers; Ticlo/Clop, Ticlopidine/clopidogrel.

that the protective effect for 2005, compared to that of 2000, stops being significant when adjusting for antiplatelet, BB and lipid lowering drug prescription upon discharge, maintaining the adjustment for other potential confounding factors. Models 3 and 5 also showed that reperfusion therapy significantly reduced mortality. On the other hand, the independent variables that increased mortality were: age, diabetes mellitus, and Killip class III/IV (maximum during hospital stay).

DISCUSSION

Our analysis shows a reduction in mortality for STEMI patients at 28 days and 6 months, from 1995 to 2005, considering crude mortality and mortality adjusted for confounding factors.

The risk of dying at 28 days in 2005 was 38% less than in 1995, which coincides with the results of other hospital registries.[1,2,15] This mortality reduction can mainly be explained because

Table 5

Odds Ratio and 95% Confidence Interval of 28-Day Mortality for the Admission Period Adjusted for Potentially Confounding Demographic, Clinical and Treatment Factors for Patients With ST-Segment Elevation Acute Myocardial Infarction

	Model 1	Model 2	Model 3	Model 4
Period				
1995	Reference	Reference	Reference	Reference
2000	0.86 (0.75–0.99)	0.88 (0.76–1.02)	0.78 (0.66-0.93)	1.15 (0.96-1.39)
2005	0.43 (0.35-0.53)	0.45 (0.37–0.56)	0.33 (0.25-0.43)	0.62 (0.44-0.88)
Adjustment variables				
Age	1.07 (1.07-1.08)	1.07 (1.06–1.08)	1.06 (1.05-1.07)	1.05 (1.04-1.06)
Female sex	1.47 (1.27-1.71)	1.44 (1.25–1.67)	1.25 (1.04-1.50)	1.28 (1.06-1.55)
Diabetes mellitus	1.41 (1.22-1.63)	1.38 (1.20–1.59)	1.06 (0.89-1.26)	1.12 (0.93-1.35)
AHT	0.91 (0.80-1.04)	0.92 (0.80–1.05)	0.79 (0.67–0.93)	0.94 (0.79-1.12)
Previous AMI/ revascularization.	1.43 (1.21-1.70)	1.46 (1.23–1.73)	1.12 (0.91-1.38)	1.16 (0.93-1.44)
Q-wave heart attack	–	1.51 (1.23–1.87)	1.33 (1.04-1.70)	1.36 (1.05-1.76)
Primary thrombolysis/reperfusion.	–	0.73 (0.64–0.84)	0.77 (0.65-0.91)	0.84 (0.70-0.99)
Anterior AMI	–	–	1.19 (1.02–1.40)	1.58 (1.33-1.87)
Max. Killip class III/IV	–	–	17.64 (14.99-20.75)	16.8 (14.0-20.1)
ASA/Clopidogrel/ GPIII/IV antagonists in CICU				0.38 (0.28-0.5)
UFH/LMWH in CICU				0.67 (0.56-0.82)
Betablockers in CICU				0.48 (0.39-0.59)
ACEI/ARB-II in CICU				0.35 (0.29-0.43)
Model deviance	5491.9	5466.1	4201.2	3927.7
P^*		<.001	<.001	<.001

ACEI, angiotensin-converting enzyme inhibitors; AHT, arterial hypertension; AMI, acute myocardial infarction; ARB-II, angiotensin II receptor blockers; ASA, acetylsalicylic acid; CICU, cardiac intensive care unit; GPIII/IV, glycoproteins III/IV; LMWH, low molecular weight heparin; UFH: unfractionated heparin.
* Compared with the 2000 model.

Table 6

Determining Factors for 28-Day-6-Month Mortality for Patients With ST-Segment Elevation Acute Myocardial Infarction, Admitted to the Cardiac Intensive Care Unit and Included in 1995, 2000 and 2005 in the PRIAMHO I, PRIAMHO II and MASCARA Registers (Survivors at 28 Days)

	Survivors (n=8652)	Death between 28 days and 6 months (n=211)	P
Age, years	62.6 ± 12.6	72.4 ± 10.8	<.001
Female sex	1736 (20.1)	62 (29.4)	.001
Risk factors			
Diabetes mellitus	1971 (22.8)	74 (35.1)	<.001
Tobacco use	4047 (46.8)	61 (28.9)	<.001
Hyperlipidemia	3258 (37.7)	62 (29.4)	.017
Hypertension	3665 (42.4)	120 (56.9)	<.001
Clinical characteristics			
Previous heart attack	1002 (11.6)	38 (18.0)	.006
History of revascularization	395 (4.6)	8 (3.8)	.713
Q-wave heart attack	7398 (85.6)	174 (82.5)	.242
Anterior AMI vs others	3824 (46.6)	106 (52.5)	.113
Symptom-monitoring time	120 [60-244]	150 [76.5-304]	.016
Maximum Killip class III/IV	627 (7.27)	61 (28.9)	<.001
AMI relapse in CICU	191 (2.2)	11 (5.2)	.009
Post-AMI angina in CICU	796 (9.3)	31 (14.7)	.011
Treatments and procedures			
Thrombolysis/Primary reperfusion	5856 (67.7)	105 (49.8)	<.001
Time to reperfusion			
<3 h	2356 (32.0)	31 (16.4)	<.001
3 h-6 h	1620 (22.0)	39 (20.6)	
>6 h-12 h	476 (6.5)	11 (5.8)	
No reperfusion or >12 h	2916 (39.6)	108 (57.1)	
ASA upon discharge[*]	4922 (87.2)	96 (71.6)	<.001
Ticlopidine/Clopidogrel upon discharge[*]	2368 (42.0)	38 (28.4)	.002
Beta-blockers upon discharge[*]	3750 (66.5)	36 (26.9)	<.001
ACEI/ARB-II upon discharge[*]	3009 (53.3)	70 (52.2)	.869
Lipid lowering drugs upon discharge[*]	3388 (60.1)	41 (30.6)	<.001
Coronary angiopathy during hospital stay[*]	2745 (32.0)	49 (23.6)	.013

ACEI, angiotensin-converting enzyme inhibitors; AMI, acute myocardial infarction; ARB-II, angiotensin II receptor blockers; ASA, acetylsalicylic acid; CICU, cardiac intensive care unit.
Data are expressed as no. (%), mean ± standard deviation or median [interquartile range].
[*] Data only available for the 6443 patients included in PRIAMHO II and MASCARA.

compliance improved with the use of GPC, a factor that justified a risk reduction of 22% during 1990-2006 in the American National Registry of Myocardial Infarction.[7] This publication included the following variables: acetylsalicylic acid, BB and heparin during the first 24 h, and reperfusion during the recommended time period. Our data (Table 5) confirm these results, and further demonstrates the positive effect of early clopidogrel administration[16] and ACEI/ARB-II.[17,18] However, after adjusting for these factors and other confounding factors, patients admitted in 2005 showed a significantly lower mortality than those hospitalized in 1995, which suggests that other factors that have not been considered in the study may have taken effect. A similar result was obtained in a European register on acute coronary syndrome, which compared 30-day mortality in 2000 and 2004, an OR: 0.85 (0.73-0.99).[19] These findings force us to reconsider the factors to be measured in future registers. It would probably be useful to include ejection fraction, given its prognostic importance for AMI.

The lower mortality observed at 28 days remained at 6 months. Even adjusting for potential confounding factors, the risk reduced by 58% for patients admitted to hospitals in 2005, as compared with 2000. This is due to more acetylsalicylic acid, clopidogrel, BB and lipid lowering drugs being prescribed upon discharge (Table 7). This result was very similar to that recently published

by Bosch et al. in a hospital register for AMI patients with follow-up at 2 years.[20] This study also confirms the importance of applying GPC, although we have not observed ACEI/ARB-II to have a beneficial effect during the first six months, probably because not enough time has passed to observe whether they are the factor which reduces the risk of dying.[21] In fact, in the study cited above[20] the protective effect is observed at two years.

Clinical and Treatment Characteristics

A high percentage of STEMI patients have a history of hypertension and hyperlipidemia[1,2] as has occurred in our study. On the other hand, we have not observed an increase in the age of onset.[1,2,22] The percentage of women remains stable[1,2,22] and the incidence of heart failure and mechanical complications during the acute AMI phase has reduced as shown in other similar studies.[1,19,23]

The greatest differences with other registers seem to lie in patient treatment. In the MASCARA[12] study, the reperfusion therapy most used in Spain was thrombolysis (48%), followed by primary angioplasty (24.2%). At that time, angioplasty was frequently used in many countries in our area,[1,15,18,19] with

Table 7

Adjusted Hazard Ratio and 95 Confidence Interval of 6-Month Mortality for 28-Day Survivors for Each Period Studied

	Model 1	Model 2	Model 3	Model 4	Model 5
Period					
1995	Reference	Reference	Reference	–	–
2000	0.92 (0.68-1.25)	0.97 (0.71-1.31)	0.97 (0.72-1.32)	Reference	Reference
2005	0.40 (0.25-0.63)	0.42 (0.26-0.67)	0.4 (0.24-0.67)	0.42 (0.25-0.68)	0.71 (0.42-1.21)
Adjustment variables					
Age	1.07 (1.06-1.09)	1.07 (1.05-1.09)	1.07 (1.05-1.08)	1.07 (1.05-1.09)	1.05(1.03-1.07)
Female sex	0.93 (0.67-1.29)	0.90 (0.65-1.25)	0.79 (0.56-1.1)	0.79 (0.52-1.22)	0.81 (0.52-1.24)
Diabetes mellitus	1.57 (1.17-2.12)	1.54 (1.14-2.07)	1.42 (1.05-1.92)	1.39 (0.95-2.05)	1.35 (0.91-1.99)
AHT	1.43 (1.07-1.92)	1.42 (1.06-1.9)	1.36 (1.01-1.83)	1.35 (0.92-1.99)	1.39 (0.94-2.05)
AMI/revascularization	1.22 (0.85-1.75)	1.20 (0.83-1.72)	0.96 (0.66-1.4)	1.01 (0.63-1.64)	0.97 (0.59-1.69)
Q-wave heart attack	–	0.87 (0.6-1.26)	0.86 (0.58-1.26)	0.95 (0.56-1.60)	0.97 (0.57-1.64)
Primary thrombolysis/reperfusion	–	0.64 (0.48-0.86)	0.66 (0.49-0.88)	0.55 (0.38-0.81)	0.61 (0.42-0.89)
Anterior AMI	–	–	1.23 (0.92-1.64)	1.35 (0.93-1.96)	1.34 (0.92-1.95)
Maximum Killip class III/IV	–	–	3.59 (2.59-4.99)	3.58 (2.36-5.42)	2.64 (1.73-4.03)
ASA/clopidogrel upon discharge[a]	–	–	–	–	0.47 (0.3-0.74)
Beta-blockers upon discharge[a]	–	–	–	–	0.35 (0.22-0.55)
Lipid lowering drugs upon discharge[a]	–	–	–	–	0.54 (0.34-0.86)
Model deviance	3250.8	3241.1	3188.3	1771	1722.7
P[b]		.008	<.001	–	<.001

AHT: arterial hypertension; AMI: acute myocardial infarction; ASA, acetylsalicylic acid.

[a] We are unable to compare this data with 1995 as treatment upon discharge data was not collected in that year.

[b] Compared with the previous model.

percentages from 39% to 72%. The median door-to-balloon time increased 15 min between 2000 and 2005, when the general tendency is for it to decrease.[15,19] That is why experiments conducted in Spain are interesting, for example in study from Mingo et al.[24] the door-to-needle time was reduced by 30 min, because the emergency transport staff was able to diagnose and advise the cardiologist of the patient's conditions. The door-to-needle time reduced in Spain in 1995-2005, although the median in 2005 was 43 min, more than the maximum of 30 min recommended by the GPC and more than other times published.[19] Furthermore, the number of non-revascularized patients in our environment continues being around 30%, as occurs in the GRACE register,[1] which is clearly an excessive figure. These data, which confirm those previously reported by García et al,[25] prove that organizational measures need to be implemented to improve health care. In this respect, primary angioplasty networks are a safe option in Spain.[26]

Administering coadjuvant drugs recommended by the GPC has improved in the CICU and upon discharge, although its use is 5%-15% lower than in other countries,[22] except for acetylsalicylic acid.

Study Limitations

The data analyzed are obtained from registers, meaning that we are unable to ensure that the sample is totally representative of Spanish hospitals, as only a small percentage of hospitals have participated. However, since hospitals were selected randomly, this limitation is weakened. Furthermore, the sensitivity analysis performed with patients from the hospitals that participated in the three registers (3892 patients) confirms the overall results. However, we are unable to guarantee that we have included all possible mortality-related factors. As such, despite having adjusted for the main determining prognostic variables, we continued to observe lower risk of dying at 28 days in 2005 than in 1995 (Table 5). This could be indicative of the confounding factors that were produced in 2005 and that were not included in the analysis.

We have studied STEMI patients admitted to the CICU, without analyzing patients attended to in other hospital areas, which could be more severe and have different treatment use rates. Furthermore, the study has not considered the patients' possible drug contraindications.

The oldest registers do not include variables that have proven interesting in later research projects. For example, the PRIAMHO I did not include data on drugs administered upon discharge.

Finally, the way that some of the variables are defined has changed over time: hypertension, hyperlipidemia, diabetes, AMI, etc., which could explain some of the changes observed. Although this limitation is common in publications of this type, the recent study by Roger et al.[22] shows that the advent of troponin in heart attack diagnosis in 2000 has not changed the trend to lower early mortality or 5-year mortality for AMI during the past two decades. As such, mortality analyses continued to have similar results with higher classic markers, with or without increased troponins. Therefore, the new AMI definition does not mean including AMI patients with a better prognosis.

CONCLUSIONS

Early and six-month mortality for STEMI patients admitted to the CICU substantially reduced in Spain between 1995 and 2005. The therapeutic factors related to these results are increasing reperfusion and using more anti-thrombotic drugs, BB, ACEI and lipid lowering drugs in the CICU, and antiplatelet agents, BB and lipid lowering drug upon discharge. All of these therapies are type I recommendations in the GPC. Nonetheless, the factors examined do not completely explain why mortality has reduced in the acute phase.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Fox KAA, Steg PG, Eagle KA, Goodman SG, Anderson FA, Granger ChB. et al.; for the GRACE Investigators. Decline in rates of death and heart failure in acute coronary syndromes, 1999-2006. JAMA. 2007;297:1892–900.
2. Rogers WJ, Frederick PD, Stoehr E, Canto JG, Ornato JP, Gibson M, et al. Trends in presenting characteristics and hospital mortality among patients with ST elevation and non-ST elevation myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. Am Heart J. 2008;156:1026–34.
3. Yeh RW, Sydney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med. 2010;362:2155–65.
4. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, et al. ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2008;51:210–47.
5. Van de Werf F, Bax G, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, et al. Guía de práctica clínica de la Sociedad Europea de Cardiología (ESC). Manejo del infarto agudo de miocardio en pacientes con elevación persistente del segmento ST [versión corregida 22-7-2009]. Rev Esp Cardiol. 2009;62:e1–47.
6. Fonarow GC, Gawlinski A, Moughrabi S, Tillisch JH. Improved treatment of coronary heart disease by implementation of a Cardiac Hospitalization Atherosclerosis Management Program (CHAMP). Am J Cardiol. 2001;87:819–22.
7. Peterson ED, Shah BR, Parsons L, Pollack CV, French WJ, Canto JG, et al. Trends in quality of care for patients with acute myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. Am Heart J. 2008;156:1045–55.
8. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet. 2003;361:13–20.
9. Widimsky P, Wijns W, Fajadet J, De Belder M, Knot J, Aaberge L, et al.; on behalf of the European Association for Percutaneous Cardiovascular Interventions. Reperfusion therapy for ST elevation acute myocardial infarction in Europe: description of the current situation in 30 countries. Eur Heart J. 2010;31:943–57.
10. Cabadés A, López-Bescos L, Arós F, Loma-Osorio A, Bosch X, Pabón P, et al.; investigadores del estudio PRIAMHO. Variabilidad en el manejo y pronóstico a corto y medio plazo del infarto de miocardio en España: el estudio PRIAMHO. Rev Esp Cardiol. 1999;52:767–75.
11. Arós F, Cuñat J, Loma-Osorio A, Torrado E, Bosch X, Rodríguez JJ, et al. Tratamiento del infarto agudo de miocardio en España en el año 2000. El estudio PRIAMHO II. Rev Esp Cardiol. 2003;56:1165–73.
12. Ferreira-González I, Permanyer-Miralda G, Marrugat J, Heras M, Cuñat J, Civeira E. en representación de los investigadores del estudio MASCARA. Estudio MASCARA (Manejo del Síndrome Coronario Agudo. Registro Actualizado). Resultados globales. Rev Esp Cardiol. 2008;61:803–16.
13. Report of the Joint International Society and Federation of Cardiology/World Health Organization Task Force on standardization on clinical nomenclature. Nomenclature and criteria for diagnosis of ischemic heart disease. Circulation. 1979;59:607–9.
14. The Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined. A consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol. 2000;36:959–69.
15. Radovanovic D, Erne P. AMIS Plus: Swiss registry of acute coronary syndrome. Heart. 2010;96:917–21.
16. López-Sendón J, Dabbous OH, López de Sá E, Stiles M, Gore JM, Brieger D, et al. Evolución hospitalaria asociada al empleo de fibrinolíticos y tienopiridinas en pacientes con infarto agudo de miocardio y elevación del segmento ST. The Global Registry of Acute Coronary Events. Rev Esp Cardiol. 2009;62:501–9.
17. Dauerman HL, Lessard D, Yarzebski J, Furman MI, Gore JM, Goldberg RJ. Ten-year trends in the incidence, treatment, outcomes of Q-wave myocardial infarction. Am J Cardiol. 2000;86:730–5.
18. Schiele F, Meneveau N, Seronde MF, Descotes-GenonV, Oettinger J, Ecarnot F, et al.; on behalf of the 'Reseau de Cardiologie de Franche Comte'. Changes in management of elderly patients with myocardial infarction. Eur Heart J. 2009;30:987–94.
19. Mandelzweig L, Battler A, Bokyo V, Bueno H, Danchin N, Filippatos G, et al. The second Euro Heart Survey on acute coronary syndromes: characteristics, treatment, and outcome of patients with ACS in Europe and the Mediterranean Basin in 2004. Eur Heart J. 2006;27:2285–93.
20. Bosch D, Masiá R, Sala J, Vila J, Ramos R, Elosua R, et al. Impacto de la apertura de un nuevo laboratorio de hemodinámica sobre la supervivencia a 30 días y a 2 años en los pacientes con infarto de miocardio. Rev Esp Cardiol. 2011;64:96–104.
21. Yusuf S, Pogue J. ACE inhibition in stable coronary artery disease. N Engl J Med. 2005;352:937–8.
22. Roger VL, Weston SA, Gerber Y, Killian JM, Dunlay SM, Jaffe AS, et al. Trends in incidence, severity, and outcome of hospitalized myocardial infarction. Circulation. 2010;121:863–9.
23. Figueras J, Alcalde O, Barrabés JA, Serra V, Alguersuari J, Cortadellas J, et al. Changes in hospital mortality rates in 425 patients with acute ST-elevation myocardial infarction and cardiac rupture over a 30-year period. Circulation. 2008;118:2783–9.
24. Mingo S, Goicolea J, Nombela L, Sufrate E, Blasco A, Millán I, et al. Angioplastia primaria en nuestro medio. Análisis de los retrasos hasta la reperfusión, sus condicionantes y su implicación pronóstica. Rev Esp Cardiol. 2009;62:15–22.
25. García-García C, Sanz G, Valle V, Molina LL, Sala J, Subirana I, et al. Evolución de la mortalidad intrahospitalaria y el pronóstico a 6 meses de los pacientes con un primer infarto agudo de miocardio. Rev Esp Cardiol. 2010;63:1136–44.
26. Estévez-Loureiro R, Calviño-Santos R, Vázquez JM, Barge-Caballero E, Salgado-Fernández J, Piñeiro M, et al. Seguridad y viabilidad del retorno precoz de pacientes transferidos para angioplastia primaria a sus centros de origen. Rev Esp Cardiol. 2009;62:1356–64.