ISCHEMIC HEART DISEASE

Trends in the Proportion of Patients Younger than 75 Years with Acute Myocardial Infarction and Killip Class III and IV. Variables Associated with Occurence and Case-Fatality: 1978-1997

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Introduction. Acute pulmonary edema (Killip III) or cardiogenic shock (Killip IV) is associated with a higher mortality in the acute phase of myocardial infarction (AMI).

Objectives. To analyze trends in the proportion of patients who developed Killip III and IV in AMI over a 20-year period in order to identify the variables associated with occurrence and case-fatality.

Methods. Hospital registry of first AMI in patients under than 75 years, from 1978 to 1997. Sociodemographic variables, cardiovascular risk factors, clinical variables, treatments, procedures, and worst Killip class were recorded.

Results. The registry included 2,590 patients. Mean age was 60 years and 17% were women. Thirteen percent (13.5%) of the patients developed Killip III and IV, and no changes in this proportion were observed over the time period studied. Age, diabetes, previous angina, and anterior location of AMI were associated with a higher risk of Killip III and IV. Case-fatality at 28 days in this subgroup was 51.7%, with a decreasing linear trend over the years. Variables associated with a higher case-fatality were age and malignant ventricular arrhythmias, whereas the periods 1990-93 and 1994-97 were associated with a lower case-fatality. This protective effect disappeared after adjusting for treatment variables (antiplatelet agents and thrombolysis).

Conclusions. The proportion of patients with AMI in which Killip class III and IV develops has remained stable in the last two decades. Although the 28-day case-fatality in these patients is high, a decrease has been observed in recent years in relation to the availability of new treatments (antiplatelet agents and thrombolysis).

Key words: *Pulmonary edema. Epidemiology. Myocardial infarction. Prognosis. Shock.*

SEE EDITORIAL ON PAGES 1111-3

This study was financed by the grants FIS-90/0672, FIS-93/0568, FIS-96/0026/001, CIRIT/1997 SGR 00218.

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Reeived 11 de March 2002.
Acepted for publication 14 de june 2002.

Tendencias en la proporción de pacientes menores de 75 años con infarto agudo de miocardio que presentan Killip III-IV. Variables asociadas con su aparición y con el pronóstico: 1978-1997

Introducción. La aparición de edema agudo de pulmón (Killip III) o shock cardiogénico (Killip IV) en la fase aguda del infarto de miocardio (IAM) se asocia con peor pronóstico.

Objetivos. Analizar la tendencia en la proporción de pacientes que presentan Killip III-IV en la fase aguda del IAM en un período de 20 años; determinar qué variables se asocian con su aparición y cuáles con la letalidad.

Métodos. Registro hospitalario de primeros IAM, menores de 75 años, del período 1978-1997. Se han recogido variables sociodemográficas, antecedentes de factores de riesgo, tratamientos, procedimientos realizados y el peor Killip durante el ingreso.

Resultados. Se incluyó a 2.590 pacientes, con una edad media de 60 años, un 17% mujeres. El 13,5% de los casos presentó un Killip III-IV, sin cambios lineales en esta proporción durante el período estudiado. La edad, la diabetes, la angina previa y el infarto de localización anterior se asociaron con un mayor riesgo de Killip III-IV. La mortalidad de estos pacientes fue del 51,7% y se observó una tendencia lineal decreciente a lo largo del tiempo. Las variables asociadas con una mayor mortalidad en este subgrupo fueron la edad y las arritmias ventriculares malignas, los períodos 1990-1993 y 1994-1997 se asociaron con una menor letalidad. Este efecto protector desaparecía al ajustar por variables de tratamiento (trombólisis y antiagregantes plaquetarios).

Conclusiones. La proporción de IAM que presentan Killip III-IV en las últimas 2 décadas se mantiene estable. Aunque la letalidad de estos pacientes es alta, se observa un descenso en los últimos años, que se explica por el tratamiento.

Palabras clave: *Edema. Epidemiología. Infarto de miocardio. Pronóstico. Shock.*

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ABBREVIATIONS

AMI: acute myocardial infarction
WHO: World Health Organization
CPK: creatinphosphokinase
PAI: platelet aggregation inhibitors
ASA: acetylsalicylic acid
OR: odds ratio
CI: confidence interval

INTRODUCTION

The Killip classification[1] is extremely useful in clinical practice and is widely used to establish the level of disease severity in patients with acute coronary syndromes. The presence of acute pulmonary edema (Killip III) or cardiogenic shock (Killip IV) is associated with a higher mortality rate in patients with acute myocardial infarction (AMI), and is the variable most strongly associated with death at 28 days.[2]

In several studies the presence of Killip classification III to IV has been associated with a series of socio-demographic and clinical characteristics, occurring most frequently in older people, women with anterior infarcts, and patients with a history of hypertension or diabetes.[3,4] On the other hand, it has been noted in some studies that there is a stable temporal tendency in patients with AMI who present with cardiogenic shock.[5,6]

The introduction of new therapeutic measures in recent years such as reperfusion,[6] early resvascularization,[7,8] or aortic contrapulsation balloon9 has meant a decrease in the mortality rate in this subgroup of patients.

The objectives of this study were to analyze, from 1978 to 1997, the percentage of patients with an initial AMI who present with Killip III to IV during their hospital stay, to determine the factors associated with presenting with level Killip III to IV as related to disease severity, and to analyze the variables associated with higher mortality at 28 days in this subgroup of patients.

MATERIAL AND METHODS

The REGICOR study was begun in 1978 as a hospital register that included all patients who presented with an AMI and were admitted to the only certified hospital in the province of Gerona.[10] From 1998 on, this study comprised the entire population,[11] and all patients with an AMI who resided in the province of Gerona from any hospital in the city or in Barcelona were registered, and all suspected cases of AMI and patients who died outside these hospitals were also registered. In this study, we have only selected those patients younger than 75 years of age with a first AMI who were seen at the hospital in question (hospital Josep Trueta) during the period from 1978 to 1997.

Patient selection

We prospectively registered all patients admitted to the coronary care unit of the Josep Trueta hospital, and we also reviewed the list of patients discharged from this hospital who had a diagnosis of AMI in order to include those cases who were not admitted to the unit. The diagnosis of AMI was based on the established criteria of the World Health Organization (WHO)[12] which specifies the appearance of abnormal Q-waves on electrocardiogram or the presence of a minimum of 2 of the following criteria: electrocardiogram showing signs of ischemia, an increase in cardiac enzymes (creatinphosphokinase [CPK] of more than double the upper limit of normal or a myocardial fraction of total CPK greater than 10%), or typical chest pain lasting for more than 20 minutes.

Variables collected

We recorded socio-demographic variables, the clinical characteristics of the event, history of risk factors and angina, treatments and procedures used during admission, and the complications that presented during the first 28 days.

Similarly, we noted the Killip classification and the maximum level reached during hospital admission. We defined five 4-year periods for analyzing the temporal tendency over the 20 years of the study (1978 to 1981, 1982 to 1985, 1986 to 1989, 1990 to 1993, and 1994 to 1997).

Follow-up

In order to evaluate mortality at 28 days, we compiled information concerning the vital statistics on the patients included in the study from the Registro de Mortalidad de Cataluña (Catalonian Mortality Register).

Statistical analysis

We used the Student t test or variance analysis to compare the continuous variables between the groups, and the χ^2 test for comparing percentages between the groups and to evaluate linear tendency during the various periods. In order to study the risk of death in patients classified as Killip III-IV, adjusted for possible confounding factors, we used logistical regression analysis.

In order to establish which variables might be confounding, we considered differences to be statistically

TABLE 1. **Characteristics of patients with acute myocardial infarction (AMI) admitted from 1978 to 1997 according to Killip classification**

	Killip I-II (n=2231)	Killip III-IV (n=348)	*P*
Women, %	14.5	32.2	<.001
Age, years	59.55	64.09	<.001
Smokers, %	58.4	43.2	<.001
AHT, %	47.2	50.0	.007
Dyslipemia, %	40.2	40.9	.432
Diabetes, %	20.8	37.6	<.001
History of dyspnea, %	1.5	13.7	<.001
History of angina, %	48.0	62.3	<.001
Anterior AMI anterior, %	43.9	61.2	.003
PAI, %	47.0	46.8	.496
Beta-blockers, %	16.5	3.8	<.001
Thrombolysis, %	23.6	12.4	<.001
Catheterization, %	21.3	16.4	.003
Revascularization, %	2.0	4.0	.029
Post-AMI angina, %	22.0	26.6	.088
Re-AMI, %	1.8	5.4	<.001
Serious arrhythmias, %	11.9	36.5	<.001
Death, %	4.9	51.7	<.001

AHT indicates arterial hypertension; PAI, platelet aggregation inhibitors.

significant when the $P<.05$ on bivariate analysis. Our calculations were performed with the SPSS program, version 9.0.

RESULTS

During the study period, 2590 cases of first AMI in patients of younger than 75 years of age were admitted, of which 16.9% were women with an mean age of 60.18 years ±9.94 years. Of the cases of AMI, 13.5% presented with a Killip grade of III or IV at hospital admission: of these, 7.6% presented with acute pulmonary edema and 5.9% with cardiogenic shock. The Killip data for 11 patients (0.4%) was unknown.

The clinical characteristics, history of risk factors, treatment administered, and AMI complications grouped by Killip grade (Killip I to II vs Killip III to IV) are shown in Table 1. The patients who presented with Killip III to IV were older; were more likely to be women; had a higher rate of a history of diabetes, hypertension, dyspnea, angina, and/or anterior infarct; and involved a lower percentage of smokers. This subgroup of patients received less thrombolitic and beta-blocker treatment, and less coronary angiography imaging, but more revascularization procedures were performed on

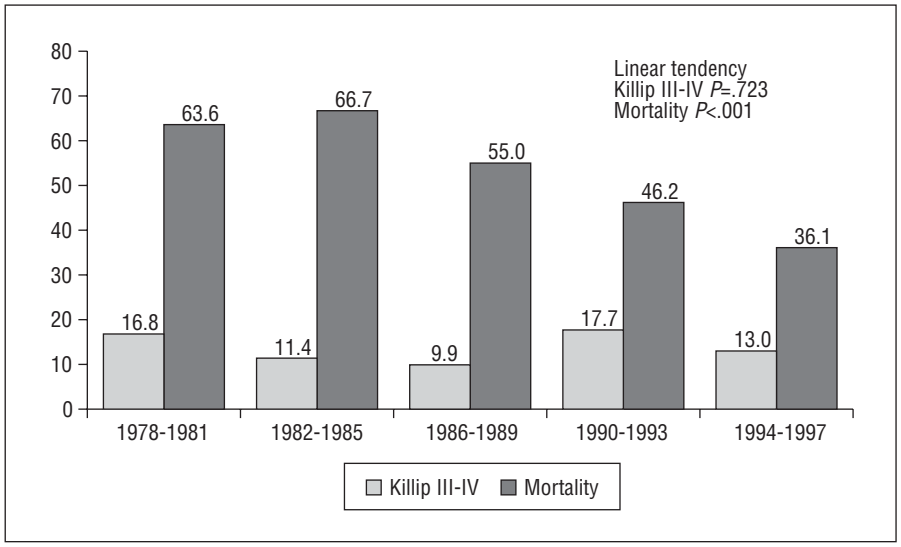

Fig. 1. Proportion of patients with a first acute myocardial infarction (AMI) who presented with Killip classification III to IV during hospital admission and mortality at 28 days in this group of patients during the various defined periods.

TABLE 2. **Variables associated with the presence of Killip III to IV during hospital admission in patients with a first acute myocardial infarct (AMI). Multivariate analysis**

	OR	95% CI
Women	1.45	0.97-2.18
Age, year	1.04	1.02-1.06
Diabetes	1.62	1.11-2.35
Angina	1.53	1.07-2.18
Anterior AMI	1.62	1.15-2.30
Period from 1978 to 1981	1	-
Period from 1982 to 1985	0.65	0.35-1.19
Period from 1986 to 1989	0.62	0.35-1.12
Period from 1990 to 1993	1.24	0.73-2.12
Period from 1994 to 1997	0.79	0.44-1.42

OR indicates odds ratio; CI, confidence interval.

the patients in this group. Similarly, this group of patients had more complications in the acute phase, and a larger percentage of re-infarct and serious ventricular arrhythmias (sustained ventricular tachycardia or ventricular fibrillation). More than half the patients with a Killip classification of III to IV died within the first 28 days (51.7%; 95% confidence interval [CI], 46.5% to 57.0%). We observed a decreasing linear tendency of mortality during the duration of the study (Figure 1). Although we did not observe a linear tendency with regard to the percentage of patients with Killip III to IV within the period analyzed (*P*=.723) (Figure 1), there were statistically significant differences between the percentages among the various periods studied (1978 to 1981, 16.8% [95% CI, 12.8% to 20.9%]; 1982 to 1985, 11.4% [95% CI, 8.6% to 14.1%]; 1986 to 1989, 17.7% [95% CI, 14.7% to 20.8%]; 1990 to 1993, 13.0% [95% CI, 10.2% to 15.8%]; 1994 to 1997: 13.5% [95% CI, 12.2% to 14.8%]). It is worth pointing out the direct relationship between Killip classification and mortality: patients with Killip I, II, III, and IV had a mortality rate of 4.3%, 7.1%, 30.5%, and 79.5%, respectively.

Table 2 shows the logistical regression model used to analyze the variables associated with the classification of Killip III to IV during hospital admission, including the 5 distinct periods analyzed (1978 to 1981, 1982 to 1985, 1986 to 1989, 1990 to 1993, and 1994 to 1997). The independent variables associated with the presence of Killip III to IV were age, history of diabetes or angina, and anterior location of the infarct. We did not observe an association with the various periods studied. We also did not find a relationship between the periods studied and the different variables associated with the risk of presenting with Killip III to IV.

When we analyzed the subgroup of patients with Killip III to IV over the 5 time periods, we observed a decrease in the percentage of patients with hypertension, dyslipemia, and a history of angina, and an increase in the percentage of patients with diabetes. The clinical treatment of these patients was notable for an increase in the use of thrombolysis, aspirin, and beta-blockers, in addition to an increase in of coronary angiography imaging. We also observed a significant crude decrease in the mortality rate of this subgroup of patients (Table 3; Figure 1). The mortality rate at 28

TABLE 3. **Characteristics of patients with acute myocardial infarct (AMI) and Killip grade III to IV treated in the hospital during various time periods**

	1978 to 1981 (n=55)	1982 to 1985 (n=57)	1986 to 1989 (n=60)	1990 to 1993 (n=104)	1994 to 1997 (n=72)	*P*
Women, %	23.6	31.6	35.0	38.5	27.8	.332
Age, years	63.91	63.63	64.33	64.60	63.67	.932
Smokers, %	59.6	42.9	35.1	36.9	47.2	.052
AHT, %	66.7	60.7	45.0	47.6	38.0	.012
Dyslipemia, %	72.1	58.7	26.0	28.0	37.9	<.001
Diabetes, %	28.8	22.8	40.0	44.0	45.5	.031
History of dyspnea, %	–	–	10.8	14.6	13.9	.848
History of angina, %	75.0	54.2	64.3	69.6	41.9	.052
Anterior AMI, %	67.3	73.7	61.7	51.9	59.7	.077
PAI, %	–	–	28.3	79.4	88.9	<.001
Beta-blockers, %	–	–	3.3	4.1	9.9	.021
Thrombolysis, %	–	–	10.0	13.5	31.9	<.001
Catheterization, %	1.9	10.5	13.5	23.5	23.9	.002
Revascularization, %	–	3.5	1.7	6.3	9.1	.154
Post-AMI angina, %	–	–	33.3	21.6	30.3	.284
Re-AMI, %	9.1	1.8	6.8	5.1	4.6	.514
Serious arrhythmias, %	23.6	31.6	42.4	39.8	40.8	.167
Deaths, %	63.6	66.7	55.0	46.2	36.1	.002

AHT indicates arterial hypertension; PAI, platelet aggregation inhibitors.

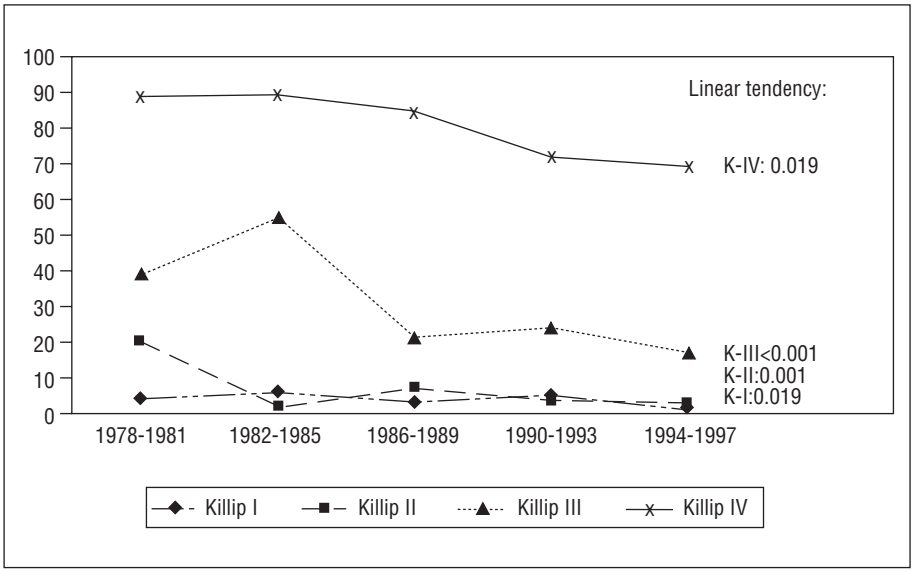

Fig. 2. Tendency for mortality in patients with a first acute myocardial infarction (AMI) according to Killip grade classification during hospital admission within the various defined time periods.

days for each Killip classification for the various defined periods is presented in Figure 2. We observed a decreasing linear tendency for death in all Killip classification groups.

In the subgroup of patients who presented with a Killip classification of III to IV, the mortality rate at 28 days was greater in older patients, patients with a history of angina, and patients who presented with serious ventricular arrhythmias (Table 4). On the other hand, in patients with a history of smoking and diabetes, Killip classification of III to IV was associated with a lower mortality rate at 28 days, and associated with the use of platelet aggregation inhibitors, beta-blockers, and thrombolysis (Table 4).

Table 5 presents 2 logistical regression models used to evaluate the association between the various time periods and mortality at 28 days in patients with Killip classification III to IV (n=348). The first model has been adjusted for the variables of personal history and clinical characteristics of acute myocardial infarct identified as confounding on bivariate analysis. Age and the presence of malign ventricular arrhythmias were associated with a higher mortality rate, while the more recent time periods studied were associated with a lower mortality rate. In the following model, this was observed as a decrease in significance of the time period on the mortality rate when adjusted for pharmacological treatment, with the use of platelet aggregation inhibitors (typically acetylsalicylic acid [ASA]) either in isolation or in combination with thrombolysis; these variables were most strongly associated with a decrease in the risk of death at 28 days.

When analyzing the independent variables associated with death in the subgroup of patients with Killip classification III and IV (data not presented), the results were similar to those presented in Table 5, and it is worth noting that in patients with cardiogenic shock the presence of malign ventricular arrhythmias was not associated with a higher mortality rate.

DISCUSSION

In our study we observed that 13.5% of patients younger than 75 years of age with a first AMI presented with Killip classification III to IV during hospital admission; this percentage did not change significantly during the 20 years of the study. On the other hand, the mortality rate of this group of patients was elevated (51.7%), but decreased over the course of the years

TABLE 4. **Characteristics of patients who presented with Killip classification III to IV during hospital admission according to their vital state at 28 days**

	Death		
	No (n=168)	Yes (n=180)	*P*
Women, %	32.1	32.2	.540
Age, years	63.00	65.11	.016
Smoking, %	49.1	37.6	.021
AHT, %	47.9	52.0	.257
Dyslipemia, %	38.5	43.3	.233
Diabetes, %	42.9	32.6	.032
History of dyspnea, %	11.7	16.3	.219
History of angina, %	54.5	68.9	.040
Catheterization, %	30.6	3.9	<.001
PAI, %	63.1	31.5	<.001
Beta-blockers, %	6.0	1.7	.037
Revascularization, %	4.9	3.2	.327
Thrombolysis, %	17.9	7.2	.002
Post-AMI angina, %	34.2	16.5	.004
Re-AMI, %	6.2	4.6	.345
Anterior AMI, %	56.5	65.6	.053
Serious arrhythmias, %	28.6	44.1	.002

ATH indicates arterial hypertension; PAI, platelet aggregation inhibitors.

TABLE 5. **Variables that were associated with mortality at 28 days in patients who presented with Killip classification III to IV during hospital admission**

	OR	95% CI
Model 1		
Women	0.92	0.50-1.68
Age	1.05	1.01-1.08
Smoking	0.63	0.35-1.11
Diabetes	0.67	0.40-1.11
Anterior AMI	1.29	0.79-2.12
Ventricular arrhythmias	2.37	1.43-3.91
Period from 1978 to 1981	1	–
Period from 1982 to 1985	1.02	0.45-2.32
Period from 1986 to 1989	0.56	0.25-1.27
Period from 1990 to 1993	0.37	0.17-0.77
Period from 1994 to 1997	0.28	0.12-0.63
Model 2		
Women	1.00	0.52-1.90
Age	1.04	1.01-1.08
Smoking	0.60	0.32-1.13
Diabetes	0.65	0.38-1.11
Anterior AMI	1.36	0.79-2.34
Ventricular arrhythmias	2.93	1.68-5.11
Period from 1978 to 1981	1	–
Period from 1982 to 1985	0.98	0.43-2.26
Period from 1986 to 1989	0.91	0.37-2.21
Period from 1990 to 1993	1.19	0.43-3.28
Period from 1994 to 1997	1.69	0.54-5.29
Aggregation inhibitors alone	0.18	0.08-0.42
Thrombolysis alone	0.75	0.13-4.34
Aggregation inhibitors+ thrombolysis	0.07	0.02-0.25
Beta-blockers	0.53	0.12-2.39

OR indicates odds ratio; CI, confidence interval; AMI, acute myocardial infarct.

studied, fundamentally due to the introduction of new therapies, namely, aspirin and its use in combination with thrombolysis. There are few studies that present the percentage of patients with Killip classification III to IV during hospital admission and the changes in these patients over time. The values observed in our study are consistent with the results from other studies performed in the Spanish population that showed a percentage of patients with Killip classification III to IV ranging from 11.1% to 26.4% according to geographic area and the study performed.[2,13] On an international scale, it has been observed that between 3% and 7% of patients present with Killip classification IV,[6,8,14] which puts the percentages from our study within the value range (5.9%). On the other hand, we did not observe a tendency for the percentage of patients with AMI who presented with Killip classification III to IV during the 20 years studied, which concurs with the results of other studies.6,14 Between 1978 and 1989, a decrease has been observed in the percentage of patients presenting with Killip classification III to IV, although this percentage begins to increase again in the periods from 1990 to 1993 and 1994 to1997; this increase may be related to better accessibility of hospital services in recent years.[15]

There is a series of variables associated with a higher risk of presenting with Killip classification III to IV in the acute phase of myocardial infarction. Women have a higher risk of presenting with signs of ventricular failure, which is one reason that explains, at least partially, the greater mortality rate in women.[16] In our register, we observed a greater risk of presenting with Killip classification III to IV in women that was only marginally significant (odds ratio [OR], 1.45; 95% CI, 0.97-2.18%). Other variables associated with a higher risk of presenting with Killip classification III to IV were age, diabetes, anterior location of the infarct, and a history of angina. These results concur with those observed in other studies.[4,17,18] The greatest risk factor of a history of angina in our study contrasts with evidence that angina occurring during the 48 hours prior to an AMI reduces the size of the infarct, preserving ventricular function after the AMI by means of a preconditioning phenomenon.[19] This apparent contradiction is probably explained by the fact that with our data we were not able to determine how long ago the angina had occurred.

The presence of Killip classification III or IV during the acute phase of a myocardial infarct is associated with an increased mortality rate (30.5% and 79.5%, respectively; 51.7% overall). In more recent series, the mortality rate during the acute phase of patients with cardiogenic shock ranged from 61% to 88%.[5,6,8,9,14,20] Upon analysis of this group of patients, a statistically significant linear tendency was observed to a decrease in the mortality rate during the period studied. Even after adjusting for confounding variables, a decreased mortality rate was observed for the periods from 1990 to 1993 and 1994 to1997 as compared with the period of 1978 to 1981. This association of decreased mortality is explained by the introduction of new therapies, namely, aggregation inhibitors and the thrombolitic agents. Beta-blockers are also associated with a decreased risk of death at 28 days but their use does not reach statistical significance, probably due to a lack of statistics and the fact that they were rarely used on this group of patients during the period studied.

Other variables that are associated with a higher mortality rate in this subgroup of patients were age and the presence of malign ventricular arrhythmias. Curiously, we did not observe an association between female sex and higher mortality rates, which is in agreement with the observations of other studies of patients with cardiogenic shock.[20] Therefore, although women have a higher risk of presenting with ventricular failure in the acute phase of a myocardial infarct, which is partially explained by the higher mortality rate in women, we did not observe a higher mortality rate in men who presented with Killip classification III

to IV. In patients with a history of diabetes this also occurs, as diabetes is associated with greater risk of presentation with Killip classification III to IV, although in this subgroup of patients those with diabetes did not have a worse prognosis.[21]

Study characteristics and limitations

One of the limitations of our study is that we did not follow patients of more than 74 years of age, although this group is one that comprises the highest number of patients with Killip classification III to IV and a higher mortality rate.[22] In addition, the aging of the population has produced an increase in the number of patients with AMI in this age group who have been admitted to Spanish hospitals in recent years.[23] Another limitation is that we did not collect data on the use of certain therapeutic measures, such as early revascularization or the use of an aortic contrapulsation balloon, which result in a decrease in the mortality rate in this subgroup of patients.[7-9]

CONCLUSION

The percentage of cases that present with Killip classification III to IV over the last 2 decades has remained stable. Although the mortality rate in this group of patients is high, there has been a decrease during recent years. This decrease is explained by the introduction of new treatment regimens.

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