Out-of-Hospital Treatment and 1-Year Survival in Patients With ST-Elevation Acute Myocardial Infarction. Results of the Spanish Out-of-Hospital Fibrinolysis Evaluation Project (PEFEX)

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Background and objectives. To investigate out-of-hospital treatment, including fibrinolysis, in patients with ST-elevation acute myocardial infarction and to determine the 1-year survival rate.

Methods. Prospective cohort study based on an ongoing out-of-hospital registry of patients with ST-elevation acute myocardial infarction who were treated by out-of-hospital emergency teams in Andalusia, Spain during 2001–2004. Patients were followed up in hospital and one year after the acute episode.

Results. The study involved 2372 patients. Out-of-hospital fibrinolysis was used in 467 (19.7%). Among these, 20.7% received treatment within the first hour, 68% within the first 2 hours, and 2 (0.4%) hemorrhagic strokes occurred. Episodes of ventricular fibrillation were recorded in 158 patients (6.7%), 106 (67%) of whom were discharged. In addition, 386 (16.3%) patients died in the short term (both out of and in hospital), with 26 (1.1%) dying before they reached hospital. The cumulative 1-year mortality rate was 22.4% (531 patients) overall, and 6.6% (29 patients) in the out-of-hospital fibrinolysis group. Increased survival at 1 year was associated with out-of-hospital fibrinolysis (odds ratio [OR]=0.368; 95% confidence interval [CI], 0.238–0.566) and percutaneous coronary intervention during admission (OR=0.445; 95% CI, 0.268–0.740).

Conclusions. In routine clinical practice, out-of-hospital fibrinolysis was performed safely, reduced short-term mortality, and improved the 1-year survival rate. The combination of appropriate out-of-hospital treatment, including early defibrillation and fibrinolysis within the first 3 hours, together with the systematic application of percutaneous coronary intervention during hospital admission is a suitable treatment strategy for the comprehensive care of patients with ST-elevation acute myocardial infarction.

Key words: *Acute myocardial infarction. ST-elevation. Ventricular fibrillation. Out-of-hospital treatment. Out-of-hospital fibrinolysis.*

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Tratamiento extrahospitalario y supervivencia al año de los pacientes con infarto agudo de miocardio con elevación de ST. Resultados del Proyecto para la Evaluación de la Fibrinólisis Extrahospitalaria (PEFEX)

Introducción y objetivos. Conocer el manejo extrahospitalario de los pacientes con infarto agudo de miocardio con elevación de ST y la aplicación de fibrinólisis extrahospitalaria y analizar la supervivencia de los pacientes al año.

Métodos. Estudio prospectivo de cohortes, sobre un registro extrahospitalario continuo de pacientes con infarto agudo de miocardio con elevación del segmento ST, atendidos por equipos extrahospitalarios de emergencia de Andalucía (España). Período 2001-2004. Se realizó seguimiento hospitalario y al año del evento agudo.

Resultados. Se incluyó a 2.372 pacientes. Se realizó fibrinólisis extrahospitalaria en 467 (19,7%) pacientes. Las realizadas en la primera hora fueron el 20,7% y en las primeras 2 h, el 68%, y se produjeron 2 (0,4%) ictus hemorrágicos. Se registraron episodios de fibrilación ventricular en 158 (6,7%) pacientes, de los que 106 (67%) recibieron el alta hospitalaria. La mortalidad inicial (extrahospitalaria y hospitalaria) fue 386 (16,3%) pacientes, 26 (1,1%) de ellos antes de llegar al hospital. La mortalidad acumulada al año fue 531 (22,4%) pacientes, 29 (6,6%) en el grupo que recibió fibrinólisis extrahospitalaria. La fibrinólisis extrahospitalaria (*odds ratio* [OR] = 0,368; intervalo de confianza [IC], 0,238-0,566) y el intervencionismo coronario percutáneo (ICP) realizado durante el ingreso hospitalario (OR = 0,445; IC, 0,268-0,740) se asociaron con mayor supervivencia al año.

Conclusiones. En la práctica habitual, la fibrinólisis extrahospitalaria se realiza de forma segura, disminuye la mortalidad inicial y mejora la supervivencia al año. La combinación de una atención extrahospitalaria adecuada, desfibrilación precoz y fibrinólisis en las primeras 3 h, junto con la realización sistemática de ICP durante el ingreso hospitalario, constituye una estrategia válida de atención integral para los pacientes con infarto y elevación de ST.

Palabras clave: *Infarto agudo de miocardio. Elevación de ST. Fibrilación ventricular. Atención extrahospitalaria. Fibrinólisis extrahospitalaria.*

ABBREVIATIONS

ihF: inhospital fibrinolysis
OHEMS: out-of-hospital emergency medical services
ohF: out-of-hospital fibrinolysis
PCI: percutaneous coronary intervention
STEMI: ST-elevation myocardial infarction

INTRODUCTION

The initial medical attention received by patients with ST-segment elevation acute myocardial infarction (STEMI) determines their final prognosis. A substantial proportion of deaths occur in the first hours following the onset of symptoms, usually out-of-hospital and before patients receive medical attention.[1,2] Immediate treatment of potentially fatal complications, primarity ventricular fibrillation (VF), together with the need to initiate reperfusion treatment quickly, has made out-of-hospital attention a basic recommendation in major clinical practice guidelines.[3,4] Moreover, it has contributed substantially to definitively consolidate the role of out-of-hospital emergency medical services (OHEMS) in the healthcare system. Out-of-hospital application of specific measures —monitoring and early defibrillation, 12-lead electrocardiography (ECG), aspirin administration and, in a more advanced phase, reperfusion treatment by intravenous fibrinolysis— has proved its efficacy in trials.[5-7]

Most data on management and survival of patients receiving out-of-hospital attention from emergency services come from hospital sources in studies that may not represent normal clinical practice. It is essential that we assess the degree of application and compliance with recommended measures and determine the true effectiveness of out-of-hospital fibrinolysis (ohF) in routine medical care of an unselected population such as that portrayed by clinical activity registers.

In a recent series, we analyzed out-of-hospital treatment of these patients in routine, OHEMS practice.[8] The present study considerably enlarges the initial cohort and completes the follow-up in order to analyze out-of-hospital treatment of STEMI and its possible impact on 1-year survival.

METHODS

Prospective cohort study, based on the Out-Of-Hospital Fibrinolysis Evaluation Project (PEFEX), an ongoing register of patients attended and diagnosed with STEMI by the OHEMS of EPES, a public company belonging to the regional government of Andalusia (Spain) and responsible for managing emergency services. The population and project methods are described elsewhere.[8]

The PEFEX register's objective is to provide quality control on out-of-hospital treatment of patients with STEMI. All patients diagnosed with STEMI are automatically included in a specific database, within the EPES general information system (PEFEX database).

The EPES OHEMS cover out-of-hospital emergencies in Andalusia and directly attend 70% of the regional population (7 750 000 inhabitants). Patients are admitted to 27 public health service hospitals of different levels and with a range of facilities. The same protocols are followed by all OHEMS,[8] although ohF was introduced progressively as agreements were reached with reference hospital coronary units.

The study lasted 3 years (January 2001 thru January 2004) with 1-year follow-up of individual patients.

We included all patients diagnosed with STEMI by the OHEMS. We defined STEMI as clinical signs and symptoms compatible with acute coronary syndrome and ECG changes compatible with acute myocardial ischemia; new or presumably new ST-segment elevation, measured from the J-point, in 2 or more contiguous leads, with a ≥0.2 mV cutoff point in V_1 through V_3 and ≥0.1 mV in the remaining leads.[3,4]

Out-of-hospital data were obtained from OHEMS clinical records, inhospital data from the corresponding discharge reports and "Rosell-Ortiz F et al. ST-elevation infarction: out-of-hospital treatment and 1-year survival follow-up" data through telephone (and/or postal) surveys, centralized thru a single questionnaire.

Variables Studied

We studied clinical, electrocardiographic and time variables corresponding to the acute episode, data on out-of-hospital treatment and its complications, and on

inhospital follow-up (diagnosis, treatment, and complications), at 1 month and 1 year (status and date of death of patients who died). We recorded reperfusion treatment: *a)* ohF, with drugs and guidelines followed: double bolus intravenous alteplase (rt-PA),[9] weight-adjusted dose single bolus intravenous tenecteplase (tnk-tpa)[10]; *b)* inhospital fibrinolysis (ihF); *c)* percutaneous coronary intervention (PCI), including any procedure performed during hospitalization for the acute episode (primary PCI, urgent PCI, programmed PCI).

Firstly, we considered ohF as a dependent variable. Secondly, we considered mortality a dependent variable, defining initial mortality (patients who died during out-of-hospital or inhospital attention for the acute episode) and 1-year mortality (patients who died at ≤1 year following onset of symptoms).

Quality Control of Data

The EPES conducts six-monthly internal audits on a randomized sample of clinical records of patients diagnosed with AMI. In addition, the regional government health department Evaluation and Quality Agency has been commissioned to conduct an external audit, (with responsibility for audit design and execution). We audited all patients enrolled in 2002 and compared variables selected by independent assessors drawn from EPES information system, out-of- and inhospital clinical records, basic inhospital records (CMBD) and the PEFEX database. The Evaluation Agency validated register quality and recommended its continued use as a quality tool.

Statistical Analysis

We conducted descriptive analysis of quantitative variables using measures of centricity and dispersion and of qualitative variables, using absolute and relative frequency distributions. We used Student *t* test in univariate analysis to compare means and χ^2, or Fisher's test when indicated, for categorical variables. A *P* value less than .05 was considered significant.

To adjust for covariates, we constructed a multiple logistic regression model for ohF adjusting for variables related to indication for ohF. We conducted multiple logistic regression analysis for initial mortality. We determined the odds ratio (OR) of each independent variable and its 95% confidence interval (CI). Finally, we conducted survival analysis for 1-year mortality. We estimated hazard ratio for 1-year mortality using a Cox regression model. For multivariate models, we included all statistically significant (*P*<.05) and clinically relevant variables (ie, confounding criterion or clinical significance).

To minimize bias in indication for ohF and its possible impact on mortality, we conducted concordance analysis of results using the propensity score technique.[11]

RESULTS

Patient Characteristics

We enrolled 2572 patients. Following hospitalization, diagnosis of STEMI was confirmed in 2206 but no diagnosis was possible in 166. In the remaining 200 patients, we recorded final diagnoses other than STEMI: cardiac etiology in 165 (6.4%) (heart failure/acute pulmonary edema, 62; no associated chest pain, 30; other, 73 [cardiac aneurysm, arrhythmias, hypertrophic cardiomyopathy, myocarditis, pericarditis]); and non-cardiac etiology, 35 (1.4%) (acute stroke, 13; digestive disease, 17; other diagnoses, 5). This group included 7 patients treated with ohF (1.5% of all ohF). Four were diagnosed with pericarditis and 3 with chest pain with altered baseline ECG and no clear associated etiology. All were discharged without complications.

We excluded the 200 patients with confirmed non-STEMI diagnoses. The final cohort consisted of 2372 patients and we achieved 1-month follow-up in 2138 (90.1%) and 1-year follow-up in 2084 (87.9%).

Baseline characteristics appear in Tables 1 and 2. Intervals as a function of reperfusion treatment administered are in Table 3. We recorded episodes of VF before reaching hospital in 158 (6.7%) patients, of whom 106 (67%) were discharged.

Reperfusion Treatment

Reperfusion treatment was administered to 1400 (59%) patients; 467 (19.7%) underwent ohF. Inhospital, 5.6% of patients received new fibrinolytic treatment and 11.1%, underwent urgent PCI. Out-of-hospital fibrinolysis was initiated at ≤1 hour following the onset of symptoms in 20.7% of patients and at ≤2 hours in 68%. We recorded 20 (4.3%) episodes of hemorrhagic complications post-ohF, 4 (0.8%) of major bleeding, 14 (3%), minor bleeding, and 2 (0.4%) strokes. We administered ihF to 848 patients (35.8%), 9% underwent urgent PCI, and 496 (20.9%) PCI during hospitalization (Table 2).

Univariate analysis shows the ohF patient clinical profile is associated with male gender (85.9% vs 73.6%; *P*<.001), younger age (58.1 [11.6] and 65.8 [13]; *P*<.001), signs and symptoms of typical chest pain (95.1% and 73.6%; *P*<.0001), normal systolic arterial pressure (90-140 mm Hg) (71.9% and 57.6%; *P*<.001), normal heart rate (60-100 bpm) (83.1% and 60.5%; *P*<.001), and Killip class I (94.2% and 85.6%; *P*<.0001). Multivariate analysis for ohF administration appears in Table 4.

Mortality

One-year cumulative mortality in the cohort was 531 (22.4%) patients. Initial mortality (out-of-hospital and inhospital) was 386 (16.3%): 26 (1.1%) died before reaching hospital, 224 (9.4%) died at ≤24 hours, and 138 (5.8%),

TABLE 1. **General and Clinical Characteristics of the 2372 Patients Included**

Variables	Distribution
Age, mean (SD), y	64.3 (13.2)
Age, mean men/women, y	62/71.6
Men, n (%)	1803 (76)
Clinical presentation: typical CP, n (%)	1831 (77.2)
Cardiovascular risk factors, n (%)	
Diabetes	568 (23.9)
High blood pressure	998 (42.1)
Dyslipidemia	685 (28.9)
Smoker	808 (34.1)
Ex-smoker	349 (14.7)
History of ischemic heart disease, n (%)	
Angina	328 (13.8)
Acute myocardial infarction	379 (16)
SAP, median (p25-75), mm Hg	120 (100-140)
Heart rate, median (p25-75), bpm	75 (60-90)
Killip-Kimball class, n(%)	
I	2059 (86.8)
II	218 (9.2)
III	60 (2.5)
IV	22 (0.9)
Ventricular fibrillation	158 (6.7)
Time intervals, median, min	
Onset of symptoms-call	51
Onset of symptoms-hospital	128
Call-to-first medical attention	14
First medical attention-to-hospital	49

SD indicates standard deviation; CP, chest pain; bpm: beats per minute; SAP; systolic arterial pressure.

TABLE 2. **Treatment Received and Mortality**[a]

	n (%)
Out-of-hospital treatment	
Aspirin	2116 (89.2)
Oxygen	2299 (96.9)
Venous access	2343 (98.8)
Nitroglycerin	1899 (80.1)
Morphine	1772 (74.7)
Reperfusion treatment	
Out-of-hospital fibrinolysis	467 (19.7)
Inhospital fibrinolysis	848 (35.8)
Primary PCI	85 (3.6)
Urgent PCI	131 (5.5)
Programmed PCI	280 (11.8)
Mortality	
Initial	386 (16.3)
At 1 month	415 (17.5)
At 1 year	531 (22.4)

[a]PCI indicates percutaneous coronary intervention.

while hospitalized. Among ohF patients, initial and 1-year mortality was 15 (3.2%) and 29 (6.6%), respectively. Multivariate analysis shows initial mortality is associated with older age, female gender, hypotension, tachycardia, Killip class >I, and episodes of VF while receiving medical attention. However, it falls with ohF or ihF and programmed PCI during hospitalization (Table 5).

The remaining variables associating with 1-year mortality in the Cox multivariate analysis were: older age, women and initial clinical variables like hypotension, tachycardia, Killip class >1 and VF episodes while receiving medical attention. Reperfusion treatment, especially ohF, is associated with improved 1-year survival (Table 6).

DISCUSSION

The PEFEX cohort studied is one of the largest, prospective series of unselected patients with STEMI and 1-year survival follow-up analyzed in the out-of-hospital context. One outstanding feature of the series is the extent to which it is representative of a healthcare system in contrast with the audit conducted, with the emergency service as a common element and different admitting hospitals with a range of facilities available for treatment, where out-of-hospital medical attention is a common factor.

TABLE 3. **Time Intervals As a Function of Reperfusion Treatment Received**

Intervals	Out-of-Hospital Fibrinolysis (n=467)	Inhospital Fibrinolysis (n=848)	Primary PCI (n=85)	Without Reperfusion (n=972)
Symptoms-call	43.5 (21-93)	48 (20-115)	53.5 (25.5-223)	59 (18-186)
Symptoms-ohF	100 (68-140)			
Symptoms-hospital	135.5 (100-180)	120 (83-186)	130.5 (86.5-315)	130.5 (83-257)
Call-to-first medical attention	17 (11-25)	15 (9-22)	15 (10-22)	13 (9-20)
First medical attention-to-ohF	27.5 (20-38)			
First medical attention-to-hospital	61 (50-76)	47 (37-59)	47.5 (37-60)	47 (37-59)

ohF indicates out-of-hospital fibrinolysis; PCI, percutaneous coronary intervention.
Intervals (min) are expressed as medians (25-75 percentiles).

TABLE 4. **Multivariate Analysis. Variables Associated With Administration of Out-of-Hospital Fibrinolysis**

Variables	OR	95% CI
Age	0.963[a]	0.950-0.977
Ex-smoker	2.332[a]	1.524-3.566
Smoker	2.870[a]	1.994-4.131
Without history of IHD	2.764	1.972-3.874
Dyslipidemia	1.921[a]	1.395-2.646
Typical chest pain	8.879[a]	5.233-15.066
Heart rate	0.992[a]	0.985-0.999
Killip >1	0.564[a]	0.328-0.970
Administration of aspirin	3.180[a]	1.660-6.093
Programmed PCI	0.636[a]	0.413-0.990
Mortality on admission	0.345[a]	0.148-0.807
Mortality at 1 year	0.527[b]	0.271-1.023

IHD indicates ischemic heart disease; CI, confidence interval; PCI, percutaneous coronary intervention; OR, odds ratio.
[a]*P*<.05.
[b]*P*=.058.

TABLE 5. **Multivariate Analysis. Variables Associated With Initial Mortality (Before and During Hospitalization)**

Variables	OR	95% CI
Age	1.048[a]	1.034-1.062
Woman	1.444[a]	1.081-1.930
Smoker	0.599[a]	0.405-0.884
Dyslipidemia	0.626[a]	0.447-0.883
Systolic arterial pressure	0.980[a]	0.977-0.984
Heart rate	1.012[a]	1.008-1.016
Killip >1	1.516[a]	1.079-2.131
Ventricular fibrillation	2.016[a]	1.236-3.287
Out-of-hospital fibrinolysis	0.237[a]	0.135-0.418
Inhospital fibrinolysis	0.432[a]	0.320-0.584
Programmed PCI	0.210[a]	0.094-0.472

CI indicates confidence interval; PCI, percutaneous coronary intervention; OR, odds ratio.
[a]*P*<.05.

TABLE 6. **Cox Regression Analysis. Variables Associated With Mortality at 1 Year**

Variables	*P*	HR	95% CI
Age	.0001	1.039	1.028-1.051
Woman	.03	1.280	1.024-1.601
Smoker	.001	0.579	0.420-0.799
High blood pressure	.014	0.768	0.622-0.948
Dyslipidemia	.0001	0.588	0.444-0.780
Without history of IHD	.002	0.715	0.579-0.883
Systolic arterial pressure	.0001	0.991	0.988-0.994
Heart rate	.0001	1.007	1.004-1.010
Killip >1	.014	1.361	1.064-1.741
Ventricular fibrillation	.013	1.833	1.135-2.959
Out-of-hospital fibrinolysis	.0001	0.368	0.238-0.566
Inhospital fibrinolysis	.0001	0.605	0.475-0.771
Programmed PCI	.002	0.445	0.268-0.740

IHD indicates ischemic heart disease; CI, confidence interval; Programmed PCI, PCI conducted while admitted to hospital; PCI, percutaneous coronary intervention; HR, hazard ratio.

The patients included in our register present epidemiologic characteristics similar to those of others in Europe,[12,13] with a 3:1 ratio of men to women and a mean age for women almost 10 years greater than that for men. Although presence of cardiovascular risk factors is important, it is striking that for almost two thirds of patients, STEMI constitutes a first coronary event. Furthermore, atypical presentation was slightly more frequent than in hospital-based series,[14] a relevant factor when the first point of contact is a telephone call.

The delays we found put arrival at hospital at ≥2 hours following the onset of symptoms and patients themselves are responsible for 50% of this. This interval was practically constant during the 3 years of enrolment. These delays mean subsequent inhospital interventions take place after the theoretical optimal margin to save myocardium has been passed.[15]

A substantial number of patients presented ≥1 VF episodes, a greater percentage than in other series that record figures of 3%-5%,[5,16] linked to interventionist treatment and fibrinolysis.[17,18] This difference contradicts data indicating a fall in incidence of VF as an early complication of AMI.[19] The disparity may be due to the strictly out-of-hospital origin of our patients. However, it is especially relevant if we consider that two thirds of these patients are finally discharged.

Reperfusion: The ohF Patient Profile

The percentage of patients treated with reperfusion is low but similar to that of European series.[12,13] This particularly limited use of primary PCI coincides in timing and context with Spanish Society of Cardiology hemodynamics register data[20] and suggests the treatment should be more widely used. Significantly, ohF is mainly used within the optimal time frame. It is initiated in 1 out of 5 patients at ≤1 hour after the onset of symptoms, in more than 2 out of 3, at ≤2 hours, and in almost all patients at ≤3 hours. With minimal complications, ohF has proven safe and effective. In our series, initially low-risk profile patients were treated with ohF but this is so early it indicates real-world use differs greatly from that generally portrayed in the analyses and comparisons of controlled trials usually used as references when applying strategies locally.[21]

Mortality

Mortality in our cohort is high, resembling that recorded in studies of non-selected populations.[22] We found high mortality at ≤24 hours, accumulating 42% of deaths at 1 year and including 1% of patients who died while receiving out-of-hospital medical attention. This data is usually omitted from studies including transport and/or hospital referral. Such high initial

mortality may be due to the inclusion of patients who would have died prior to reaching hospital had they not received out-of-hospital attention. It follows a pattern similar to that of series comparing inhospital mortality from STEMI by patient mode of access.[23] Variables associated with greater mortality are well-known: age, female gender, unstable clinical condition (tachycardia, hypotension, and Killip >I). Furthermore, we know dyslipidemia, hypertension, and smoking, once the acute event has occurred, is associated with lower 1-year mortality. Primary VF is associated with greater risk of death at ≤1 year (OR=1.83) which contrasts with earlier studies on the impact of VF in discharged patients.[24] Like the recorded rate of VF, this may be related to the strictly out-of-hospital origin of our cohort.

When we analyze mortality, comparing the groups with and without ohF, we find a statistically significant difference in favor of the ohF group. The risk profile is clearly different but these significant differences hold after adjusting for indication for ohF to compensate for the possible effect of bias. Mortality in the ohF group is comparable to that found in studies with substantial repercussion in clinical practice[10,21,25] and even lower than in recent data provided by registers like the Swedish RIKS-HIA, which reports >7% and >10% annual mortality, depending on the period analyzed.[26,27]

In fact, in the Cox regression, reperfusion treatments, especially ohF, is associated with greater 1-year survival. However, primary PCI does not. On current evidence, this contradiction seems incoherent considering the limited use of primary PCI in our cohort. At <4%, the lack of significance seems clinically or statistically irrelevant but, as use of PCI increases in Andalusia and the rest of Spain, its contribution to survival will prove of interest.[20]

Notwithstanding, the fact that PCI during hospitalization, whenever it occurs, is associated with survival is highly relevant. This was highlighted by the GRACE register[28] which indicates it is a strategy most hospitals can easily adopt.

Although debate on the most adequate treatment for patients with STEMI continues,[29] a substantial distance remains between the theoretical model of maximum efficacy and the most efficient strategy to attend a specific population. The divergences between trial populations and real life are increasingly evident,[30] meaning real options for improvement should reflect available local resources and the clinical characteristics of each patient.[31]

Limitations

We must stress that, as we are dealing with a register and not a clinical trial, we cannot ignore the possibility that factors we have not considered (eg, treatment at discharge and during the first year of evolution) or inadequately controlled confounding factors may explain these results, albeit in part only. Their influence on effectiveness but not efficacy should be considered.

We have been unable to record the times of key inhospital interventions such as inhospital infusion of the fibrinolytic and balloon inflation time in PCI, in enough patients to permit a reliable analysis. We do have access to OHEMS arrival at hospital times as our computer system records this automatically, revealing the basic pattern of the first 120-180 minutes of evolution.

Information lost in the follow-up is mainly that of the nonresident population. This should clearly have been considered a criterion for exclusion in the original design.

CONCLUSIONS

Ventricular fibrillation as a complication of STEMI is associated with lower initial and 1-year survival although more than two thirds of patients attended were finally discharged from hospital. Out-of-hospital fibrinolysis is performed safely; mortality decreases and survival improves. In daily practice, the combination of adequate out-of-hospital attention, early defibrillation and ohF at ≤3 hours, together with systematic PCI during hospitalization, constitutes a valid strategy in a balanced approach when attending patients with STEMI.

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