

## Out-of-Hospital Treatment of Acute Myocardial Infarction in Andalusia, Spain

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**Introduction and objectives.** Clinical trials and meta-analyses have shown that out-of-hospital thrombolysis is effective. Our objectives were to investigate out-of-hospital emergency management of acute myocardial infarction by paramedical teams and to identify factors associated with out-of-hospital use of fibrinolytic therapy.

**Patients and method.** The study made use of a registry of all patients with ST-segment elevation acute coronary syndrome who were diagnosed and treated out of hospital by emergency paramedical teams in Andalusia, Spain in the 2-year period: 2001-2002. Follow-up was carried out during hospital admission and after one month.

**Results.** The study included 981 patients, mean age 65 [13] years, 777 male (79.2%). In total, 152 (15.5%) received out-of-hospital thrombolysis; 18% within the first hour, and 68% within the first 2 hours following symptom onset. No hemorrhagic stroke was observed following thrombolysis. During hospitalization, 206 (21%) patients died, eight (0.8%) of whom had received out-of-hospital thrombolysis. Factors associated with the administration of out-of-hospital thrombolysis included: age under 55 years ( $P < .0001$ ), normal systolic blood pressure (odds ratio=6.825; 95% confidence interval, 2.442-19.069), and an in-hospital diagnosis of anterior acute myocardial infarction ( $P < .022$ ).

**Conclusions.** The administration of out-of-hospital thrombolysis by emergency paramedical teams enables treatment to be administered within the optimum time interval. Mortality during hospital admission is lower in this sub-

group of patients than in those who did not receive out-of-hospital thrombolysis. Moreover, the low complication rate observed indicates that the procedure is safe. However, the patients who received out-of-hospital thrombolysis appeared to be those at a lower risk.

**Key words:** Acute coronary syndrome. Myocardial infarction. Thrombolysis. Fibrinolysis. Medical emergency. Out-of-hospital treatment.

### Tratamiento extrahospitalario del infarto agudo de miocardio en Andalucía

**Introducción y objetivos.** En ensayos clínicos y metaanálisis se ha demostrado que la trombólisis extrahospitalaria es eficaz. Nuestro objetivo es analizar el manejo del infarto agudo de miocardio por equipos de emergencias extrahospitalarios, así como evaluar los factores asociados a la aplicación de fibrinólisis extrahospitalaria.

**Pacientes y método.** Registro prehospitalario continuo de pacientes atendidos y diagnosticados de síndrome coronario agudo con elevación del segmento ST por los equipos de emergencias extrahospitalarios de Andalucía. Duración: 2 años (2001-2002). Se realiza un seguimiento al ingreso hospitalario y al mes de éste.

**Resultados.** Se atendió a un total de 981 pacientes, con una edad media de  $65 \pm 13$  años, de los que 777 (79,2%) eran varones. Se realizaron 152 (15,5%) fibrinólisis extrahospitalarias. El 18% de éstas se realizó en la primera hora de evolución y el 68% en las primeras 2 h, sin que se produjeran accidentes cerebrovasculares hemorrágicos posfibrinólisis. La mortalidad en el ingreso hospitalario fue de 206 pacientes (21%), de los cuales 8 (0,8%) fueron tratados con fibrinólisis extrahospitalaria. Las variables asociadas a la administración de fibrinólisis extrahospitalaria fueron la edad  $< 55$  años ( $p < 0,0001$ ), la presión arterial sistólica normal (odds ratio = 6,825; intervalo de confianza del 95%, 2,442-19,069) y el diagnóstico hospitalario de infarto agudo de miocardio anterior ( $p < 0,022$ ).

**Conclusiones.** La fibrinólisis extrahospitalaria realizada por los equipos de emergencias permite aplicar el tratamiento dentro de los intervalos óptimos de tiempo. La

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## ABBREVIATIONS

ECG: electrocardiogram.  
AMI: acute myocardial infarction.  
PEFEX: project to evaluate out-of-hospital fibrinolysis in acute myocardial infarction.  
STEACS: ST-segment elevation acute coronary syndrome.  
SBP: systolic blood pressure.  
DBP: diastolic blood pressure.

mortalidad en el ingreso hospitalario en este subgrupo de pacientes es menor que en los no tratados con fibrinólisis extrahospitalaria. Además, la baja tasa de complicaciones muestra la seguridad del procedimiento. No obstante, los pacientes tratados con fibrinólisis extrahospitalaria parecen ser los de menor riesgo.

**Palabras clave:** *Síndrome coronario agudo. Infarto agudo de miocardio. Trombólisis. Fibrinólisis. Emergencias sanitarias. Extrahospitalaria.*

## INTRODUCTION

Early treatment of patients with ST-segment elevation acute coronary syndrome (STEACS) is fundamental as maximum mortality occurs within the first hours of evolution,<sup>1</sup> in a high percentage of cases prior to reaching hospital, and the most frequent cause is ventricular fibrillation.<sup>2</sup> Furthermore, reperfusion treatment has been shown to reduce mortality from acute myocardial infarction (AMI). Its efficacy depends on the time between symptom onset and start of treatment and maximum benefit is obtained from earliest possible treatment, above all when this occurs within the first hours of evolution.<sup>3,4</sup>

Pre-hospital thrombolysis has been effective in clinical trials and several meta-analyses have found better survival rates when compared with in-hospital therapy.<sup>5</sup> Its effectiveness in routine pre-hospital care has been evaluated<sup>6</sup> in other countries but in Spain it is little used at present. To analyze the efficacy of pre-hospital thrombolysis, registries of activity recording parameters of real world practice are needed. Although there are many AMI registries of in-hospital care or of the population at large (PRIAMHO, ARIAM, REGICOR, NRMI),<sup>7-10</sup> this is not the case for out-of-hospital treatment.

In Andalusia, a public company (EPES) belonging to the regional government and responsible for managing emergency services, has constructed a continuous registry of patients attended for AMI since January 2001. It is known by the acronym PEFEX, which represents the Spanish for "Project to evaluate out-of-hospital fibrinolysis in acute myocardial infarction." Analysis of the registry will enable us to describe the population attended, establish differences between patients who receive out-of-hospital fibrinolysis and those who do not, and study variables associated with therapy.

## PATIENTS AND METHOD

We constructed a 3-year long, continuous registry (PEFEX) from 1 January 2001 thru 31 December 2003 with a 1-year follow-up and included patients attended and diagnosed with AMI by EPES emergency paramedical teams (established in the 8 provinces in Andalusia), Codes 410 of the International Diseases Classification.<sup>11</sup>

All the patients are registered in a special EPES database (PEFEX database). Variables recorded include clinical and electrocardiogram (ECG) data and time intervals relating to acute episodes as well as 1-month and 1-year in-hospital follow-up data.

### Design, Period, and Patients in the Study

Preliminary analysis of PEFEX data was carried out and all patients included from January 2001 thru December 2002 were enrolled.

### Inclusion Criteria

Evaluation of biochemical markers of myocardial necrosis is not standard procedure and patients are considered to present AMI if they fulfill 2 criteria:

- Patients of any age who present signs and symptoms compatible with acute coronary syndrome.
- ECG changes that indicate myocardial ischemia: new or presumably new ST-segment elevation measured from the J-point, in 2 or more contiguous leads, with cutoff point  $\geq 0.2$  mV in leads V1-V3 or  $\geq 0.1$  mV in the other leads.<sup>2</sup>

### Variables and Data Collection

We used the following variables recorded in the database<sup>12</sup>:

- Age (within ranges as found in other studies on treatment of AMI<sup>13,14</sup>).
- Gender.
- Cardiovascular risk factors expressed as self-

reported variables (smoker: active or during the year pre-event; ex-smoker: stopped smoking >1 year post-event; dyslipidemia: history of dyslipidemia diagnosed and/or treated by a physician; high blood pressure: history of high blood pressure diagnosed and/or treated by a physician; diabetes: history of diabetes diagnosed and/or treated by a physician).

- Antecedents of ischemic heart disease: angina or AMI; systemic systolic blood pressure (SBP), and diastolic blood pressure (DBP) prior to treatment (in mm Hg).

- Heart rate (HR) prior to treatment (in beats/minute).

- Killip and Kimball class evaluation (Killip): we used a combined variable, depending on presence or not of heart failure (Killip >I or Killip I, respectively).

- General measures: continuous follow-up, treatment with acetylsalicylic acid (aspirin), administration of oxygen, treatment with (sublingual or intravenous) nitroglycerin, analgesia (opiates).

- Emergency paramedical team diagnosis: previous AMI (anterior), inferoposterior AMI (inferior, posterior or lateral), non-specific site AMI (nss AMI).

- In-hospital diagnosis: anterior AMI, inferoposterior AMI, nss AMI and STEACS with final diagnosis of unstable angina (by enzyme diagnosis), and other (in-hospital diagnosis not compatible with SCA).

- Reperfusion treatment: out-of-hospital fibrinolysis (out-of-hospital administration of fibrinolytic drugs). Indication: typical pain >30 minutes and <6 hours evolution which does not remit with sublingual nitroglycerin in patients <75 years and initial ECG with ST elevation >2 mm in more than 2 contiguous leads, without absolute or relative contraindications for fibrinolysis.<sup>15</sup> Drug regimens: double bolus intravenous alteplase (rt-PA) as in ARIAM<sup>16</sup>; single bolus intravenous tenecteplase (tnk-tpa) as in ASSENT III<sup>17</sup>; in-hospital fibrinolysis (ihF); percutaneous transluminal coronary angioplasty (PTCA) (including primary PTCA, urgent and programmed).

- Ventricular fibrillation (VF): number of patients presenting VF episodes.

- Bleeding complications following fibrinolysis: ≤72 hours following fibrinolytic agent infusion (minor bleeding: i.e. blood transfusion not needed; major bleeding: i.e. blood transfusion needed; including strokes attributed to cerebral hemorrhage diagnosed clinically and by computerized tomography).

- Time intervals in minutes: clinical, out-of-hospital fibrinolysis interval (time from symptom onset to administration of out-of-hospital fibrinolysis, time of out-of-hospital fibrinolysis); clinical, arrival at hospital interval (time from symptom onset to arrival at hospital, time of arrival), care-start of out-of-hospital fibrinolysis interval (time from start of treatment to administration of out-of-hospital fibrinolysis, “out-of-hospital door-to-needle time”).

- Mortality: initial mortality (deaths occurring during out-of-hospital and in-hospital treatment of acute episodes), 30-day mortality (including initial mortality and mortality between discharge and day 30 post-treatment).

## Statistical Analysis

We used SPSS-10.0 (Spanish version) software. We performed descriptive analysis of quantitative variables using measures of centeredness and dispersion, and of qualitative variables using absolute and relative frequency distributions. We analyzed normality of distributions using graphic tests and evaluated variable symmetry and homogeneity of variance using the Levene test. In univariate analysis we used Student's *t* test to compare means and chi-squared and the Fisher test for categorical variables. We performed binary multivariate logistic regression analysis and included all variables presenting statistically significant and clinically relevant differences. We calculated the odds ratio (OR) of each independent variable and 95% confidence intervals (CI). Values of the quantitative variables are presented as mean±standard deviation (SD) and values of qualitative variables as absolute numbers (n) and percentages (%). Values of *P*<.05 were considered statistically significant.

## RESULTS

### Descriptive Analysis

The study included 981 patients whose general characteristics appear in Table 1. The most frequent age range was 65-74 years and approximately 75% of patients were <75 years. We found 94.3% (n=921) of patients presented a cardiovascular risk factor.

TABLE 1. General and Clinical Characteristics of the 981 Patients Enrolled\*

|                                  |               |
|----------------------------------|---------------|
| Age, mean±SD                     | 65±13 years   |
| Men, n (%)                       | 777 (79.2)    |
| Antecedents, n (%)               |               |
| Diabetes                         | 223 (22.7)    |
| Hypertension                     | 412 (42)      |
| Dyslipidemia                     | 298 (30.4)    |
| Smoker                           | 339 (34.6)    |
| Ex-smoker                        | 161 (16.4)    |
| Angina                           | 142 (14.5)    |
| Acute myocardial infarction      | 170 (17.3)    |
| Systolic blood pressure, mean±SD | 120±39 mm Hg  |
| Heart rate, mean±SD              | 78±28 lat/min |
| Killip and Kimball class I       | 851 (86.7)    |

\*SD indicates standard deviation.

**TABLE 2. Univariate Analysis in the Groups of Patients With or Without Administration of Out-of-Hospital Fibrinolysis\***

| Variables                                       | Without ohF<br>829 (84.5%) | With ohF<br>152 (15.5%) | P      |
|-------------------------------------------------|----------------------------|-------------------------|--------|
| Age range, year, n (%)                          |                            |                         | <.0001 |
| <55                                             | 170 (20.5)                 | 54 (35.5)               |        |
| 55-64                                           | 157 (18.9)                 | 49 (32.2)               |        |
| 65-74                                           | 258 (31.1)                 | 39 (25.7)               |        |
| 75-84                                           | 198 (23.9)                 | 10 (6.6)                |        |
| >84                                             | 46 (100)                   | 0 (0)                   |        |
| Gender, n (%)                                   |                            |                         | .022   |
| Men                                             | 646 (77.9)                 | 131 (86.2)              |        |
| Women                                           | 183 (22.1)                 | 21 (13.8)               |        |
| Mean time to arrival<br>at hospital, min        | 66.3                       | 58.24                   | <.0001 |
| Cardiovascular risk factors,<br>n (%)           |                            |                         |        |
| Diabetes                                        | 188 (22.7)                 | 35 (23)                 | .916   |
| Smoker                                          | 261 (31.5)                 | 78 (51.3)               | <.0001 |
| Ex-smoker                                       | 134 (16.2)                 | 27 (17.8)               | .634   |
| AHT                                             | 343 (41.4)                 | 69 (45.4)               | .372   |
| Dyslipidemia                                    | 233 (28.1)                 | 65 (42.8)               | <.0001 |
| Antecedents of ischemic<br>heart disease, n (%) |                            |                         |        |
| Angina                                          | 128 (15.4)                 | 14 (9.2)                | .045   |
| AMI                                             | 153 (18.5)                 | 17 (11.2)               | .035   |
| SBP, mm Hg, n (%)                               |                            |                         | <.0001 |
| <90                                             | 158 (19.1)                 | 5 (3.3)                 |        |
| 90-140                                          | 484 (58.4)                 | 114 (75)                |        |
| >140                                            | 187 (22.6)                 | 33 (21.7)               |        |
| Heart rate, beats/min,<br>n (%)                 |                            |                         | <.0001 |
| <60                                             | 192 (23.2)                 | 15 (9.9)                |        |
| 60-100                                          | 502 (60.6)                 | 135 (88.8)              |        |
| >100                                            | 135 (16.3)                 | 2 (1.3)                 |        |
| Killip and Kimball class,<br>n (%)              |                            |                         | <.0001 |
| I                                               | 705 (85)                   | 146 (96.1)              |        |
| >I                                              | 124 (15)                   | 6 (3.9)                 |        |
| Aspirin administration,<br>n (%)                | 690 (83.2)                 | 147 (96.7)              | <.0001 |
| Emergency paramedical<br>team diagnosis, n (%)  |                            |                         | <.041  |
| Anterior AMI                                    | 359 (43.3)                 | 66 (43.4)               |        |
| Inferoposterior AMI                             | 437 (52.7)                 | 86 (56.6)               |        |
| nss AMI                                         | 33 (4)                     | 0                       |        |
| In-hospital diagnosis,<br>n (%)                 |                            |                         | <.0001 |
| Anterior AMI                                    | 223 (31.7)                 | 56 (37.6)               |        |
| Inferoposterior AMI                             | 311 (44.2)                 | 80 (53.7)               |        |
| nss AMI                                         | 142 (20.2)                 | 12 (8.1)                |        |
| Other                                           | 28 (4)                     | 1 (0.7)                 |        |
| Mortality, n (%)                                |                            |                         | <.0001 |
| Initial                                         | 198 (23.9)                 | 8 (5.3)                 |        |
| 1-month                                         | 221 (26.6)                 | 9 (5.9)                 | .066   |

\*ohF indicates out-of-hospital fibrinolysis; AHT, arterial hypertension; nss AMI, non-specific site acute myocardial infarction; other, diagnoses not compatible with acute coronary syndrome; SBP, systolic blood pressure.

Hemodynamic constants were normotension 598 (61%) and normal heart 637 (64.9%).

General measurements: continuous monitoring, oxygen, and analgesia with opiates were administered to 100%, 97%, and 73% of patients, respectively. Aspirin was administered to 865 patients (88.2%) and nitroglycerin to 846 (86.3%). We recorded FV episodes in 53 patients (5.4%). We recorded the following in-hospital procedures: fibrinolysis, 404 patients (41.2%); coronary angiography, 220 (22.4%); PTCA, 168 (17.1%). Initial mortality was 206 (21%) and 1-month mortality was 230 (23.4%).

Out-of-hospital fibrinolysis was administered to 152 (15.2%) patients. Therapy was started at  $\leq 1$  hour in 18% of these patients and at  $\leq 2$  hours in 68%. Median intervals for time to out-of-hospital fibrinolysis, time of arrival and "out-of-hospital door-to-needle" time were 100, 120, and 30 minutes, respectively. We used tnk-tpa as fibrinolytic agent in 69 patients (45.4%) and rt-PA in 83 patients (54.6%). We detected 8 bleeding complications (5.2%), 2 major bleeding and 3 minor bleeding in patients treated with tnk-tpa, and 3 minor bleeding in those administered rt-PA. No patients suffered stroke attributed to hemorrhage.

Emergency paramedical team diagnoses were inferoposterior AMI in 523 patients (53.3%), anterior AMI in 425 (43.3%), and nss AMI in 33 (3.4%). We obtained discharge reports on 853 patients (87%) and in-hospital, the emergency paramedical team diagnoses of AMI were confirmed in 96.6% of patients. In the remaining 3.4%, final in-hospital diagnoses were: congestive heart failure, 12 patients (1.4%); angina, 6 (0.7%); cardiomyopathy, 3 (0.4%); arrhythmia, 3 (0.4%); cardiac arrest, 2 (0.2%); and pericarditis, 2 (0.2%).

## Univariate and Multivariate Analysis

Univariate analysis of patients with and without out-of-hospital fibrinolysis is shown in Table 2. Patients receiving out-of-hospital fibrinolysis are more frequently men with ages in the younger ranges (<65 year), with a shorter time to arrival at hospital, and with antecedents of dyslipidemia and smoking but without a prior history of ischemic heart disease. They usually present normal SBP, HR and Killip class, and a higher rate of aspirin administration. They are mainly patients diagnosed with anterior or inferoposterior AMI. Patients without out-of-hospital fibrinolysis are more frequently diagnosed with nss AMI or other AMI and have a lower survival rate following admission.

We performed binary multivariate logistic regression analysis for "result of out-of-hospital fibrinolysis" and the other variables (Table 3). The variables associated with out-of-hospital fibrinolysis continued to be age, SBP and in-hospital diagnosis of AMI. Out-of-hospital



fibrinolysis was administered more frequently in younger, normotensive patients with in-hospital diagnosis of anterior AMI, and less frequently in patients aged 65-84 years.

## DISCUSSION

The population included in our registry presents clinical and epidemiologic characteristics similar to that of the most important European registries.<sup>6,18,19</sup>

Pre-hospital diagnosis of AMI was later confirmed in-hospital in 97% of patients. This is a high proportion and is slightly above that of other recent pre-hospital studies which highlight the difficulty of extrapolating the possible benefits of a treatment such as fibrinolysis to any out-of-hospital care context that does not guarantee highly effective classification and stratification of patients.<sup>20</sup>

The use of general measures, termed type I recommendations in principal clinical practice guidelines,<sup>15,21,22</sup> such as follow-up, ECG, administering sublingual/intravenous nitroglycerin, analgesia, and aspirin, was adequate. Specifically, aspirin administration in our series was above that of other estimates for the out-of-hospital context<sup>23</sup> and similar to that reported for in-hospital series.<sup>18</sup>

The rate of in-hospital fibrinolysis coincides with other series.<sup>18</sup> Administration of out-of-hospital fibrinolysis follows the inclusion criteria defined in our protocol and the profile of patients treated is similar to that reported in other studies and registers.<sup>6,18</sup> The percentage of out-of-hospital fibrinolysis in our study is 15.5%. Overall, we cannot estimate the adequacy of the figures as the principal data come from comparative studies, not registries of specific activity; moreover, in Spain no data are available on use of out-of-hospital fibrinolysis as standard practice. By way of comparison, we can use data from in-hospital series although they vary substantially from study to study and region to region. In general, fibrinolysis is employed in 40% of patients with AMI, ranging between 37% and 58%.<sup>18</sup> In this context, maintaining an out-of-hospital registry clearly facilitates our learning about clinical practice.

The times involved in general management of patients, i.e. symptom onset to start of out-of-hospital fibrinolysis time, or time to transfer to hospital if treatment is not administered, are below those recorded in other studies.<sup>24,25</sup> One important finding is the time taken to perform out-of-hospital fibrinolysis: 18% of out-of-hospital fibrinolysis procedures start in ≤1 hour and 68% in ≤2 hours. This situates start of treatment within the optimal range. Two out of 3 patients receive treatment in ≤120 minutes of evolution, a proportion notably higher than that reported in other recent studies.<sup>6,20,26</sup> This enables us to transfer to the real world these impressive findings on fibrinolysis in very

**TABLE 3. Variables Associated With Out-of-Hospital Fibrinolysis\***

| Variables                        | OR     | CI 95%         |
|----------------------------------|--------|----------------|
| SBP, mmHg                        |        |                |
| <90 (reference)                  | 1      |                |
| 90-140                           | 6.825† | 2.442-19.069   |
| >140                             | 5.347† | 1.821-15.701   |
| AMI                              |        |                |
| In-hospital anterior (reference) | 1      |                |
| In hospital inferoposterior      | 0.980  | 0.657-1.473    |
| In-hospital nss                  | 0.410† | 0.209-0.805    |
| In-hospital others               | 0.191  | 0.025-1.471    |
| Age, years                       |        |                |
| <55 (reference)                  | 1      |                |
| 55-64                            | 1.051  | 0.663-1.667    |
| 65-74                            | 0.527† | 0.326-0.852    |
| 75-84                            | 0.235† | 0.114-0.48     |
| >84                              | 0.001  | 0.0001-127.867 |

\*nss AMI indicates non-specific location acute myocardial infarction; CI, confidence interval; OR, odds ratio; other, diagnoses not compatible with acute coronary syndrome; SBP, systolic blood pressure.

†*P*<.05.

early phases of AMI, revealed in a recent analysis of CAPTIM data.<sup>27</sup>

These results on time intervals have a fundamental incidence on the management of AMI. They put out-of-hospital fibrinolysis within the window of greater benefits for the great majority of patients treated and, in patients who are not treated out-of-hospital, rapid transfer gives them access to in-hospital fibrinolysis and/or the option of whatever other reperfusion techniques may be available, with shorter delays, which is a clear indicator of and criterion for quality in pre-hospital care of AMI.<sup>15,21,22</sup>

Bleeding complications after out-of-hospital fibrinolysis have been fewer than reported in other series.<sup>6,16</sup> Finally, we would highlight the fact that no patient has suffered stroke attributed to cerebral hemorrhage while recognizing that we are dealing with a relatively small series.

Mortality in our series is high and lies between that reported in in-hospital registries and population studies, probably because these deal with different populations.<sup>7,9</sup>

The limitations of our study include the reduced sample size, which has not enabled us to confirm tendencies indicated in univariate analysis, obliges us to go into fine detail over the incidence of complications, and impedes more detailed survival analysis. Moreover, many variables, as in the vast majority of registries, are self-reported. These limitations will be largely overcome with the larger sample derived by maintaining the continuous registry and using the same methodological approach.

## Conclusions and Clinical Implications

Out-of-hospital fibrinolysis performed by emergency paramedical teams as routine clinical practice enables initiating therapy within the optimal time intervals in a high proportion of patients and initial mortality in this subgroup is less than that in patients not treated out-of-hospital. However, patients receiving out-of-hospital fibrinolysis seem to be those at less risk. The low rate of complications shows the safety of the procedure.

These results show the viability of implanting out-of-hospital fibrinolysis in emergency services with a structure similar to ours. The out-of-hospital context offers opportunities to improve management of SCA, both in the implantation of treatments and in the reduction of the time of care.

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