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REVIEW ARTICLE

Pre-hospital fibrinolysis in the patient with acute coronary syndrome with ST-segment elevation: history and recommendations

ANDRÉS PACHECO RODRÍGUEZ, JUAN JOSÉ LARA SÁNCHEZ

Médicos de Ambulancia Medicalizada. Consorcio Público SCIS-Emergencia Ciudad Real/Gerencia Regional de Emergencias-GUETS-SESCAM, Servicio de Salud de Castilla La Mancha. Ciudad Real, Spain.

CORRESPONDENCE:
Andrés Pacheco Rodríguez
C/ Jaraíz, 1
13300 Valdepeñas. Ciudad Real
E-mail:
apacheco1701@telefonica.net

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Fibrinolytic therapy has been called one of the most important advances for achieving coronary reperfusion in the management of acute coronary syndrome with ST-segment elevation. The efficacy of this measure depends on how quickly it is implemented, however. Percutaneous coronary intervention has since been shown to be more efficatious than fibrinolysis. Timely provision of this treatment within the therapeutic window is not available to a large proportion of patients, however, given that it is provided only in specialized centers, a situation responsible for long delays. Prehospital fibrinolytic therapy therefore continues to be an efficatious measure for many. We review the history of fibrinolysis in acute coronary syndrome with ST-segment elevation and offer recommendations for approaches to coronary reperfusion, discussing key points to consider in deciding between fibrinolytic therapy or percutaneous coronary intervention. [Emergencias 2009;21:441-450]

Key words: Prehospital fibrinolysis. Out-of-hospital emergency medical services. Acute coronary syndrome. Thrombolytic therapy. Acute myocardial infarction.

Magnitude of the problem

Cardiovascular diseases remained the leading cause of death in Spain (32.5%) in 2006. By sex, cardiovascular diseases were the leading cause of death in women, and second leading cause in men, although ischemic heart diseases were the main cause of death in men[1] and in women aged over 65 years.

The three leading cardiovascular causes (cardiac ischemia, cerebrovascular disease and other heart diseases) decreased in the period 1989-98 at the expense of the latter two, because cardiac ischemia increased by 2.8% in women aged 35-44 years and 4.4% in men aged 75-85 years[2]. Acute coronary syndrome (ACS) is especially dramatic because of the fact that 65% of ACS patients who die do so in the pre-hospital setting, mostly without having received any medical care[3]. Hospital resources therefore do not alter this mortality rate.

Acute coronary syndrome and acute myocardial infarction

The term ACS applies to the syndromic spectrum covering the sudden compromise of myocardial perfusion generated by an absolute or relative deficit in coronary artery blood flow. In 95% of cases, this is due to partial or total obstruction, lasting or intermittent, of the coronary artery affected.

The obstruction results from the erosion-breakage of intracoronary atheromatous plaque, which causes a thrombus that compromises the perfusion of the affected cardiac area. This is a dynamic process which, if prolonged (more than 15-30 minutes) and continues for hours, leads to necrosis of the area. The initial obstruction is due to platelet aggregation, but fibrin is important to stabilize this early and fragile platelet thrombus.

Acute myocardial infarction (AMI), unstable angina and sudden cardiac death are part of a spectrum called ACS[4]. The size of the myocardial infarction is not predetermined from the outset, but advances with time, and becomes definitive about six hours after onset[5,6]. Reimer showed that restoration of coronary flow after 40 minutes occlusion allowed recovery of 60-70% of the affected myocardium, 33% after three hours and 15% after

six hours[5,7]. For this reason, therapeutic interventions to prevent or reduce necrosis should be initiated during the first 3-4 hours of symptom onset.

Mortality and historical evolution

In-hospital mortality in AMI in the 1950s was 30-35%, especially due to malignant arrhythmia[8]. With the creation of Intensive Care Units and Coronary Units, this fell to 15-20%, and to 14% as from the early 1970's with the development of strategies to treat arrhythmias and to limit the size of MI.

However, this reduction had little impact on overall mortality[9], since approximately 50-70% of deaths occurred outside the hospital in the first two hours[10] after symptom onset, before these patients could receive adequate coronary care.

In those patients surviving the pre-hospital phase, a number of potentially beneficial measures have been tested. Of these, fibrinolytic agents have been the most effective, and are considered the biggest advance in the treatment of AMI since the creation of Coronary Units. The study Fibrinolitic Therapy Trialist[11] showed the benefit of fibrinolysis in terms of mortality, and that the earlier it was administered the greater the benefit; also, after 12 hours, its additional benefit was slight.

Boersma et al[12], in a meta-analysis of fibrinolysis in AMI, reported that the reduction of mortality was significantly higher in patients treated during the first 2 hours than those treated later. The proportional reduction in mortality was highest in patients treated within the first hour (48%), with almost twice the number of lives saved (per thousand), when compared with those treated during the second hour (65% vs. 37%). This established that the decrease in mortality with early treatment was not linear but significantly greater in the early hours.

Pre-hospital mortality of AMI patients in Spain

The BEECIM study showed that approximately 70% of AMI deaths occurred outside the Hospital[13]. In Spain, Iturralde et al showed that 61.1% of AMI deaths occurred at home[14]. It therefore became obvious that our emergency outpatient care system was not effective, so adequate mobile resources were deemed necessary[15].

Pre-hospital therapeutic possibilities for AMI

The early 1960s saw the first Mobile Intensive Care Units with medical staff to administer advanced cardiac life support. Among the pioneers were the Pantridge group in Belfast (1966)[16]; this system soon spread to other Western cities and countries[17]. Among their results, the Pantridge group eliminated pre-hospital mortality of AMI and thus decreased total AMI mortality in this community. Furthermore, pre-hospital treatment within 3 hours of symptom onset decreased in-hospital mortality by half[18].

The benefits of pre-hospital care in AMI and sudden cardiac death provided by Emergency Medical Systems (EMS) came to light in our country in 1988[19,20]. In the late 1970s, knowledge that AMI mortality was associated with infarct size, and that size was not predetermined from the start but advanced with ischemia time, led to the use of various techniques and pharmacological methods to limit the volume of affected myocardium and reduce morbidity and mortality: percutaneous transluminal angioplasty, percutaneous coronary intervention (PTCA-PCI)[21], beta-blockers[22], early reperfusion surgery[23], and intracoronary and intravenous fibrinolysis[24].

The latter is notable for its effectiveness and simplicity of application compared to the others which require very expensive logistical support, and is more effective the sooner it is administered[11,12].

Fibrinolysis in AMI

Two studies of in the late 1970s indicated the possibility of reducing mortality in patients with AMI. Rentrop et al, in 1979, demonstrated the efficacy of intracoronary administration of streptokinase on the dissolution of coronary thrombi[25], and Wood et al, in 1980, the role of coronary thrombosis in the pathogenesis of AMI[5]. The lysis of the thrombus allows reperfusion of the ischemic zone, limits the extent of the MI and improves prognosis, and the earlier the better[11,12].

In fact, to be truly effective the maximum delay for these techniques is approximately 4-6 hours, without implying that delayed treatment is not also more effective, but less so. Unfortunately, epidemiological studies show that, in most cases, hospitalization in the Coronary Care Unit is delayed, which undermines the potential benefits of fibrinolytic therapy.

Pre-hospital fibrinolysis in STE ACS. Results of studies

In geographic areas where prolonged delay in care may occur, pre-hospital administration of fib-

rinolytics in patients with STE ACS or new left branch block avoids quality of care discrimination, is socially just and represents adequate healthcare to help reduce the effect of delays[26].

Using established EMS, either in the form of ambulances, medical staff (EMIP)[27], paramedical staff (MITI)[28], or primary care physicians (GREAT)[29], the era of pre-hospital fibrinolysis (PHF) began in the mid 1980s. The first known published PHF experience was by the Koren group[30].

Since then various authors have published the results of their experiences, especially in European countries. Thus, the 1980's witnessed the publication of the results of studies carried out in Israel, Germany, Holland, Belgium and France.

Among these pioneering studies, the following results refer to patients receiving PHF: the use of streptokinase (SK) in the study by Koren et al[30] showed greater left ventricular ejection fraction (LVEF), and increased permeability in the study by Oemrawsingh et al[31]; with the use of APSAC, Dubois-Rand et al[32] showed greater permeability; with Rt-PA, McNeill et al[33] showed higher permeability and LVEF. These experiences extended during the 1990s, and new studies appeared in Ireland, Sweden and Spain[34,35].

In summary, the studies of these two decades showed time gains of 55 minutes, diagnostic accuracy of 97.38%, higher LVEF, higher rates of diffusion and/or reperfusion (90% vs 81.4%, with statistical significance) and lower total mortality (almost with statistical significance).

During this period, results of the clinical trials GREAT[29], and the multicentre studies EMIP[27] and MITI[28] were published.

Results of clinical trials comparing pre-hospital versus hospital thrombolysis

EMIP Study (The European Myocardial Infarction Project Group)[27]: This was a multicentre (Europe and Canada), randomized double-blind study on the efficacy and safety of fibrinolysis with APSAC, comparing pre-hospital (medicalized ambulances) versus hospital fibrinolysis in AMI, analyzing 5469 patients within the first six hours of symptom onset. The primary endpoint was mortality at 30 days.

With a diagnostic accuracy of 87% and a time gain of 55 minutes, the study reported a non-significant reduction in mortality in the pre-hospital group (9.7%) vs hospital (11.1%), with a risk reduction of 13% (p = 0.08). In the subgroup of patients where the time gain was greatest (90 minutes or more between the two injections), a significant reduction in total mortality was observed (p = 0.047).

The EMIP study also analyzed the results of studies by Castaigne et at (with APSAC)[36]; Schofer et al (with urokinase)[37], GREAT group (APSAC)[29], the MITI group (rt-PA)[28] and the EMIP study itself (with APSAC)[32], showing a 17% reduction in 30-day mortality (with proportional risk adjustment) (95% CI: 2-29%, p = 0.03).

Regarding diagnostic accuracy in the pre-hospital setting, 90% of patients were diagnosed with AMI or probable AMI and, additionally, 7% with acute coronary disease. Since 2000, the studies included a larger number of cases. Among these, Benger38 showed that 6% of patients receiving PHF died, compared to 12% of those receiving hospital fibrinolysis.

Morrow's study[39], comparing delayed EMS contact-PHF (31 minutes) with the delay in EMS contact-hospital fibrinolysis the (previous-historical) control group (63 minutes), found an estimated time gain of 32 minutes. In the first 30 minutes after contact with the EMS, 49% of patients in the study had received the first fibrinolytic bolus, compared with only 5% of the control patients in the hospital.

Once demonstrated the greater effectiveness of PHF versus hospital fibrinolysis for STE ACS, other studies have removed doubts about the application of PHF which provides time gain and improvement in mortality, ejection fraction and reperfusion.

Several meta-analyses have analyzed the results of previous studies on PHF compared with hospital fibrinolysis. Fath-Ordoubadi et al[40] showed significantly reduced mortality rate of 16% (p = 0.01) in the pre-hospital group. Morrison[41] concluded that pre-hospital fibrinolysis, compared to hospital fibrinolysis, reduces the relative risk for all-cause hospital mortality by 17%.

But the evidence that PCI was more effective than fibrinolytic treatment when performed early[42] led to the comparative study of PHF versus immediate PCI in the hospital, as carried out by Bonnefoy et to[43] in France in the Service d'Aide Medicale Urgente (SAMU).

Patients were excluded if the delay in transport time to the hospital was over an hour. PHF was compared with immediate PCI. The suspected diagnosis of AMI was confirmed by the medical coordinator in 94.8% of patients. The study concluded that primary PCI was not better than PHF in STE ACS in the first 6 hours. An exponential decrease in mortality was observed when PHF was initiated within the first 3 hours, and this reduc-

tion was much higher in patients treated within 2 hours than in those treated later.

Pre-hospital fibrinolysis in Spain

In Spain, pioneering studies in PHF began in the mobile ICU service (medicalized ambulances) of the Public Consortium for Fire and Rescue Service, "SCISEmergencia Ciudad Real" that has provided coverage for the entire province of Ciudad Real since 1987.

These studies performed in Ciudad Real[26,44] showed that approximately two thirds of the delay in initiating FPH were attributable to the patient, that EMS response times ranged between 7 and 11 minutes and that the delay in triage (arrival-fibrinolysis) was 26 minutes. This highlights the successful management of hospital cardiac arrest in 85.7% (6 out of 7 cases) and a 1-hour gain in fibrinolytic therapy time. In fact, if these patients had not been treated by mobile ICU staff with fibrinolytic agents, 19.8% of them would not have reached the hospital ICU within 6 hours from symptom onset.

The study by Pacheco et al[34,45] compared LVEF in three groups of patients diagnosed with STE ACS receiving fibrinolysis, administered by mobile ICU (UVIMG), Regional Hospital (HOSPITALCG) or the Coronary Care Unit (UCIHG) between the years 1989-92. Its findings include: mobile-ICU response time of 11 ± 14 minutes, triage time (patient contact to initiation of fibrinolysis) of 35 ± 23 minutes, and time to receiving care (patient contact to the Coronary Care Unit) of 91 ± 48 minutes. The gain in time (time difference between pain and fibrinolysis in each area of care) in the UVIMG group was 61.8 minutes, and diagnostic accuracy was 98.85%. For the primary endpoint, LVEF, the results were as follows: HOSPITALCG: 56.7% vs UVIMG: 56.7% vs UCIHG: 50% ($p < 0.05$ between UVIMG and UCIHG). On relating the results of LVEF with therapeutic delays, referring to the pain-fibrinolysis interval, times of less than three hours showed an LVEF of 56.4 ± 12.1% while the times greater than three hours showed an LVEF of 51.6 ± 12.3% ($p < 0.1$).

A comparative analysis was performed by Lara Sanchez[46] on the safety of applied PHF in the province of Ciudad Real, during the decade 1992-2002, compared with cumulative world experience and the previous Pacheco study on this aspect. The main objective was to analyze out-of-hospital complications in terms of rhythm and hemodynamic alterations in the PHF group. It also analyzed the management of complications and diagnostic accuracy. This was an open study, with three intervention groups: the first group, consisting of 143 patients with suspected diagnosis of STE ACS (1992-2002), the second was an international reference group consisting of 5056 patients, and the third was the group of 86 patients studied by Pacheco (1989-1992). All were treated with PHF. Its findings include: arrival-fibrinolysis (triage), 31 ± 17.7 minutes, pain-fibrinolysis 149.7 ± 131 minutes, range 93.4 ± 39.2, and ambulance distance of 68.1 ± 33.1 Km.

In the first group, it took more than an hour (99 minutes) to request assistance from the onset of symptoms. This delay was much higher than in international reference group (56 minutes), however it had decreased with time, by 22 minutes compared to the delay reported by Pacheco (120 min.).

EMS response time was 19 minutes. This delay was higher than that for the international reference group (11 minutes) and the Pacheco study. Triage delay was 32 minutes and symptom-onset to PHF was 2 hours (150 minutes), in this case, similar to that of the international reference group and the Pacheco group. The main source of delay in receiving treatment (66% of the total delay) was still attributable to the patient and/or bystanders. In addition, only 20.3% of the cases included in the study initially requested mobile-ICU physician attention, although this does represent a slight increase when compared with that of Pacheco (16%). The delay in receiving medical attention was far higher that of the reference group (34 minutes) largely due to the different distances.

Diagnostic accuracy was 91%, similar to the international reference group (90.6%) and the study by Pacheco (89.9%). Successful cardiopulmonary resuscitation in cardiac arrest was 100%, similar to that of the Pacheco study (85.7%), although this variable is not explicitly reported for the international reference group but could be deduced from the variable out-of-hospital mortality: 0% in our study, which is lower than that of the international reference group (1.8%) and similar to that reported by Pacheco (1.16%).

Several Spanish EMS have also published their experiences of outpatient fibrinolysis[47,48]. Recently, the Andalusian PEFEX group has published their results of a study on STE ACS PHF, which analyzes the data obtained in the period 2001-4[49]. They conclude that in daily practice, out-of-hospital fibrinolysis is safe, reduces mortality and improves 1-year survival rates.

Current Recommendations

The recommendations cited here include those of the European Resuscitation Council (2005)[50] whose text referring to PHF states that its application is beneficial in patients with STE ACS or presumed new left branch block. Fibrinolytic therapy can be safely administered by trained paramedics, nurses or physicians using an established protocol. Its efficacy is greatest within the first three hours of onset of symptoms. A safe and effective system for out-of-hospital thrombolytic therapy requires facilities for accurate diagnosis and treatment of STE ACS and its complications. Ideally, the intervention should be performed in communication with experienced hospital physicians (eg. emergency physicians or cardiologists).

Recommendations of the International Liason Commitee On Resusctitation (ILCOR) (2005)[51]

Particular emphasis is placed on evaluating the best strategy for early coronary reperfusion. This set of recommendations outlines symptom onset-physician contact, risks or contraindications for fibrinolysis and anticipated delays for PCI. ILCOR recommends adopting a medical strategy (fibrinolysis) or an immediate, invasive strategy (PCI) and the cutoff point for making the decision is the delay of more or less than three hours after symptom onset (Table 1) (Figure 1). The administration of pre-hospital fibrinolytics in STE ACS patients whose symptoms have lasted between 30 minutes and 6 hours and without contraindications, is safe, feasible and reasonable (Class IIa). This intervention can be performed by paramedics, nurses or trained physicians.

Consensus Conference on management of AMI in the acute phase, outside of cardiology units (Paris, November 2006), published in 2007[52]

This was hosted by SAMU of France, the Société francophone de médecine d'urgence and the Société française de Cardiologie. The conference was organized and developed according to the methodological rules laid down by the Haute Autorité de Santé (HAS) and received funding. The recommendations were drafted by the conference Jury independently. It is a consensus document specifically directed at the Emergency Services and Emergency out-of-hospital care. In summary the following considerations are presented:

The cornerstone of STE ACS reperfusion strategy is to reduce the time between the onset of symptoms and achieving coronary permeability, i.e. the delay between first contact with the physician and balloon inflation (PCI). Physician contact is understood to be with one able to perform an ECG and a diagnosis of STE ACS. This delay in Physician contact- PCI balloon inflation should be broken down into two intervals:

a) delay between first contact with a physician (here called MedContact) and arrival at the door of an interventional cardiology unit (here called

Table 1. Evaluation of reperfusion strategy in acute coronary syndrome with ST elevation (STE ACS)[51]

– Step 1: Assess time and risk, time from symptom onset, STE ACS risk, risk of fibrinolysis, and time required for transfer to experienced catheterization unit for percutaneous coronary intervention (PCI).	
– Step 2: Select reperfusion strategy (fibrinolysis or invasive).	
If the presentation is within 3 hours and there is no delay to PCI, either of the two strategies may be preferred.	
Fibrinolytic strategy is preferred if:	– There is early presentation early within 3 hours from symptom onset and delay in invasive strategy (PCI) is expected, and if – Invasive strategy is not possible: a) Space occupied or not available. b) Vascular access difficult. c) Staff with little training. – Delay in the invasive strategy: prolonged transfer time: a) Difference MedContact-Balloon minus MedContact-needle > 1 hour. b) Delay in MedContact-Balloon or door-Balloon > 90 minutes.
PCI is preferred if:	– Trained staff present, with cardiac surgery support: a) MedContact-Balloon or door-Balloon < 90 min. b) Difference MedContact-Balloon minus MedContact-needle < 1 hour. – High risk STE ACS: a) Cardiogenic shock. b) Killip Class ≥ 3. – Contraindications for fibrinolysis (including increased risk of bleeding). – Late presentation of the patient: symptom onset > 3 hours. – Diagnosis of STE ACS is doubtful.

Source: Stabilization of the Patient With Acute Coronary Syndromes. Circulation. 2005, 112: IV-89-IV-110 (modified ACC/AHA, 2004). (Updated Recommendations). ACC/AHA: American College of Cardiology/American Heart Association.

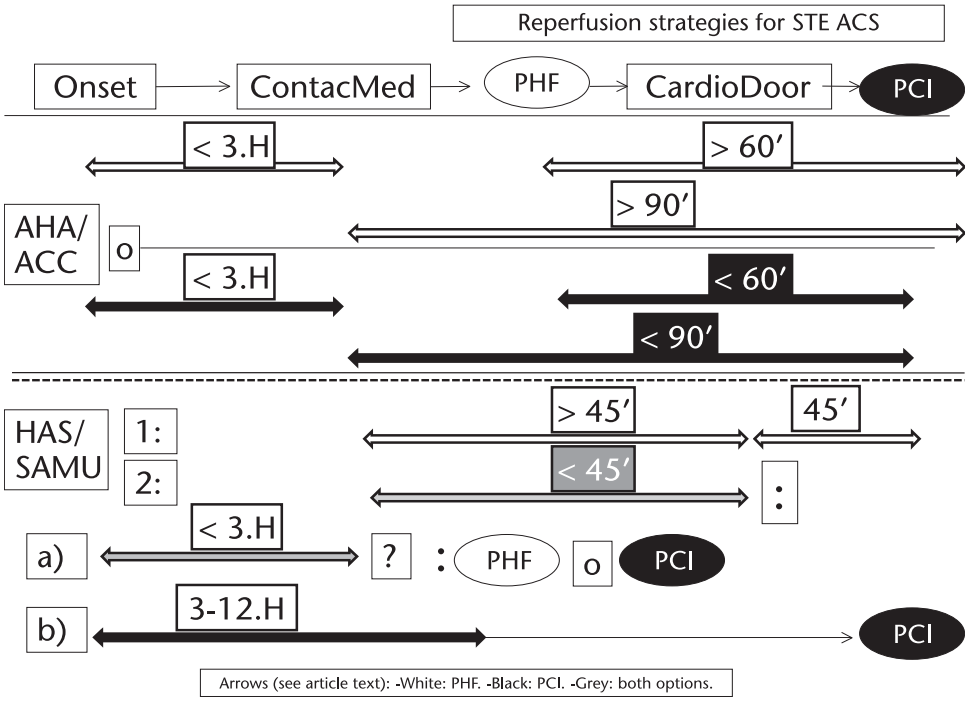

Figure 1. Reperfusion strategies for STE ACS. Recommendations by AHA/ACC and HAS-SAMU. References: 51 and 52. PHF: Pre-hospital Fibrinolysis. PCI: percutaneous coronary intervention. AHA/ACC: American Heart Association/American College of Cardiology. HAS/SAMU: Haute Autorité Santé/Service Aide Medicale Urgent. H: Hours. ('): Minutes. MedContact: first Contact with a Physician; CardioDoor: Door of Cardiology Unit.

CardioDoor) (MedContact-CardioDoor delay), and

b) delay between CardioDoor and PCI balloon inflation (called CardioDoor-Balloon delay).

To respect the international guidelines on overall delay of 90 minutes (MedContact-Balloon delay), the jury recommended a maximum MedContact-CardioDoor delay of 45 minutes.

The choice of PHF or PCI is based on risk-benefit assessment in a given clinical situation. PHF administration has the advantage of simplicity, since it is achievable anywhere. Optimal effectiveness is within the first 3 hours of symptom onset.

The recommendations include the preferential use of tenecteplase, a fibrin-specific fibrinolytic that can be administered as a single intravenous (iv) bolus in ten seconds, adapted to the weight of the patient and not exceeding 10,000 iu (50 mg). Streptokinase is not recommended.

Choice of strategy (Figure 1):

1. Knowing delay intervals: MedContact-CardioDoor and CardioDoor-Balloon.

2. If the delay MedContact-CardioDoor is greater than 45 minutes, the probability of the delay MedContact-Balloon being more than 90 minutes is very high, and this justifies the use of PHF for any patient with symptom onset less than 12 hours. The strategy is the same whether the delay from the onset of symptoms is greater or less than 3 hours.

3. If the MedContact-CardioDoor delay is less than 45 minutes, and if the sum of this delay plus the CardioDoor-Balloon delay is less than 90 minutes, the strategy depends on the interval from the onset of symptoms:

a) If the MedContact delay is less than 3 hours, the attending physician may select either PHF or primary PCI, based on written and proven procedures.

b) If the MedContact delay is between 3 and 12 hours, the preference is primary PCI.

Recommendations of the American Heart Association for the management of patients with STE ACS (2008)[53]

Regardless of the mode of reperfusion, the concept is to minimize total ischemia time, defined as the interval from symptom onset to initiation of reperfusion therapy. The crucial objective is to ensure that the delay between first contact with the physician and initiation of PCI balloon inflation should be 90 minutes. The emphasis on primary PCI does not compromise the importance of fibrinolytic therapy. Efforts should be made to

Table 2. Anticoagulants as adjunctive therapy to reperfusion therapy. AHA-2008[53]

Class I	Level of evidence
1. Patients treated with fibrinolytics should receive anticoagulant therapy for at least 48 hours	C
Anticoagulation regimens with established efficacy:	
a) UFH (initial iv bolus of 60 IU/kg (maximum 4,000 IU) followed by iv infusion of 12 IU/Kg/hour (max. 1,000 IU/h)	C
b) Enoxaparin (provided serum creatinine is < 2.5 mg/dL in men and < 2.0 in women):	A
– In patients < 75 years, initial bolus dose of 30 mg iv, followed 15 minutes later by subcutaneous bolus of 1.0 mg/kg/every 12 hours.	
– In patients aged ≥ 75 years, the initial iv bolus is not to be administered and the subcutaneous dose should be reduced to 0.75 mg/Kg every 12 hours.	
– NOTE: regardless of patient age, if creatinine clearance is < 30 mL/min, the subcutaneous dose should be 1.0 mg/Kg/every 24 hours.	
c) Fondaparinux (when serum creatinine is < 3.0 mg/dL): loading dose 2.5 mg/iv; then doses of 2.5 mg/sc/24 hours	B

AHA: American Heart Association. UFH: Unfractionated heparin.

reduce the delay to thrombolytic therapy after first contact with the physician, when this treatment is considered the appropriate therapeutic strategy.

PHF: EMS-fibrinolysis in 30 minutes, if the professionals are able to do so. MedContact-needle or door-needle in 30 minutes, MedContact-Balloon or door-Balloon in 90 minutes. Standards for coronary reperfusion (fibrinolysis or PCI) from the onset of symptoms: the main objective is that total ischemia time = 120 minutes and the golden hour is the first 60 minutes (ideal).

Adjunctive therapy: Anticoagulants

The ExTRACT-TIMI 25 study[54] compared the therapeutic strategy of using enoxaparin versus unfractionated heparin (UFH) in patients during the first 6 hours after STE ACS symptom onset, in which fibrinolytic therapy was planned. The recommendations for use are summarized in Table 2.

Recommendations on the use of thienopyridines in the patient with STE ACS

Two studies, COMMIT-CCS-2[55] and CLARITYTI-MI 2856, have provided sufficient evidence on the benefit of adding clopidogrel to aspirin (ASA) in STE ACS patients treated with fibrinolytics. Their recommendations are summarized in Table 3.

Contraindications for fibrinolytic therapy

The recommendations on contraindications for fibrinolytic therapy in STE ACS (recommendations of the American Heart Association and European Society of Cardiology) are shown in Table 4.

Guidelines on the administration of tenecteplase, enoxaparin and ASA in STE ACS

Table 5 shows when this treatment is indicated.

Conclusions

PHF in STE ACS patients remains a therapeutic option of great interest and efficiency. Its effectiveness, in terms of mortality, is higher the sooner it is applied. EMS systems have demonstrated high diagnostic accuracy and safety in implementation and in monitoring complications. The recent international recommendations stress the importance of minimizing delay intervals from the onset of symptoms to medical contact with the patient, where PHF may be the most effective option when compared to PCI.

Table 3. Updated recommendations on use of thienopyridines in acute coronary syndrome with ST elevation (STE ACS). AHA-2008[53]

Class I	Level of evidence
1. Clopidogrel at doses of 75 mg/oral/24 hours should be added to ASA in patients with STE ACS, regardless of whether they receive fibrinolytic therapy or do not receive reperfusion therapy.	A
2. In patients taking clopidogrel, and where coronary bypass surgery is planned, administration should be suspended for at least 5 days before surgery and preferably for 7 days.	B
Class IIa	
1. In patients under 75 years who receive thrombolytic therapy or do not receive reperfusion therapy, it is reasonable to administer a loading dose of 300 mg/oral.	C

AHA: American Heart Association.

Table 4. Contraindications for receiving fibrinolytic therapy in acute coronary syndrome with ST elevation (STE ACS)

American College of Cardiology/American Heart Association. **2004-5****	*European Society of Cardiology.* **2003*****
ABSOLUTE contraindications	**ABSOLUTE contraindications**
– Any previous intracranial haemorrhage.	– Previous haemorrhagic ACVA or ACVA of unknown origin.
– Acute ischemic stroke in the past 3 months EXCEPT acute ischemic stroke within the last 3 hours.	– Acute ischemic stroke in the previous 6 months.
– Known structural cerebral vascular lesion (eg. arteriovenous malformation).	
– Known intracranial malignancy (primary or metastatic).	– Damage or neoplasm of central nervous system.
– Closed head trauma or major facial trauma in the previous 3 months.	– Major trauma/surgery/head injury in the last 3 weeks.
– Suspected aortic dissection.	
– Active bleeding or bleeding diathesis (excluding menstruation).	– Aortic dissection.
	– Known bleeding disorders.
Relative contraindications	**Relative contraindications**
– Uncontrolled hypertension on presentation (SBP> 180 mmHg or DBP> 110 mmHg)*.	– Refractory hypertension (SBP> 180 mmHg).
– History of chronic hypertension, severe, poorly controlled.	
– History of previous acute ischemic stroke > 3 months, dementia or known intracranial pathology not specified in the contraindications.	– Acute ischemic stroke in the previous 6 months.
– Cardiopulmonary resuscitation, traumatic or prolonged (> 10 minutes) or major surgery (<3 weeks).	– Trauma resuscitation.
– Recent internal bleeding (previous 2-4 weeks).	
– Non-compressible vascular punctures.	– Non-compressible puncture.
– Active peptic ulcer.	– Active peptic ulcer.
– Pregnancy.	– Pregnancy including 1 week postpartum.
– Habitual use of anticoagulants: > International Normalized Ratio (INR), greater risk of bleeding.	– Treatment with oral anticoagulants.
– For streptokinase/Anistreplase: prior exposure (> 5 days) or previous allergic reaction to these drugs.	
	– Advanced liver disease.
	– Infective endocarditis.

*This could constitute an absolute contraindication in patients with low risk ACS STE. ACVA: acute stroke. SBP: systolic blood pressure. DBP: diastolic blood pressure.

**ACC/AHA.2004. update guidelines. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC Jr, Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction— executive summary: a report of the American College of Cardiology/American Heart Association. Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). Circulation. 2004;110:588-636 (cited in Stabilization of the Patient With Acute Coronary Syndromes. Circulation. 2005; 112: IV-89-IV-110).

***European Society of Cardiology: 2003. Van de Werf F, Ardissino D, Betriu A, et al. Management of acute myocardial infarction in patients presenting with STsegment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 2003;24:28-66.

Table 5. Guidelines on the administration of tenecteplase, enoxaparin and aspirin in acute coronary syndrome with ST elevation (when fibrinolysis is indicated). AHA-2005[51]

Patients aged less than 75 years:	
Aspirin +	150-325 mg (oral).
Enoxaparin iv +	30 mg +.
Subcutaneous Enoxaparin +	15 minutes after intravenous bolus: 1 mg/kg/every 12 hours (maximum dose 100 mg). Note: If estimated creatinine clearance is < 30 ml: the dose of enoxaparin is 1 mg/kg/every 24 h.
Tenecteplase	Weight-adjusted dose (kilograms –Kg–).
(INCOMPATIBLE with dextrose)	6.000 units < 60 Kg.
Administration: bolus in 10 seconds	7.000 units ≥ 60 Kg to < 70 Kg.
	8.000 units ≥ 70 Kg to < 80 Kg.
	9.000 units ≥ 80 Kg to < 90 Kg.
	10.000 units ≥ 90 Kg.
Patients aged ≥ 75 years	
ALL the same EXCEPT:	
Intravenous Enoxaparin:	Bolus is NOT administered.
Subcutaneous Enoxaparin:	Dose of 0.75 mg/kg/every 12 hours.

AHA: American Heart Association.

References

1 INE. Instituto Nacional de Estadística. Año 2006. Datos provisionales. 2008.
2 Yacer A, Fernández-Cuenca R, Martínez de Aragón MV. Mortalidad en España en 1998. Evolución en la década 1989-98 II. Mortalidad general, principales causas de muerte por sexo y edad. Boletín Epidemiologico Semanal. 2001;24:249-56.
3 Norris RM. The natural history of acute myocardial infarction. Heart. 2000;83:726-30.
4 Fuster V, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes (1). N Engl J Med. 1992;326:242-50.
5 De Wood MA, Spores J, Notsker R, Mouser LT, Buroughs R, Goleen MS, et al. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. N Engl J Med. 1980;303:897-902.
6 Reimer KA, Jennings RB. The "wavefront phenomenon" of myocardial ischemic cell death. II, transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. J Lab Invest. 1979;40:633-44.
7 Reimer KA, Lower JE, Rasmussen MM, Kennings RB. The "wavefront phenomenon" of ischemic cell death. I, Myocardial infarct size vs duration of coronary occlusion in dogs. Circulation. 1977;56:786-94.
8 Shah PK. Las Unidades Coronarias desde la perspectiva de EEUU. En Asin Cardiel E, López Bescós: Tratamiento de las Cardiopatías en fase aguda. Sociedad Española de Cardiología. Madrid: Edit ELA-grupo Arán; 1991. p. 211-220.
9 Pantridge JF, Adgey AAJ. Pre-Hospital Coronary Care. The Mobile Coronary Care Unit. Am J Cardiol. 1969;24:666-73.
10 Armstrong G, Duncan B, Oliver MF. Natural history of acute coronary attack community study. Br Heart J. 1972;34:67-80.
11 Fibrinolitic Therapys Trialist (FTT) Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet. 1994;343:311-22.
12 Boersma E, Maas A, Deckers J, Simoons M. Early thrombolytic treatment in acute myocardial infarction: reapraisal of the goleen hour. Lancet. 1996;348:771-5.
13 BEECIM. Balance Epidemiológico Español Contra el Infarto de Miocardio. Informe General. Madrid: Edit Egraf, S.A.; 1991.
14 Iturralde Yañiz J. Estudio sobre el infarto agudo de miocardio en Navarra. [Tesis Doctoral]. Pamplona: Universidad de Navarra; 1987.
15 Navarro-López F, Caminal J, Oriol A, Soler J, Esplugas E, Masia R, et al. Registro de infartos de miocardio y anginas inestables hospitalizados en Barcelona (II). La calidad de la asistencia comunitaria. Rev Esp Cardiol. 1988;41:70-7.
16 Pantridge JF, Geddes JS. A mobile intensive-care unit in the management of myocardial infarction. Lancet. 1967;ii:271-3.
17 McLeod BA, Seaberg DC, Paris PM. Prehospital Therapy Past, Present and Future. En: Roush WR, Fontanarosa PB (eds). EMS/Prehospital Care. Emerg Med Clin North Am. 1990;8:57-74.
18 Pantridge JF. Mobile Coronary Care. Chest. 1970;58:229-34.
19 Alises JM, Castellanos J, Corral E, Matesanz J. Arritmias observadas en el IAM, evolución y tratamiento en ambulancia medicalizada. Emergencias. 1990;2:300.
20 Pascual Ramírez J. Muerte súbita cardíaca y resucitación cardiopulmonar extrahospitalaria. Resultados mediante UCI móvil en Ciudad Real. Med Intens. 1991;15:474-82.
21 Meyer J, Merz W, Schimtz H. Percutaneous transluminal coronary angioplasty inmediately after intracoronary streptolysis of transmural myocardial infarction. Circulation 1982;66:905-13.
22 Yusuf S, Sleight P, Rossi IRF. Reduction in infarct size, arrhythmias, chest pain, and morbidity by early intravenous beta-blockade in suspected acute myocardial infarction. Circulation. 1983;67:32-41.
23 De Wood MA, Notske RN, Hensley GR. Exercice tolerance in late survivors of balloon pumping and surgery for cardiogenic shock. Circulation. 1980;62(Suppl I):38.
24 Yusuf S, Collins R, Peto R, Furberg C, Stampfer MJ, Goldhaber SZ, et al. Intravenous and intracoronary fibrinolityc therapy in acute myocardial infarction: Overview of results on mortality, reinfarction and side-effects from 33 randomized controlled trials. Eur Heart J. 1985;6:556-85.
25 Rentrop KP, Blanke H, Karsch KR, Kreuzer H. Acute myocardial infarction: Intracoronary application of nitroglyicerin and streptokinase. Clin Cardiol. 1979;2:354-63.
26 Ortega Carnicer J, Hermoso Gadeo FE, Fernández Medina V. Fibrinolisis prehospitalaria en el infarto agudo de miocardio. Med Clin (Barc). 1991;97:278.
27 EMIP, The European Myocardial Infaction Project Group. Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction. N Engl J Med. 1993;329:383-9.
28 Weaver WD, Cerqueira M, Hallstrom AP, Litwin PE, Martin JS, Kudenchuk PJ, et al for the Myocardial Infarction Triage and Intervention Project Group. Prehospital-Initiated vs Hospital-Initiated Thrombolytic Therapy. JAMA. 1993;270:1211-6.
29 GREAT Group. Feasibility, safety and efficacy of domiciliary thrombolytis by general practitioners: Grampian region early anistreplase trial. Br Med J. 1992;305:548-53.
30 Koren G, Weiss AT, Hasin Y, Appelbaum D, Welber S, rozenman Y, et al. Prevention of myocardial damage in acute myocardial ischemia by early treatment with intravenous streptokinase. N Engl J Med. 1985;313:1384-9.
31 Oemrawsingh PV, Bosker HA, Van der Laarse A, Cats VM, Bruskchke AVG. Early Reperfusion by Initiation of Intravenous Streptokinase Infusion Prior to Ambulance Transport. Circulation. 1988;78(suppl II):110.
32 Dubois Rande JI, Duval AM, Herve C, Lellouche D, Jan F, Boesch C, Castaigne A. At home trhombolysis in Acute Myocardial Infarction. Circulation. 1988;78(Suppl II):276.
33 McNeill AJ, Cunningham S, Flannery D, Dalzell G, Wilson C, Tsoi E, et al. Pre-admission recombinant tissue Plasminogen Activator. Eur Heart J. 1988;9(suppl I):214.
34 Pacheco Rodríguez A, Ortega Carnicer J, Hermoso Gadeo FE, Muriel Villoria C. Fibrinolisis extrahospitalaria versus Unidad Coronaria en el infarto agudo de miocardio. Emergencias. 1997:9:14-24.
35 Pacheco Rodríguez A. Fibrinolyse extrahospitalière de l'Infarctus Aigu Du Myocarde Par les Services de Santé des Pompiers en Europe. Urgence Pratique. 1994;9:43-4.
36 Castaigne AD, Herve C, Duval-Moulin AM, Gaillard M, Dubois-Randé JL, Oesch C. Prehospital use of APSAC: results of a placebo-controlled sutyd. Am J Cardiol. 1989;64:30A-33A.
37 Schofer J, Buttner J, Geng G, gutschmidt K, Herden HN, Mathey DG, et al. Prehospital thrombolysis in acute myocardial infarction. Am J Cardiol. 1990;66:1429-33.
38 Benger JR, Karlsten R, Eriksson B. Prehospital thrombolysis: lessons from Sweden and their application to the United Kingdom. Emerg Med J. 2002;19:578-83.
39 Morrow DA , Antman EM, Sayah A, Schuhwerk KC, Giugliano RP, de Lemos JA, et al. Evaluation of the time saved by prehospital initiation of reteplase forST-elevation myocardial infarction. Results of the early retavase-thrombolysisin myocardial infarction (ER-TIMI) 19 trial. J Am Coll Cardiol. 2002;40:71-7.
40 Fath-Ordoubadi F, Al-Mohammad A, Huehns TY, Beat KJ. Meta-analysis or Randomised Trials of Prehospital versus Hospital Thrombolysis. Circulation. 1994;90:I-325.
41 Morrison LJ, Verbeek PR, McDonald AC, Sawadsky BV, Cook DJ. Mortality and Prehospital Thrombolysis for Acute Myocardial Infarction. A Meta-analysis. JAMA. 2000;283:2686-92.
42 Boersma E. Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. Eur Heart J. 2006;27:779-88.
43 Bonnefoy E, Lapostolle F, Leizorovicz A, Steg G, McFadden EP, Dubien PY et al, on behalf of the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) study group*. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. CAPTIM. Lancet. 2002;360:825-9.
44 Ortega Carnicer J, Pacheco Rodríguez A, Hermoso Gadeo F, Ambrós A. Fibrinolisis prehospitalaria en España. Med Clin (Barc). 1997;108:518.
45 Pacheco Rodríguez A. Estudio Epidemiológico sobre reanimación del paciente crítico en medicina extrahospitalaria: Asistencia en UVI-móvil en el estudio comparativo de la Fibrinolisis Extrahospitalaria versus Hospital Comarcal versus Unidad Coronaria en el Infarto Agudo de Miocardio. [Tesis Doctoral]. Universidad de Salamanca; 1995. ISBN: 84-8499-974-2.
46 Lara Sánchez JJ. Fibrinólisis extrahospitalaria en pacientes con infarto agudo de miocardio: estudio comparativo de la experiencia de Emergencia Ciudad Real con la experiencia mundial acumulada [Tesis Doctoral]. Ciudad Real: Universidad de Alcalá de Henares; 2005.
47 Huidobro Ubierna J, Batista Llano I, Sepúlveda Santana M, Rodríguez de la Sierra Tanti S, Purriños González A, Fernández Ortiz. Acortar tiempo es salvar miocardio. Fibrinolisis prehospitalaria. Emergencias. 1999;11(extra):179-80.
48 Roqué M, Magriñá J, Huguet M, Lopez A, Bosch X, García A, et al. Estudio comparativo mediante gammagrafía cardíaca de perfusión con 99mTc-MIBI de la fibrinolisis pre o intrahospitalaria en enfermos con infarto agudo de miocardio. Rev Esp Med Nuclear. 1995;14:222-6.
49 Rossell-Ortiz F, Mellado Vergel FJ, Ruíz-Bailén M, Perea Milla E, en representación del grupo de investigadores del proyecto PEFEX. Tratamiento extrahospitalario y supervivencia al año de los pacientes con

infarto agudo de miocardio con elevación del ST. Resultados del Proyecto para la Evaluación de la Fibrinólisis Extrahospitalaria (PEFEX). Rev Esp Cardiol. 2008;61:14-21.
50 Arntz HR, Bossaert L, Filippatos GS. Section 5. Initial management of acute coronary syndromes. European Resuscitation Council Guidelines for Resuscitation 2005. Resuscitation. 2005;67S1:S87-S96.
51 Stabilization of the Patient With Acute coronary Syndromes (part 8). 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2005;112:IV-89-IV-110.
52 Prise en charge de l'infarctus du myocarde à la phase aiguë en dehors des services de cardiologie. Conference de consensus 23 novembre 2006 Paris (Faculté de médecine Paris V. Urgence Pratique. 2007;84:45-9.
53 Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, et al. 2007 focused update of the ACC/AHA 2004 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 (Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction). Circulation. 2008;117:296-329.
54 Antman EM, Morrow DA, McCabe CH. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. N Engl J Med. 2006;354:1477-88.
55 Chen ZM, Jiang LX, Chen YP. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005;366:1607-21.
56 Sabatine MS, Cannon CP, Gibson CM, López-Sendón JL, Montalescot G, Theroux P, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med. 2005;352:1179-89.

Fibrinolisis prehospitalaria en el enfermo con síndrome coronario agudo con elevación del ST. Historia y recomendaciones

Pacheco Rodríguez A , Lara Sánchez JJ

El tratamiento fibrinolítico en el síndrome coronario agudo con elevación del segmento ST (SCACEST) ha sido considerado como uno de los mayores avances en su manejo para lograr la reperfusión coronaria. Su efectividad es tiempo dependiente: a mayor precocidad mejores resultados. Con posterioridad, se demostró que la intervención coronaria percutánea (ICP) tiene superior eficacia que la fibrinolisis. Pero esta última técnica no está disponible para un porcentaje elevado de enfermos durante el periodo en la que es verdaderamente efectiva, ya que se realiza en centros especializados. Y ello provoca demoras superiores. Por esto, el tratamiento fibrinolítico prehospitalario sigue siendo una terapia efectiva para muchos enfermos. En este artículo, se revisa la historia de la fibrinolisis en el SCACEST y se presentan las recomendaciones para la estrategia de la reperfusión coronaria, junto a las claves para decidirse por el tratamiento fibrinolítico o por la ICP. [Emergencias 2009;21:441-450]

Palabras clave: Fibrinolisis prehospitalaria. Servicios de Emergencia Médica Extrahospitalaria. Síndrome coronario agudo. Terapia trombolítica. Infarto agudo de miocardio.