Universitat de Girona

FINAL DEGREE PROJECT

EXTERNAL VALIDATION OF THE PREDICTION TIME FROM THE FIRST MEDICAL CONTACT UNTIL THE ARTERY'S OPENING

Hospital Universitari Dr. Josep Trueta

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ABBREVIATIONS

- **ACS:** acute coronary syndrome.
- **AMI:** acute myocardial infarction.
- **STEMI:** ST- segment elevation myocardial infarction.
- **NSTEMI:** non- ST- segment elevation myocardial infarction.
- **ECG:** electrocardiographic.
- **PCI:** percutaneous coronary intervention.
- **pPCI:** primary percutaneous coronary intervention.
- **tPA:** tissue plasminogen activador.
- **TNK:** Tenecteplase.
- **rPA:** Reteplase.
- **NRMI:** National Registry of Myocardial Infarction.
- **EMS:** Emergency Medical System.
- **ESC:** European Society of Cardiology.
- **FMC:** first medical contact.

ABSTRACT

Background: *Ischemic heart disease remains the most important cause of mortality, morbidity and hospitalization in the world.*

When acute myocardial infarction occurs, the opening time of the clogged artery is essential to reduce the degree of myocardial necrosis. For this reason, European Cardiology Guidelines advise coronary opening treatment as soon as possible.

The current recommendation is to prioritize primary angioplasty over fibrinolysis, as it is more effective and safer. However, in the same way, that an early angioplasty is more effective than early fibrinolysis, this superiority disappears when angioplasty is late.

Because of this, the guidelines recommend "calculating" the ideal time until primary angioplasty and, if it exceeds 120 minutes, opt for fibrinolytic treatment in patients who do not have contraindications.

The cardiology service of the Dr. Josep Trueta University Hospital has been working on this prediction model for years. Finally, and based on data from 2.000 patients, it has been possible to create a linear prediction model from the first medical contact until the opening of the artery with primary angioplasty. An internal validation has been implemented satisfactory and is currently being published.

Objective: *Externally validate, in the towns of Lleida and Tarragona, the prediction function of time from the first medical contact to the opening of the artery (primary angioplasty time) obtained with the sample data of the Dr. Josep Trueta University Hospital.*

Methodology: *A multicentre, retrospective cohorts study will be carried out from 2007 to 2018; with the data registered in Arnau de Vilanova University Hospital and Joan XXIII University Hospital. Variables related to the patient, the heart attack and the transfer to the centre with hemodynamics will be recollected. The sample will be included in a validation set for the validation of the predictive score.*

Keywords*: STEMI, pPCI, Fibrinolysis, Time, Validation*

1. INTRODUCTION

1.1 ACUTE CORONARY SINDROME:

1.1.1 DEFINITION:

Acute coronary syndrome (ACS) is the acute phase of coronary heart disease; (1) so it is considered a real medical emergency. It includes three entities with a high morbidity and mortality rate:

1. Unstable angina,
2. Acute myocardial infarction without ST-elevation (NSTEMI) and
3. Acute myocardial infarction with ST- elevation (STEMI).

The primary clinical manifestation of this syndrome is chest pain, one of the most frequent reasons for consulting in the emergency department, but also part of the clinical manifestations of other pathologies. Quickly identifying patients with ACS and performing the early pharmacological and interventional treatment is essential to obtain good clinical results with decreased morbidity and mortality. (2)

When there is evidence of myocardial damage, with the elevation of cardiac troponins to values higher than the 99th percentile of the upper reference limit, we use the term acute myocardial infarction (AMI), with the presence of necrosis in a context compatible with myocardial ischemia. (3)

STEMI is a clinical syndrome defined by characteristic symptoms of myocardial ischemia in association with persistent electrocardiographic (ECG) ST elevation and subsequent release of biomarkers of myocardial necrosis.

Diagnostic ST elevation in the absence of left ventricular hypertrophy or left bundle-branch block is defined by the European Society of Cardiology / ACCF/ AHA / World Heart Federation, as:

New ST elevation at the J point in at least two contiguous leads of ≥ 2 mm (0.2 mV) in men or ≥ 1.5 mm (0.15 mV) in women, in leads V2–V3 and/ or of ≥ 1 mm (0.1 mV) in another contiguous chest leads or the limb leads. The majority of patients will evolve ECG evidence of Q-wave infarction. (4)

Reperfusion treatment strategies will begin immediately in patients with STEMI. (3)

1.1.2 EPIDEMIOLOGY:

Coronary artery disease is the single most frequent cause of death. Over seven million people every year die from coronary artery disease, accounting for 12.8% of all deaths. Every sixth man and every seventh woman in Europe will die from myocardial infarction.

The mortality of STEMI is influenced by many factors, among them: age, Killip class, time delay to treatment, mode of treatment, history of prior myocardial infarction, diabetes mellitus, renal failure, number of diseased coronary arteries, ejection fraction and treatment. The in-hospital mortality of unselected STEMI patients in the national registries of the European Society Countries varies between 6% and 14%.

Several recent studies have highlighted a fall in acute and long-term mortality following STEMI, in parallel with greater use of reperfusion therapy, primary percutaneous coronary intervention, modern antithrombotic therapy and secondary prevention treatments. Still, mortality remains substantial, with approximately 12% of patients die within six months, but with higher mortality rates in higher-risk patients. (3)

1.1.3 ETIOLOGY:

Atherosclerosis of the epicardial arteries is the leading cause of coronary artery disease.

Nevertheless, there are other causes due to alterations of coronary microcirculation and endothelial dysfunction:

- Coronary spasm (Prinzmetal Angina).

- Coronary embolisms.
- Ascending aortic aneurysm that dissects proximally.
- Aortic stenosis.
- Congenital alterations of coronary anatomy
- Increased demands for hypertrophic cardiomyopathy due to hypertrophic heart disease, aortic stenosis, hypertrophic cardiomyopathy, tachycardias.
- Decreased oxygen supplies due to anemia or significant elevations of carboxyhemoglobin. (1)

1.1.4 CARDIOVASCULAR RISK FACTORS:

Table 1. Cardiovascular risk factors. They predispose to the development of atherosclerosis and therefore to coronary heart disease. (5) (6) (7)

NOT MODIFICABLE	
Male sex	
Age (♂≥ 45 years; ♀post-menopause)	
Family background of early ischemic cardiopathy (♂ < 55 years; ♀< 65 years)	
MODIFICABLE	
ESTABLISHED	**OTHERS**
Smoking	**Hyperhomocysteinemia**
Arterial Hypertension (≥140/90 mmHg)	**Hyperfibrinogenemy**
Diabetes Mellitus	**↑ Lipoprotein A**
Hypercholesterolemia (↑ LDL, ↓ HDL)	**↑ C- reactive protein**
Obesity (ICM> ≥ 30%)	**↑ Brain natriuretic peptide**
Sedentary	**ECA gene**
Microalbuminuria	**Chronic inflammation, as in rheumatoid arthritis**
Glumeral filtration <60mL/min	**Hyperparathyroidism**

1.1.5 PHYSIOPATHOLOGY OF THE ATHEROSCLEROTIC PROCESS:

The rupture of an atheroma plaque and erosion on it causes the exposure of collagen, cholesterol and tissue factor (among others), which are poured into the bloodstream.

That entails the activation of the platelets, leading to the activation of the coagulation cascade, aggregation and secretion of vasoactive substances such as thromboxane.

All this produces intravascular thrombus formation and vasoconstriction.

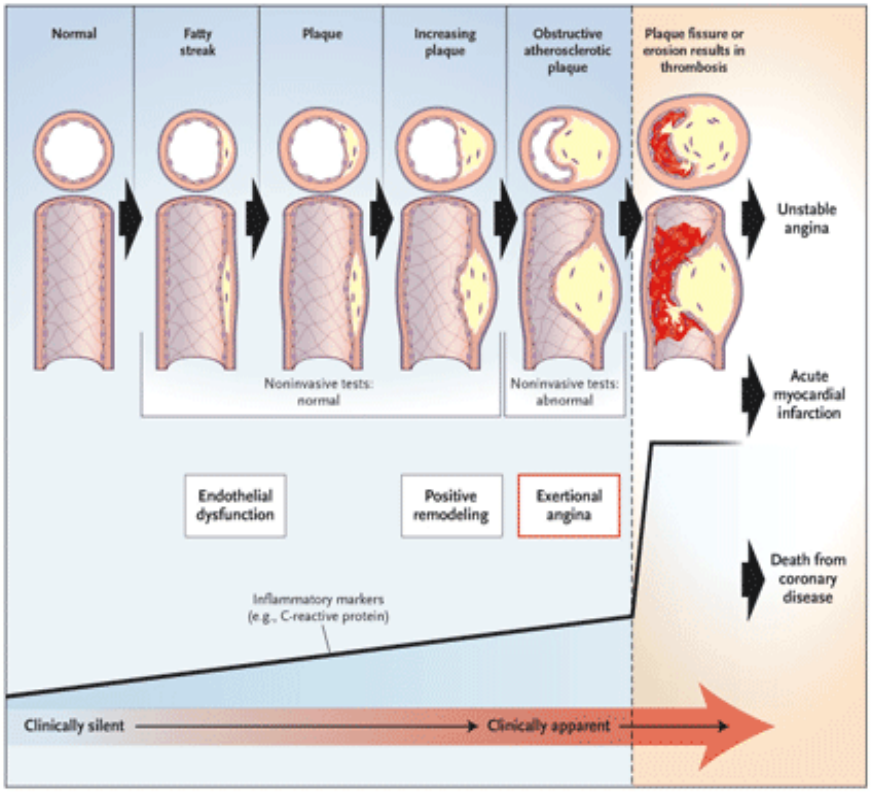


Illustration 1. Development of atherosclerosis (8)

Everything described will eventually cause a distal embolization:

- If the distal embolization is suboclusive, we will be in front of partial arteriolar obstruction and microinfarction, where the most affected layer is the subendocardium.

- If the distal embolization is total, we will have complete arteriolar obstruction of the irrigated area resulting in an immediate loss of the ability to perform contractile work of the affected area, a process known as stunned myocardium.
- If the ischemia, not however endures, we will finally have necrosis where the most affected layers are usually subepicardial and subendocardial, that is, transmural infarction. (6)

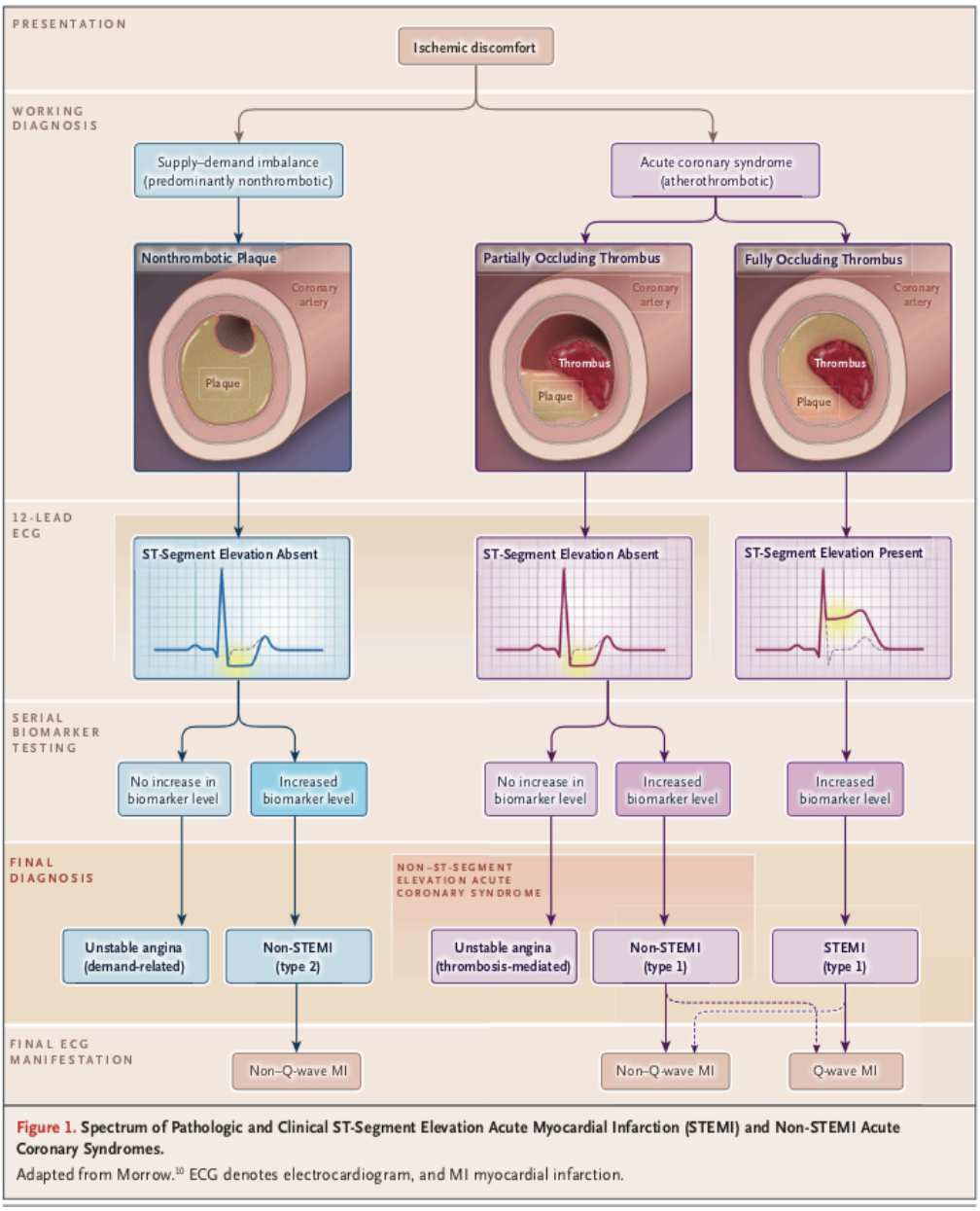


Figure 1. Spectrum of Pathologic and Clinical ST-Segment Elevation Acute Myocardial Infarction (STEMI) and Non-STEMI Acute Coronary Syndromes.
Adapted from Morrow.[10] ECG denotes electrocardiogram, and MI myocardial infarction.

Illustration 2. The spectrum of pathologic and clinical STEMI and non-STEMI acute coronary syndrome. (9)

1.2 REPERFUSION THERAPIES IN STEMI:

1.2.1 THERAPEUTIC ALTERNATIVES FOR EARLY OPENING OF CORONARY ARTERY:

Time is myocardium, a familiar adage in the cardiovascular community; it is central to the controversy of the best modality of reperfusion after AMI. (10)

The goal of reperfusion therapy in STEMI is to achieve early, full and sustained coronary blood flow in the infarct artery. (11)

The rapid restoration of coronary flow can reduce the degree of myocardial muscle necrosis, to preserve ventricular function, the appearance of malignant arrhythmias, reduction of mortality and improve the quality of life.

The extension of AMI is definitive about six hours after arterial occlusion. (12)

As myocardial reperfusion therapy, we understand interventional reperfusion and endovenous reperfusion:

1.2.1.1 INTERVENTIONAL REPERFUSION:

Percutaneous coronary intervention (PCI), usually balloon angioplasty, stenting, or both methods, without prior fibrinolysis, a technique called primary percutaneous coronary intervention (pPCI), is an effective procedure to restore blood flow to STEMI if performed immediately (urgency) in the first hours of the infarction. (13)

The procedure is nothing more than applying a balloon that is made to reach the occluded coronary artery, swelling and dilating the affected artery, the aspiration of the thrombus that generates arterial occlusion and the possibility of establishing a stent to prevent reocclusion. Therefore, the term percutaneous coronary intervention currently encompasses the use of the necessary balloons, stents and complementary devices to perform a safe and effective percutaneous revascularization in complex coronary lesions. (12)

Although it is always recommended to treat the artery responsible for the infarction, the evidence in favour of the immediate (preventive) revascularization of other significant coronary stenosis is not convincing. (3)

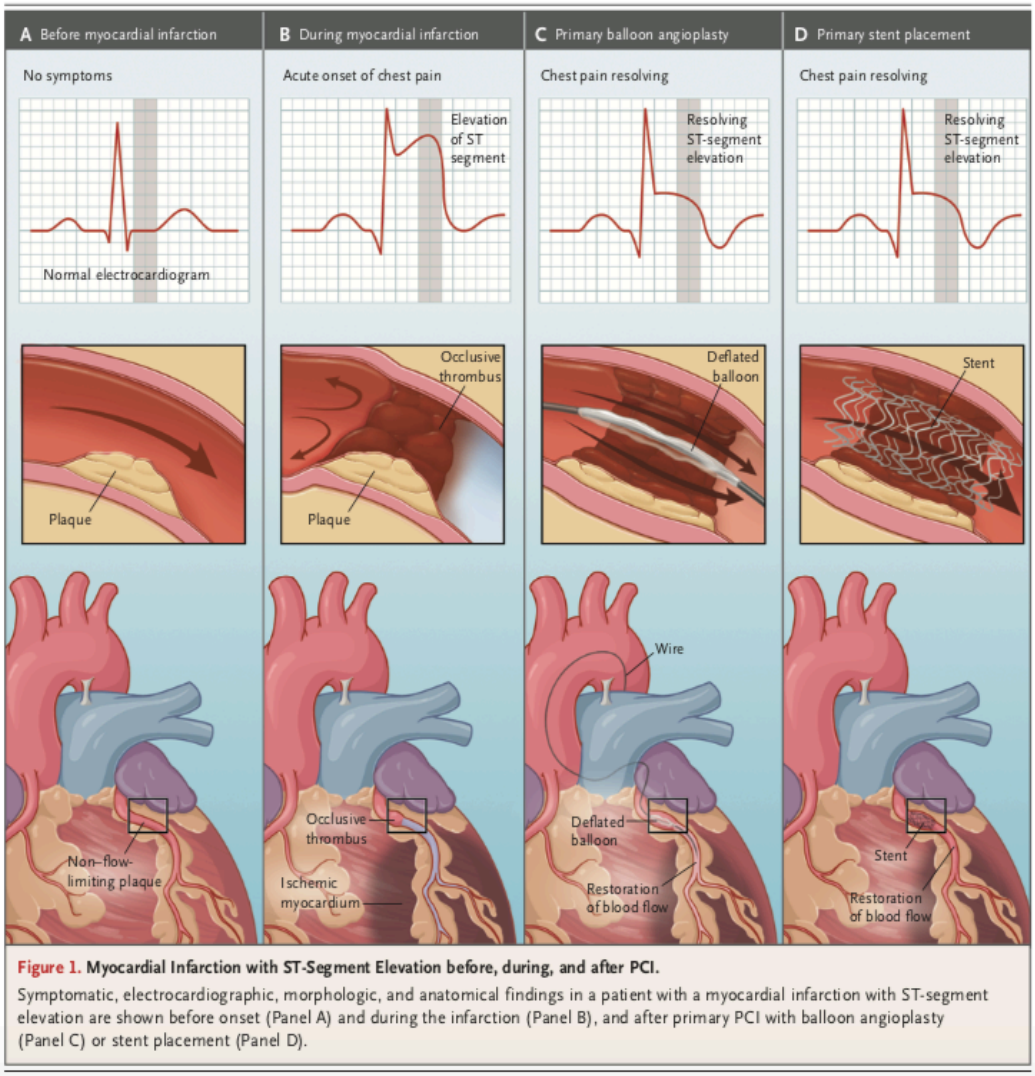


Figure 1. Myocardial Infarction with ST-Segment Elevation before, during, and after PCI.
Symptomatic, electrocardiographic, morphologic, and anatomical findings in a patient with a myocardial infarction with ST-segment elevation are shown before onset (Panel A) and during the infarction (Panel B), and after primary PCI with balloon angioplasty (Panel C) or stent placement (Panel D).

Illustration 3. STEMI before, during and after PCI (14)

1.2.1.2 ENDOVENOUS REPERFUSION:

If there are no contraindications under optimal circumstances, the administration of fibrinolytics should be performed within 10 min of the diagnosis of acute myocardial infarction. With fibrinolysis, the main objective is to restore free transit through the coronary artery immediately. The tissue plasminogen activator (tPA), streptokinase, tenecteplase (TNK) and reteplase (rPA), for intravenous use, are drugs that stimulate plasminogen conversion into plasmin, which will exert a lytic action on the fibrin thrombi.

TNK and rPA are called immediate-use fibrinolytics because their administration does not need prolonged intravenous venoclysis. (13)

1.2.2 ADVANTAGES AND DISADVANTAGES OF pPCI AND FIBRINOLYSIS:

Table 2. Advantages and disadvantages

	ADVANTAGES	DISADVANTAGES
pPCI	♦ Better rates of reperfusion flow than fibrinolytic therapy. (11) ♦ It can be applied to individuals who show contraindications to the use of fibrinolytics. (15) ♦ pPCI, at optimal times, has shown a significant decrease in mortality, the rate of reinfarction and the incidence of cerebral haemorrhage (16)	♦ pPCI is an expensive technique in terms of specialized personnel and facilities. (15) ♦ The possibility of applying it is slight because it is done only in a few hospitals 24 hours. (15) ♦ Although normal coronary flow may be achieved in the epicardial arteries, flow in the distal microvascular beds may be compromised in a considerable portion of patients by microscopic atherosclerotic debris which becomes dislodged during the procedure. (10) ♦ There are often delays in restoring successful reperfusion. (11)

FIBRINOLYSIS	♦ Appropriate treatment decreases the size of the infarction, limit the dysfunction of the left ventricle and reduce the incidence of serious complications such as the ruptured interatrial or interventricular septum, cardiogenic shock and malignant ventricular arrhythmias. (13) ♦ Fibrinolytic therapy includes the secure and consistent performance of the administration. (11) ♦ Fibrinolysis used early, followed by study and early invasive treatment has the same results as pPCI.(17) ♦ Fibrinolysis does not require a cardiac catheterization room or a hemodynamic trained in angioplasty. Any doctor, not necessarily specialist in cardiology or intensivist, can perform it. (18)	♦ Absolute contraindications: - Previous intracranial haemorrhage or stroke of unknown origin at any time. - Previous ischaemic stroke in the preceding six months. - Central nervous system damage or neoplasms or arteriovenous malformation. - Recent significant trauma/ surgery/ head injury (within the preceding month). - Gastrointestinal bleeding within the past month. - A known bleeding disorder (excluding menses). - Aortic dissection. - Non-compressible punctures in the past 24 hours. (3) ♦ 0.5-1.5% risk of a fatal cerebral haemorrhage. (13) ♦ Thrombolysis in the flow of myocardial infarction is restored in only 29% to 54% of arteries. (10)

1.2.3 pPCI vs FIBRINOLSYS:

In 2003, the PRAGUE-2 study compared the two reperfusion strategies (intravenous fibrinolytic treatment or pPCI) randomly assigned in 850 patients with STEMI less than 12 hours of evolution. The patients received fibrinolytic treatment in 42 hospitals without PCI or PCI after an interhospital transfer (distances less than 120 km and an average of 48 minutes and commencement of transfer of fewer than 30 minutes). In general, there was a benefit in favour of PCI quantified in the number of deaths/reinfarctions/ cerebral vascular accidents (15.2% for fibrinolysis treatments and 8.4% for those transferred; p <0.003).

Thus, the results obtained in the PRAGUE-2 study showed that when performed by expert teams, at the right time and place, pPCI produces more significant clinical benefit and lower mortality than endovenous thrombolysis. (12)

However, in the same way, that an early angioplasty is more effective than early fibrinolysis, this superiority disappears when the angioplasty is late. (16)

Highlight the STREAM study where 1,892 patients were randomized to these two reperfusion strategies, provided that the patients were diagnosed early and the pPCI could not be performed in less than 1 hour. Of the patients with prehospital fibrinolysis, 36% needed rescue PCI, and in the rest, angiography was performed on the first day. In the study, the meantime from the onset of symptoms to the performance of reperfusion therapy was 100 minutes for intravenous-TNK and 178 minutes for PCI. The primary objective (death, shock, congestive heart failure or reinfarction in the first month) was similar with both strategies, although there were more intracranial haemorrhages with fibrinolysis. The authors concluded that this drug-invasive strategy might be a very appropriate option when it is not possible to achieve good times with primary angioplasty. (19)

Today, we know that the option of prehospital fibrinolysis reperfusion therapy has to be present in the different action protocols when the time of completion of the pPCI exceeds the recommended times. The administration of fibrinolytics can reduce the relative risk of in-hospital death by up to 50% if it is done following the appropriate times.

The objective of reaching a door-to-balloon time[1] of ≤ 90 minutes, begins with the concept that a shorter interval between ischemia and reperfusion saves myocardium, and this, in turn, causes better clinical results.

Improvement actions to increase the number of patients receiving reperfusion therapies in a time adjusted to the guidelines is essential. In the USA, The National Registry of Myocardial Infarction shows data in which only 15% of patients receive pPCI in less than two hours from the onset of chest pain and that 65-80% of patients with STEMI transferred from a centre without pPCI capacity take more than 120 minutes of total door-to-balloon time. (12)

1

[1] We defined door-to-balloon time as "*the time from arrival at the hospital to first balloon inflation during PCI*". (25)

1.3 HEALTHCARE NETWORKS IN THE ACUTE TREATMENT OF STEMI AND ITS APPLICATION IN THE HEALTH REGION OF CATALONIA:

1.3.1 STEMI CARE NETWORK:

Optimal treatment of STEMI should be based on the implementation of networks between hospitals with various levels of technology, linked by a prioritized and efficient ambulance service. The goal of these networks is to provide optimal care while minimizing delays, thereby improving clinical outcomes.

The main features of such a network are:

- Integrate and coordinate all professionals who assist a patient with a STEMI.
- Increase the number of patients treated in the acute phase.
- Reduce the reperfusion treatment time of the patient with STEMI.
- Improve survival.
- Record the activity to correct potential errors. (3)

1.3.2 AMI CODE:

The infarction Code of Catalonia began in June 2009 with the creation of a protocol, unique to all of Catalonia. It was promoted by the Catalan Society of Cardiology and was developed jointly with the Department of Health, CatSalut and the Emergency Medical Service (EMS).

AMI Code is an urgent action protocol that includes the activation of a series of assistive devices that allow urgent attention in the acute phase of the disease when a patient is suspected of having an infarct and is a candidate for immediate reperfusion (desobstruction of arteries that are causing a heart attack).

The code is activated when a patient, who is suspected of having an ACS, comes into contact with the EMS, which sends an advanced life support unit.

The EMS can be activated from primary care, another hospital, the patient's home or any public place.

If it has been previously agreed, once the patient arrives at the hospital, it does not stop at the emergency department but enters into the coronary unit directly. There cardiologist medical team will expect to intervene most appropriately.

This program is based on a series of premises:

- Change in the decision centre: the SEM doctor or the doctor who makes the FMC decides which treatment perform.
- Sectorization territory that uniquely defines a predetermined destination for each patient, depending on the place where the infarction occurred.
- Mandatory acceptance of the case by the infarction referral hospital.
- Mandatory return of the treated and stablished patient in the centre of the origin or the intensive/intermediate care unit closest to the patient's home, to avoid overloading the infarction reference hospital.
- Mandatory to declare the cases of activation of the AMI Code by the infarction reference centres.
- Continuous evaluation: it is a stimulus for the improvement of the results and for the detection of the inefficiency of the system to take corrective measures and plan the assistance (20)

Annexe III shows us the EMS'S operating procedure.

1.3.3 SELECTION OF REPERFUSION STRATEGIES:

The recommended mode of patient presentation is by alerting the EMS (call the national emergency number: 112). When STEMI diagnosis is made in the out-of-hospital setting (via EMS) or a non-PCI centre, the decision for choosing reperfusion strategy is based on the estimated time from STEMI diagnosis to PCI-mediated reperfusion (wire crossing). System delay for patients alerting the EMS starts at the time of phone alert, although FMC occurs when EMS arrives at the scene. Patients with fibrinolysis should be transferred to a PCI centre immediately after administration of the lytic bolus.

Components of the ischaemic time, delays of initial management, and selection of reperfusion strategy are shown in the next figure:

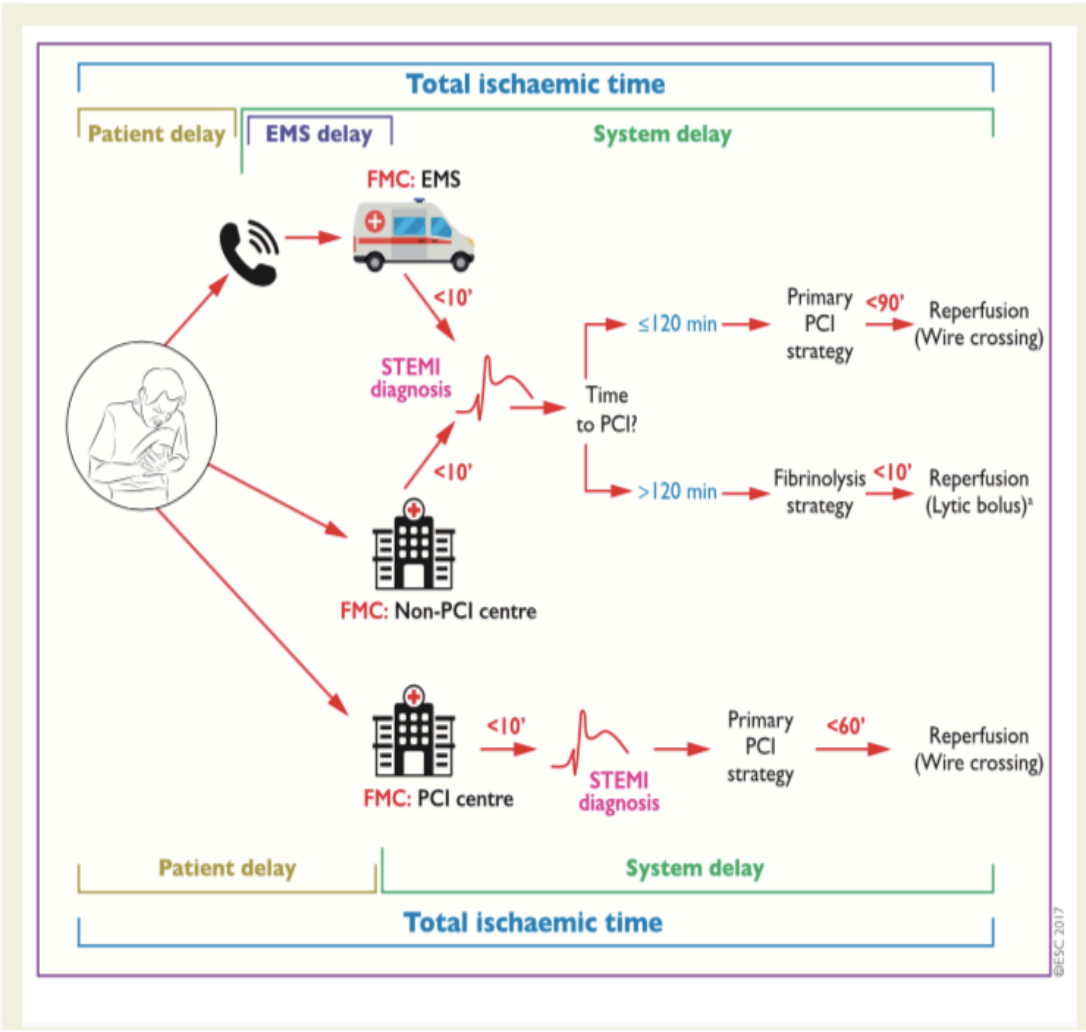


Illustration 4. Patient presentation, components of ischemia time and flowchart for reperfusion strategy selection. (3)

The new guides recommend evaluating the STEMI assistance process according to the new diagnostic and therapeutic strategy based on the time intervals between the ECG practice and the therapeutic decision in the first assistance and the guide step in treated patients with pPCI.

The picture shows us the maximum target times according to reperfusion strategy selection in patients presenting via the EMS or in a non-PCI centre. STEMI diagnosis is time 0 for the strategy clock. Target times from STEMI diagnosis represent the maximum time to do specific interventions. (3)

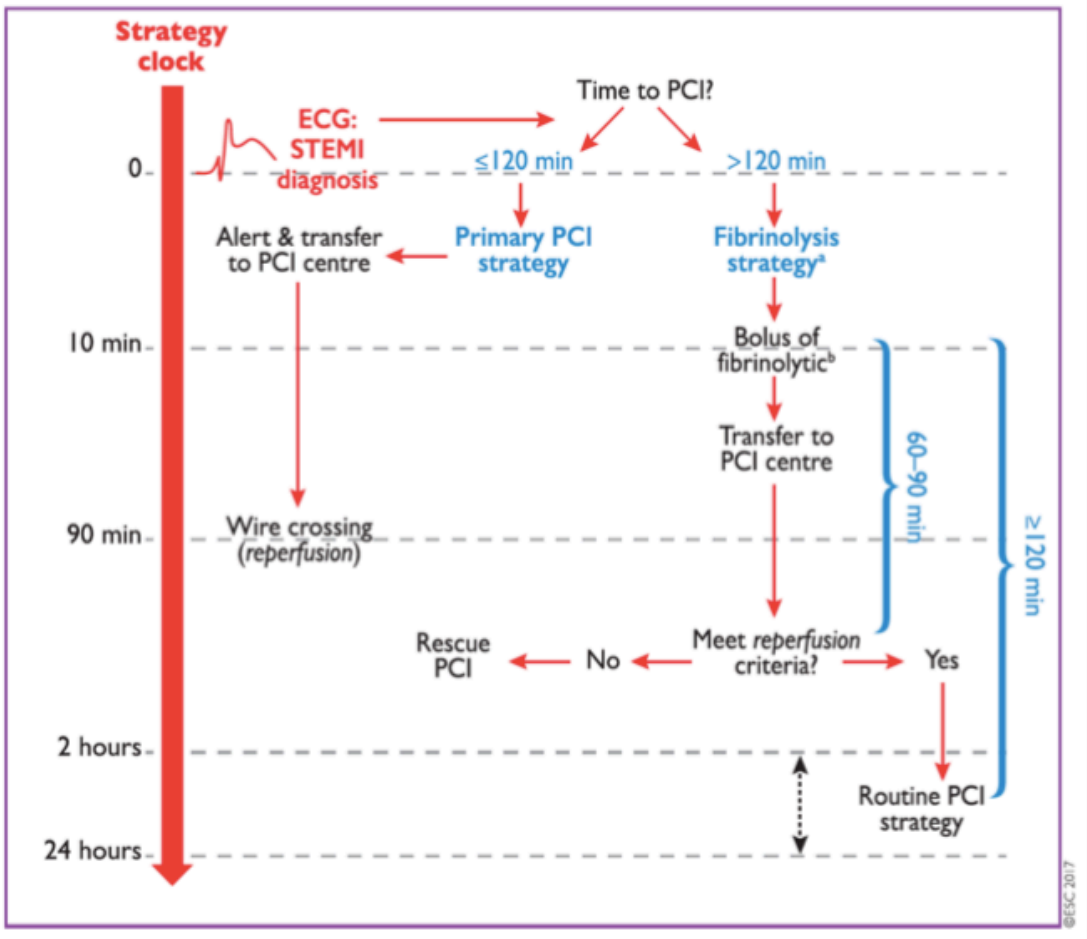


Illustration 5. Maximum target times according to reperfusion strategy selection in patients presenting via EMS or in non-PCI centre. (3)

1.3.4 SUMMARY OF IMPORTANT TIME TARGETS:

Table 3. Time Targets (3)

INTERVALS	TIME TARGETS
Maximum time from FMC to ECG and diagnosis	- ≤ 10 min
Maximum expected delay from STEMI diagnosis to pPCI (wire crossing) to choose pPCI strategy over fibrinolysis (if this target time cannot be met, consider fibrinolysis)	- ≤120 min
Maximum time from STEMI diagnosis to wire crossing in patients presenting at pPCI hospitals	- ≤60 min
Recommended time from STEMI diagnosis to wire crossing in transferred patients	- ≤90 min
Maximum time from STEMI diagnosis to bolus or infusion start of fibrinolysis in patients unable to meet pPCI target times	- ≤10 min
The time delay from the start of fibrinolysis to the evaluation of its efficacy (success or failure)	- 60-90 min
The time delay from the start of fibrinolysis to angiography (if fibrinolysis is successful)	- 2-24 hours

1.3.5 HOWEVER, IS THE IAM CODE APPROPRIATE FOR ALL CATALAN GEOGRAPHY AND ITS AVAILABLE RESOURCES?

The population of Catalonia is distributed in a non-homogeneous way around the big cities, especially around the Sanitary Region of Barcelona, equivalent to the vast metropolitan area of Barcelona, which has about 5 million inhabitants (70% of the total). In this area, there are seven public hospitals with an interventional cardiology unit, five with a PCI 24 hours/7 days program and two with a PCI program from 8.00 to 20.00-22.00 hours from Monday to Friday.

However, although the population density is much lower in the rest of the country, with sparsely populated areas, the fact of being far from the capitals of each province where the public hospitals have hemodynamics laboratory and 24 hours programs can result in a significant inconvenience.

Highways and motorways are located especially along the coast, with only two fast roads connecting Barcelona-Lleida-Zaragoza, on the one hand, and Lleida-Girona on the other. That causes a severe problem of urgent sanitary transport of the resident population outside the large metropolitan areas. (21)

A study carried out at the Josep Trueta Hospital in Girona, confirmed how long travel distances determine a low percentage of patients treated within the recommended time standards for pPCI. The record made showed very long FMC-to-balloon times (only 15.1% was made in less than 120 minutes).

The interpretation of the results gave two possible explanations for these delay times:

- It should be taken into account that these were patients who lived far away from the centre with hemodynamics (93.8 km on average) and,
- Further, a high percentage of patients had their first hospital assistance without hemodynamic availability (54.5%).

Long FMC-to-balloon times, associated with long transport distances, are linked to a significant increase in mortality. (16)

Taking into account everything explained, in terms of population density and distances to the different hospitals, it was clear from the beginning that the AMI Code would result in two different geographical areas. One around the urban centre, in which it was estimated that it could be carried out pPCI in 90% of cases, and another away from them, in which thrombolysis and rescue PCI should be performed.

This estimate was based not only on distances, type and quality of roads but mostly on the estimated transport isochrons (the time it takes from the base to the place of assistance). This point is especially crucial since the isochrons are not fixed, but mobile-based on many factors, such as the location of the nearest ambulance, their occupation or unemployment at the necessary time, the proximity to a fast track and the existing traffic.

It was considered that the optimal means of achieving a STEMI diagnosis-to-pPCI time <120 min was to change the role of the EMS and maximize it to become the central axis of the entire program. For this, each sector had to have a sufficient and well-distributed number of medicalized ambulances with trained doctors who were able to diagnose a STEMI correctly.

Besides, to be efficient, they had to be able to make the treatment decision based on the protocol and the corresponding isochron.

In this way, the role of the transport system of patients with heart attack changed completely, from being a mainly secondary means of transport to a primary means of transport with full diagnostic and treatment capacity. So, the EMS was given the ability to decide on the type of reperfusion treatment to be administered and the ability to activate an automatic procedure with direct transport of patients to the interventional cardiology units without prior consultations.

The only requirement that was established was that, in order to shorten the door-to-balloon time, they would communicate the estimated time of arrival at the reference hospital at the time of initiating the transfer. (21)

2. JUSTIFICATION

Ischemic heart disease remains the most important cause of mortality, morbidity and hospitalization, both in high-income and low-income countries. (22)

When acute myocardial infarction occurs, the opening time of the clogged artery is essential to reduce the extent of myocardial necrosis. For this reason, the European Cardiology Guidelines advise coronary opening treatment as soon as possible and choose the most appropriate reperfusion strategy for each clinical scenario.

Regarding reperfusion therapies, the current recommendation is to prioritize primary angioplasty over fibrinolysis since it is more effective and safer. However, primary angioplasty has a notable drawback, sometimes patients undergoing this procedure are long distances from the centre with hemodynamic availability 24 hours a day, these transfers generate significant delays that impact on the time of artery opening. Because of this, the guidelines recommend "calculating" the ideal time until primary angioplasty and if it exceeds 120 minutes, opt for fibrinolytic treatment in patients who do not have contraindications (low risk of bleeding).

Following this recommendation, having information that allows predicting the theoretical time of primary angioplasty is relevant and would allow choosing the best reperfusion treatment for each clinical scenario. Having this information from the first medical contact (FMC) could provide valuable information for the doctors who perform this first assistance.

The cardiology service of the Dr. Josep Trueta University Hospital has been working on this prediction model for years. Finally, and based on data from 2.000 patients, it has been possible to create a linear prediction model from the first medical contact until the opening of the artery with primary angioplasty. An internal validation has been implemented satisfactory and is currently being published.

Thus, the main objective of this study will be to externally validate the prediction function of time from the FMC to the opening of the artery (primary angioplasty time) obtained with the sample data of the Dr. Josep Trueta University Hospital.

3. HYPOTHESIS AND OBJECTIVE

3.1 HYPOTHESIS:

The hypothesis is to confirm that the function created from the first medical contact until the artery's opening, based on data from the Dr. Josep Trueta University Hospital, is precise and accurate in an external population.

3.2 OBJECTIVE:

3.2.1 PRINCIPAL OBJECTIVE:

Externally validate, in the towns of Lleida and Tarragona, the prediction function of time from the first medical contact to the opening of the artery (primary angioplasty time) obtained with the sample data of the Dr. Josep Trueta University Hospital.

4. THEORETICAL FRAMEWORK AND BACKGROUND

Since 2007, at the Dr. Josep Trueta University Hospital, Dr. Aboal works on the creation of a tool, based on a retrospective record of more than 10 years of patients with STEMI transferred for primary angioplasty; which allows predicting from the STEMI diagnosis (with variables available at that point) an estimated time of primary angioplasty time. The goal is to become a useful instrument in clinical practice for the doctor who makes the FMC.

The theoretical applicability can be in different ways:

- It allows estimating the probability of reaching an optimal time of primary angioplasty (<120 minutes) so that in patients with very long estimated times the possibility of alternative reperfusion treatments such as fibrinolysis may be considered.
- Coordination with the hemodynamic receiving centre, allowing to reduce possible interference with the elective case program.
- Potentially it can help in the creation of future STEMI assistance networks, providing a device that can be useful for coordinating medical teams and improving reperfusion times.

In order to create such a tool, we first studied those variables, which independently showed to be predictors of delays. These turned out to be:

- Clinical variables: severe heart failure upon admission, being a woman and a history of previous cardiac surgery bypass and other situations.
- First contact with a hospital without hemodynamics availability.
- Distance to the receiving centre with hemodynamics.

With these variables, a linear model of prediction of primary angioplasty time (first medical contact-artery opening) was created and was validated internally with satisfactory results.

It is currently in the publication phase, and an application has been created so that it can be consulted in a generalized way.

5. METHODOLOGY

5.1 STUDY DESIGN:

A multicentre study of analytical, descriptive and retrospective cohorts will be carried out from 2007 to 2018; with the data registered in the Coronary Units of the following hospitals:

- Arnau de Vilanova University Hospital, Lleida.
- Joan XXIII University Hospital, Tarragona.

5.2 STUDY POPULATION:

Patients admitted into the Coronary Unit because of a STEMI and transferred to primary angioplasty between January 2007 to December 2018.

5.2.1 INCLUSION CRITERIA:

The study included those patients with STEMI who were transferred to undergo acute reperfusion therapy with primary angioplasty.

5.2.2 EXCLUSION CRITERIA:

The following patients were excluded:

- Patients who required a transfer by air.
- Patients treated with fibrinolytic therapy.
- Patients with times of first medical contact - excessive artery opening (> 360 minutes) and not justified.

5.3 SAMPLE AND SAMPLING:

We expect a study population of around 7.000 patients since every year there are about 430 admissions related to STEMI at the Joan XXIII University Hospital in Tarragona and almost 270 admissions at the Arnau Hospital in Vilanova de Lleida.

That means 700 patients each year in our database that becomes a sample of approx. 6000 patients; after discarding patients with exclusion criteria.

A method of consecutive non-probabilistic sampling will be carried out, and the recruitment of the sample will be carried out in the database of the Coronary Units of the Hospitals of Lleida and Tarragona.

Thus, accepting an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral contrast, 4428 subjects are required to detect a difference equal to or greater than 4 units. A standard deviation of 95 is assumed. A follow-up loss rate of 0% has been estimated. Data obtained according to the free online application, Calculadora de la Grandària Mostral (GRANMO) was used to calculate the sample size. (23)

5.4 VARIABLES:

5.4.1 INDEPENDENT VARIABLES:

Variables related to the patient:

- Age.
- Sex.
- Cardiovascular risk factors: arterial hypertension, dyslipidemia, diabetes mellitus, smoker / ex-smoker, peripheral vasculopathy, history of lung disease and chronic renal failure.
- History of heart disease, previous infarction, previous angina, previous percutaneous or surgical revascularization, previous atrial fibrillation, previous ventricular dysfunction.

Variables related to heart attack:

- Type of infarction (previous / not previous).
- Killip degree upon admission.
- Serious complications before primary angioplasty (severe arrhythmias, clinical instability and orotracheal intubation requirement).
- Treatment received in the hemodynamics laboratory.
- Time of first medical contact: defined as the time in which the patient comes into contact with the healthcare system.
- Time between the first medical contact and the opening of the artery in hemodynamics.

Variables related to the transfer to the centre with hemodynamics:

- The place of the first medical contact will be collected and may be a hospital without hemodynamics, outpatient or public address/place.
- Distance (in kilometres) from the first medical contact post to the centre with hemodynamic availability.
- Estimated transfer time: for this calculation, the Google MapsTM application (Google Inc., California) will be used with the choice of the fastest route option.
- Meteorological weather when the transfer is initiated. Data to be obtained from Meteocat.
- Transfer schedule labour (weekdays from 8-17h) and non-work (other days).

5.4.2 DEPENDENT VARIABLE:

Time until the artery's opening in patients with STEMI, transferred to a hemodynamic centre, for the performance of primary angioplasty.

5.5 DATA COLLECTION METHOD:

Demographic data, history of interest, clinical characteristics, infarction data, complications during the transfer, means of transport, place of first medical contact (hospital without hemodynamics, primary care centre or domicile / public road) and distance (in kilometres) will be collected to the centre with hemodynamic availability.

Collection of temporary variables:

- The first medical contact will be recorded from the patient's contact with a doctor, both in hospital emergencies or in medicalized ambulances.
- Balloon time will be measured from the moment of balloon inflation in angioplasty.
- The FMC-balloon will be the reperfusion time. The FMC-balloon less than 120 minutes according to current standards will be taken as optimal times.

Distance pickup:

- The exact place of FMC will be recorded, and the distance by land will be calculated in kilometres to the centre with hemodynamic availability.

6. STATISTICAL ANALYSIS

6.1 DESCRIPTIVE ANALYSIS:

At the descriptive level, the information will be provided on the available variables and the response variable (time to reperfusion).

- Continuous variables will be described with location statistics (mean and median) and dispersion (standard deviation and interquartile range).
- Categorical variables will be described with their relative and absolute frequencies.

The descriptions will be made by the derivation and validation set. A correct randomization will be attempted using the likelihood ratio test (logistic model for binary variables and Gaussian model for continuous variables).

6.2 VALIDATION ANALYSIS:

For the validation of the predictive score, the entire available sample will be included in a validation set.

As a first validity test, a comparison of the predicted and observed times will be made. For make it possible, the entire test set will be divided into deciles. Subsequently, the estimated probability will be compared with the likelihood observed using a t-Student of paired data.

As a second validity test, we will study how the variables used in the original predictive model are associated with the current sample. That will result in a new time prediction function, adjusted to the populations of Tarragona and Lleida. Then, a coefficient comparison will be made.

A value of $p > 0.05$ indicates that the model fits the data accurately and, therefore, correctly predicts.

Analyses will be performed using IBM SPSS (Statistical Package for the Social Sciences).

7. ETHICS

The project will be evaluated by the appropriate Ethics Committee of each site; in this case of the Hospitals, Arnau de Vilanova, de Lleida and Joan XXIII, of Tarragona.

Patients or the legal substitute (for those who cannot give their consent) will be informed about the project and will be asked for informed consent before the inclusion of their data (Annex I and II). Participants will have to sign the informed consent voluntarily according to *"Ley 41/2002 Básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica".*

According to "*Ley Orgánica 15/1999 de Protección de Datos de Carácter Personal",* the anonymity of patient data will be guaranteed; for this reason, the data manager will use the medical record number instead of the names of the patients.

8. STUDY LIMITATIONS

The most important limitations of the project are:

- Impossibility of obtaining the time intervals that conform the FMC-artery opening time. The first time is the FMC and opening of the artery; this time is formed by different times:
    - Diagnosis time, time of activation of the CODI IAM, time of transfer to the centre with hemodynamics and time of artery-opening in hemodynamics.

  We only have the FMC-artery opening time, and we cannot study the different times that make up this time.

- Impossibility of obtaining information about the availability of sanitary transport at the time of transfer to the centre with hemodynamics. It is unknown if the ambulance was nearby or had to take a tour to collect the patients.

9. FEASIBILITY, SCHEDULE AND CHRONOGRAM

The study is expected to last about three years. All the activities executed during this period will be organized in 4 stages, detailed below:

Stage 1: Preparation, coordination and training:

The principal investigator will perform the literature review and the elaboration of the work protocol.

Also, coordination and training in statistics and methodology of the research team will be accomplished in this stage.

Indispensably, the protocol will be evaluated and approved by the Ethics Committee (CEIC) of each Hospital.

Stage 2: Data collection, data extraction and database development:

The data of patients suffering from STEMI transferred to the Arnau de Vilanova and Joan XXIII Hospitals, during the periods between 2007-2018, which meet the inclusion criteria and none of the exclusion criteria will be offered entry into the study.

They will be included after reading and signing the informed consent.

For a year, the data will be collected from the medical records that appear in the SAP, following the instructions in the data collection section.

This task will be carried out by the study coordinators of each Hospital.

Once the data collection is finished according to our sampling, the study's data manager will organize the data collected from the two Hospitals, into a single database. Six months will be destined to perform this work.

Stage 3: Data analysis and interpretation of the results:

Finally, a person qualified in statistics will process the data with the appropriate software. Subsequently, the principal investigator will dedicate nine months to the analysis, interpretation of results and conclusions.

Stage 4: Article writing and publication of the results:

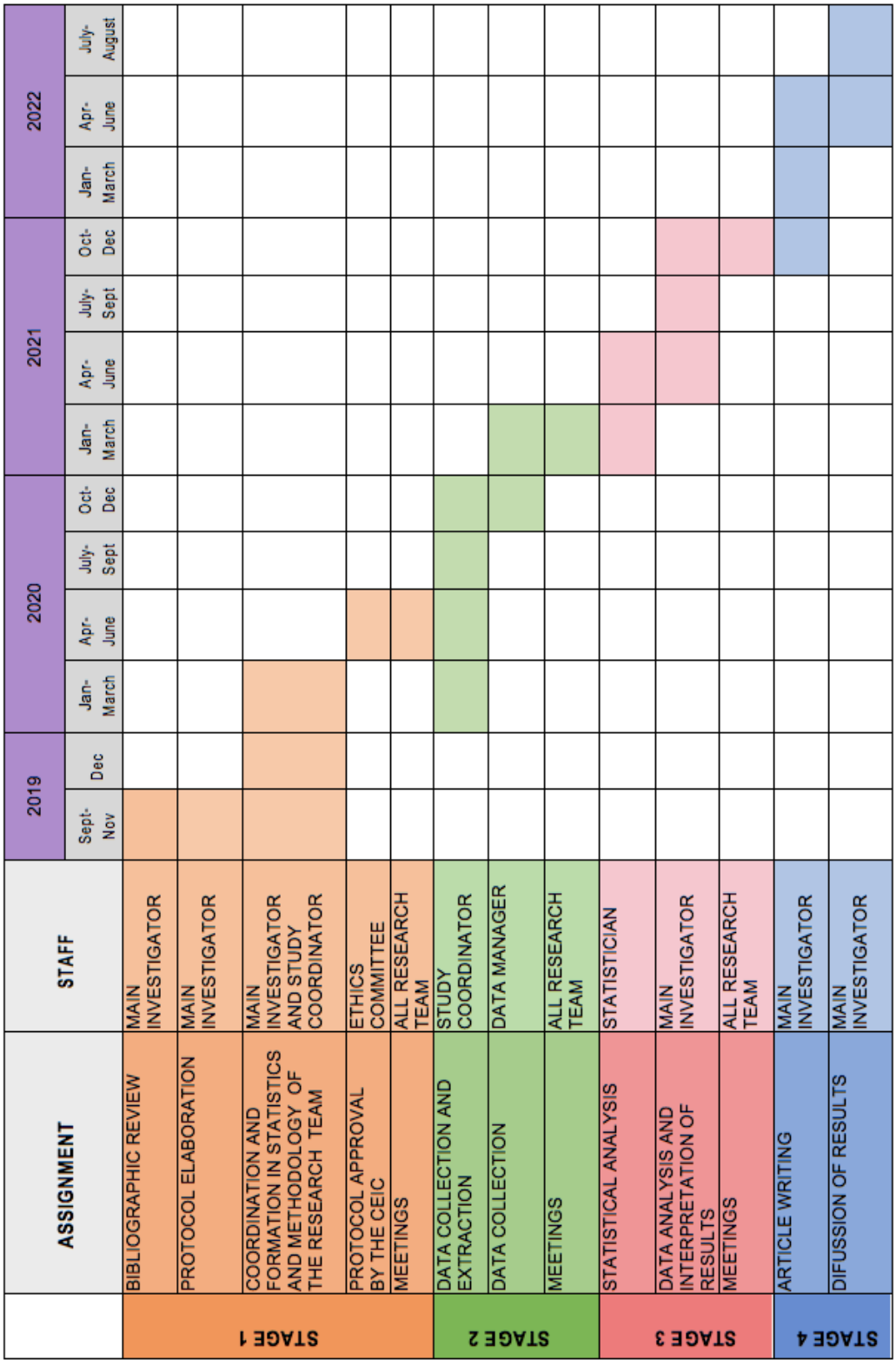
The final article will be published in the Spanish Journal of Cardiology to disseminate the results of the study adequately.

As the study is longitudinal and will last about three years, the researchers will meet in the first phase to coordinate the project well, at the end of the period of data collection, data analysis and interpretation of results. The purpose of these meetings is to identify deficiencies in the study and correct methodological errors.

Members of the research team:

- Principal investigator: responsible, protocol development, study supervision, coordination and training of the research team, interpretation of the results, writing of conclusions, publication and dissemination of results.
- Study coordinators: responsible for the coordination and training of the research team. Also, it will handle the extraction and collection of data. There will be a study coordinator at each hospital.
- Co-researchers:
    - Expert statistician: responsible for the statistical analysis of the study.
    - Data manager: will be responsible for the creation of a database of smooth understanding and interpretation.

Table 4. Schedule and chronogram



10. BUDGET

The research team will assume the tasks related to coordination, data collection and interpretation of the results as part of their normal activities.

Table 5. Budget

	Unit/Cost (€)	Time/Units/ Words	Subtotal
Personnel - Statistician - Data Manager	 35€/h 35€/h	 40h 80h	 1.400€ 2.800€
Translation	0,120€/w	17.500w	2.100€
Meeting - Coordination Meetings	300€	7u	2.100€
Publication and difussion - Publication - National Congress	 1.000€ 1.500€	 1u 2u	 1.000€ 3.000€
		TOTAL	12.400 €

11. IMPACT ON THE NATIONAL HEALTH SYSTEM

According to the finding of the National Registry of Myocardial Infarction (NRMI), less than 30% of patients with pPCI had a door-to-balloon time fewer than 90 minutes. Transfers from other institutions significantly lengthened the time from door to balloon, with less than 5% of displaced patients undergoing PPCI within 90 minutes after the first medical contact. (10)

Although recent efforts have reduced reperfusion delays, patients with STEMI who require interhospital transfer for primary PCI represent a considerable population that is still far from reaching established reperfusion parameters.

With this study, we could demonstrate that the predictive score can be applied to other populations and thus obtain a useful and powerful tool in the estimated calculation of arterial opening time, in the prehospital phase.

Also, the main characteristics of the patient would be taken into account so that the time calculation would be individualised avoiding in this manner, the application of population standardised parameters in a particular way. That would entail being able to decide on an appropriate treatment for each patient in question.

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13. ANNEXES

13.1 INFORMATION DOCUMENT FOR THE STUDY:

CONSENTIMIENTO INFORMADO

Nos dirigimos a usted para informarle sobre un estudio de investigación al que se le invita a participar. El presente estudio ha sido aprobado por el Comité Ético de Investigación Clínica del Hospital, de acuerdo con la legislación vigente, Real Decreto 1090/2015, de diciembre, sobre la investigación biomédica.

Nuestra intención es que usted reciba la información correcta y suficiente para que pueda evaluar si quiere o no que sus datos participen en este estudio. Antes de decidir si desea participar o no, le rogamos lea detenidamente este documento que incluye la información sobre este proyecto.

Puede formular todas las preguntas que le surjan y solicitar cualquier aclaración sobre cualquier aspecto.

Puede consultar la decisión con las personas que considere oportunas.

Debe saber que su participación en este estudio es voluntaria y que puede decidir no participar o cambiar su decisión y retirar el consentimiento en cualquier momento, sin que ello altere la relación con su médico ni se produzca ningún perjuicio en su atención sanitaria.

TÍTULO DEL PROYECTO

Validación externa de la función predictiva del tiempo desde el primer contacto médico hasta la apertura arterial.

LUGAR DE REALIZACIÓN

Unidades Coronarias de los siguientes hospitales:

- Hospital Universitario Arnau de Vilanova, de Lleida.
- Hospital Universitario Joan XXIII, de Tarragona.

OBJETIVO DEL ESTUDIO

Con este estudio, podríamos demostrar que el score predictivo puede aplicarse a otras poblaciones y obtener de esta forma, una herramienta eficaz y potente en el cálculo estimado de tiempo de la apertura arterial, en la fase prehospitalaria.

Además, se tendrían en cuenta las principales características del paciente, por lo que el cálculo del tiempo sería individualizado. Evitándose de esta forma, la aplicación de parámetros estandarizados poblacionales de manera particular. Esto conllevaría, poder decidir un tratamiento adecuado, para cada paciente en cuestión.

Por esta razón el objetivo del estudio será validar externamente, en las poblaciones de Lleida y Tarragona, la función predictora del tiempo desde el primer contacto médico hasta la apertura de la arteria (tiempo de angioplastia primaria) obtenida con los datos de la muestra del Hospital Universitario Dr. Josep Trueta.

BENEFICIOS Y RESULTADOS DERIVADOS DE SU PARTICIPACIÓN EN EL ESTUDIO

Pretendemos conseguir una mejora del tiempo del tratamiento de reperfusión, en aquellos pacientes que son trasferidos desde centros sin disponibilidad de hemodinámica cuando presentan un infarto agudo de miocardio con elevación del ST.

Es posible que los conocimientos adquiridos con la investigación no lo beneficien a usted personalmente, sino a futuros pacientes que padezcan la misma enfermedad.

Usted tiene derecho a conocer los resultados de los estudios que se obtengan. Y también tiene derecho a la no información de estos resultados.

CONFIDENCIALIDAD, PROTECCIÓN DE DATOS Y DERECHOS DEL PACIENTE

Los datos recogidos serán estrictamente confidenciales. Sólo se autorizará para la recogida de datos de su historial médico a personas sometidas al secreto profesional siempre con el previo conocimiento del investigador principal.

La comunicación y la cesión de los datos de carácter personal de todos los participantes se ajustará a la Ley de confidencialidad 03/2018, de protección de datos de carácter personal. De acuerdo a lo establecido en la legislación mencionada, usted puede ejercer los derechos de acceso, modificación, oposición y cancelación de datos, por eso se ha de dirigir a su médico del estudio. Los datos recogidos por el estudio estarán identificados mediante un código y sólo los miembros del equipo de investigación podrán relacionar estos datos con usted y con su historia clínica.

En ningún caso su nombre aparecerá en la publicación de los resultados.

Si usted decide retirar el consentimiento para participar en este estudio, ningún dato nuevo será añadida a la base de datos y se procederá a destruir toda la información personal obtenida.

CONTACTO CON EL INVESTIGADOR

Para cualquier duda, información adicional que precise o sobre sus derechos como participante en el proyecto, debe contactar con el investigador.

Le agradecemos su participación.

13.2 INFORMED CONSENT:

CONSENTIMIENTO INFORMADO

Yo (nombre y apellidos) .....con DNI .....

- He leído la hoja informativa que se me ha entregado sobre el estudio.
- He podido hacer preguntas sobre el estudio.
- He recibido suficiente información sobre el estudio.
- He hablado con: (nombre del investigador) .....
- Comprendo que mi participación es voluntaria.
- Comprendo que puedo revocar mi consentimiento en cualquier momento, sin tener que dar explicaciones y sin que ello altere mi asistencia sanitaria.

Accede a que los investigadores principales del proyecto puedan contactar con usted en un futuro si lo consideran oportuno.

☐ Sí ☐ No

Doy libremente mi conformidad para participar en el estudio y doy mi consentimiento para el acceso y utilización de mis datos en las condiciones detalladas en la hoja de información.

Firma del paciente:

Fecha: ____ / _____ / _____

Firma del investigador:

Fecha: _____/ _____/_____

Firma del representante legal, familiar o persona vinculada de hecho

Fecha: ____/_____/_____

Firma del investigador

Fecha: ____/_____/_____

13.3 EMS'S OPERATING PROCEDURE:

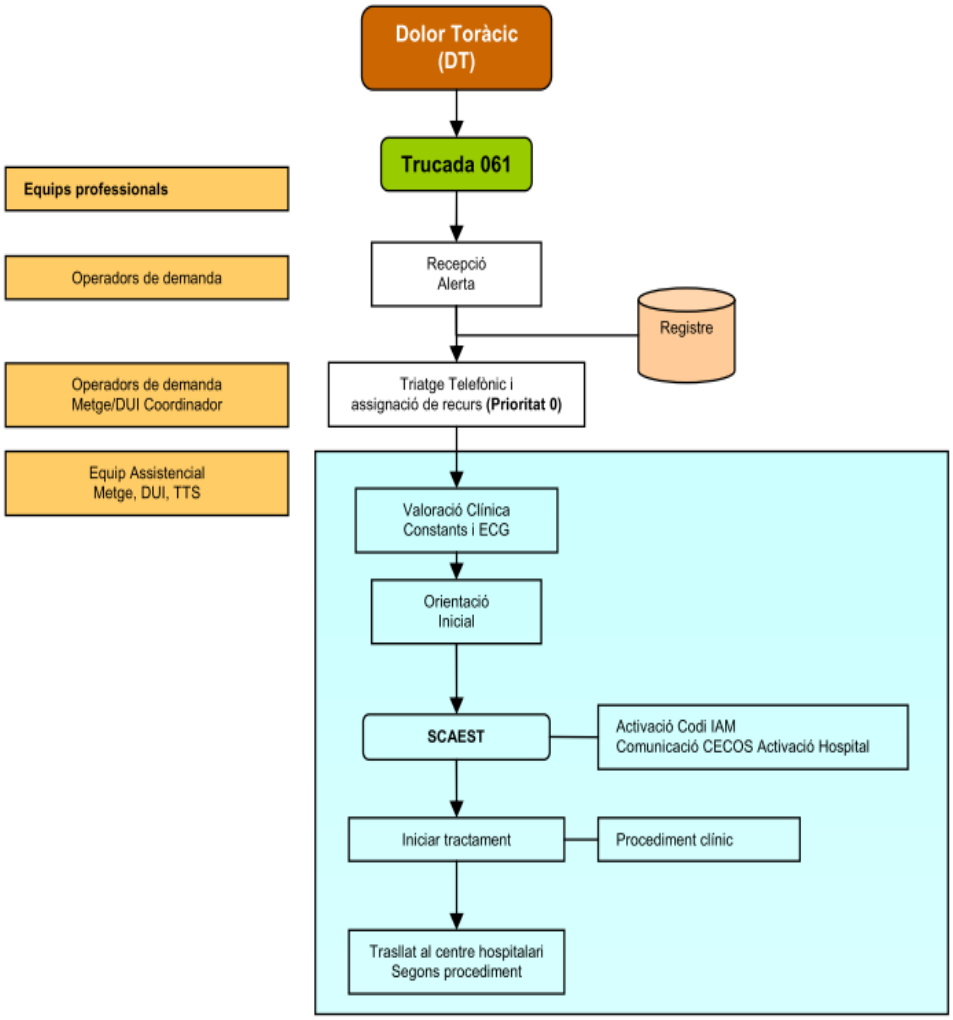

Illustration 6. EMS's operating procedure. [2] (24)

[2] DUI: Universitari en Infermeria i TTS: Tècnic en Transport Sanitari.