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ST-elevation myocardial infarction: gaps in current knowledge

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ABBREVIATIONS

ACS: Acute Coronary Syndromes

AV Blockade: Atrio Ventricular Blockade

BSM: Bare metal stent

DES: Drug-eluting stent

DI-DO: Door In-Door Out time

ECG: Electrocardiogram

EMS: Emergency Medical Service Ambulance

ESC: European Society of Cardiology

FIRB: Family Income Ratio of Barcelona

FMC: First Medical Contact

HR: Hazard ratio

IHD: Ischemic Heart Disease

INE: Instituto Nacional de Estadística

LBBB: Left Bundle Branch Blockade

LVEF: Left Ventricular Ejection Fraction

MI: Myocardial infarction

OR: Odds ratio

SO: Onset of Symptoms

PCI: Percutaneous Coronary Intervention

PPCI: Primary Percutaneous Coronary Intervention

SES: Socioeconomic Status

STEMI: ST-elevation myocardial infarction

TIMI: Thrombolysis in Myocardial Infarction

VF: Ventricular Fibrillation

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REVIEW AND ABSTRACT

Ischemic heart disease (IHD) is the leading cause of deaths in the world. In Europe ischemic heart disease is also the leading cause of death in both women and men. The disruption of an atherosclerotic lesion is the most common etiopathogenic finding of this

entity. Myocardial infarction is a main complication within the IHD body given the fact that it results in myocardial necrosis. ST-elevation myocardial infarction (STEMI) is precipitated by the persistent occlusion of an epicardial coronary vessel. Limiting myocardial necrosis is based on a timely treatment with reperfusion in which the thrombus that is occluding the coronary artery is retrieved by means of mechanical or lytic-drugs. Benefits of STEMI reperfusion treatment are therefore time-depedent. Health systems have organized networks to treat patients with STEMI within a time window in order to obtain benefits from extensive early reperfusion and decrease complications at population level.

The aim of this work has been to investigate: 1) the benefits for women of a contemporary STEMI network "Codi-IAM" which treats STEMI patients in the region of Catalonia, and 2) the relationship of socioeconomic status with treatment and prognosis after STEMI treated within this network in Barcelona city. The results of the analysis of the prospective cohort of "Codi IAM" from 2010 to 2017 showed the benefits of the standardization of treatments for all society and the inclusion of citizens into a secondary prevention measures. Neither women nor patients with low socioeconomic status had worse prognosis than men or those with higher income. The results of these two studies constitute an important and encouraging achievement to prevent health inequalities, however it also reveals that there is still room to improvement by ameliorating atherosclerosis detection and treatment especially for those who are less advantaged in society.

RESUMEN

Las enfermedades isquémicas del corazón son la principal causa de muerte en el mundo y en Europa. El fenómeno etiopatogénico fundamental en la cardiopatía

isquémica es la aterosclerosis y la inestabilización de las lesiones ateroscleróticas comporta, eventualmente, un síndrome coronario agudo. El infarto de miocardio es una de las complicaciones más frecuentes de la enfermedad isquémica del corazón y se traduce en necrosis miocárdica. El infarto agudo de miocardio con elevación del segmento ST (IAMEST o STEMI) se precipita por la oclusión persistente de un vaso coronario epicárdico. La extensión del daño miocárdico resultante depende del tiempo de oclusión coronaria que, si no se resuelve, produce finalmente necrosis. El beneficio del tratamiento de reperfusión es por tanto tiempo-dependiente; el tratamiento trombolítico o mecánico, mediante angioplastia primaria, reduce la necrosis miocárdica. Los sistemas de sanitarios actuales organizan redes distribuidas en el territorio para tratar pacientes con IAMEST dentro del periodo temporal en el que la reperfusión es beneficiosa en cuanto a disminuir la morbi-mortalidad a nivel poblacional. El objetivo de este trabajo doctoral es investigar 1) como la implantación y el despliegue de la red de tratamiento "Codi IAM" en Cataluña ha repercutido en la administración del tratamiento de reperfusión y en la mortalidad por IAMEST en mujeres y, 2) si la implantación de esta red de tratamiento urgente de IAMEST, "Codi IAM", guarda alguna relación significativa con el nivel socioeconómico de los pacientes con IAMEST tratados en la ciudad de Barcelona dentro de esta red, tanto en cuanto al tratamiento como en cuanto al pronóstico. Los resultados del análisis de la cohorte prospectiva de "Codi IAM" desde 2010 hasta 2017 muestran los beneficios de la estandarización de los tratamientos para toda la sociedad y la inclusión de los pacientes en el sistema de prevención secundaria. Pese a que tanto las mujeres como los pacientes con menor nivel socioeconómico presentan tiempos más prolongados hasta el tratamiento, ni las mujeres ni los pacientes de bajo nivel socioeconómico tuvieron peor pronóstico que los hombres o los pacientes con rentas más elevadas.

Los resultados de estos dos estudios constituyen una muestra de la importancia de la puesta en marcha de las redes de tratamiento urgente del IAMEST ya que implican un avance alentador en la prevención de las desigualdades a nivel poblacional; sin embargo, también revela que todavía hay margen de mejora para la detección precoz, diagnóstico y el tratamiento de la aterosclerosis, especialmente para las personas menos favorecidas de la sociedad.

1. Background

1.1 Epidemiology of Ischemic Heart Disease

Ischemic heart disease (IHD) is the leading cause of mortality in Europe [1]. This entity is an aggregate of clinical syndromes ranging from chronic coronary syndromes, acute coronary syndromes, ischemic cardiomyopathy and cardiac arrest. All these entities have a major common pathophysiology: the atherosclerosis. Despite the fact that mortality due to IHD has declined since the mid XX Century in the whole spectrum of European countries, the decline is less pronounced in southern European countries [2]. However, the burden of IHD does not decline because of longer life expectancy and increased risk factor prevalence [3] .

IHD has been the most frequent cause of death of Spaniards since current available Instituto Nacional de Estadística (INE) data published online. The percentage of death attributable to IHD ranges from 10.7% in 2002 to 7.3% in 2018 [4]. In 2018, the number of IHD in Spain ranged from 37.7 to 110 per 100.000 inhabitants depending on geographical location.

Acute coronary syndromes (ACS) are most commonly secondary to destabilization of an atherosclerotic plaque (rupture, ulceration, fissure or erosion) that leads to thrombus formation and decrease of myocardial blood flow, resulting in persistent or transient myocardial ischemia. Myocardial infarction (MI) is defined as myocardial ischemia leading to cardiomyocyte necrosis defined by an increase and/or decrease of sensitive/ultrasensitive cardiac biomarkers, preferably high-sensitive cardiac troponin, with at least one value above the 99th percentile of the upper reference limit [5].

Persistent myocardial ischemia is usually clinically identified by acute chest pain or pain-equivalent symptoms such as dyspnea, epigastric or left arm pain. Prior to the onset of ischemic symptoms, molecular changes start in myocardial cells of the left ventricle sub-endocardium's due to a sudden, strong decline of myocardial oxygen tension and eventually impairment in left ventricular function [6]. Molecular ischemic changes are

reflected in the electrocardiogram: a gradient between normal and ischemic zones that lead a current of injury that is represented by a deviation of the ST segment from the isoelectric line [7]. The location and severity of the ischemia are indicated by the amount and direction of ST segment deviation and generally reflects an acute total or subtotal epicardial coronary occlusion [8]. At this stage reperfusion treatment can salvage or limit the damage to the jeopardized area. If the injury persists longer than 20 minutes myocardial necrosis will develop.

The diagnosis of myocardial infarction has increased since the year 2,000 due to new European guidelines [9] resulting in a universal method of diagnosing myocardial infarction. The relative incidence of diagnosed/treated ST-segment elevation myocardial infarction is decreasing with a current incidence rate of STEMI ranging from 58 per 100,000 per year in Sweden in 2015[10] to 50 per 100,000 year in USA in 2010. In Spain there is no official registry to know the annual incidence of acute myocardial infarction; however, in 2010 there were 120.000 hospitalized MI patients and one third of them were patients with a STEMI diagnosis [11] [12].

Mortality of STEMI patients is known to be related to two types of factors: i) those related to the health administration, such as existence of public networks of emergency treatment of STEMI and access and timing to evidence-based treatments; and ii) those related to the patient such as age, Killip class, previous MI, left ventricular ejection fraction (LVEF), diabetes mellitus, severity and extension of atherosclerosis, renal dysfunction or ventricular fibrillation [13] [14]. In-hospital reported mortality in Europe varies from 3% to 17%. In European countries with robust-confirmation health systems and registries, the in-hospital mortality rates were between 3.1% to 4.8% [15]. The crude mortality of patients in the first year after STEMI hospitalization and primary percutaneous coronary intervention (PPCI) is still around 10% in most European countries [16].

However, STEMI mortality rates are probably underestimated due to the difficulties of merging data of pre-hospital sudden cardiac death rates, which still account for more than 30% of all IHD events in real-world population registries, with that from STEMI hospitalized patients [2] [17].

1.2 Current evidence-based treatments for STEMI reperfusion

Atherosclerosis prevention and reduction is the cornerstone of IHD treatment. Once atherosclerosis develops there is still no deep knowledge on who will develop an unstable plaque that will result in a persistent occlusion of an epicardial coronary vessel.

The optimal STEMI treatment that has proved to improve prognosis of patients is early administration of reperfusion [18] [19] [20].

The initial step of the treatment is the diagnosis which is based on clinical typical symptoms consistent with chest pain or atypical symptoms such as dyspnea, epigastric pain, syncope or sudden cardiac death. Patients presenting ACS without chest pain are frequently underdiagnosed and undertreated [21]. This point in the continuum of STEMI treatment in which a health technician, nurse, general practitioner or doctor can initially assist the patient and make the initial diagnosis of ACS is known as First Medical Contact (FMC). The time elapsed since the FMC agent suspects ACS, obtains a 12-lead ECG and detects persistent ST-segment elevation is known as FMC to ECG/diagnosis and is other cornerstone for a successful treatment to guide appropriate therapy [14]. Equivalent ECG changes that may hide an epicardial coronary occlusion such as left or right bundle branch blockade or pacemaker rhythm, should be identified and resolved as ST-segment elevation. The time between FMC and diagnosis should be as short as possible, with a gold standard set at 10 minutes [14]. Even those patients who survived a cardiac arrest should be immediately transferred for emergency treatment if ST-elevation is observed

or if there is high suspicion of ongoing infarction (presence of chest pain prior to cardiac arrest, previous history of IHD or uncertain ECG).

The goal of STEMI treatment is to reduce pain and to salvage as much myocardium as possible by a reperfusion treatment, that has shown to reduce mortality if administered within the first 12 hours after onset of symptoms [22]. Implementation of a reperfusion strategy in STEMI is a public health need and should be well organized in order to permit the administration of reperfusion treatment in a targeted time, which depends on where the FMC takes place. If the FMC takes place out of a PPCI center, the FMC agent has to decide whether to administer an immediate intravenous fibrinolytic treatment (if the presumed delay to perform PPCI is longer than 120 minutes) or transfer the patient to a capable PPCI center otherwise. This 120 minutes- time threshold for effective treatment from FMC to open artery/first device has been derived from observational studies and secondary analysis of "old" clinical trials [23] [24] [25]. Data from newer trials suggest that PPCI with an FMC to reperfusion within 120 minutes is comparable to prehospital fibrinolysis followed by an early angiography (less than 24hs), the so-called pharmaco-invasive treatment [26].

Reperfusion delay at any point of the process and with any of the reperfusion treatments, PPCI-related or fibrinolysis-related, is associated to increased mortality [27] [24] [28] [29] [30]. Observational data show that with FMC- to open artery times ranging from 60 to 180 minutes, each 10-minute delay led to an additional 3.3 deaths among 100 STEMI PPCI treated patients, but this increased mortality was even higher in patients presenting in cardiogenic shock [31].

1.2.1 Reperfusion by PPCI

Reperfusion by PPCI was first performed in 1982 by Meyer et al. and nowadays it is the preferred reperfusion strategy in those patients presenting within the first 12 hours from onset of symptoms and in those in whom treatment could be performed in less than 120 minutes from FMC in a high-volume PPCI center with an experienced team [32]. The time is set at 120 minutes because longer delays seem to decrease the benefit over fibrinolysis without routine early angiography; however more recent data showed only a chance of benefit of PPCI over fibrinolysis followed by routine early angiography if PPCI could be performed in less than 80 minutes from FMC [26]. What's more, there is currently a debate to find a reliable base to set the time threshold for choosing the most suitable treatment. Despite the fact that the rate of artery patency after fibrinolysis is higher than without, there is no reduction in mortality in post-hoc analysis and in propensity-matched cohorts [33] [34]. PPCI should be prioritized in cases with non-interpretable ST-segment on ECG (bundle branch block, ventricular pacing), symptoms lasting for more than 12 hours and electrocardiographic ischemic changes, recurrent pain, heart failure, shock or malignant arrhythmias. Reperfusion treatments in patients presenting without symptoms after 12 hours have less current evidence than conservative medical treatment alone [35].

Specific aspects of reperfusion treatments have also shown benefits in mortality in patients with STEMI undergoing reperfusion by PPCI. The radial access route used to PPCI has shown benefits compared to femoral access in reducing bleeding, a consequence of less vascular complications, and mortality [36] [37]. PPCI by coronary stenting instead of coronary balloon angioplasty has shown to reduce acute abrupt vessel occlusion, reinfarction and repeated revascularization. Drug-eluting stents (DES) in STEMI settings have also shown to reduce the need for reintervention compared to bare-metal stents

(BMS) [38] [39] [40]. However, there is still discrepancy on its effect on mortality [40] [41] at 5-year follow up.

About half of the patients presenting with acute STEMI have significant multi-vessel coronary heart disease according to the initial coronary angiography. Those patients have worse prognosis than patients with less extensive coronary disease [42]. Complete revascularization of significant non-culprit lesions before hospital discharge is recommended to reduce the number of new revascularizations after hospital discharge, but there are no significant effects on mortality with this strategy [43] [44] [45] [46]. In cases of cardiogenic shock complicating STEMI, there is evidence that treating only the culprit lesion is superior to multivessel PCI [47] [48].

1.2.2 Reperfusion by Fibrinolysis

Fibrinolysis was first administered in STEMI by Chavoz et al. in 1976 and it is currently a bail-out strategy for reperfusion in patients in whom PPCI cannot be offered in a timely manner, ideally in less than 120 minutes, except when there are formal contraindications. Fibrin-specific agents have shown lower mortality rates than non-specific agents [49]. The largest benefits from fibrinolysis are shown when it is administered in a pre-hospital setting among patients presenting within the first 3 hours from symptom onset in whom PPCI cannot be performed within the first hour after FMC [50] [51]; these benefits are reduced with increasing time elapsed since the onset of symptoms to treatment due to reduced efficacy compared to PPCI [52] [23]. After fibrinolysis, early angiography (less than 24 hours) and subsequent stenting, if indicated, has been established as standard of care to reduce early reinfarction and recurrent ischemia [53]. Fibrinolysis is associated to a significant excess of bleeding strokes that are more frequent in patients with lower weight, females, advanced ages, previous stroke and hypertension at admission [54].

Intracranial bleeds occurred in 1% of the population treated and major non-cerebral bleeds in 4-13% [55]. Lowering the fibrinolytic dose has reduced the rate of intracranial bleeding by 50% [51].

1.2.3 Reperfusion in cardiogenic shock

About 10% of patients with STEMI present with cardiogenic shock and about 50% of them die. Little improvements have been made in this sense in recent years. The first step in successful management of cardiogenic shock in STEMI is to rapidly identify it and treat the reversible causes such as ischemia, hypovolemia, mechanical complications and severe LV dysfunction. Early reperfusion (in less than 120 minutes) may prevent the development of cardiogenic shock and establish reperfusion within a time frame that allows rapid restoration of left ventricular function. European guidelines recommend reperfusion by PPCI in cases of cardiogenic shock. Nevertheless, this recommendation is not based on enough evidence because there is a lack of contemporary data comparing both reperfusion treatments. In the SHOCK trial, patients receiving fibrinolysis appeared to have a lower proportion of occluded culprit artery than non- treated [56]. However, PPCI-mediated reperfusion, when feasible, only of the culprit artery should be prioritized in cardiogenic shock patients, according to recent published evidence [48] [47]. Devices to decrease myocardial workload (Intra-aortic balloon pump counterpulsation and Impella devices) have been tested without any clear benefit in survival. A small benefit may be observed in those patients receiving fibrinolysis and intra-aortic balloon pump, although it is of importance to decrease loading pressures and increase perfusion pressures in such cases [57] [58]. Despite this, there is no strong evidence to recommend one reperfusion strategy over the other due to important methodological issues and lack of randomization in current available evidence.

Other devices such as intracardiac pumps and arterial-venous extracorporeal membrane oxygenation devices have been used in patients unresponsive to standard therapies and evidence regarding its effectiveness is scarce. Notwithstanding, and on an individual basis, short-mechanical circulatory support devices may be considered as a bridge towards myocardium recovery or cardiac transplantation [59].

1.2.4 Patients without reperfusion

Despite overwhelming evidence of the benefits of STEMI reperfusion on mortality and morbidity, there is still a high rate of patients who do not receive either PPCI or fibrinolysis. Registries from the late 90s of the previous century showed that at least 30% of the patients did not receive any treatment. Data from this century showed that no-reperfusion rate is still high but it is probably underestimated due to the absence of unified criteria for compiling data on non-admitted patients. In 2010-2011 the rates of STEMI patients not receiving reperfusion treatments ranged from 526 per million inhabitants (Ukraine) to 19 (Finland) [15]. No-reperfusion rates declined to 19% in countries/areas which implemented PPCI-facilities [60].

Factors associated to absence of reperfusion therapy relate to factors that determine to poorer outcomes: age > 75 years, high blood pressure, late presentation and geographical areas far from PPCI-facilities [61]. Moreover, patients in whom reperfusion has not been performed are often subsequently undertreated despite the fact that they should receive the same secondary prevention therapies as reperfused patients. The deployment of reperfusion networks has decreased the proportion of patients with STEMI receiving no reperfusion.

1.2.5 Reperfusion networks

In a real world setting, not all patients with STEMI can be treated in a timely manner due to multiple barriers. The main barrier is the absence of a universal and effective STEMI

network linking the pre-hospital environment, general practitioners and the Emergency Medicalized ambulance system (EMS), with PPCI hospitals. Regional STEMI networks have been promoted by European and American Societies of Cardiology [62] [14]. The aim of these networks is to minimize delays in reperfusion by streamlining the flow of patients, optimizing and standardizing treatments and to continuously audit data to readdress newly detected problems and maintain quality indicators. The main features of STEMI networks should be to define clearly geographic areas of responsibility, to share protocols of risk stratification in the pre-hospital setting and consequent transportation to an adequate institution depending on the area, to by-pass non-PPCI capable centers/emergency departments or to administer fibrinolysis at the FMC with subsequent transportation to a PPCI center [14]. The coordination of care between EMS and hospitals is associated with reductions in time to reperfusion and to decreased in-hospital STEMI mortality [63].

In most European countries, PPCI is the leading reperfusion therapy and its use has increased over time. In 2010, some European countries such as Germany and the Czech Republic were already treating 70-90% of all STEMI patients by PPCI [11]. At that time, Spain treated 58% of STEMI diagnosed patients by PPCI and 13% by fibrinolysis [12]. Spain reached the average of 417 PPCI per million of inhabitants in 2017 [64] consistently with the increase observed in Europe [65]. Stent for Life initiative, supported by the European Society of Cardiology, recommended a European average of 600 PPCI per million. However, different velocities in the introduction and implementation of reperfusion programs still exist in Europe and other world regions (Table 1).

One of the main delays in STEMI treatment is due to the available resources of the Health System and to the unawareness of IHD symptoms among the general population: this is

usually referred to as “patient-delay” in seeking medical help. This delay is calculated as the time from symptom-onset to FMC. Strategies in order to decrease this “patient-delay” have been investigated. Public media campaigns may increase the awareness of the community about heart attack symptoms and may also increase the number of diagnosed STEMI cases [66] [67]. However, public media campaigns usually fail to decrease care delivery delays [68]. Patients who take longer to seek help are older, with overnight symptom onset and they are usually not initially attended by an EMS. Presentation with severe symptoms such as unbearable symptoms, rapid development, self-attributed as cardiac or that matches the expectations to be cardiac, lead patients to seek earlier treatment than those with less severe symptomatology [69] [70]. Patients directly admitted to PPCI centers had shorter ischemic times and lower mortality rates compared to those who were admitted through an inter-hospital transfer [71]. New technologies associated to smartphones or smartwatches may help to decrease delays by prompt detection of ECG changes and direct contact with the STEMI network.

Once the STEMI patient is admitted to a PPCI-facility, the shortening of the door-to-open artery time is associated with lower mortality rates [72]. American accepted delays from FMC to reperfusion (or first device or open artery) are longer (≤ 90 minutes) [73] [63] than those recommended in Europe (<70 minutes, ≤60 minutes if counted from ECG) [14]. In the United States of America, where the organization of STEMI networks is delayed in comparison to most European countries, a 7% increase in the proportion of patients undergoing PPCI in less than 90 minutes was associated with a 50% reduction of in-hospital mortality. This reduction was obtained after the introduction of Lifeline STEMI systems Accelerator-1 and 2 projects [63]. Those projects were implemented throughout the country with grant funds to develop regional leaderships, systematic

implementation of processes, data collection and analysis and feedback in coordination with the American Heart Association.

The implementation of STEMI networks is highly variable worldwide due to several barriers: medical, organizational, patient-related, regulations and economic factors. Initiatives such as Stent for Life, a coalition between the European Association of Percutaneous Intervention and the EuroPCR, or STEMI Accelerator-1 and 2 projects served as models for organizing STEMI networks in different countries such as India (STEMI India project), China (China PEACE-Retrospective Acute Myocardial Infarction Study), Jakarta (Jakarta Acute Coronary Syndrome Registry) or Brasil (Salvador's STEMI Registry-RESISST) [74] .These projects resulted in an increase of number of reperfused STEMI patients, a reduction in delays, more patients transferred to adequate hospitals and better knowledge of the regional delays and barriers. Data from China revealed substantial gaps in the quality of cardiovascular care in both rural and urban areas [75] . In European countries with a strong reperfusion tradition such as the Czech Republic, France and Austria, the population's mean rate per PPCI- center is lower and report lower in-hospital mortality rates [15]. However, Sweden and Denmark have higher population mean per PPCI center but similar in-hospital mortality rates. Multiple factors interact across countries to explain these differences: the lack of good nationwide registries with standardized data collection, the prevalence of co-morbidities, supply factors, the country's health budget, reimbursement schemes, the definition of PPCI, data collection and registration of cases from both public and private systems, etc. One of the supply factors studied is the number of cardiovascular health professionals in the country or region. Data on this subject is scarce but whereas European countries have a median of 73 cardiologists per million inhabitants, developing regions such as Indonesia, have 2.7 [76] [77] and other countries have huge variations between rural and urban areas [75]

in terms of qualified interventional cardiologists. To agglutinate cases and maximize staff experience, European guidelines recommend that all PPCI facilities should perform the procedure systematically on a 24 hours and 7 days a week basis rather than daily/weekly rotation of PPCI facilities or multiple primary PCI centers in the same region [14].

Once a STEMI patient is admitted to a non-PPCI setting (e.g., an EMS, a general practitioner or in a non-PCI center), both the presence of an appropriate EMS and the geographical distance to a PPCI-facility, determine the optimal individualized strategy for each STEMI patient. For instance, in Canada, most of the population reside within 120 minutes of a PPCI facility but most Canadians with a STEMI first present to non-PPCI hospitals [78] [79].

Regional strategies around the world have been developed to increase the proportion of patients living in non-PCI capable areas who can receive timely appropriate PPCI or alternatively on-site fibrinolysis [80] [81]. General practitioners play an important role in the early care of STEMI patients because they can establish the diagnosis, alert the EMS, administer thrombolytic/opioid/anti-thrombotic medications and proceed to defibrillation if needed. However, in most settings the consultation with any actor other than the EMS will increase pre-hospital delay. If the diagnosis is directly made by the EMS, immediate activation of the catheterization laboratory is shown to reduce not only delays but also in-hospital mortality [72]. The EMS should be easily accessed by the general population to speed up any acute health process. The EMS access telephone number should be periodically advertised and the number should be easily recalled, preferably with the same number in a country/region. Parallel circuits for STEMI transportation that bypass the EMS should be avoided. The EMS should play not only the transportation role but also to diagnose, triage, treatment and coordination with the available resources [30]. EMS ambulances or transportation units should be equipped with technology such as ECG

recorders, defibrillators and with trained personnel able to register and transfer/analyze an ECG and administer initial medications (oxygen or opioids) and provide basic life support. Pre-hospital expert assessment ECG enables early identification of STEMI cases and allows early notification to the receiving PPCI-facility or ensures early fibrinolytic therapy. A strategy of obtaining pre-hospital or on-site ECG has shown to decrease reperfusion time and subsequent mortality, regardless of the patient being treated with PPCI or fibrinolysis [82] [83]. The diagnosis of STEMI by ECG can be performed by a paramedic, by an on-line health care provider or it can be interpreted by automated means with a computerized pre-specified algorithms. Nevertheless, available evidence shows that human interpretation is more sensitive to ECG STEMI identification than computer assisted interpretation [84] [82]. "On-line" ECG evaluation by a trained physician is feasible but it has two potential aspects to consider: it may add delays due to technical issues both in ECG transmission and ECG reading transmission but it also may decrease the rate of false positive STEMI diagnosis [85]. Each STEMI network should strive to optimize the diagnostic accuracy of the prehospital ECG by education programs, standardized updated guidelines and quality improvement programs.

Paramedics or nurses can also be safely trained to administer fibrinolysis when the PPCI is not feasible, the patient presents within the first 2-3 hours from symptom onset [86] and has no formal contraindication to fibrinolysis. On the basis of time-dependent mortality benefits of fibrinolysis, European guidelines recommended lysis therapy within less than 10 minutes from STEMI diagnosis [14]. Other regional guidelines recommend FMC to needle (fibrinolysis administration) within less than 30 minutes [73]. Recent data from randomized controlled trials show that fibrinolysis administration followed by very early angiography within less than 120 minutes [87] or early angiography within less than 18 hours [88] with subsequent PCI have similar favorable outcomes than PPCI. The

STREAM 2 clinical trial is still recruiting high risk patients (older than 70 years) to PPCI vs., pharmaco-invasive strategy with a half dose of a direct-thrombin lytic drug within the first 3 hours of symptom onset [89].

However, when a patient in a non-PPCI setting is triaged to be managed by PPCI, the EMS should bypass any non-PPCI facility or emergency department and take the patient straight to the catheterization laboratory. This bypassing strategy has been associated to reductions in total ischemic time (from FMC to device crossing/open artery) of about 20 minutes [90]. In many countries, however, patients first seek help into the closest non-PPCI facility [73] [91] [92] including the region of Catalonia in which at least 50% of patients with PPCI indication were first admitted into a non-PPCI hub [93] . The waiting time between the non-PPCI and the PPCI-facility (known as Door In-Door Out time, DI-DO) is an important parameter; it determines the overall delay to PPCI and correlates with total ischemic time [71]. If diagnosis is first performed in a non- PPCI facility, it is recommended that the maximum time until transfer to a PPCI center should be less than 30 minutes and inter-hospital transfer time less than 60 minutes [94]. Interventions that may help in reducing DI-DO times to the minimum include: training of non-PPCI personnel to promptly diagnose a STEMI even while the EMS is bringing the patient to the emergency room, endorse rapid ECG transmission and receive rapid answer to guarantee transfer bypassing the non-PPCI facility, rapid ambulance coordination and in some areas introducing fibrinolytic agents when long delay until PPCI facility is suspected.

1.3 Reperfusion treatment in Spain/Catalonia/Barcelona

In 1981, in accordance with the principle of territorial decentralization of the Spanish Constitution of 1978, the transfer of competencies in health care from the Social Security

to the autonomous communities began. The process culminated in 2001 following the development of the General Health Law 14/1986 [95]. Following decentralization, the different autonomous communities started to launch different strategies in health care. The Foral Region of Navarre was the pioneer in Spain with the first STEMI network initiated in 2002 after the constitution of the "Área Clínica del Corazón de Navarra" in 2001. Before that, individual interventional cardiologists performed PPCI without financial compensation. The creation of this consortium involved a budget to build a new catheterization laboratory and new hospitalization beds. The initial objectives of this strategy were to administer ready reperfusion treatment (PPCI or fibrinolysis) depending on where the STEMI patient was first cared for and the potential delays in patient referral to a PPCI facility. With this strategy, PPCI was adopted as the choice reperfusion method in the area corresponding to the PPCI reference center (Complejo Hospitalario de Navarra) and fibrinolysis in regional areas of Tudela and Estella [96]. However, the corresponding official registry did not start monitoring delays and impacts on health until 2010. Data from the Euro Heart Survey ACS registry showed that in 2007-2008, the rate of reperfusion in Spain was 74% (compared to 75% in Europe), whereas Navarre achieved a reperfusion rate of 81% mainly by PCCI (specifically 79% PPCI and 1.6% fibrinolysis). Within this period, mortality declined from the 7.2% to 4.8%. In 2009, Navarre region was performing 448 PPCI per million inhabitants whereas at the same time, the average in Spain was 261 PPCI per million [97]

A year later, the region of Murcia launched the APRIMUR network to cover the entire Murcia region. This was possible because of internal agreements between emergency department services, intensivists, cardiologists and interventional cardiologists. Cardiologists took the responsibility of treating patients with STEMI and interventional

cardiologists started to be paid for on-call nights. The number of PPCI tripled in six years and in-hospital mortality declined by 8% (from 14.6% to 6.6%) [98].

The PROGALIAM program started in 2005 in Galicia, with a population of 2,6 million. The aims of this program were similar to those of described above: i) to reduce morbidity and mortality and improve the quality of life of patients with STEMI; and, ii) to promote equity in access to health system services, to reduce variability in the use of resources and diagnostic and therapeutic technologies. When the program started, only 60% of patients were admitted to hospitals because 30% of them died before admission [99]. Recently, the IPHENAMIC study analysed data on 10,495 patients with STEMI, treated before and after implementation of the PROGALIAM network (2001-2005 and 2005-2013). The proportion of patients with no reperfusion treatment decreased from 37% to 27%, the rate of fibrinolysis declined from 40.3% to 11.4% and the number of PPCI increased from 22.7% to 61.7%. Unadjusted 30-day mortality decreased from 16.4% in 2001 to 7.7% in 2013. Rates of adjusted mortality decreased significantly throughout the 4 health regions of Galicia [100].

In Spain, the initiative of Stent for Life helped to launch regional strategies through the country in 2008, emphasizing the high number of STEMI patients that were not receiving any kind of reperfusion treatment (30%) and the low number of PPCI (169 per million of inhabitants) compared to the needs estimated by the European Society of Cardiology of about 600 per million or at least 70% of patients with STEMI treated with PPCI [101].

In Catalonia, a region with more than 7.5 million inhabitants, in 2003 there was one single center which performed PPCI in Barcelona. At that time, the *Consorci Sanitari de Barcelona* created a working group on ACS with representatives from the Public Health Agency, General Practitioners, EMS and public hospitals from Barcelona city. As a result, a common protocol on STEMI patients integrated management and treatment was

developed [102]. The Catalan Health Department created the Director Plan of Cardiovascular Diseases in 2004 which compiled epidemiological data, decided future objectives and designed plans to be achieve them. STEMI network was created and called "Codi IAM" and several regions were created around a PPCI facility. Several difficulties were encountered and in 2007 Catalunya still had a number of PPCI per million below the median of Spain. In 2008, a new Committee was commissioned to re-design the previous work and establish a new "Codi IAM" structure with the consensus of all parts including the Catalan Society of Cardiology, heads from interventional cardiology and coronary units from all the participating Catalan hospitals as well as the Public Health Administration. The new, re-designed, "Codi IAM" was finally launched under the protection of the 4/2009 Order from Servei Català de Salut. The Catalan Society of Cardiology and Stent For Life both played a key role in the development and deployment of the plan. There was a common protocol for the whole territory and it was based on the 2008 European Guidelines in which PPCI was the elective reperfusion treatment in patients in whom reperfusion could be achieved in less than 120 minutes and fibrinolysis was the bail-out strategy in cases without contraindications.

Seven Health Regions were designed and Barcelona's Area condensed more than 5 million inhabitants. Taking into account the isochrones of transportation to PPCI-facilities, 11 zones of STEMI treatment were planned around 5 PPCI-facilities working 24hours 7 days a week plus five hospitals with 7-12 hours , 5 days per week. The EMS was considered the cornerstone of the whole system, leading the decision of transportation versus on-site fibrinolysis and clinical streaming of the patients to the PPCI-center. Other relevant features of the "Codi IAM" network included the fact that STEMI patients were returned to their home reference hospital once treated and stabilized and that, from 2010 onwards, all patients were consecutively recorded through an on-line

case report form, which is audited periodically. The initial objectives of the network were: 1) to achieve a 90% successful reperfusion in STEMI patients presenting within less than 12 hours from onset, by using PPCI in at least 60% of patients; 2) that the 75% of patients who were initially cared at a PPCI-facility should be successfully treated in less than 50 minutes; 3) that the 75% of patients without complications should return to the residence reference hospital in less than 6 hours, and the 100% in less than 12 hours; 4) that FMC to diagnosis, Door-to-Balloon time and transfer should be less than 40, 30 and 50 minutes respectively; 5) that fibrinolysis should be administered in less than 30 minutes in at least 75% of the STEMI patients who had no contraindications and were expected to have long transfer delays, 6) all these measures should decrease 30-day in-hospital mortality [20]. During the first complete year of implementation of "Codi IAM" Network, 2,140 STEMI patients were treated: the rate of non-reperfused patients declined from 21% in 2006 (data from IAM CAT III) to 6% in 2011, PPCI increased from 31% to 86% and fibrinolysis treatment decreased from 37% to 3.6%. Crude 30-day STEMI mortality decreased from 7.7% in 2002 (data from IAM CAT II) to 5.6% in 2011 in patients receiving PPCI, but also decreased from 10.5% to 3.6% in patients treated with fibrinolysis [103].

Over the last few years the "Codi IAM" Network has increased its PPCI- facilities. There are currently 8 PPCI hospitals working 24 hours and 7 days a week. The EMS organization coordinates the link between patients, out-hospital-moving ambulances and PPCI-facilities according to delays until treatment. Fibrinolysis is only considered if transfer delays for PPCI are not acceptable and there is no contraindication. PCI post-fibrinolysis (rescue PCI) is carried out urgently in patients with evidence of absence of effective reperfusion. In patients with effective fibrinolysis, PCI takes place between 3 and 24 hours as recommended by ESC Guidelines [14]

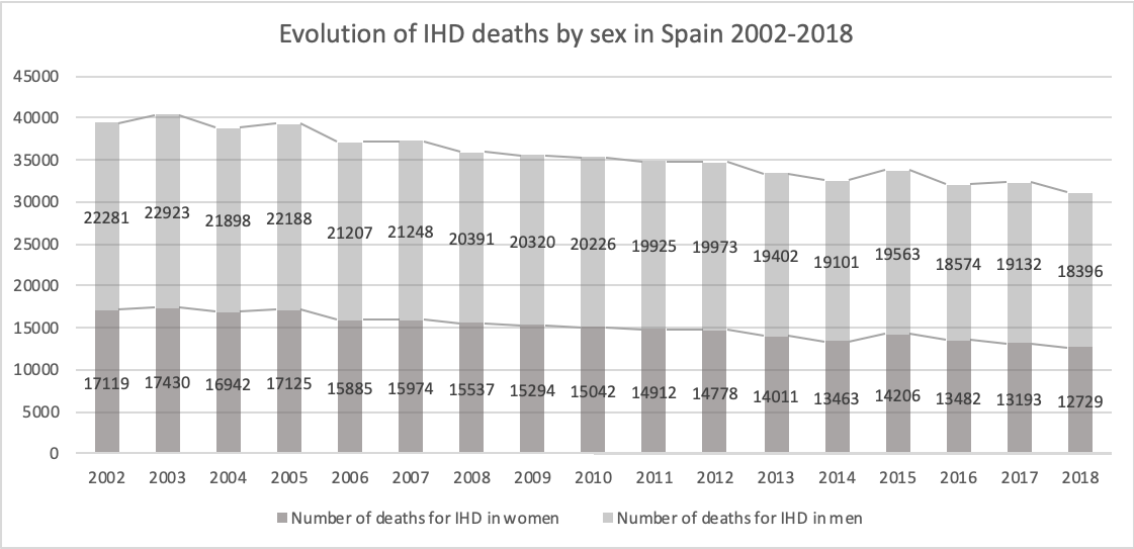
The “Codi IAM” registry started in 2010 and included demographic, clinical, care and therapeutic data and discharge data of patients with STEMI that evolved within ≤12 hours. Patients with cardiac arrest or death during first health care contact were included in the registry if ST elevation or new left bundle-branch block was diagnosed in any ECG during first medical contact. The Principal Investigator of the “Codi IAM” team of each participating hospital enters the data into an electronic database.Data collection was extended to new variables in 2012, 2015 and 2020. The registry is periodically validated by external audits to assure the quality of the data registered and analysed. Compilation of data on antiplatelet therapy during the first hours of admission to the Coronary Unit from the PPCI-facility was initiated in 2015. Data on vascular access, initial haemoglobin and renal function, SARS-CoV2 infection, left ventricular systolic function, arrhythmias during PPCI and cause of in-hospital death have been collected since 2020 alone.

1.4. Gender and STEMI

The effect of gender on STEMI prognosis is still a matter of debate. The multifaceted influence of age on access to health care and vital prognosis probably contributes to confound this gender effect which is not limited to the social and cultural influence on biological sex, but also includes the genetic determinants of sex and the concurrent effects of older age with sex such as lower use of invasive and medical treatments and more complications after interventions [104] .

Although IHD presents in women 7-10 years in average later than in men in western societies, it remains a leading cause of death in that gender. In Spain, the overall burden of IHD on mortality has progressively declined; nevertheless, IHD is still the leading cause of death in men during the 2002-2018 period whereas IHD resulted the second cause of death in women (until 2015) and nowadays is the third cause of death after cerebrovascular disease and non-specific dementia [4] (Figure 1). ACS occurs three to four times more frequently in men below 60 years whereas at older ages (75 and above) the majority of patients are women [105]. In effect, the risk of STEMI in men increases with age in a linear way but exponentially in women [106].

Figure 1. Evolution of the number of ischaemic heart disease (IHD) deaths by sex, 2002-2018 in Spain.



Therefore, in general, women who present with IHD are typically older. Advanced age already confers a higher mortality risk in itself. In addition, the female sex also carry a cluster of heavy risk factors due to age (diabetes, hypertension or heart failure) and they may also have social conditionings such as delayed or different access to health care. Some reports showed that women present more often without typical symptoms [21] which may add diagnostic and treatment delays [107].

Some reports have actually also described lower rates of guideline-indicated coronary angiography [108] and pharmacological therapies prescribed at discharge in women with STEMI; the latter can be only partially explained by the higher rates of non-obstructive coronary heart disease [109]. RCT show that women treated with DES have better prognosis in terms of all-cause death or recurrent myocardial infarction or repeated revascularization at 2 years [110] despite worse clinical features than men. A meta-analysis has shown that this benefit extends to all women with infarction-ACS over a 3-year period [111].

However, women are still underrepresented in current cardiovascular randomized controlled trials. On average, women represent 38% of all participants but this underrepresentation is more pronounced in trials with devices or with multi-interventions,

in trials with acute coronary syndromes, performed in Europe and for ages below 60. Effective strategies are needed to improve women representation in randomized controlled trials. In parallel, those randomized controlled trials should also include practical and innovative psychological, cultural and gender-specific measurements.

There is an ongoing debate on whether outcomes are poorer in women and whether these poorer outcomes are due to older ages and comorbidities. The last European Society of Cardiology (ESC) STEMI Guidelines reinforced the fact that women benefit at least equally from evidence-based treatments and that both genders should be managed with the same intensity. Applying timely IHD-treatments derived from evidence-based medicine could benefit women even more than men.

Similarly, the ESC suggested the need for publication of observational data and real-world evidence in order to measure and compare the quality of health care to promote initiatives with an improved quality.

1.5. Socioeconomic status and STEMI

Socioeconomic status (SES) is described in the Oxford Dictionary of Public Health as a "descriptive term that defines the position of persons in society, based on a combination of occupational, economic, and educational criteria, usually expressed in ordered categories, that is, on an ordinal scale. Many classification systems have been proposed, from a simple division according to occupation, which usually relates closely to income and educational level, to more complex systems based on specific details of educational level, income, occupation, and sometimes other criteria, such as whether the usual place of dwelling is owned or rented and the ratable value of the dwelling. Other factors, including ethnicity, literacy, and cultural characteristics, influence socioeconomic status, which is an important determinant of health may also be included" [112].

Until recently, the SES has been the forgotten actor when assessing cardiovascular prognosis.

Evidence coming from real-world registries has recently and progressively shown the importance of SES on cardiovascular medicine. CVD morbidity and mortality are strongly linked to SES conditions [113]. Patients with lower SES not only have higher rates of treatable cardiovascular risk factors and high needs of primary prevention, but also "unequal" access to treatments during and after admission [114]

In a global world perspective, it is easy to understand that SES is linked to prognosis of CVDs when we observe the IHD mortality secular trends that have decreased in high-income countries, due to detection of high risk population and improvements in health care systems. Whereas, in developing countries, there has been an increase of deaths attributable to IHD [115]. Scarce deployment of a country's resources on health produces inadequate access to health care, lack of health professionals and essential medical technology, and low adherence to evidence-based medicine. Real world reports on the management of IHD across the different regions of the world provide a benchmark for improving care and survival by comparing the management strategies and outcomes used in each region. There is, however, a connection between low-income and high-income countries: the nature of the health system and the financial status of its inhabitants to pay for treatments. For instance, PPCI reperfusion treatment was performed in an extremely low rate in Sri Lanka (<6%) [116] and in the United States PPCI treatment was used at lower rates in low income groups compared to the wealthiest (40% vs 45%) [117]. Data from the Nationwide Inpatient Sample of the USA during 2003-2011 period, demonstrated that SES, assessed by zip-code, was independently associated to longer delays from symptom-onset to reperfusion, lower rates of reperfusion by PPCI and higher mortality in STEMI patients [118]. Moreover, SES, assessed by zip-code, is not only

associated to worse outcomes after STEMI but, in general, the lack of access to health care due to economic reasons results in higher all-cause death rates. The private nature of health system and the incapacity of patients to pay for treatments is independently associated with increased in-hospital mortality after STEMI in the United States of America (3.4% in insured patients and 5% in non-insured, propensity-matched cohort) [119]. However, these data, generated by studies performed before reperfusion networks were deployed. More recent ACS cohorts show that there has been a decrease in mortality across all SES levels in the USA and that use of PPCI in STEMI patients has increased [117].

The standardization of treatments driven by evidence-based medicine and its consequent universalization allows countries with different income levels and different health systems to progressively organize emergency networks for early management of high-incidence, hospitalization and case-fatality rate diseases such as STEMI [116, 120].

The city of Barcelona offers annually through the Department of "Gabinet tècnic de programació" an extensive on-line document with an per-capita income index of the inhabitants of the 73 neighborhoods of the city which had a population with 1,664.182 inhabitants in 2020 [121]. The county of Barcelona has the leading in terms of income per capita in Catalonia; and the town of Barcelona is the second city with more than 50,000 inhabitants in per-capita income. The income in Barcelona city comes from wage incomes (60%), social benefits (21%) and from gross operating surplus (19%). After the loss of income of the inhabitants during the 2009-2013 period due to the Global financial crisis of 2008, triggered directly by the collapse of the housing bubble in the United States in 2006, which led to the so-called subprime mortgage crisis around October 2007, the GDP increased in Barcelona with a higher speed than in rest of Catalonia (the income per capita at Barcelona was 19,600 euros and in Catalonia was 16,500 euros in 2014). The

"*Índex de la Renta familiar a Barcelona*" or "Family income ratio at Barcelona" (FIRB) is an indicator of the relative income of residents in different neighborhoods and provides an annual snapshot of social inequalities referred to an average value of the city. The FIRB has been calculated annually since 2007 by the Technical Office of the Barcelona City Council and it can be accessed online [122]. This indicator combines five concepts: 1) population proportion of university graduates, 2) population proportion of unemployed to employable inhabitants, 3) number of vehicles per inhabitant, 4) engine power of the new vehicles acquired and 5) price of the second-hand housing.

Combining 2010-2016 "Codi IAM" registry data with Barcelona town hall FIRB information allows us to address the two key potential inequality issues in STEMI prognosis: the role of sex and SES.

2. HYPOTHESES

The aim of this work has been to investigate the effect of the implementation of the emergency network for diagnosing and treatment of STEMI in Catalonia and its effect on gender and its relationship with socioeconomic status in the city of Barcelona.

Main hypotheses:

2.1.1 The hospitalization rate of incident STEMI cases has increased with the implementation of the "Codi IAM" network both in women and men during the 2010-2016 period.

2.1.2 Ischemic time (from onset of symptoms to open artery) has decreased in women with the "Codi IAM" network implementation during the 2010-2016 period.

2.1.3 Female STEMI patients have similar 30-day mortality or complications or one-year mortality rates as compared to men after adjustment for confounding factors.

2.2.1 FIRB, as a SES surrogate, correlates with total ischemic time and 30-day mortality in patients treated in Barcelona city by the "Codi IAM" network during the 2010-2016 period.

2.2.2 SES is an independent predictor of mortality in Barcelona's STEMI patients treated within the "Codi IAM" network during the 2010-2016 period.

3. OBJECTIVES

The four objectives of this work are:

3.1. To analyze the trend in the hospitalization rate of number of cumulated STEMI cases diagnosed and treated by the "Codi IAM" network in Catalonia

3.2. To compare the trend of the total ischemic time between women and men with first STEMI treated within "Codi IAM" network through the 2010-2016.

3.3. To determine whether women with STEMI have different basal characteristics, delay times to treatment, treatment, 30-day complications or one-year mortality than men in the "Codi IAM" cohort recruited from 2010 to 2016.

3.4. To determine whether patient-SES is associated to total ischemic time, 30-day complications and one-year mortality in the "Codi IAM" cohort recruited from 2010 to 2016.

4. METHODS

4.1. Type of study

Retrospective multicenter cohort study

4.2. Population

For gender analysis, data from patients with first STEMI were retrospectively analyzed from the "Codi IAM" registry from the 2010 to 2016 period. Patients with previous myocardial infarction or any revascularisation were excluded to avoid the effect of previous learning.

For SES analysis, data from patients from the "Codi IAM" registry with a discharge diagnosis of STEMI from 2010 to 2016 that were inhabitants of Barcelona were included. Patients treated outside Barcelona's hospitals or non-residents were excluded because the complete follow-up was not available.

All patients included were diagnosed of acute myocardial infarction with ST-elevation (STEMI), with the criteria from the current guidelines when ST elevation of ≥1mm in at least 2 contiguous leads (2mm in precordial leads) in the qualifying ECG [14].

Fibrinolysis was only considered if transfer delays for PPCI were not acceptable and there was no contraindication. Rescue PCI (PCI performed after lysis) was considered in patients with ineffective reperfusion. In those with effective fibrinolysis, PCI took place before 24 hours as recommended by the ESC guidelines [14]. The local health system provides universal health coverage and, in addition it provides partial subsidy of medication costs depending on patients' income and working status. Mortality registry was analysed up to 2017 in order to obtain one-year mortality of cases from 2016.

The "Codi IAM" registry started in 2010 and included: demographic, clinical, treatment delays, therapeutic and discharge data of patients with STEMI seeking help

within ≤12 hours after symptom-onset. Epicardial coronary flow in the STEMI culprit artery was graded according to the Thrombolysis in Myocardial Infarction (TIMI) flow grade [123] and optimal reperfusion was considered if TIMI 3 flow was obtained at the culprit lesion. The number of data collected through the registry's electronic form was extended in 2012 and in 2015: in 2012 compilation of the variables number of diseased vessels and TIMI flow began, and in 2015 compilation was extended to include previously treated hypertension or dyslipidaemia, current smoking, previous stroke, previous antiplatelet or anticoagulant treatment and type and number of stents used during PPCI. Bleeding was considered only when a transfusion was required.

The Family Income Ratio of Barcelona (FIRB) is an indicator of the mean income ratio of the inhabitants of the 73 districts in Barcelona city and shows the imbalances relative to the mean income ratio of the city, set at 100. The FIRB has been calculated annually since 2007 by the Technical Office of the Barcelona City Council and it can be accessed via online [122]. This indicator combines five concepts: 1) ratio of university graduates, 2) ratio of unemployed to employable inhabitants, 3) number of vehicles per inhabitant, 4) engine power of the new vehicles acquired and 5) price of the second-hand housing. The FIRB of patients included in the "Codi IAM" registry was assigned to patients according to their address and consequent neighborhood by the Technical Office of Barcelona. In this study the FIRB has been used as a surrogate of socioeconomic status (SES). Three categories of SES were analyzed according to the FIRB classification used by the Technical Office: low SES (low and very low SES corresponding to FIRB values below or equal to 80), mid SES (mid-low and mid-high SES corresponding to FIRB to values from 81 to 125) and high SES (high and very high SES corresponding to FIRB values equal or above 126) [122].

Thirty-day and one-year all-cause mortality data were obtained from the Spanish mortality registry.

For this project, patients that were no-residents in Catalonia were excluded because the collection of follow up data from other regions of Spain or other countries was not feasible.

This project was approved by the ethics committee of Hospital del Mar (2020/9134 and 2020/9056). Data was not available to investigators because it was analysed by external statisticians who maintained data anonymized. Procedures and data collection comply with the Declaration of Helsinki and Spanish Data Protection Laws.

4.3. Endpoints

The primary end-points were: 30-day mortality and one-year all-cause mortality.

The secondary end-point was: a composite end-point including 30-day mortality and complications. This secondary end-point was assigned to patients that died within the first thirty days or suffered ventricular fibrillation, pulmonary oedema or cardiogenic shock during admission.

4.4. Statistical analysis

Dichotomous variables are shown as number and percentages, and continuous variables as mean and standard deviation or as median and interquartile range if they were non-normally distributed.

The comparison between groups was done by Student's t-test or the Mann-Whitney U-test for continuous variables, and Chi-Squared or Fisher exact test for categorical variables. The comparison of percentages over the years was performed with a Chi-squared for trends test.

Univariate analysis of patients with and without end-points was performed: death at 30-days or the composite end-point (cardiogenic shock, pulmonary oedema, ventricular fibrillation or death), and death at one year in 30-day STEMI survivors.

Objective 1:

Cumulated STEMI hospitalization rates per 100,000 inhabitants were calculated as annual total number of MI cases divided by census population by year, sex, and age group. Rates for the group aged >35 years were age-standardized (weights were 14, 14, 11, 7, 3 and 1 for age groups 35-44, 45-54, 55-64, 65-74, 75-84 and 85+ respectively) using the 1976 European Standard Population (ESP) [124], chosen over the 2013 ESP to allow direct comparison with previous publications.

Annual changes (95%CI) in the adjusted hospitalization rates were calculated with meta-analysis technique in the 2010-2016 period. Population trends were represented with smoothed curves obtained by nonparametric regression using the LOESS function from R (LOcally wEighted Scatterplot Smoothing).

Objectives 2, 3 and 4:

Logistic regression models were fit to obtain the odds ratios (OR) of the association between gender and complications at 30 days adjusted for potential confounders.

Cox proportional-hazards regression models were fit to obtain the hazard ratios (HR) of the association between gender or SES and one-year mortality in 30-day survivors.

Gender analysis

As compiled data has increased over time within the registry, there is a considerable percentage of missing values from the first years such as: initial TIMI (31.1%), final TIMI (33.4%), number of diseased vessels (31.2%), left main disease (25.0%), bare metal stent use (83.7%), drug-eluting stent use (82.3%), Killip class (1.5%), current smoking (54.5%), hypertension under treatment (54.5%), and dyslipidemia under treatment (54.5%), previous stroke (54.5%) and previous treatments (69.4%).

In the process of modelling, data with more than 5% of missing values were excluded. Finally, a robust model was analysed including age, diabetes mellitus, recruitment year and time from symptom-onset to the opening of the culprit coronary artery, and Killip class.

Due to extensive missing data, an age-matched analysis by age (+/- 2 years) with two men for each woman was also performed. This subset of patients was used to confirm the female effect in models adjusted for comorbidity (diabetes) and delay (time for symptom-onset to open artery) variables, as well as year of registration and centre of care (they were assigned to the hospital in which they spent most of their stay). Analyses were performed using the R software: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, and also using the SPSS software version 24.0. A p-value <0.05 was considered statistically significant.

SES analysis

Models were adjusted considering the confounding variables associated to STEMI prognosis which had <8% missing values: age, sex, diabetes mellitus, recruitment year, type of initial care, place of treatment, time from electrocardiogram to PPCI and Killip

Class. Patients' assignment to hospital was done according to the hospital in which they spent most of their hospital stay.

Analyses were performed using the SPSS software version 24.0.

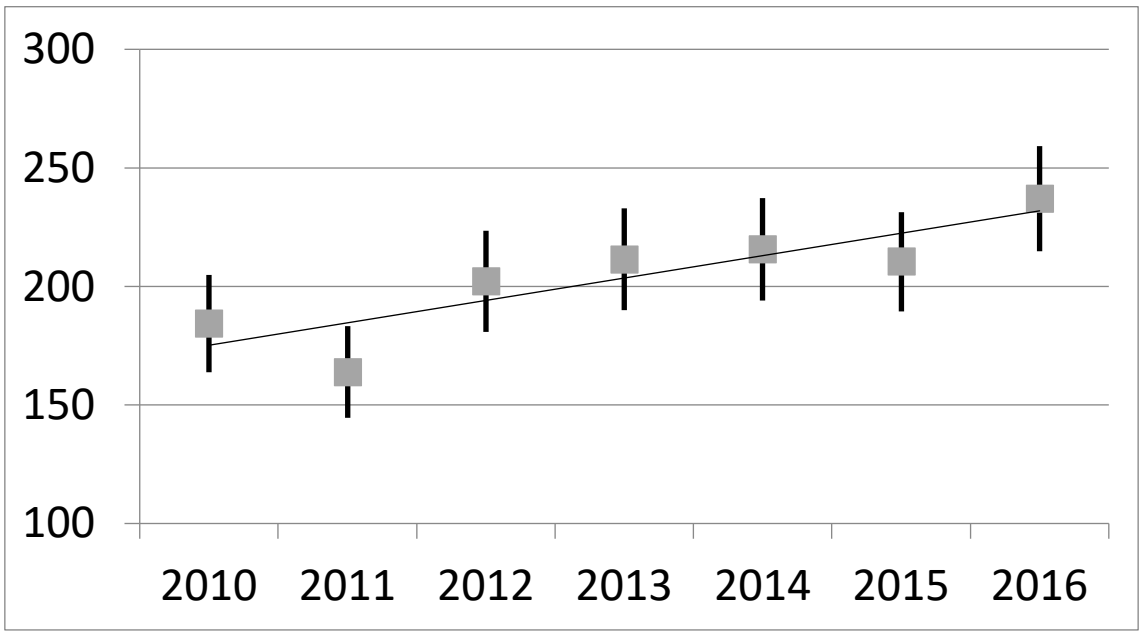
5. RESULTS

Objective 1: To analyse the trend in the hospitalization rate of cumulated STEMI cases diagnosed and treated by the "Codi IAM" network in Catalonia

The annual hospitalisation rate has increased in both men and women diagnosed and treated within the "Codi IAM" network during the first seven years of the implementation of the network (Figure 2). The annual hospitalisation rate in 2010 was 956 [95% CI, 909-2003] in men and increased up to 1,052 [95% CI, 1005-1099], p<0.001. The annual hospitalisation rate in 2010 was 184 [95% CI, 164-205] and increased up to 237 [95% CI, 215-259] in women, p-value<0.001.

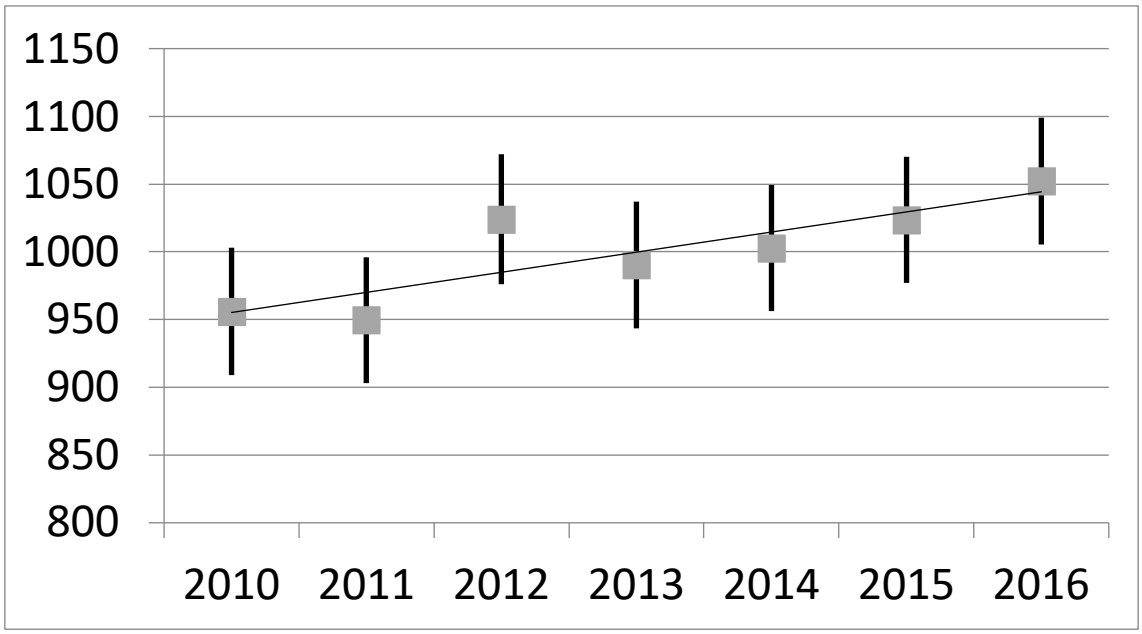
Figure 2. Annual "Codi IAM" standardized hospitalization rates per 100.000 Inhabitants with 95% confidence intervals for STEMI for female (panel A) and male patients (panel B), 2010-2016

Panel A) Females



Annual change 19.5 [95%CI 4.5-14.5], p-value < 0.001

Panel B) Males



Annual change 14.9 [95%CI 6.1-23.8], p-value < 0.001

Objective 2: Differences in 30-day complications and one-year mortality by gender in patients with a first STEMI managed by "Codi IAM", a population network of emergency triage, between 2010 and 2016

Population

From a total number of cases 23,507: 1,116 (4.75%) were excluded because they were not residents of the cathment area, 2,599 (11.1%) because they were not diagnosed of myocardial infarction at discharge, 2,329 (9.91%) because of previous myocardial infarction, 396 (1.75%) because of previous angioplasty, 90 (0.38%) because of previous

coronary surgery and 2,278 (9.7%) because of non-ST elevation on the electrocardiogram. The total number of patients included were 14,690: 3,452 women (23.5%) and 11,065 men (75.3%). During the 7 years of the study period the number of patients treated within the "Codi IAM" network with the final diagnosis of STEMI increased from 1,748 in 2010 to 2,250 in 2016 ($p<0.05$). The percentage of women did not vary significantly during the whole period (24%, $p=0.12$).

Clinical and initial care characteristics

Women were nine years older than men on average (69.9±13.7 vs 60.9±12.6, $p<0.001$) and had more comorbidities as expected from their age (more hypertension -34% vs 24%, diabetes -24% vs 17%- and dyslipidaemia -25% vs 21%-, $p\leq0.01$ for all) (Table 1) and were already taking anti-thrombotic treatments more frequently than men (chronic anticoagulants 1.9% vs 1.8%, antiplatelet therapy 6.5% vs 4.3%, $p\leq0.003$). Men were more frequently active smokers (13.6% vs 24.2%, $p=0.001$). Finally, women had more frequently severe heart failure at presentation (Killip III-IV 11.2% vs 7.8%, $p=0.001$).

Women first contacted the system differently than men did: they were first cared for more frequently by a facility without PPCI (38.9% vs 35.9%) and less by the EMS or General Practitioner (29.9% vs 31.2%, 19.2% vs 20.6%, $p=0.01$). During the FMC or first care, men had more ventricular fibrillation (4.7% vs 6.9%, $p=0.001$) and were more often sedated and intubated for controlled respiratory support (3.6% vs 4.9%, $p=0.001$). The FMC agent chose fibrinolysis less frequently for women than for men (2.5% vs 3.9%, $p=0.001$), both genders were transfer directly to a PPCI facility in a similar proportion (96% vs 95%), (Table 1).

Table 1 . Baseline patient and first care characteristics by gender in the "Codi IAM" network 2010-2016.

	Women N=3,486	**Men N=11,204**	**p-value**
Age,years mean (standard deviation)	69.9±13.7	60.9±12.6	0.001
Smoking*	13.6%	24.2%	0.001
Hypertension*	34.2%	24.3%	0.001
Dyslipidaemia*	25.2%	21.2%	0.01
Diabetes Mellitus	24.2%	17.2%	0.001
Previous stroke*	2.0%	1.4%	0.08
Chronic oral anticoagulant*	2.9%	1.8%	0.003
Previous antiplatelet treatment*	6.5%	4.3%	0.001
First contact			
General Practitioner	19.2 %	20.6 %	0.01
Emergency medical system	29.9 %	31.2 %	
Non-PPCI-centre	38.9 %	35.9 %	
PPCI-centre	12.1 %	12.2 %	
Left bundle branch block	1.78%	0.9%	0.001
Therapeutic decision			
Transfer to PPCI hospital	96.0 %	95.0%	0.001
Transfer to nearest hospital	1.2%	0.8%	
Fibrinolysis	2.5%	3.9%	
Complications			
Mechanical ventilation	3.6%	4.9%	0.001
Ventricular Fibrillation	4.7%	6.9%	0.001
Atrial Fibrillation	1.8%	1.4%	0.29
Atrio-ventricular Blockade	5.9%	4.5%	0.002
Pulmonary oedema**	1.5%	1.0%	0.03
Killip III-IV at presentation	11.2%	7.8%	0.001

(*)Data available since 2015 only.(**)Data available since 2012

ECG: electrocardiogram; **PPCI**: primary percutaneous coronary intervention

Treatment delays

The median delay times and trends by sexes during the study period are shown in Table 2. We observe that women have longer and significant delay treatment times throughout each of the intervals of treatment compared to men: 20 minutes in the median time from onset of symptoms to first medical contact, 16 minutes in the median time from onset of symptoms to hospital, 4 minutes in the median time to interpret an ECG, 8 minutes in the median time from ECG to open artery and a final 31 minutes of difference in the total ischemic time (<0.001).

Table 2. Median delay times and trends by sexes during the study period 2010-2016.

	Women	**Men**	**P-value for comparisons between sex**	**P-value for time comparisons**
SO-FMC, min	89.0 [40.0;193]	69.0 [29.0;158]	<0.001	p=0.016
SO-Hospital, min	143 [80.0;276]	117 [67.0;225]	<0.001	p=0.006
FMC-ECG, min	9.00 [4.00;18.0]	7.00 [4.00;15.0]	<0.001	p=0.004
ECG-therapeutic decision, min	24.0 [11.0;45.0]	20.0 [10.0;40.0]	<0.001	p=0.99
ECG-open artery, min	109 [83.0;144]	101 [78.0;138]	<0.001	p=0.001
Total ischemic time, min	231 [160;375]	200 [140;320]	<0.001	p=0.044

ECG: electrocardiogram; SO: onset of symptoms; FMC: First Medical Contact; Total ischemic time: from onset of symptoms to open artery.

The treatment delays varied during study period in the whole cohort. The so called "patient-delay" or time from symptom onset to FMC (or First assistance) decreased during the study period (p=0.016). And the majority of the "system-delays" tend to decrease in the whole cohort: FMC to ECG (p=0.004), ECG to open artery time -as a surrogate of achieving reperfusion- (p=0.001) and the final total ischemic time (that includes the whole delay from onset of symptoms to reperfusion) (p=0.044). The delay from ECG and the decision of treatment is taken did not vary significantly during the study period in the whole cohort.

The treatment delays varied during the study period in both genders (Table 3). The "patient-related" delay (SO to FMC) did decrease significantly in women (21 minutes of difference between 2010 and 2016, p=0.009) but did not decrease significantly in men (p=0.27). In parallel, a significant reduction in median delay from SO to hospital first care was observed in women (26 minutes of difference between 2010 and 2016, p=0.012) but no significant decrease was found in men. The median time between the ECG and its interpretation did not vary significantly in either gender (p > 0.267). The median and interquartile range regarding the time between electrocardiogram and open artery decreased significantly throughout the study period in both women vs men (119 min [85-160] vs 109 min [80-153] in 2010, 102 min [81-133] vs 96min [74-124] in 2016, all *p*-values<0.001.

Total ischemic time (from symptom onset to open artery) tend to decrease in both genders from 250 min [176-374] vs 224 min [155-1344] in 2010, 203 min [148-350] vs 190min [136-309] in 2016 but the decrease was only significant in men (p=0.006) but not in women (p=0.279).

Table 3. Temporal trends in delays at different levels of care over the 7 years spanned by the "Codi IAM" emergency care organization for ST-elevation myocardial infarction patients.Panel A,women and Panel B,men)

Panel A

Women	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**P for trend**
SO-FMC, min	94.0 [42.0;190]	80.0[40.0;168]	90.0[36.0;206]	90.0[42.0;212]	90.0[41.5;180]	85.0[40.0;195]	73.0[36.0;179]	p=0.009
SO-Arrival to hospital, min	155 [89.0;268]	130 [78.0;254]	149 [84.0;300]	150 [84.0;274]	149 [80.0;288]	135 [75.0;280]	129 [78.0;270]	p=0.012
FMC-ECG, min	10.0 [5.00;20.0]	8.00 [4.00;15.0]	9.00 [4.00;20.0]	8.00 [4.00;18.0]	10.0 [5.00;20.0]	9.00 [4.00;15.0]	8.00 [3.00;15.0]	P=0.027
ECG-therapeutic decision, min	24.0 [10.0;49.0]	22.0 [10.0;45.0]	22.0 [13.0;48.0]	24.0 [11.0;47.0]	24.0 [12.0;42.0]	24.0 [10.0;40.0]	24.0 [11.0;44.0]	p=0.267
ECG-open artery, min	119 [85.0;160]	113 [85.0;150]	110 [83.0;147]	110 [83.0;147]	110 [84.0;146]	104 [81.0;135]	102 [81.0;133]	p=0.000
Ischemic time, min	250 [176;374]	227 [159;375]	245 [160;419]	235 [163;376]	248 [165;392]	220 [152;354]	203 [148;350]	p=0.279

Panel B

Men	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**P for trend**
SO-FMC, min	80.0 [35.0;170]	67.0 [31.0;150]	65.0 [29.0;150]	69.0 [29.0;157]	65.0 [29.0;150]	63.0 [29.0;160]	69.0 [33.0;160]	p=0.276
SO-Arrival to hospital, min	125 [73.0;230]	114 [65.0;219]	114 [67.0;214]	115 [64.0;226]	115 [66.0;224]	110 [64.0;227]	118 [68.0;230]	p=0.11

FMC-ECG, min	8.00 [3.00;15.0]	7.00 [3.00;15.0]	7.00 [3.00;15.0]	7.00 [4.00;15.0]	7.00 [4.00;15.0]	7.00 [4.00;15.0]	7.00 [3.00;15.0]	p=0.062
ECG-therapeutic decision, min	20.0 [10.0;42.0]	20.0 [10.0;44.0]	22.0 [11.0;42.0]	20.0 [10.0;38.0]	20.0 [10.0;40.0]	20.0 [10.0;40.0]	20.0 [10.0;40.0]	p=0.558
ECG-open artery, min	109 [80.0;153]	110 [83.0;150]	105 [80.0;145]	101 [76.0;134]	102 [78.0;137]	94.0 [74.0;125]	96.0 [74.0;124]	p<0.001
Ischemic time, min	224 [155;344]	210 [149;330]	204 [145;325]	200 [140;326]	197 [140;313]	190 [134;305]	190 [136;309]	p=0.006

Data expressed with median [IQR]. SO: symptom onset; **FMC**: first medical contact **ECG:** electrocardiogram**; PPCI:** primary percutaneous intervention; Ischemic time: from SO to open artery.

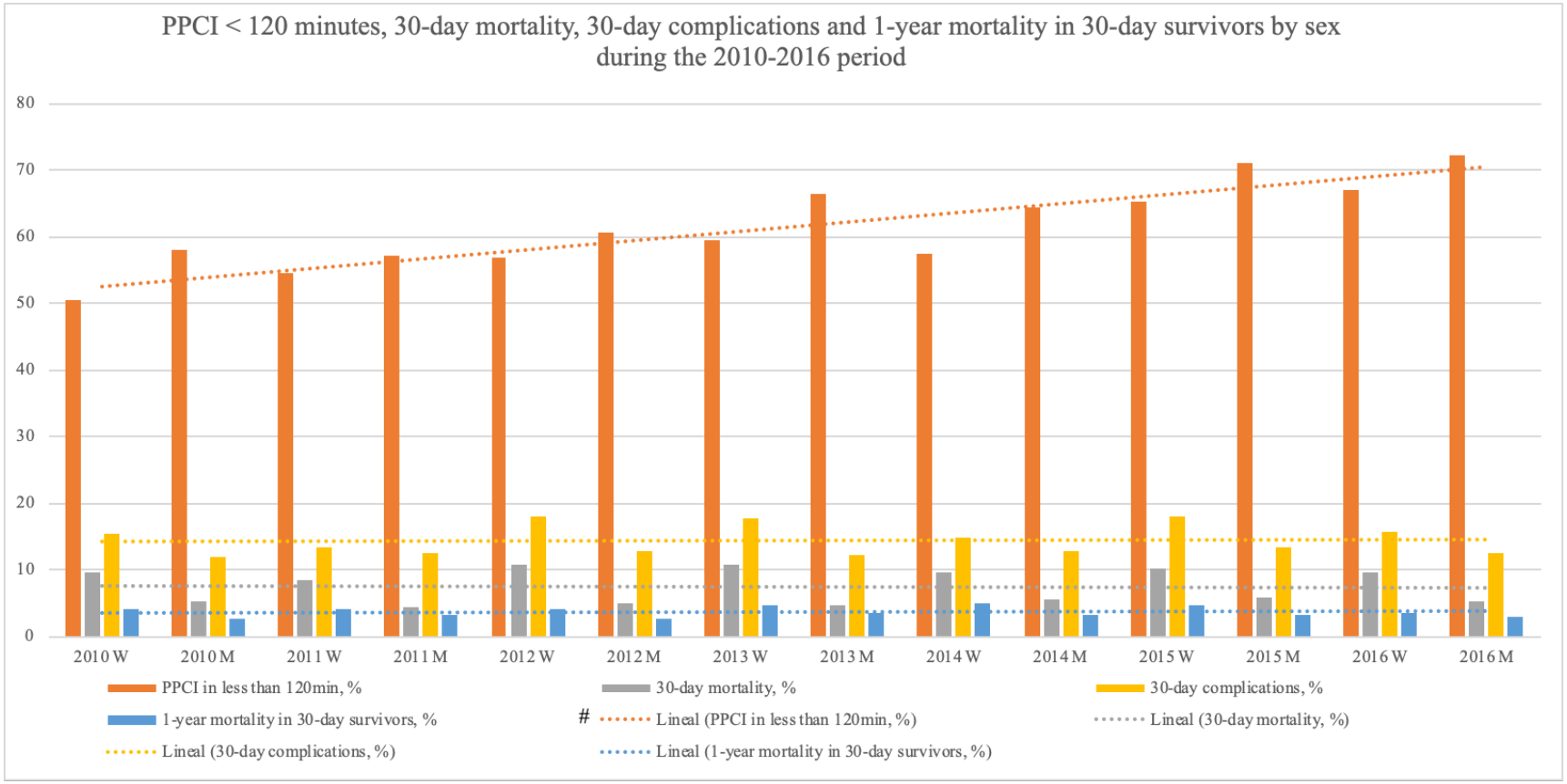
Women had lower rates of PPCI in less than 120 minutes than men in the whole study period (59.2% vs 64.7%, p<0.001), (Table 4). The proportion of patients treated with PPCI in less than 120 minutes increased over time for both genders: in 2010 only 50.4% of women were treated within 120 minutes and at the end of the period 67% of women were treated within this time-frame (p<0.001) (Figure 3). The proportion of male STEMI patients treated with PPCI in less than 120 minutes did also increase from 57.9% to 72.1% (p<0.001). The gender gap was reduced: in 2010 there was a 7.5% difference in the proportion of patients treated within 120 minutes and in 2016, there was a 5.1% difference (Table 5).

Table 4. PPCI in less than 120 minutes and end-points by gender in the "Codi IAM" network period 2010-2016.

	Women N= 3,486	**Men N=11,204**	**P-value for comparisons between sex**
PPCI in less than 120 minutes, %	59.2%	64.7%	<0.001
30-day mortality, %	9.93%	5.12%	<0.001
30-day complications, %	16.3%	12.6%	<0.001
1-year mortality in 30-day survivors, %	4.3%	3.08%	0.001

PPCI: Primary Percutaneous Coronary Intervention

Figure 3 . Temporal trends of rates of PPCI performed in less than 120 minutes, rates of 30-day mortality, 30-day complications and 1-year mortality in 30-day survivors by sex during the 2010-2016 period.



<0.05 in temporal trend

Table 5 . Temporal trends in delays at different levels of care and endpoints over the 7 years spanned by the "Codi IAM" emergency care organization for ST elevation myocardial infarction patients. Panel A, women and Panel B ,men.

Panel A

Women	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**P for trend**
PPCI in <120 minutes, %	50.4%	54.6%	56.9%	59%	57.5%	65.0%	67.0%	<0.001
30-day mortality, %	9.7%	8.3%	10.8%	10.7%	9.5%	10.2%	9.7%	0.906
30-day composite endpoint, %	15.5%	13.4%	18.0%	17.6%	14.8%	18.0%	15.7%	0.357
1-year mortality, %**	4.2%	4.0%	4.0%	4.7%	4.9%	4.6%	3.6%	0.952

Panel B

Men	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**P for trend**
PPCI in <120 minutes, %	57.9%	57.2%	60.7%	66.5%	64.3%	71.1%	72.1%	<0.001
30-day mortality, %	5.2%	4.4%	4.8%	4.7%	5.4%	5.9%	5.3%	0.539
30-day composite endpoint, %	11.9%	12.6%	12.8%	12.2%	12.8%	13.3%	12.4%	0.941
1-year mortality, % **	2.5%	3.2%	2.7%	3.6%	3.2%	3.3%	3.0%	0.668

**** in 30-day survivors; PPCI:**primary percutaneous intervention

Objective 3: To determine whether women with STEMI have different basal characteristics, delay times to treatment, treatment, 30-day complications or one-year mortality than men in the "Codi IAM" cohort recruited from 2010 to 2016.

Crude mortality rates were higher in women than in men: at 30-days the mortality of women doubled that of men (9.93% vs 5.1%) and the one-year mortality in those surviving at 30-days was also significantly higher, 4.3% vs 3% ($p \leq 0.01$ for both comparisons). Rates of complications at 30-days were also higher in women than in men ($p<0.001$) (Table 5).

There was no significant decrease trend in 30-day mortality, 30-day complications or one-year all-cause mortality in 30-day survivors during the study period in either women (p-values 0.906, 0.357, 0.952, respectively) or men (p-value 0.539, 0.941, 0.668, respectively) (Table 4).

Effect of Female Gender on STEMI prognosis

To analyze the effect of female gender on STEMI prognosis, several models of multivariate analysis were studied. The effect of female gender on 30-day mortality was initially analyzed with a model that included significant univariate data (Table 6) and excluded age and heart failure at admission.

Table 6. Univariate analysis of factors associated to 30-day mortality (A),30-day mortality or ventricular fibrillation or pulmonary oedema or cardiogenic shock (B) and 1-year all-cause mortality in 30-day survivors (C).

A)

30-day follow-up	**No 30-day complications N=13770**	**Death N=920**	**p-value**
Sex (women)	23%	38%	0.001
Age, years	62±13	73±13	0.001
Diabetes	18%	28%	0.001
Smoking	23%	10%	0.001
Hypertension	26%	33%	0.002
Dyslipidaemia	22%	33%	0.140
Previous stroke	1.35%	4.6%	0.001
Killip class I-II	94%	50%	0.001
OS-ECG (min)*	192 (379)	216 (401)	0.090
OS-Hospital arrival (min)*	234 (395)	264 (432)	0.040
OS-Open artery (min)*	319 (438)	348 (468)	0.100
ECG-Open artery (min)*	138 (282)	142 (110)	0.300
PPCI	91%	82%	0.001
Final TIMI 3	94%	72%	0.001
3-vessel disease	12%	22%	0.001
Left main disease	2%	9%	0.001
Bleeding	0.8%	3.7%	0.001
Left bundle branch block	0.9%	2.7%	0.001

B)

30-day follow-up	**No 30-day complications N=12714**	**Death or VF/Pulmonary Oedema/Cardiogenic shock N=1976**	**p-value**
Sex (women)	23%	29%	0.001
Age, years	62±13	66±15	0.001
Diabetes	18%	22%	0.001
Smoking	23%	16%	0.001
Hypertension	27%	28%	0.490
Dyslipidaemia	22%	22%	0.800
Previous stroke	1.32%	3%	0.001
Killip K I-II	97%	55%	0.001
OS-ECG (min)	197 (383)	168 (358)	0.002
OS-Hospital arrival (min)*	234 (400)	216 (384)	0.006

OS-Open artery (min)*	320 (438)	348 (467)	0.100
ECG-Open artery (min)*	136 (282)	142 (234)	0.300
PPCI	91%	85%	0.001
Final TIMI 3	94%	84%	0.001
3-vessel disease	12%	19%	0.001
Left main disease	2%	6%	0.001
Bleeding	0.6%	3.5%	0.001
Left bundle branch block	0.9%	2.6%	0.001

C)

1-year all-cause mortality in 30-day survivors	**No 1-year complications N=13275**	**Death or reinfarction N=495**	**p-value**
Sex (women)	23%	30%	0.001
Age	62±13	75±13	0.001
Diabetes	18%	29%	0.001
Smoking	23%	12%	0.001
Hypertension	26%	39%	0.001
Dyslipidaemia	22%	24%	0.500
Previous stroke	1.1%	6%	0.001
Killip K I-II	95%	79%	0.001
OS-ECG (min)*	190 (374)	262 (499)	0.002
OS-Hospital arrival (min)*	234 (390)	306 (512)	0.002
OS-Open artery (min)*	319 (438)	392 (493)	0.002
ECG-Open artery (min)*	138 (288)	139 (122)	0.700
PPCI	91%	88%	0.008
Final TIMI 3	94%	90%	0.003
3-vessel disease	12%	21%	0.001
Left main disease	2%	6%	0.001
Bleeding	0.8%	2%	0.007
Left bundle branch block	0.9%	2.6%	0.001

* Mean (standard deviation)

The resulting OR was significant (OR 1.9, 95% CI 1.63-2.2). But, when age and Killip Class were included in the model, the effect of female sex disappeared (OR 1.06, 95% CI 0.92-1.33). (Figure 4, panel A). Similarly, the effect of female gender disappeared when analyzing the effect of confounders on the secondary end-point of 30-day complications (OR 1.05, 95% CI 0.91-1.21) when age and heart failure at admission were included (Figure 4, panel B). At 1-year, when the effect of age or Killip Class were

excluded, women had increased risk of mortality. But when both age and Killip Class were included in the model, women had higher chance to survive than men in the whole cohort (HR 0.78, 95% CI 0.63-0.97) (Figure 4, panel C). The absence of effect of female gender on the three different end-points were further established by the analysis paired by-age with 2 men (Figure 4).

Figure 4. Panel A) Female ST-elevation patients adjusted 30-day mortality in the whole cohort and in the matched by age cohort adjusted odds ratio (OR) in the "Codi IAM" network during 2010-2016.

30-day mortality risk for female STEMI patients in the whole cohort		
MODEL 1 (n=13,468)	**OR**	**95% CI**
Female gender	1.90	1.63-2.23
MODEL 2 (n=13,468)	**OR**	**95% CI**
Female gender	1.06	0.92-1.33
30-day mortality risk for female STEMI patients paired by age with men		
MODEL 1 (n=8,313)	**OR**	**95% CI**
Female gender	1.04	0.85-1.26
MODEL 2 (n=8,313)	**OR**	**95% CI**
Female gender	0.98	0.79-1.22

Model 1 adjusted for adjusted for diabetes mellitus,recruitment year,center of recruitment and time from symptom-onset to the opening of the culprit coronary artery. Model 2 adjusted for Model 1 + Killip Class and age.

Figure 4. Panel B) Female ST-elevation patients adjusted 30-day complications in the whole cohort and in the matched by age cohort adjusted odds ratio (OR) in the "Codi IAM" network during 2010-2016.

30-day composite endpoint risk for female STEMI patients in the whole cohort		
MODEL 1 (n=14,690)	**OR**	**95% CI**
Female gender	1.29	1.15-1.45
MODEL 2 (n=14,690)	**OR**	**95% CI**
Female gender	1.05	0.91-1.21
30-day composite end-point risk for female STEMI patients paired by age with men		
MODEL 1 (n=8,313)	**OR**	**95% CI**
Female gender	1.00	0.87 – 1.15
MODEL 2 (n=8,313)	**OR**	**95% CI**
Female gender	0.94	0.79 – 1.11

Figure 4. Panel C). Female ST-elevation patients adjusted one-year mortality in 30-day survivors in the whole cohort and in the matched by age cohort hazard ratio (HR) in the "Codi IAM" network during 2010-2016.

1-year mortality in 30-day survivors risk for female STEMI patients in the whole cohort		
MODEL 1 (n=13,770)	**HR**	**95% CI**
Female gender	1.57	1.28-1.93
MODEL 2 (n=13,770)	**HR**	**95% CI**
Female gender	0.78	0.63-0.97
1-year mortality in 30-day survivors risk for female STEMI patients paired by age with men		
MODEL 1 (n=7,724)	**HR**	**95% CI**
Female gender	0.85	0.66-1.08
MODEL 2 (n=7,724)	**HR**	**95% CI**
Female gender	0.84	0.65-1.08

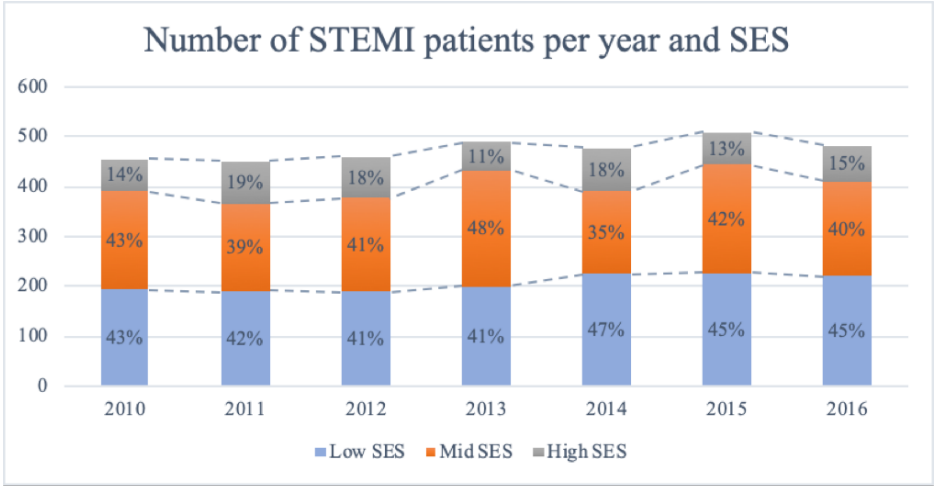
Model 1 adjusted for adjusted for diabetes mellitus,recruitment year,center of recruitment and time from symptom-onset to the opening of the culprit coronary artery. Model 2 adjusted for Model 1 + Killip Class and age.

Objective 4: Socioeconomic status and prognosis of ST elevation myocardial infarction patients managed by the emergency-intervention "Codi IAM" network.

Population

During the period from 2010 to 2016, a total of 4,691 inhabitants of Barcelona were included in the "Codi IAM" registry as treated STEMI cases. From these, 488 patients were excluded (10%) because it was not possible to confirm their usual residence, a further 1,369 (29%) of the patients were excluded because the final diagnosis was different from myocardial infarction. The final cohort used in the study resulted in 3,322 patients, that were distributed into the following SES categories: 1,443 patients (43%) were low SES, 1,366 patients (41.1%) were mid SES and 513 patients (15.4%) were high SES. During the period of the study there was a trend for an increase of STEMI patients treated within the "Codi IAM" network in the low SES group (p-value=0.1), (Figure 5).

Figure 5. Proportion of STEMI patients per year and Socioeconomic Status during the 2010-2016 period, "Codi IAM" registry.



p<0.1 for temporal trend

Clinical and first attention characteristics

Basal clinical characteristics showed that patients in lower SES were younger and had a worse clinical profile in terms of cardiovascular risk factors such as hypertension, dyslipidemia and diabetes mellitus (Table 7). Low SES patients were first cared for more frequently by general practitioners and less frequently cared in hospital facilities (Table 8). Patient-delays, as well as "system-delays", were longer in the low SES group than in the high SES group and there was a gradation from low to medium and high SES. Finally, the quality system indicator of PPCI in less than 120 minutes was achieved in higher rates in the high SES group (83% vs 78.6% vs 77%, p = 0.034).

Table 7. Baseline clinical characteristics according to socioeconomic status (SES) classification within the "Codi IAM" network during the years 2010-2016

	All **N=3,322**	**Low SES** **≤80** **N=1,443**	**Mid SES** **81-125** **N=1,366**	**High SES** **≥126** **N=513**	**p-value**
Age,years	65.3±13.5	64.4±13.9	65.8±13.3	66.6±13.0	0.002
Women,%	26.3	27.0	25.9	25.3	0.720
Smokers,% *	26.5	27.1	27.0	23.2	0.460
Hypertension,% *	40.8	43.0	41.8	30.4	0.024
Dyslipidemia,% *	32.1	35.2	31.9	22.5	0.008
Diabetes Mellitus,%	20.7	23.3	20.2	14.4	<0.005
Previous stroke, % *	2.6	2.9	2.2	2.9	0.790
Oral anticoagulant,% *	1.9	2.5	1.0	2.9	0.720
Antiplatelet drugs,% *	8.0	9.6	5.9	8.7	0.280

* Data since 2015, N=991.

Table 8. First medical contact and delays in initial medical care, diagnosis, and revascularization according to socioeconomic status (SES) during the period 2010-2016.

	All **N=3,322**	**Low SES** **≤80** **N=1,443**	**Mid SES** **81-125** **N=1,366**	**High SES** **≥126** **N=513**	**p-value**
First Medical Contact, **General Practitioner, %** **EMS, %** **Non-PPCI center, %** **PPCI center, %**	 15% 47.6% 11.4% 26%	 18.9% 49.1% 8.9% 23.1%	 13.4% 44.8% 13.2% 28.6%	 9.0% 51.1% 14.4% 25.5%	 <0.005
SO-FMC, min	69 [33-165]	74 [36-165]	69 [33-170]	60 [27-157]	0.005
FMC-ECG, min	9 [5-15]	8 [5-18]	10 [5-18]	9 [5-15]	0.030
ECG-open artery, min	85 [67-115]	87 [69-117]	83 [65-115]	81 [63-105]	<0.005
SO -Arrival to hospital, min	130 [82-240]	135 [85-240]	128 [80-254]	120 [75-225]	0.033
SO -open artery, min	184 [127-305]	190 [133-310]	180 [125-312]	165.5 [118-269]	0.003
PPCI <120 min from ECG, %	78.7	77.3	78.6	83.0	0.034

SO: Onset of symptoms. ECG: Electrocardiogram; Min: Minutes: median [Interquartilic range]; FMC: First Medical Contact; EMS: Emergency Medical System; ECG: electrocardiogram; PPCI: Primary Percutaneous Coronary Intervention

Reperfusion characteristics

Thrombolysis was administered in less than 0.3% of the population from the cohort (Table 9). Patients in the higher SES group had higher prevalence of initial complete occlusion of the culprit artery but also had a higher rate of less significant coronary disease in the angiogram. There were no significant differences in terms of three vessel disease (p=0.67) or prevalence of left main disease (p=0.3), anterior myocardial infarction (p=0.89) or need of transfusion (p=0.92). Patients with lower SES were less often treated with DES than those with mid-high SES (65.8% vs 81.8% vs 82.5%, p<0.005). An analysis was performed in order to understand which patients were treated more frequently with DES (Table 10). Patients in which a DES was implanted were younger (63.3 vs 70.7) and had a median SES of 81.6 compared to patients in whom non-DES was used that had a median SES of 80.6. The difference in median SES was one point. Patients with DES use were less frequently on oral anticoagulant treatment (0.9% vs 3.3%), more frequently had a complete occluded artery and more frequent had an anterior myocardial infarction (Table 10). Patients treated with DES had shorter treatment delays and less 30-day mortality or complications or 1-year mortality.

Table 9. Reperfusion procedure in the "Codi-IAM" network during the period 2010-2016 according to socioeconomic status (SES).

	All **N=3,322**	**Low SES ≤80 N=1,443**	**Mid SES 81-125 N=1,366**	**High SES ≥126 N=513**	**p-value**

Coronary angiogram without PCI, %	5.0	4.6	5.5	5.0	0.640
PPCI, %	93.4	94.2	92.7	92.5	
Thrombolysis, %	0.2	0.3	0.2	0.2	0.240
Initial TIMI 0, % *	68.3	66.3	69.0	72.2	0.035
Initial TIMI 3, % *	11.0	12.1	10.2	9.6	0.120
Final TIMI 0, % *	2.1	2.2	1.6	3.0	0.630
Final TIMI 3, % *	91.6	92.1	91.5	90.6	0.390
No significant epicardial coronary disease, % *	5.3	4.3	5.5	7.6	0.023
3-vessel disease, % *	15.0	15.2	15.1	14.0	0.670
Left main disease, % *	4.2	3.9	4.2	5.2	0.300
BMS use, % **	49.7	46.7	55.8	45.9	0.480
DES use, % **	74.3	65.8	81.8	82.5	<0.005
Anterior STEMI, %	41.8	42.4	40.6	43.1	0.890
Inferior STEMI, %	43.8	42.2	45.2	44.6	0.180
Bleeding with transfusion, %	0.6	0.7	0.3	1.0	0.920

* Data available since 2012. ** Data available since 2015.

PPCI: Primary Percutaneous Coronary Intervention. TIMI: Thrombolysis In Myocardial Infarction Flow; BMS: Bare Metal Stent; .DES: Drug Eluting Stent. STEMI: ST Elevation myocardial

Table 10. Clinical, procedural and endpoints by DES/BMS use.

	DES use **N= 460**	**Non-DES use** **N= 210**	**p-value**
Age,years	63.3 (12.5)	70.7 (14.4)	<0.005
Female gender, %	25.7	29.0	0.360
SES, **Median+-IQR** **Percentage into lower SES (<80), %**	81.6 (68.3 – 98.6) 42.6	80.6 (61.0 – 101.9) 49.5	0.027

Percentage into middle SES (81-125), % **Percentage into higher SES (>126), %**	44.6 12.8	39.0 11.4	0.250
Smoker*, %	36.5	22.9	<0.005
High Blood Pressure*, %	44.3	50.0	0.170
Dyslipidemia*, %	36.3	35.7	0.880
Diabetes Mellitus, %	23.5	21.9	0.650
Previous stroke*, %	1.5	3.3	0.130
Chronic oral anticoagulant*, %	0.9	3.3	0.020
Previous antiplatelet treatment*, %	6.5	9.5	0.170
Killip III-IV at presentation, %	11.8	14.8	0.280
First medical contact **General Practitioner, %** **Emergency Medical System (EMS), %** **Non- PPCI centre, %** **PPCI centre, %**	 19.0 49.0 9.8 22.1	 14.3 50.0 10.0 25.7	0.440
LBBB, %	1.3	0.5	0.330
Oral intubation and mechanical ventilation, %	6.7	6.7	0.970
Ventricular Fibrillation, %	8.3	5.7	0.240
Atrial Fibrillation, %	1.3	1.9	0.550
AV Blockade, %	4.6	8.6	0.040
Pulmonary oedema, %**	2.0	3.3	0.280
Shock, %	7.0	5.7	0.55
Initial TIMI 0, %**	35.4	26.7	0.025
Initial TIMI 3, %**	9.3	8.6	0.75
Final TIMI 0, %**	100.0	9.5	0.31
Final TIMI 3, %**	97.4	96.2	0.40
3-vessel disease, %**	15.4	15.2	0.95
Left main disease, %**	4.8	2.9	0.2
Anterior STEMI, %	49.3	29.0	<0.005

Inferior STEMI , %	41.7	60.0	<0.005
Bleeding requiring transfusion, %	0.0	0.5	0.31
SO-First assistance, min	60 (35–148)	90 (40–225)	0.016
SO -ECG, min	72 (43 – 163)	105 (52.5–263.5)	0.002
ECG-open artery, min	80 (63 – 110)	90 (71 – 115)	0.002
SO -Arrival to hospital, min	122 (80–220)	150 (95–317.2)	0.002
SO -open artery,min	169 (121– 278)	203 (144.5– 383.5)	< 0.005
PPCI in less than 120 min, from ECG %	80.0	76.9	0.37
30-day mortality, %	5.0	11.0	0.005
30-day composite, %	16.7	23.3	0.043
One-year mortality in 30-day survivors, %	2.7	7.5	0.007

LBBB: Left Bundle Branch Blockade; ECG: electrocardiogram; PPCI: Primary Percutaneous Coronary Intervention.; AV Blockade: Atrio Ventricular Blockade. TIMI: Thrombolysis In Myocardial Infarction Flow; BMS: Bare Metal Stent; .DES: Drug Eluting Stent. STEMI: ST Elevation myocardial infarction; OS: Onset of symptoms. ECG: Electrocardiogram; min: minutes: median [Interquartilic range]

(*) Data available since 2015

(**) Data available since 2012

The end-points are shown in Table 11: there was no difference in mortality at 30-days or at one-year, nor was there any difference between SES groups on the 30-day composite end-point. After adjusting for confounders (age, sex, diabetes mellitus, Killip class III/IV vs I/II, first medical care, coronary percutaneous intervention, hospital, year of treatment, time from electrocardiogram to coronary percutaneous intervention (> 120min) and type of initial medical care), it was found that low SES was not associated to 30-day mortality or complications or one-year mortality in 30-day survivors (Figure 6).

Table 11. End-points according to SES in the "Codi-IAM" network during the period 2010-2016 according to socioeconomic status (SES).

	All **N=3,322**	**Low SES ≤80** **N=1,443**	**Mid SES 81-125** **N=1,366**	**High SES ≥126** **N=513**	**p-value**
30-day mortality, %	7.7%	7.6%	8.3%	6.6%	0.430
30-day composite, % **	19.9%	19.4%	20.7%	19.1%	0.600
1-year mortality in 30-day survivors, %	4.7%	5.2%	4.9%	5.1%	0.810

** death, pulmonary oedema, cardiogenic shock or ventricular fibrillation

Figure 6. Low socioeconomic status (SES) patients with ST-elevation myocardial infarction (STEMI) adjusted odds ratio (OR) of 30-day mortality (model 1); a 30-day composite endpoint (death, ventricular fibrillation, acute pulmonary oedema or cardiogenic shock) (model 2); and hazard ratio (HR) of one-year mortality in 30-day survivors (model 3) in the "Codi IAM" network during 2010-2016.

MODEL 1: **30-day mortality risk for STEMI patients in the whole cohort**		
n=3,078	OR	95% CI
Low SES	0.95	0.70 – 1.30
MODEL 2: **30-day composite endpoint risk for STEMI patients in the whole cohort**		
n=3,078	OR	95% CI
Low SES	1.03	0.84-1.26

MODEL 3: **One-year mortality risk for STEMI patients in the whole cohort in 30-day survivors**		
n=2,720	HR	95% CI
Low SES	1.09	0.76 – 1.56

Models 1 and 3 were adjusted for age, sex, diabetes mellitus, Killip III/IV vs I/II, first medical care, coronary percutaneous intervention, hospital, year of treatment, time from electrocardiogram to coronary percutaneous intervention (> 120min) and type of initial medical care.

Model 2 was adjusted for age, sex, diabetes mellitus, first medical care, coronary percutaneous intervention, hospital, year of treatment, time from electrocardiogram to coronary percutaneous intervention (> 120min) and type of initial medical care.

6.DISCUSSION

The implementation of the “Codi IAM” network has resulted in the progressive increase in the number of patients diagnosed of STEMI diagnosed patients treated within this network (Figure 2). This finding concurs with the most recent published data about other reperfusion networks operating over the world, shown in Table 12.

Table 12 . Contemporary existing reperfusion networks over the world.

	France [125]	**Vienna [126]**	**USA [91]**	**Sweden [127]**	**Tamil Nadu-India [128]**	**China [129]**	**Jakarta [130]**	**Australia[92]**	**Brasil [131]**	**Korea [132]**	**Japan [133]**
Time frame	1995-2015	2002-2004	2008-2012	1995-2014	2013-2014	2001-2011	2008	2009-2016	2011	2005	2011-2013
Increase in STEMI admissions or population included,			18,583->41,644	5567->9749	898->1522	46,773->212,666			520	32,211	20,462
Initial PPCI rate, %	12%	16%	61.7% (transfer patients)/ 93% (direct PPCI-facility patients)	4.5%	21.8%	10.2%		43%		67.8%	
Final PPCI rate, %	76%	60%	89.9%/97.5%	78%	40.7%	27.6%		71%		99.1%	87.9%
Mortality decline, %	11.9% (17.2%->5.3% at 6-months mortality)	6.5% (in-hospital mortality)	1.6% (decline in in-hospital excluding cardiogenic shock)	In-hospital: 5.8% (13.6%->7.8%) 30-day:6.6% (15.8%->9.2%) 1-y mortality: 8% (22.1%->14.1%)	In-hospital: 0.2% 1-year mortality: 3.4%	8.4%->7% (2011)	6.6%->4.1%	6% (in-hospital) without changes, 6months 5%->4%	15% adjusted	0.9% in-hospital, 4% at 1-y (11.9->7.9%)	
Any reperfusion therapy, %	60%	66%->87%		67%->81%	88.5%->90.1%	13%->54%			40.7%		
Non-reperfused patients, %		34%->13%	6.2%->3.3			44.8%->45%	60%				

According to this data, when a health resource is implemented for a particular disease, the number of diagnosis increases, the delays due to the "system" decrease and the crude mortality decreases. However, in the "Codi IAM" series shown in this work, neither the 30-day mortality nor the one-year mortality of survivors decreased during the study period in either gender. This discrepancy between the reduction of the system-delays and the stabilization of the fatality within this cohort may be due to several reasons. The first reason is that Catalonia, as a community in Southern Europe, already had low fatality AMI rates in population-based studies where the population AMI incidence and mortality were among the lowest in Europe between 1990 and 2010 [2]. Similar findings were obtained from registries of patients admitted to hospitals for mortality during the 2008-2010 period [12]. In countries with lower AMI incidence, the declines in the population mortality rates although significant, are slower and less pronounced [3]. Moreover, the decline in population AMI incidence and mortality may have a limit that cannot be further reduced by any treatments unless the main cause of IHD, the atherosclerosis, is prevented or cured. However, there are some hints in previous population registries that show that there is still a chance to reduce mortality related to AMI, and specifically to STEMI. Population registries showed that whereas the total case-fatality and in-hospital mortality for acute myocardial infarction was declining, a significant increase in pre-hospital mortality in women older than 65 years was observed [2]. Cardiac arrest is the first IHD presentation form in up to 26% [134], most of due to ventricular fibrillation (VF). During the course of a witnessed STEMI it occurs in 8.7% of patients, 74% of the cardiac arrests occurring out-of-hospital [13]. Despite the fact that in attended STEMI patients VF has a higher incidence in men, women with acute coronary syndromes (ACS) have higher rates of pre-hospital mortality [135]. This increased out-of-hospital fatality rate in young

women with ACS could be due to different perceptions of health/disease that lead to different self-response to symptoms, to longer time until diagnosis and reperfusion and to increased ischemia burden or susceptibility to arrhythmia. Women are more likely than men to face delays between the onset of symptoms and FMC. In fact, longer "patient-related delays" are associated with female gender, older ages, diabetes and overnight presentation [136],[137]. However, exclusion of patients not transported by the EMS or with a delay of more than 6 hours, could have biased the results of one the previously mentioned works [136]. The patient-related delays observed in this study, with a mean difference of 20 minutes between genders, are similar to those reported in recent literature [107].

One of the causes of delayed care in women has been the interpretation of women symptoms' as atypical. Firstly women tend not to recognize this pain as being an IHD symptom and they managed it differently than men do [69]. And, the non-typicality of IHD symptoms in women, frequently attributed to higher diabetes prevalence in women with AMI, have been extensively described using retrospective data from clinical records in patients with confirmed ACS. However, these reports come from clinician-reported symptoms not from patient data reported from the patients themselves. When the patient reports the symptoms, chest pain is the most common symptom reported in both genders with myocardial infarction [138]. And, when standardized criteria for identifying ACS symptoms are applied, based on patient-reported symptoms such as the nature of pain, its location or radiation, "typical" symptoms are more common in women and have greater predictive value than in men [138] and atypical features in AMI presentation are more often self-reported by men. Self-reporting symptoms may increase the affirmation of associated symptoms in women but also help to disclose symptoms usually masked by guided interviews by clinicians. Therefore, the Cardiology Societies should make an

effort to eliminate the idea of gender-related atypicality and make the entire scientific community aware of the importance of self-reporting in the symptoms classification in the diagnosis of STEMI.

Despite the differences in times to diagnosis, some other delays should be kept in mind when considering the overall treatment delay in women with STEMI. System-related delays have also been reported. Some authors reported longer delays from FMC to ECG in women [107] while others reported similar delays (mean 8 minutes of difference between genders) [139]. The "Codi IAM" registry data did not show clinically relevant differences between genders in the time between FMC and ECG [140]

The ISACS-TC study is, an international observational registry aiming at providing a full spectrum of the management of ACS in countries with transition economy to help to improve outcomes by reforming healthcare systems. In 2017 this study reported an effect of gender on access to care and treatment delays for STEMI patients. Its main finding was that women with a STEMI treated in a timely manner (<120 minutes from onset of symptoms) do have the same 30-day mortality as men. The secondary finding was that women treated with a delay from onset of symptoms to hospital (equivalent to onset of symptoms until FMC and FMC to ECG, and diagnosis and transfer to PPCI-Fibrinolysis Center) longer than 120 minutes have worse 30-day mortality than men. They suggested that treatment delays should always be included into modelling due to the fact that reperfusion treatments are time-dependent and women are usually treated with longer delays. Moreover, they suggest that there may be biological differences in the response to myocardial ischemia that may have a deleterious effect on female prognosis [141]. This registry, however, excluded patients that did not know the time of symptoms onset (20% of the whole cohort) and, in addition, there were no available data on Killip Class at presentation in more than 30% of the cohort and therefore it was not entered into

adjustment models (despite Killip Class is usually the most powerful mortality predictor). The conclusions of this study may be added to those of Alabas et al. in which they analyzed the Swedeheart AMI registry [109]. Alabas et al. found differences in excess mortality that increased with age in both men and women with STEMI (Table 13). They found that excess mortality decreased after adjustment for co-morbidities and the additional adjustment for the use of evidence-based guideline treatments in women did further reduced excess mortality. Expected survival rates, however, were calculated by comparing STEMI patients from the Swedeheart registry to Swedish individuals matched only by age, sex and year of hospitalization. Similar results were obtained by a German study that revealed that older women received a coronary angiography less frequently than men although they finally received similar rates of percutaneous intervention to men (89.0% vs 91.2%) [142]. A further study, the TETAMI multicentered randomized trial showed that old age (>75 years) was a predictor of not receiving any reperfusion treatment as well as a predictor of 30-day mortality whereas female gender was not [61]. In the same direction, Otten et al [143] and the Leeds UK PPCI registry [144], both registries only including patients treated with PPCI, observed no influence of gender on MACE (myocardial infarction, unplanned revascularization or death) but an important effect of age was seen when stratifying patients by age, below 60, from 61-79 and above 80, respectively. The Vienna STEMI registry also showed that women had longer delays in treatment and lower rates of reperfusion (but similar to men in terms of PPCI rates). However, when adjusting for not only age and comorbidities but also for the use of reperfusion and "patient-delays" (SO-FMC), female gender was not associated to excess mortality (at 3 years) compared to men [145]. Treatments according to guidelines have been introduced over a period of time and this may also be an important confounder as shown by Zandecki et al. in the Polish ACS registry [146] and in the Swiss registry [147].

Table 13 . Most recent registries on STEMI and gender disparities

	Muhrbeck [107]	**Alabas [109]**	**Sambola [148]**	**Piackova[145]**	**Freisinger [142]**	**Zandecki [146]**	**Venetsanos [149]**	**Bugiardini [141]**	**Krishnamurthy [144]**	**Radovanovic [147]**	**Manzo-Silberman [150]**
Study dates	2010-2015	2003-2013	2005-2015	2003-2009	2009	2005-2011	2011-2013	2010-2016	2009-2011	1997-2016	2005-2012
Number of patients	539	60,712	277,281	4,593	124,995	111,148	1,862	6,022	3,049	30,398	16,733
Type of patients	STEMI	STEMI and NSTEMI	STEMI	STEMI	STEMI and NSTEMI	STEMI and NSTEMI	STEMI (Atlantic)<6hs	STEMI	STEMI treated with PPCI <12hs	STEMI and NSTEMI	STEMI<12hs
Prospective STEMI registry,	Yes (AMI)	Yes (AMI)	No	Yes	No	Yes (AMI)	No, RCT	Yes (AMI)	Yes	Yes (AMI)	Yes
STEMI network	Yes	Yes	Only 31% of patients	Yes	No	No	No	No	Yes	No	Yes
Publication	2020	2017	2020	2017	2014	2017	2017	2017	2019	2017	2017
Ages, w/m	74[65-81]/65[57-74]*	74(12)/67(12)*	74.7(13)/64(13)	67.2(13)/58.9(12)*	≥75yo: 50%/21.2%	2011: 69(12)/62.6(11)*	69(13)/59(11)*	64.8(11)/59.3(11)*	69(20)/60(19)*	71.3(12.7)/62.8(12)	70.6(14)/60.6(13)
HBP, w/m	61%/44%*	48%/36%*	59.7%/46%	59%/49%*	64.5%/60.3%	70.8%/63.6%	51.5%/40.5%*	71.4%/58.3%	47%/35%*		58.7%/38.8%
Diabetes Mellitus %, w/m	21%/19%	18%/15%*	35%/25.8%	23.4%/19.7%*	27.4%/20.6%	29.9%/20.8%*	13%/13.7%	29%/19%	14.4%/12.5%		19.6%/15.4%
Patient-delay min, w/m	61[29,156]/4[15,115]*			109[60-202]/90[50-180]*		232[126-490]/205[120-420]*	88(49-169)/70(41-129)*	60[15-180]/50[20-180]			20 min delay
FMC-ECG min, w/m	30/28										
Door to balloon min, w/m	28[18,40]/27[16,48]							45 [25-75]/45[27-80]			
Total ischemic time min, w/m				240[148-378]/220[146-360]							
Reperfusion rate, %		69%/79%*	95.4%/	93.2%/ 96.3%*							86.6%

PPCI rate, %			51.7%/68% (2015)	81.2%/82.9%	58.6%/70.3 %	92.5%/95.2% (coronary angiography)	83.7%/88.5%				66.7%/67.6%
No reperfusion, %				12%/3.8%*		7.5%/4.8%*					18.3%/11.6%
Heart failure during admission, %		29%/20%*	Shock 8%/5.3%	Shock 10.9%/7.8%*			Shock 0.5%/0.2%				
In-hospital mortality, %			18.7%/9.3%	11.2%/6.3%*	16.9%/9.9 %	7.7%/4.6%					9.6%/3.9%
30-day mortality, %						11.4%/7.5%	5.7%/1.9%				
Cox HR at 1 year after adjustments,		0.92(0.89-0.96)*	OR 1.23 (1.19-1.23)	3-year 1.7(0.59-4.9)		1.05 (0.86-1.29)	Cox at 1 month 2.08(1.03-4.2)	OR 1month <2hs 1.29(0.65-2.58) >2hs 1.77(1.05-2.99)	OR 12 month 0.99 (0.76-1.3)	OR in-hospital 0.95(0.93-0.96)	OR in-hospital mortality 1.85(1.32-2.6)
Adjustments		Age, sex, year of hospitalization, comorbidities (DM, HBP, previous MI, CRF, COPD) and reperfusion.	Comorbidities, cardiogenic shock, mechanical complications	Age, sex, diabetes mellitus, hypertension, smoking status, previous MI, GPIIb/IIIa inh, reperfusion, OS-FMC and shock		Age, sex, year of admission, HBP, DM, DLP, smoking, obesity, previous MI, Cardiac arrest, PPCI or emergent CABG, thrombolysis, previous PCI or CABG, anterior MI	Age, sex, comorbidities, access site, patient-delay, Killip Class, revascularisation	Age, sex, comorbidities and time to presentation < or > than 2hours, but no Killip Class (only available in 4003 patients)	Age, sex, race comorbidities and cardiogenic shock	Age, gender and year of treatment	Age, sex, comorbidities and patient delay and ischemic time Only included if FMC was a PPCI-hub or EMS No Killip Class included

*p-value < 0.05 for comparisons

For example, in those two studies, relative changes in treatments and outcomes are enormous: during the 7 year-period, comprised between 2005 to 2011, an 80% relative increase in coronary angiography in women was observed and age-adjusted mortality decreased in women at a rate of 5% per year, respectively. The Polish registry showed no effect of gender on STEMI mortality after a complete adjustment for clinical baseline characteristics, indicated invasive treatments and the year of hospitalization. They did not, however, included timely-manner treatments in the multivariate modeling [146]. The Atlantic (Administration of Ticagrelor in the catheterization Laboratory or in the Ambulance for New ST elevation myocardial Infarction to open the Coronary artery) prespecified study on the effect of gender on short-term STEMI prognosis. In this study, the effects of a randomized controlled trial in terms of population selection, such as only including STEMI patients with less than 6 hours from onset of symptoms, 0.5% of shocked patients and 75% with FMC being the EMS, indicated that gender had a marginal effect of sex on 30-day all-cause mortality (p=0.04) but no effect on primary end-points.

Sambola et al. (2020) published a Spanish registry of patients from the minimum data set of the National Health System that had been diagnosed of STEMI during the period from 2005 to 2015 [148]. Patients discharged to other hospitals after reperfusion were excluded. PPCI was considered when PCI was performed during the admission without thrombolysis administration. The end-point was in-hospital mortality related to the influence of network systems on reperfusion. As previously seen, the spread of reperfusion networks has not been homogeneous through Spain. In 2009, the mean PPCI per million inhabitants was 216, Navarra was at the lead with 427 and Asturias was the last with only 65. However, at the end of the study period (2015) women were less often treated with PPCI than men, 51.7% in women vs 68% in men. Compared to the work

presented in this thesis, Sambola et al. included patients codified as STEMI at discharge. This criterion may have resulted in inclusion of patients without a final AMI diagnosis. In the paper presented in this thesis, a 20% of the initially diagnosed STEMI patients were not confirmed and were therefore excluded from the analysis. This fact could also explain the different ages from both studies: mean age of women in the Sambola et al. work was 74.7±13 whereas in this thesis women who presented STEMI (first) had a mean age of 69.9±13. Older mean ages are consistent in the literature among cohorts with all kinds of ACS, not only STEMI. In consequence, higher rates of comorbidities (ie, diabetes mellitus) are encountered compared to other series. Besides, we excluded patients with previous AMI to better understand the initial responses of patients and of the health system in both genders and eventually decreasing the mean age of the final cohort.

Women, according to Sambola et al. registry, had a higher chance to undergo reperfusion if they resided in a region with a STEMI network (46.6% vs 32.4%), however, only 32% of all patients were managed through a network system. In addition, the study of Sambola et al. excluded patients transferred to other centers (12% of the initial cohort) and they were not included into the analysis of in-hospital mortality. Discarding the transferred patients and only including the non-transferred, usually with a higher severity burden, may have resulted in increasing the bias towards worse risk profiles of the patients included. Moreover, the in-hospital mortality is highly dependent on the ability of each network to discharge less severe patients to other hospitals. Sambola et al. described that the effect of gender on in-hospital mortality was significant when adjusted for only comorbidities and heart failure at admission (OR 1.23, 95%CI 1.19-1.26). There was no additional adjustment for reperfusion treatments or PPCI but lower in-hospital mortality in women was observed when reperfusion was performed during admission by PPCI through a network system. In the cohort from the study presented [140] the age was

a determining factor in the adjustment models (9 years of difference between men and women) and so, since it was not possible to assess other measures linked to age and associated with management (due to absence of data recompiled at the registry), it was decided to pair by age. For this reason, and to reduce the effect of potential unmeasured confounding factors, a sensitivity study with semi-restriction and matching by approximate age (± two years) was performed .In these models, no significant effect of the year of recruitment or the hospital in which primary angioplasty was performed was detected. This secondary analysis matching by age reinforced the idea that the gender has no effect at 30-day mortality or complications and a tendency towards better prognosis at 1-year, despite non-significance due to a probably decrease in statistical power secondary a decrease in the number of the population in the matched-cohort.

Several factors may explain the reduction of the "gender gap" previously observed some decades ago [151]: the first is that the vast majority of patients underwent coronary angiography catheterisation during the acute phase (97.4% of women and 96.4% of men) reflecting the extensive implantation of systematic reperfusion .It may also reflect the different nature of the underlying CHD affecting women: less angiographical evidence of significant epicardial disease than men [152] with more plaque disruption or coronary dissection [153] and CHD affecting smaller vessels with less ischemia burden [143].It may also reflect the incorporation of evidence-based therapies for both genders in terms of primary prevention and baseline risk factors and cardiovascular secondary prevention treatments after the first ischaemic event [154] [127].

In our study, first STEMI one-year crude mortality was higher in women than in men.This finding was mostly accounted by women's age and co-morbidities as shown in the adjunsted analysis of regression in which,after one year,women actually had better prognosis than men. The worse one-year prognosis of men after STEMI has been

previously reported and it may reflect the higher cardiovascular risk burden and the higher risk of reinfarction within the first year [154] [155].

The differences in the AMI treatment between sexes that were found in patients from Catalonia in reports from last century [151] seem to have progressively decreased until vanishing thanks to a structured universal health system and the implementation of networks to effectively administer evidence based treatments [156] [140].

Further research has been performed to evaluate the influence of race and female gender on STEMI prognosis. The recent Leeds PPCI registry showed no effect of Asian race or gender, compared to white, on MACE or mortality [144]. The effect of race on the prognosis of AMI has been extensively studied at the USA where blacks Americans bear a high burden of poverty and inequality compared with whites Americans [157]. During the previous century, black women were at higher risk of mortality after AMI even after adjustment for co-morbidities and SES indicators such as the level of education [158]. Nevertheless, many confounders had arisen to explain such racial disparities. Many studies have shown that racial disparities in health outcomes are mainly driven by carefully measured SES factors [159] [160]. In fact, a systematic review and meta-analysis found that socioeconomic deprivation was a strong predictor of IHD in both sexes but the association was a 24% greater in women than in men [161]. The effect of economic deprivation on health is more evident in countries without universal health coverage, such as the USA, in which population has to pay for a private health insurance to have a minimum health coverage: higher coverage or more technified treatments result in increased costs for the health insurance. In such an environment, the absence of an insurance due to economic deprivation is a significant predictor of mortality after AMI [162]. In fact, studies performed at the USA before reperfusion networks started to be

implemented reflected poor rates of reperfusion treatments among all SES groups (47.0% for the lowest SES and 53.6% for the highest SES) and nature of insurance (33.9% in Medicare and 53.9% with private insurances) [119].

However, the effect is also seen in Europeans such as in the Netherland's population in which there was an apparent increase of AMI risk in socioeconomic disadvantaged population that was more evident in women and young people [163]. Thus, economic deprivation and universal health are not the only mediators of such differences in AMI prognosis.

The relationship between SES and both short and long term prognosis after ACS has been studied at least since late 90s and early XXI Century, showing that low SES is associated with increased mortality after ACS [164], [165].

A wealth of more recent studies have shown that SES, measured by education level, occupation or income, is associated with increased prevalence of cardiovascular risk factors and worse outcomes after AMI [166], [167], [168]. However, SES may also reflect the characteristics of the health system of the region (universal vs private coverages) and neighborhood disadvantages such as difficulties in access to health, immigration status, social network and support [159]. Both individual-SES and the neighborhood-SES are independently and significantly associated with incidence of AMI [169]. The association between neighborhood-SES and AMI is generally well documented in western countries, indicating that those living in deprived areas experience the largest burden of cardiovascular risk factors with higher incidence [170], prevalence [171] and mortality [172] rates after AMI. Neighborhood-level SES is often used in population-based studies where individual-level SES is not available or where only economic data is available. Moreover, the interest in neighborhood-SES has also arisen because of the recognition of the importance of the environment in which people live for the risk of CHD. These

concepts are particularly important in the context of the present study because individual SES was imputed from neighborhood SES in Barcelona.

Neighborhood disadvantage, defined as low neighborhood education, income and living resource deprivation, is a risk factor of incident acute myocardial infarction all over the world: the incidence of AMI increases for those living in a neighborhood with socioeconomic deprivation [173]. Residing in areas with low economic resources may not only increase the risk of AMI due to a higher burden of cardiovascular risk factors but it may also determine a delayed care in acute processes and a reduced post-admission follow-up care such as cardiac rehabilitation [174]. Immigration status has a non-homogeneous effect: whereas the incidence of acute myocardial infarction seems increased in Sweden for the immigrated citizens [175] the contrary effect is found in Canadian immigrants [176]. Moreover, the survival after an AMI in Sweden is increased for immigrants compared to natives depending on its country of origin [177]. These data suggest that the immigration status on AMI risk depends not only of the SES level but also of the own/country of origin burden/protection. Social isolation, lack of emotional support, menial job strain or single status are associated to higher AMI incidence according to most of the published evidence [173]. Several reasons have been given to explain this relationship, for instance a higher inflammation level of markers associated with anxiety-depression, less participation in supportive resources that may reinforce self-care and health promoting behaviors including quitting smoking promoted in turn by cardiac rehabilitation programs [178]. Survival after an AMI is greater for those with high or medium social support than those with low support [179]. However, all these data come from heterogeneous studies with different time frames, different definitions, and may reflect inequalities in disease incidence, access to health care systems and poor compliance with secondary prevention medications [180]. Moreover, different SES

indicators were used in previous studies: household income [181], highest educational level [182], geographical area [180], racial aspects [159] and various composite indexes [183-186] (Table 14). The composite indexes can include varying combinations of household income, educational level, unemployment rate, vehicle ownership and engine power, prices of housing, proportion of families with >4 children, community services, environmental conditions and crime level. These composites indexes reflect a multilevel neighborhood-SES or strata of social, educational and economic data which can give a better picture of the concurring effects that determine health, acute and chronic treatment and follow up, compared to strictly economic information.

Table 14. Most recent registries evaluating the effect of SES in AMI-STEMI patients

	Stirbu [180]	**Biswas [183]**	**Denvir [185]**	**Shimorny [186]**	**Jackobsen [187]**	**Steele [184]**	**Fournier [188]**
Geographical area	Netherlands	Melbourne	Scotland, two hospitals	Soroka Med Centre, Israel	Western Denmark	UK, single center	French Swiss, single center
Determinant,	Income	Composite, by postal-code	Composite, by postal code	Composite, by area of residence	Income, individual	Composite, by postal code	Composite, individual
Timeline	2003-2005	2005-2015	2001-2002	2004-2006	2002-2008	2009-2014	2009-2010
Number of patients		5665	1346	1397	4856 (only PPCI)	3298	222
Mean age, low/high	65	62.1/64.3	63/69	59/65	68.6±12.9	14% of <45yo inlow/4.5% in high	
Female, %		23.1-21.3	37/31	20/15	35.1/17.9	30.1/24.5	27.9
Diabetes Mellitus low/high, %		19.5/13.8	13/10	46/28	11.6/7.5	15.9/13.6	22.9
Diagnosis	Acute myocardial infarction	STEMI treated with PPCI or post-fibrinolysis PCI	Patients with PCI	44% STEMI, 38%NSTEMI 13% SA	STEMI who underwent PPCI <12hs SO	STEMI treated with PCI	STEMI treated by PCI, fibrinolysis excluded
Structural network for STEMI	No mention	Yes			Yes, PPCI as standard STEMI tt		
Killip class III-IV low/high, %				13/5			
PTCA in lower/higher income group, %	18.6/26.5	65.8/96.3			100%		
SO-OA, min (lower/higher groups)		105(62-205)/100(65-168)					
30-d mortality, %	10.5					37/10.2	
1-y mortality, %	16.5					34.6/11.7	3.1/1.8

30-d mortality in lower/higher income group, %	14.2/8.3	7.1/7.1			Unadjusted/adjusted HR 2.05 (1.56-2.7/1.13(0.83-1.54) for med, 3.27 (2.53-4.23)/1.16(0.84-1.6) for low	HR (low) 1.35(0.79-2.33) or 1.2 (0.69-2.14)/(mid) 1.18(0.68-2)	
1-y mortality in lower/higher income group, %	22.3/12	10.3/9.2	2.6/2.7			HR (low) 1.1(0.7-1.65)/ mid 1 (0.69-1.5)/0.9(0.64.1.45)	
2-y mortality in lower/higher income group, %				10/11			
Medications at discharge		Yes	No	Yes	Yes	Yes	No
Interaction		No, SES HR 1.01 (0.96-1.08)	No	Yes, low SES HR 1.52(1.03-2.25)	No interaction when adjusting for baseline characteristics	No interaction when adjusting for baseline characteristics	No studied

Studies from various geographical areas have found that access to revascularization procedures in AMI patients is reduced in groups with lower SES [189]. The population analyzed and presented in this thesis represents a sample of homogeneously-treated STEMI patients: most of them (> 93%) were treated by PPCI in a universal integrated medical system, but also features the inclusion of patients not treated with PPCI (fibrinolysis and those who finally were not treated with angioplasty+stenting). The use of PPCI in STEMI patients varies largely by regions, and as mentioned above can be explained by several factors such as limited supply, number of physicians and number of available hospitalization beds for acute conditions, as well as constraining measures and "patient-level" factors [190]. Network organization and public access to care and health may result in neutralization of both the higher incidence of the disease and adverse clinical baseline characteristics in low SES groups [118, 119]. In the data from the "Codi IAM" study, the low SES group had a worse cardiovascular profile, longer treatment delays and different access routes to the health system, which did not however translate into a worsen 30-day complications or one-year mortality. Besides, when adjusting for potential confounders, SES data was not associated with either endpoint. Similar findings have been described in international more recent cohorts in different studies performed in single-center fashion [184], [188] , in groups of hospitals within a geographical area [185] [187] or within a city [183] (Table 14). Those studies have in common the inclusion of patients with STEMI treated with PPCI as a standard treatment within a structural universal STEMI network and showed no interaction of SES with mortality. However, most of these registries reported results from cohorts of patients from before 2010. Other previous registries also included patients with other conditions such as non-ST elevation myocardial infarction [186] or excluded patients treated with fibrinolysis [188]. The exclusion of patients treated with fibrinolysis or patients who did not received PPCI may

however bias the results of any study aiming to clarify the importance of socioeconomic factors in STEMI prognosis because of the geographical gradient towards the periphery for lower income groups and its relationship with the optimal timing of treatment for PPCI [30] [183] [191] . The lower use of DES in the low SES group observed in our study has also been reported in USA cohorts [192-194] and is called a "treatment-risk paradox". This condition means that higher risk patients are not treated with optimal or evidence-based strategies and use of highly technified devices such as mechanical support devices is reduced [184]. This finding may reflect the fact that differences in outcomes may not only be related to the use of a specific treatment/device in the acute period but to a whole standardized medical approach in which access to a secondary prevention resources may be of utmost importance [127].

Limitations

Both projects have several limitations. Firstly, data is derived from the first seven years of implementation of a regional STEMI network in which management guidelines and clinical practice have evolved very rapidly during the study period [195], [196], [197], [14]. Consequently, and in parallel, the registry has also evolved including progressively new data: during the study period, three updates of the variables collected in the on-line registry electronic case report form were carried out (2010, 2012 and 2015) to collect more detailed information on the patients background and the treatments used in the acute phase. For instance, the pulmonary edema as a complication during the FMC was not available during the 2010-2011 period. However, those events may correspond to as little as 60 events out of the 1,979 considered in the study in the 30-day complication endpoint, corresponding to 3% of all events. Data on FMC medications and intensive coronary unit

first medications were only registered from 2015 on, and previously there are no records on the pharmacological therapy administered during admission or at discharge. These treatments as well as patients' adherence to the prescriptions, have been shown to have a direct impact on in-hospital and one-year mortality [127] in both genders and may be also related to SES [186]. A standardized protocol of data collection on antiplatelet therapy at discharge was added to the "Codi IAM" registry electronic form after new data on antiplatelet therapy were published [196]. Furthermore, the registry still had no records on gender-related risk factors such as menopausal status which have shown to have a strong impact on the pathophysiology of cardiovascular diseases [198]. The cause of death is not available either, therefore the weight of cardiovascular mortality on the total death rate cannot be inferred and assumed to be cardiovascular during the hospitalization for the acute phase. However, the secondary end-point (30-day complications) from both projects is an attempt to reflect not only the cardiovascular death during the first 30-days but also the cardiovascular events most frequently related to death after STEMI during the first 30-days (pulmonary edema, cardiogenic shock and ventricular fibrillation).

The FIRB index is a composite surrogate of SES that aggregates data from all the inhabitants of a given district, not strictly the zip-code, so it does not allow us to analyze the effects of individual-level SES. However, the FIRB as a surrogate of neighborhood-SES, similar to zip-code, results in a useful tool. Several previous studies have validated this approach of imputing individual SES in epidemiologic studies to reflect aggregate characteristics of the population and the prevailing habits as well as its environmental attributes (such as available health resources) that impact on residents' health [199] [200].

7.CONCLUSIONS

1. The number of hospitalized STEMI cases per 100.000 inhabitants treated within the "Codi IAM" network has increased during the first seven years of implementation of the network.
2. Despite the fact that treatment times related to system such as ECG to open artery have decreased in the whole cohort and by gender, total ischemic time for women has not decreased significantly during the study period.
3. In a STEMI network with standardized protocols founded on evidence-based medicine, women have no greater risk of death or complications at 30-days, but an increased survival rate at one-year compared to men. The inequalities in mortality between sexes detected more than 20 years ago have been overcome thanks, in large part, to the structured reperfusion system, the "Codi IAM" in Catalonia.
4. Low SES patients with STEMI treated in Barcelona by the "Codi IAM" emergency network have a higher burden of cardiovascular risk factors and longer treatment delays than patients with a higher SES. However, low SES was not associated to higher risk of mortality or complications at 30-day or one-year mortality. A STEMI network within a specific geographical area with universal health coverage may confer a "health vehicle for equity" that offers non-restricted diagnostic and treatment also for those with low SES life conditionings.

8.FUTURE RESEARCH

Future lines of research in this field should include population-based registries to allow to calculate the real case-fatality of STEMI, including those patients suffering from sudden cardiac death before EMS-STEMI network activation. In that sense, we would be able to understand the "stabilization" of the mortality rates after STEMI of the "in-network" patients and we would be able to observe a more pronounced decline in sudden cardiac death secondary to STEMI, and at the end due to global STEMI, because of the implementation of primary/secondary prevention and evidence-based treatments as well as the spread of the street defibrillators.

Due to the increasing prevalence of insurance companies medicine, the number of STEMI patients treated in private clinics has increased. Delays in treatment and their related mortality should be registered and monitoring should be performed to optimize resources.

Another future line of research would focus on predicting in which moment an atherosclerotic plaque would become unstable and in which patients the destabilization of an atherosclerotic plaque would carry a complete thrombotic occlusion of a coronary artery.

Research also should be carried out to reduce the time from the onset of symptoms to FMC. The current level of technological advances should be able to detect continuous ECG from watches or phones, diagnose and send an ECG to the EMS center if the automated algorithm detects an ST-elevation. Randomized trials should be performed in order to implement targeted effective strategies to reduce the delays from onset of symptoms to FMC in selected populations such as women or patients with low SES.

Further research should be done in order to better understand the underlying connections between age, gender and SES in our community, if there are any. As cardiac rehabilitation is currently a treatment with a high level of evidence in decreasing mortality after STEMI, it should be mentioned and entered into modelling for detecting confounders that affect STEMI outcomes. Research on SES, age and gender referral to cardiac rehabilitation and program completion should be performed in order to understand the causes of non-referral or early discontinuation. In that way, targeted rehabilitation programs should be implemented to eliminate baseline conditionings.

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10. ANNEX

10.1 Supplementary material I

Helena Tizón-Marcos, Beatriz Vaquerizo, Jaume Marrugat, Albert Ariza, Xavier Carrillo, Juan Francisco Muñoz, Mérida Cárdenas, Joan Garcia-Picart, Sergio Giovanni Rojas, Carlos Tomas-Querol, Mònica Massotti, Rosa Maria Lidón, Josep Jiménez,Julio Martí-Almor, Núria Farré, Sílvia Pérez-Fernández, Antoni Curós,Josepa Mauri Ferré

Differences in 30-day complications and one-year mortality by gender in patients with a first STEMI managed by *"Codi IAM"*, a population network of emergency triage, between 2010 and 2016.

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10.2 Supplementary material II

Reperfusion in a STEMI program, still a gender issue? Results from the STEMI program in Catalunya

H. Tizon Marcos, X. Carrillo, J. Garcia-Picart, A. Ariza, J. Guarinos, M. Cardenas, J.F. Munoz, M.F. Borras, M. Massoti, R.M. Lidon, J. Jimenez, A. Curos Abadal, J. Mauri Ferre

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10.ANNEX

10.3. Supplementary material III

H Tizon Marcos, J Marrugat, B Vaquerizo, A Ariza, R.M Lidon, X Carrillo, J Garcia-Picart, J.F Garcia-Munoz, R Millan, N Ribas, E Menendez, X Duran, P Poirier, F Mauri Ferre on behalf of Codi IAM investigators

The Family Income Ratio of Barcelona and its impact on treatment delays and one-year mortality in 3173 cases of STEMI treated at the Codi IAM network

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