Original article

Differences in 30-day complications and 1-year mortality by sex in patients with a first STEMI managed by the *Codi IAM* network between 2010 and 2016



Helena Tizón-Marcos,^{a,b,*} Beatriz Vaquerizo,^{a,b} Jaume Marrugat,^c Albert Ariza,^d Xavier Carrillo,^e Juan-Francisco Muñoz,^f Mérida Cárdenas,^g Joan García-Picart,^h Sergio-Giovanni Rojas,ⁱ Carlos Tomás-Querol,^j Mònica Massotti,^k Rosa-Maria Lidón,^{1,m} Josep Jiménez,ⁿ Julio Martí-Almor,^{a,b} Núria Farré,^{a,b} Sílvia Pérez-Fernández,^c Antoni Curós,ⁿ and Josepa Mauri Ferré^{e,n}

^a Servicio de Cardiología, Hospital del Mar, Grupo de Investigación Biomédica en Enfermedades del Corazón, Instituto Hospital del Mar de Investigaciones Médica (IMIM), Barcelona, Spain ^b Facultat de Medicina, Universitat Autònoma de Barcelona, Bellaterra, Barcelona, Spain

^c Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares, Grupo de Trabajo en Epidemiología y Genética Cardiovascular, Instituto Hospital del Mar de Investigaciones Médica (IMIM), Barcelona, Spain

^d Servicio de Cardiología, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain

^e Servicio de Cardiología, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain

^fServicio de Cardiología, Hospital Universitari Mútua de Terrassa, Terrassa, Barcelona, Spain

^g Servicio de Cardiología, Hospital Universitari Dr. Josep Trueta, Girona, Spain

^h Servicio de Cardiología, Hospital de la Santa Creu I Sant Pau, Barcelona, Spain

ⁱ Servicio de Cardiología, Hospital Joan XXIII, Tarragona, Spain

^j Servicio de Cardiología, Hospital Universitari Arnau de Vilanova, Lleida, Spain

^k Servicio de Cardiología, Hospital Clínic i Provincial, Barcelona, Spain

¹Servicio de Cardiología, Hospital Universitari de la Vall d'Hebron, Barcelona, Spain

^m Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Spain

ⁿ Departament de Salut, Generalitat de Catalunya, Barcelona, Spain

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ABSTRACT

Introduction and objectives: ST-segment elevation myocardial infarction (STEMI) emergency care networks aim to increase reperfusion rates and reduce ischemic times. The influence of sex on prognosis is still being debated. Our objective was to analyze prognosis according to sex after a first STEMI.

Methods: This multicenter cohort study enrolled first STEMI patients from 2010 to 2016 to determine the influence of sex after adjustment for revascularization delays, age, and comorbidities. End points were 30-day mortality, the 30-day composite of mortality, ventricular fibrillation, pulmonary edema, or cardiogenic shock, and 1-year all-cause mortality.

Results: From 2010 to 2016, 14 690 patients were included; 24% were women. The median [interquartile range] time from electrocardiogram to artery opening decreased throughout the study period in both sexes (119 minutes [85-160] vs 109 minutes [80-153] in 2010, 102 minutes [81-133] vs 96 minutes [74-124] in 2016, both P = .001). The rates of primary PCI within 120 minutes increased in the same period (50.4% vs 57.9% and 67.1% vs 72.1%, respectively; both P = .001). After adjustment for confounders, female sex was not associated with 30-day complications (OR, 1.06; 95%CI, 0.91-1.22). However, female 30-day survivors had a lower adjusted 1-year mortality than their male counterparts (HR,0.76; 95%CI, 0.61-0.95).

Conclusions: Compared with men, women with a first STEMI had similar 30-day mortality and complication rates but significantly lower 1-year mortality after adjustment for age and severity.

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* Corresponding author: Hospital del Mar, Passeig Marítim 25-29, 08003 Barcelona, Spain. *E-mail address:* htizon@parcdesalutmar.cat (H. Tizón-Marcos).

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Complicaciones y mortalidad a 30 días y al año en pacientes con primer IAMCEST tratados en la red Codi IAM en 2010-2016: análisis del efecto del género

RESUMEN

Introducción y objetivos: Las redes de tratamiento del infarto agudo de miocardio con elevación del segmento ST (IAMCEST) han incrementado la tasa de reperfusión y reducido los tiempos de isquemia. Nuestro objetivo fue analizar la diferencia en el pronóstico entre géneros en pacientes con un primer IAMCEST.

Métodos: Se realizó un estudio de cohorte multicéntrico de pacientes con primer IAMCEST durante 2010-2016 para determinar el efecto del género/sexo ajustado sobre la mortalidad, la combinación de mortalidad, fibrilación ventricular, *shock* cardiogénico o edema agudo de pulmón a 30 días, y sobre la mortalidad al año.

Resultados: Entre 2010 y 2016 se incluyeron 14.690 pacientes, un 24% fueron mujeres. En el periodo de estudio, la mediana [rango intercuartílico] de tiempo entre electrocardiograma y apertura de arteria descendió en ambos sexos (119 min [85-160] frente a 109 min [80-153] en 2010 en mujeres, y 102 min [81-133] frente a 96 min [74-124] en 2016 en mujeres, ambos valores p = 0,001). En el mismo periodo, el porcentaje de angioplastia primaria en < 120 min aumentó (50,4% frente a 57,9% en mujeres; 67,1% frente a 72,1% en varones, ambos p = 0,001). Tras ajustar por confusores desaparecieron las diferencias entre géneros en las complicaciones a los 30 días (OR = 1,06; IC95%, 0,91-1,22). Las supervivientes a 30 días presentaron menor mortalidad al año (HR = 0,76; IC95%, 0,62-0,95) que los varones.

Conclusiones: Las mujeres con un primer IAMCEST presentan un porcentaje de muerte o complicaciones al mes similar a la de los varones y, en cambio, menos mortalidad al año tras ajustar por edad y gravedad. © 2020 Sociedad Española de Cardiología. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Abbreviations

CHD: coronary heart disease ECG: electrocardiogram PCI: percutaneous coronary intervention PPCI: primary percutaneous coronary intervention STEMI: ST-segment elevation myocardial infarction TIMI: Thrombolysis in Myocardial Infarction

INTRODUCTION

Although coronary heart disease (CHD) mortality has markedly fallen in Europe in the last 20 years, it is still the leading cause of death in most countries.¹ Despite an increase in the number of incident ST-segment elevation myocardial infarction (STEMI) cases as the population ages, the number of STEMI patients in Europe has declined and stabilized.^{2,3}

Data from the latest European registries show that men are at higher risk of incident STEMI at any age vs women but that STEMI incidence with age increases linearly in men but exponentially in women.⁴ Recent studies have shown that improvements in STEMI prognosis are due to both the implementation of a standard of care for reperfusion programs and the universalization of evidencebased medical treatments.⁵ STEMI networks increase reperfusion rates, reduce mortality, improve survival, and decrease the risk of recurrent ischemic events. Nationwide registries are essential to monitor STEMI treatments and outcomes, to evaluate the true effectiveness of treatments, and to account for changes in outcomes.³ Besides the exponential increase in STEMI in women, various studies have shown that women's prognosis after STEMI is worse than men's, not only because the condition affects women at older ages⁶ and those with clustering of risk factors,⁷ but also due to longer delays before medical help is sought,^{8,9} lower use of evidence-based treatments, and higher rates of kidney disease and bleeding.10

The aim of this study was to investigate the effect of sex on 30day mortality and complications and on 1-year mortality in first STEMI patients during the first 7 years of implementation of the *Codi IAM* Emergency STEMI Care network (2010-2016) in Catalonia, Spain.

METHODS

The Codi IAM Catalan Emergency STEMI Care network was launched in 2010 in a region with 7.6 million inhabitants. The 3 main objectives of the network are to increase the rate of reperfusion therapy among STEMI patients, to achieve primary percutaneous coronary intervention (pPCI) in less than 120 minutes from first contact with the health system,⁵ and to monitor the results of the program through a registry. The network was initially integrated into 5 hospitals with a 24-hour a day, 7-day a week pPCI facility and 5 daytime pPCI facilities. From 2015, the network spread across Catalonia, with 9 pPCI hospitals open 24 hours a day, 7 days a week and 2 hospitals with daytime pPCI. The operational details of the Codi IAM have been published elsewhere.¹¹ Briefly, the Emergency Medical Service organization coordinates the link between patients, ambulance transfers, and pPCI facilities according to the delay until treatment. Fibrinolysis is only considered if the pPCI transfer delay is unacceptable and there are no prior contraindications. Postfibrinolysis PCI (rescue PCI) is urgently performed in patients with no evidence of effective reperfusion. In those with effective fibrinolysis, PCI is performed after between 3 and 24 hours, in line with ESC guidelines.⁵ STEMI was defined according to guidelines as acute myocardial infarction with STsegment elevation \geq 1 mm in at least 2 contiguous leads (2 mm in precordial leads) in the qualifying electrocardiogram (ECG).⁵

The *Codi IAM* registry was started in 2010 and includes demographic, clinical, care, therapeutic, and discharge data on patients with a STEMI onset \leq 12 hours. The Principal Investigator of the *Codi IAM* team of each participating hospital entered the data into an electronic case report form. Epicardial coronary flow in the STEMI culprit artery was graded according to the Thrombolysis in Myocardial Infarction (TIMI) flow grade,¹² and reperfusion was considered optimal when TIMI 3 flow was obtained at the culprit

Palabras clave: Infarto agudo miocardio con elevación del segmento ST Mujer Género Reperfusión Angioplastia primaria Mortalidad lesion in less than 120 minutes from first medical contact. Data collection was extended to new variables in 2012 (acute pulmonary edema, number of diseased vessels, and TIMI flow) and in 2015 (hypertension, dyslipidemia, smoking status, previous stroke, previous treatment, and type and number of stents). Bleeding was only included in the registry when the patient required transfusion.

The study included patients from the *Codi IAM* Registry who had been diagnosed with a STEMI from 2010 to 2016. Patients with cardiac arrest or death during first medical contact were also included if ST-segment elevation or a new left bundle branch block was diagnosed in any ECG during the initial care. All patients with known previous CHD (previous myocardial infarction or any revascularization) were excluded.

Patients' mortality data were obtained from the Spanish mortality registry. The quality of the data included in the registry is periodically verified by external audits.

This project was approved by the ethics committee of *Hospital del Mar* (2020/9134) and all data are anonymous. Procedures and data collection were performed in accordance with the Declaration of Helsinki and Spanish Data Protection Laws.

End points

The primary assessment end points were all-cause mortality within 30 days and 1 year. In addition, the composite end point comprised 30-day complications, adjudicated as mortality during the first 30 days or ventricular fibrillation, pulmonary edema, or cardiogenic shock during the admission.

Statistical analysis

Dichotomous variables are shown as numbers and percentages, whereas continuous variables are shown as mean and standard deviation or, if nonnormally distributed, as median and interquartile range. Patient characteristics and treatment times were compared for each assessment end point: 30-day mortality or 30-day complications (cardiogenic shock, pulmonary edema, ventricular fibrillation, or death), and death of 30-day STEMI survivors within the first year after the intervention. Student *t* test or Mann-Whitney U test was used for continuous variables, whereas the chi-square or Fisher exact test was used for categorical variables. The association between sex and 30-day mortality or complications was evaluated with odds ratios (ORs) obtained by logistic regression models, and 1-year mortality in 30-day survivors was evaluated with hazard ratios (HRs) using Cox proportional hazards regression models. Models were adjusted for confounding variables associated with STEMI prognosis that had < 8% missing values (ie, age, diabetes mellitus, recruitment year, time from symptom onset to culprit coronary artery opening, and Killip class). Symptom onset to artery opening and ECG to artery opening time variables had 7.6% missing data. The numbers of missing values for other variables were as follows: initial TIMI (31.1%), final TIMI (33.4%), no angiographical epicardial disease or 3-vessel disease (31.2%), left main disease (25.0%), bare-metal stent (83.7%), drug-eluting stent (82.3%), Killip class (1.5%), smoking (54.5%), hypertension (54.5%), dyslipidemia (54.5%), previous stroke (54.5%), and previous treatments (69.4%).

Survival curves were fit for both sexes and P values were obtained using the log-rank test.

An age-matched analysis (\pm 2 years) with 2 men for each woman was also performed. This subset of patients was used to confirm the effect of female sex in models adjusted for comorbidity (diabetes) and delay (time from symptom onset to artery opening) variables, as well as the year of registration and care center. Patients were assigned to the hospital in which they spent most of their hospital stay. One-year mortality was analyzed up to 2017 to obtain the 1-year mortality rates of patients from 2016.

Analyses were performed using R software version 3.6.0 (R Foundation for Statistical Computing, Austria). P < .05 was considered statistically significant.

RESULTS

From January 2010 to December 2016, 23 507 STEMI patients were included in the *Codi IAM* registry. The selection flowchart for the present study is shown in figure 1. The final cohort consisted of 14 690 patients (24% women) without previous CHD and with a



Figure 1. Flowchart of the inclusion of Codi IAM STEMI. pPCI, primary percutaneous intervention; STEMI, ST-segment elevation myocardial infarction.

Baseline patient and first medical contact characteristics by sex in the Codi IAM registry 2010-2016

	Women n = 3486	Men n = 11 204	Р
Age, y	69.9 ± 13.7	60.9 ± 12.6	.001
Smoking ^a	13.6%	24.2%	.001
Hypertension ^a	34.2%	24.3%	.001
Dyslipidemia ^a	25.2%	21.2%	.01
Diabetes mellitus	24.2%	17.2%	.001
Previous stroke ^a	2.0%	1.4%	.08
Chronic oral anticoagulant ^a	2.9%	1.8%	.003
Previous antiplatelet treatment ^a	6.5%	4.3%	.001
Killip III-IV at presentation	11.2%	7.8%	.001
First medical contact			
General practitioner	19.2%	20.6%	.01
Emergency medical system	29.9%	31.2%	.01
Non-pPCI center	38.9%	35.9%	.01
pPCI center	12.1%	12.2%	.01
Left bundle branch block	1.78%	0.9%	.001
Therapeutic decision			
Transfer to pPCI hospital	96.0%	95.0%	.001
Transfer to nearest hospital	1.2%	0.8%	.001
Fibrinolysis	2.5%	3.9%	.001
Complications			
Mechanical ventilation	3.6%	4.9%	.001
Ventricular fibrillation	3.6%	4.9%	.001
Atrial fibrillation	1.8%	1.4%	.29
Atrioventricular blockade	5.9%	4.5%	.002
Pulmonary edema ^b	1.5%	1.0%	.03
30-d mortality	9.9%	5.1%	.001
30-d composite end point	16.3%	12.6%	.001
1-y mortality in 30-d survivors	4.3%	3.0%	.001

pPCI, primary percutaneous coronary intervention.

Data are expressed as % or mean \pm standard deviation.

^a Data available since 2015.

^b Data available since 2012.

discharge diagnosis of myocardial infarction and 1-year follow-up data.

The proportion of women was similar over the 7-year study period (P = .12).

The baseline and complication characteristics of the cohort are shown in table 1. Women were older and had higher prevalence of diabetes mellitus, hypertension, and dyslipidemia and higher rates of heart failure. Women tended to be more frequently first attended in non-pPCI centers and less often cared for by the emergency ambulance system (P = .01). Women more frequently had left bundle branch block and had higher rates of heart failure and atrioventricular blockade (P < .01). Men had higher rates of ventricular fibrillation and need for mechanical ventilation.

Crude 30-day mortality, 30-day composite end point, and 1year mortality rates were significantly lower in men than in women. Univariate analysis of factors associated with 30-day complications and 1-year mortality are shown in table 1 of the supplementary data.

First medical contact and angiography and pPCI characteristics according to sex are shown in table 2. Time delays in STEMI care were longer in women than in men. Compared with men, women undergoing pPCI had significantly less initial TIMI 0 at the initial coronary angiography and less TIMI 3 at the final coronary angiography. Significant coronary disease (< 70% stenosis in epicardial vessels) was significantly less frequent in women; however, the coronary disease extension and severity (3-vessel disease or left main involvement) did not differ according to sex. Women waited a significant median of 22 minutes longer for the first ECG than men and the time from ECG to reperfusion or to hospitalization was longer in women than in men.

The trends in treatment delays, mortality, and the composite end point at 30 days are shown in table 3. Times from ECG to artery opening decreased during the study period for both sexes but the total ischemic time decreased only in men. At the end of the study period, a significantly lower proportion of women were reperfused in less than 120 minutes than men (table 3). Survival curves at 30 days and 1 year are shown in figure 2: no significant differences were observed in these crude mortality curves between men and women.

The effects of female sex on 30-day mortality and complications and 1-year mortality were tested with multivariate analyses with progressive adjustment for potential confounders: for the whole cohort in table 4A and for the male-female 2:1 age-matched subcohort in table 4B. Female STEMI patients had no increased risk

Primary reperfusion procedure characteristics in men and women in the Codi IAM network from 2010 to 2016

	Women n = 3486	Men n=11 204	Р
Coronary angiogram without PCI	7.6%	3.7%	.001
pPCI	87.4%	91.5%	.001
Rescue PCI	1.4%	2.3%	.001
Initial TIMI 0	63%	66%	.003
Initial TIMI 3	15%	13%	.080
Final TIMI 0	2.6%	1.4%	.001
Final TIMI 3	90%	94%	.001
No significant epicardial coronary disease ^a	5.4%	3.8%	.001
3-vessel disease ^a	13.0%	12.7%	.600
Left main disease ^a	3.7%	3.3%	.490
BMS use ^b	73%	70%	.100
DES use ^b	65%	73%	.001
Anterior STEMI, %	42%	41%	.700
Inferior STEMI, %	45.7%	48%	.019
Bleeding requiring transfusion/treatment	1.2%	0.9%	.700
Symptom onset to ECG time, min	104 [51-219]	82 [42-179]	.001
Symptom onset to artery opening time, min	231 [160-375]	200 [140-320]	.001
Hospital arrival to artery opening time, min	30 [21-50]	30 [22-45]	<.001
ECG to artery opening time, min	109 [83-144]	101 [78-128]	.001
pPCI in < 120 min	59.2%	64.7%	.001

BMS, bare-metal stent; DES, drug-eluting stent; ECG, electrocardiogram; PCI, percutaneous coronary intervention; pPCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction flow score.

Data are expressed as No. (%) or median [interquartile range]. ^a Data available since 2012.

^b Data available since 2012.

of 30-day mortality or complications but had a significantly lower risk of 1-year mortality after adjustment for diabetes mellitus, year and center of recruitment, time from symptom onset to culprit coronary artery opening, age, and Killip class. Interestingly, the model not adjusted for age and Killip class showed an increased risk of 1-year mortality in women, indicating that age and STEMI severity are determinants of mortality in 30-day STEMI survivors (table 4A). The models fit to the age-matched cohort showed results of a similar magnitude and consistency to the findings for the full cohort but did not reach statistical significance due to lower statistical power.

DISCUSSION

Our results show that women with a first STEMI are older, have more cardiovascular risk factors, and have longer delays vs men. In addition, although mortality and a composite of mortality and other complications (ventricular fibrillation, acute pulmonary edema, or cardiogenic shock) at 30 days are similar in men and women with a first STEMI, women have significantly lower mortality within 1 year.

Previous studies have evaluated the influence of female sex on STEMI prognosis. Female sex is generally considered to be a prognostic confounder due to its multiple divergent interactions with age and the related clinical profile and due to sex-related increases in treatment delays.^{8,9} However, the relationship between sex and outcomes after STEMI may also be due to global undercare or sex-based treatments: increased treatment delays and ischemic times,¹³ lower reperfusion rates, and underuse of evidence-based treatments during all STEMI phases.⁶ Optimal care is therefore a

cornerstone of a favorable STEMI prognosis and of the utmost importance in female patients. In our cohort, women had longer treatment times than men. Delayed diagnoses are driven by sexrelated pathophysiological differences such as an absence of typical male-related symptoms (chest pain) and less frequent ST-elevation on first ECG.¹⁴ In our cohort, female patients waited longer to ask for help (mean, 22 minutes) and the ECG was performed with a longer delay than in men. The time between symptom onset and first medical contact accounted for 38% of the total ischemic time in women and for 34% of that in men. "Patient-related" delays are consistent across time periods and throughout literature and are challenging to reduce.¹⁵ Decreases in prehospital delays might have tremendous benefits on STEMI morbidity and mortality prognoses because many deaths occur in the very early phase from malignant arrhythmias¹⁶ and other acute-phase complications, which are known to be sex-specific, such as heart failure. Despite a general tendency for a decrease in pretreatment delays during the study period, women had a longer pretreatment delay than men. This may be partially because, compared with men, women more frequently first attended a non-pPCI center¹⁷ and also less frequently called emergency medical services, resulting in longer delays to STEMI revascularization treatment.¹⁸ Recent data from European registries showed that a decrease in delays could be influenced by media campaigns tailored not only to help women to identify the symptoms of CHD and thus rapidly access the health care system, ¹⁹ but also to alert all health care providers participating in STEMI emergency care networks of the need to prevent possible gender gaps. In previous work, patients with prior myocardial infarction or prior revascularization had a shorter treatment delay, underlining the importance of knowledge or understanding of CHD pathophysiology to promote STEMI treatment.²⁰

Trends in delays to different levels of care and in end points over the 7-year period of the Codi IAM emergency care network for ST-elevation myocardial infarction patients

	Women	2010	2011	2012	2013	2014	2015	2016	P for trend
	SO to first medical contact	94 [42-190]	80 [40-168]	90 [36-206]	90 [42-212]	90 [41.5-180]	85 [40-195]	73 [36-179]	.276
	First medical contact to ECG	10 [5-20]	8 [4-15]	9 [4-20]	8 [4-18]	10 [5-20]	9 [4-15]	8 [3-15]	.029
	SO to hospital	155 [89-268]	130 [78-254]	114 [67-214]	150 [84-274]	149 [80-288]	135 [75-280]	129 [78-270]	.012
	ECG to artery opening	119 [85-160]	113 [85-150]	110 [83-147]	110 [83-146]	110 [84-146]	104 [81-135]	102 [81-133]	.001
	SO to artery opening	250 [176-374]	227 [159-375]	245 [160-419]	235 [163-376]	248 [165-392]	220 [152-354]	203 [148-350]	.279
	pPCI in < 120 min	50.4%	54.6%	56.9%	59%	57.5%	65.0%	67.0%	<.001
	30-d mortality	9.7%	8.3%	10.8%	10.7%	9.5%	10.2%	9.7%	.906
	30-d composite end point	15.5%	13.4%	18.0%	17.6%	14.8%	18.0%	15.7%	.357
	1-y mortality*	4.2%	4.0%	4.0%	4.7%	4.9%	4.6%	3.6%	.952
I	Men	2010	2011	2012	2013	2014	2015	2016	P for trend
1	SO to first medical contact	80 [35-170]	67 [31-150]	65 [29-150]	69 [29-157]	65 [29-150]	63 [29-160]	69 [33-160]	.009
	First medical contact to ECG	8 [3-15]	7 [3-15]	7 [3-15]	7 [4-15]	7 [4-15]	7 [4-15]	7 [3-15]	.06
	SO to hospital	125 [73-230]	114 [54-219]	114 [67-214]	115 [64-226]	115 [66-224]	110 [64-227]	118 [68-230]	.11
	ECG to artery opening	109 [80-153]	110 [83-150]	105 [80-145]	101 [76-134]	102 [78-137]	94 [74-125]	96 [74-124]	.0001
	SO to artery opening	224 [155-344]	210 [149-330]	204 [145-325]	200 [140-326]	197 [140-313]	190 [134-305]	190 [136-309]	.006
	pPCI in < 120 min	57.9%	57.2%	60.7%	66.5%	64.3%	71.1%	72.1%	<.001
	30-d mortality	5.2%	4.4%	4.8%	4.7%	5.4%	5.9%	5.3%	.539
	30-d composite end point	11.9%	12.6%	12.8%	12.2%	12.8%	13.3%	12.4%	.941
2	1-y mortality*	2.5%	3.2%	2.7%	3.6%	3.2%	3.3%	3.0%	.668

ECG, electrocardiogram; pPCI, primary percutaneous intervention; SO, symptom onset.

Data are expressed as No. (%), mean ± standard deviation, or median [interquartile range].

In 30-day survivors.



Figure 2. Survival curves for 30-day mortality in women and men with STEMI (A) and 1-year mortality in 30-day STEMI survivors (B) in the *Codi IAM* network from 2010 to 2016. STEMI, ST-segment elevation myocardial infarction.

There is strong evidence that health care system delays are associated with mortality and heart failure-related readmission.²¹ However, despite the decrease in the ECG to artery opening time and the increase in the rate of pPCI in less than 120 minutes during the study period, we observed no significant reduction in mortality in either sex in our cohort. The absence of a mortality decrease from 2010 to 2016 may be explained by the short study period and a slight increase in the mean age but warrants further and longer studies. Previous work from the same decade showed no further reduction in mortality, reinforcing the idea of a plateau in mortality after STEMI.³

In our cohort, sex did not have a significant effect on 30-day mortality or complications. Similar results were obtained in a subanalysis of age-matched male and female patients. The absence of a significant association remained after adjustment for time to treatment and year and hospital of treatment.

Women were about 9 years older than men in the STEMI cohort. The lack of an association of female sex with 30-day complications after age-matching of men and women is in contrast to some studies^{2,22} but in accordance with others.^{23–27} Several factors may explain this inconsistency. The first is that the vast majority of patients underwent coronary angiography catheterization during the acute phase (97.4% of women and 96.4% of men), reflecting the extensive implementation of systematic reperfusion, which reduced the "gender gap" observed several decades ago.^{26,28} It may also reflect the distinct nature of the underlying CHD affecting women: less angiographical evidence of significant epicardial disease than in men,²⁹ with more plaque disruption or coronary dissection³⁰ and CHD that affects smaller vessels with less ischemic burden.³¹ It may also reflect the incorporation of evidence-based therapies for both sexes in terms of primary prevention, baseline risk factors, and cardiovascular treatments after the first ischemic event.^{3,32} In our study, the 1-year crude mortality rate was higher in women than in men. This association was mostly accounted for by women's higher age and more comorbidities, as reflected by the regression analysis, which

Female STEMI patients in the *Codi IAM* network from 2010 to 2016 in the whole cohort (A) and in an age-matched subsample of 2 men: 1 women (B): adjusted risks of 30-day mortality (models 1 and 2), the 30-day composite end point (mortality, ventricular fibrillation, acute pulmonary edema, or cardiogenic shock) (models 3 and 4), and 1-year mortality in 30-day survivors (models 5 and 6)

A. 30-d mortality risk for female STEMI patients in the whole cohort							
MODEL 1, n=13 468	OR	95%CI					
Female sex	1.90	1.63-2.23					
MODEL 2, n=13 468	OR	95%CI					
Female sex	1.06	0.92-1.33					
	30-d composite end point risk for female STEMI patients in the whole cohort						
MODEL 3, n = 14 690	OR	95%CI					
Female sex	1.29	1.15-1.45					
MODEL 4, n = 14 690	OR	95%CI					
Female sex	1.05	0.91-1.21					
1-y mortality risk for female 30-d STEMI survivors in the whole cohort							
MODEL 5, n = 13 770	HR	95%CI					
Female sex	1.57	1.28-1.93					
MODEL 6, n = 13 770	HR	95%CI					
Female sex	0.78	0.63-0.97					
	B. 30-d mortality risk for female STEMI patients paired by age with men						
MODEL 1, n=8313	OR	95%CI					
Female sex	1.04	0.85-1.26					
MODEL 2, n=8313	OR	95%CI					
Female sex	0.98	0.79-1.22					
	30-d composite end point risk for female STEMI patients paired by age with men						
MODEL 3, n=8313	OR	95%CI					
Female sex	1.00	0.87-1.15					
MODEL 4, n=8313	OR	95%CI					
Female sex	0.94	0.79-1.11					
1-y mortality risk in 30-d female STEMI survivors paired by age with men							
MODEL 5, n = 7724	HR	95%CI					
Female sex	0.85	0.66-1.08					
MODEL 6, n = 7724	HR	95%CI					
Female sex	0.84	0.65-1.08					

95%CI, 95% confidence interval; HR, hazard ratio; OR, odds ratio; STEMI, ST-segment elevation myocardial infarction.

Models 1, 3, and 5 were adjusted for diabetes mellitus, recruitment year, center of recruitment, and time from symptom onset to culprit coronary artery opening. Models 2, 4, and 6 were adjusted as in models 1, 2, and 3 but with Killip class and age.

showed that women actually have better prognosis after 1 year than men after a first STEMI. The worse prognosis of men after STEMI has previously been reported and may reflect the higher cardiovascular risk burden and the higher risk of reinfarction^{25,33} at 1 year.

Limitations

Several important limitations should be considered. First, all data were derived from the first 7 years of a regional STEMI transportation network. Thus, some treatment and management variables are available for only a few years of the *Codi IAM* registry. For instance, the number of unavailable pulmonary edema events from 2010 to 2011 may represent as many as 60 events out of 1979 (3%). In addition, no records were available for medical treatment administered by the emergency medical system or at discharge. These treatments have a net beneficial impact on mortality both in-hospital and at 1 year of follow-up.³ In contrast, the network has a STEMI protocol for medications such as antithrombotic

agents administered to all participants. Data regarding left ventricle ejection fraction was not available at the time of the study. The cause of death was also not available. Therefore, we cannot know the weight of cardiovascular diseases in the all-cause mortality. Optimal epicardial reperfusion was considered TIMI grade 3 at the end of the procedure but there were no details on ST resolution at ECG or TIMI myocardial blush grade to further evaluate reperfusion. In addition, and of note, the registry still has no records available on the menopausal status of women, which has a clear impact on the pathophysiology of cardiovascular diseases.³⁴ Sex-related risk factors should be considered and recorded.

CONCLUSIONS

In the *Codi IAM* emergency STEMI transportation network, women underwent PCI with a greater delay than their male counterparts but showed similar 30-day mortality and complication rates and lower mortality 1 year after STEMI.

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WHAT IS KNOWN ABOUT THE TOPIC?

- Previous evidence showed that women with STEMI had worse prognosis than men.
- This gender gap has been partly explained by women's older age, more comorbidities, and lower receipt of evidence-based treatments.

WHAT DOES THIS STUDY ADD?

- The implementation of the STEMI network *Codi IAM* has progressively reduced treatment delays.
- Despite worse risk profiles and longer delays in treatment, women showed similar 30-day cardiac complications vs men and lower 1-year all-cause mortality when age and comorbidities were considered.

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CONFLICTS OF INTEREST

None declared.

APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.rec.2020.06.002

REFERENCES

- Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. *Eur Heart J.* 2016;37:3232–3245.
- Freisinger E, Fuerstenberg T, Malyar NM, et al. German nationwide data on current trends and management of acute myocardial infarction: discrepancies between trials and real-life. Eur Heart J. 2014;35:979–988.
- Szummer K, Wallentin L, Lindhagen L, et al. Improved outcomes in patients with ST-elevation myocardial infarction during the last 20 years are related to implementation of evidence-based treatments: experiences from the SWEDEHEART registry 1995-2014. Eur Heart J. 2017;38:3056–3065.
- Kytö V, Sipilä J, Rautava P. Gender, age and risk of ST segment elevation myocardial infarction. Eur J Clin Invest. 2014;44:902–909.
- Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39:119–177.
- EUGenMed Cardiovascular Clinical Study Group, Regitz-Zagrosek V, Oertelt-Prigione S, et al. Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. *Eur Heart J.* 2016;37:24-34.
- Arnold SV, Smolderen KG, Kennedy KF, et al. Risk factors for rehospitalization for acute coronary syndromes and unplanned revascularization following acute myocardial infarction. J Am Heart Assoc. 2015;4:e001352.

- 8. Her AY, Shin ES, Kim YH, Garg S, Jeong MH. The contribution of gender and age on early and late mortality following ST-segment elevation myocardial infarction: results from the Korean Acute Myocardial Infarction National Registry with Registries. J Geriatr Cardiol. 2018;15:205–214.
- 9. Piackova E, Jäger B, Farhan S, et al. Gender differences in short- and long-term mortality in the Vienna STEMI registry. *Int J Cardiol.* 2017;244:303–308.
- Berger JS, Elliott L, Gallup D, et al. Sex differences in mortality following acute coronary syndromes. JAMA. 2009;302:874–882.
- Carrillo X, Fernandez-Nofrerias E, Rodriguez-Leor O, et al. Early ST elevation myocardial infarction in non-capable percutaneous coronary intervention centres: in situ fibrinolysis vs. percutaneous coronary intervention transfer. *Eur Heart J.* 2016;37:1034–1040.
- TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. N Engl J Med. 1985;312:932-936.
- Bugiardini R, Ricci B, Cenko E, et al. Delayed Care and Mortality Among Women and Men With Myocardial Infarction. J Am Heart Assoc. 2017;6:e005968.
- Sederholm Lawesson S, Isaksson RM, Thylén I, et al. Gender differences in symptom presentation of ST-elevation myocardial infarction - an observational multicenter survey study. Int J Cardiol. 2018;264:7–11.
- Dracup K, McKinley S, Riegel B, et al. A randomized clinical trial to reduce patient prehospital delay to treatment in acute coronary syndrome. *Circ Cardiovasc Qual Outcomes*. 2009;2:524–532.
- García-García C, Oliveras T, Rueda F, et al. Primary ventricular fibrillation in the primary percutaneous coronary intervention ST-segment elevation myocardial infarction era (from the "Codi IAM" Multicenter Registry). Am J Cardiol. 2018;122:529–536.
- Sederholm Lawesson S, Isaksson RM, Ericsson M, et al. Gender disparities in first medical contact and delay in ST-elevation myocardial infarction: a prospective multicentre Swedish survey study. *BMJ Open.* 2018;8:e020211.
- Thylén I, Ericsson M, Hellström Ängerud K, et al. First medical contact in patients with STEMI and its impact on time to diagnosis; an explorative cross-sectional study. *BMJ Open*. 2015;5:e007059.
- 19. Nielsen CG, Laut KG, Jensen LO, et al. Patient delay in patients with ST-elevation myocardial infarction: time patterns and predictors for a prolonged delay. *Eur Heart J Acute Cardiovasc Care.* 2017;6:583–591.
- Radovanovic D, Maurer L, Bertel O, et al. Treatment and outcomes of patients with recurrent myocardial infarction: a prospective observational cohort study. J Cardiol. 2016;68:498–503.
- Terkelsen CJ, Sørensen JT, Maeng M, et al. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. JAMA. 2010;304:763–771.
- Hurtado-Martínez J, Pinar-Bermúdez E, Teruel-Carrillo F, et al. In-hospital and long-term mortality in women with acute myocardial infarction treated by primary angioplasty. *Rev Esp Cardiol.* 2006;59:1113–1122.
- Schiele F, Meneveau N, Seronde MF, et al. Propensity score-matched analysis of effects of clinical characteristics and treatment on gender difference in outcomes after acute myocardial infarction. *Am J Cardiol.* 2011;108:789–798.
- 24. Krishnamurthy A, Keeble C, Burton-Wood N, et al. Clinical outcomes following primary percutaneous coronary intervention for ST-elevation myocardial infarction according to sex and race. *Eur Heart J Acute Cardiovasc Care*. 2019;8:264–272.
- García-García C, Molina L, Subirana I, et al. Sex-based differences in clinical features, management, and 28-day and 7-year prognosis of first acute myocardial infarction. RESCATE II study Rev Esp Cardiol. 2014;67:28–35.
- Kang SH, Suh JW, Yoon CH, et al. Sex differences in management and mortality of patients with ST-elevation myocardial infarction (from the Korean Acute Myocardial Infarction National Registry). Am J Cardiol. 2012;109:787–793.
- 27. Grau M, Sala C, Sala J, et al. Sex-related differences in prognosis after myocardial infarction: changes from 1978 to 2007. *Eur J Epidemiol.* 2012;27:847–855.
- 28. Marrugat J, Sala J, Masiá R, et al. Mortality differences between men and women following first myocardial infarction. RESCATE Investigators. Recursos Empleados en el Síndrome Coronario Agudo y Tiempo de Espera. JAMA. 1998;280:1405–1409.
- 29. Chokshi NP, Iqbal SN, Berger RL, et al. Sex and race are associated with the absence of epicardial coronary artery obstructive disease at angiography in patients with acute coronary syndromes. *Clin Cardiol.* 2010;33:495–501.
- **30.** Reynolds HR, Srichai MB, Iqbal SN, et al. Mechanisms of myocardial infarction in women without angiographically obstructive coronary artery disease. *Circulation*. 2011;124:1414–1425.
- **31.** Otten AM, Maas AH, Ottervanger JP, et al. Is the difference in outcome between men and women treated by primary percutaneous coronary intervention age dependent? Gender difference in STEMI stratified on age. *Eur Heart J Acute Cardiovasc Care.* 2013;2:334–341.
- Puymirat E, Simon T, Steg PG, et al. Association of changes in clinical characteristics and management with improvement in survival among patients with ST-elevation myocardial infarction. JAMA. 2012;308:998–1006.
- Lawesson SS, Stenestrand U, Lagerqvist B, Wallentin L, Swahn E. Gender perspective on risk factors, coronary lesions and long-term outcome in young patients with ST-elevation myocardial infarction. *Heart*. 2010;96:453–459.
- Rich-Edwards JW, Kaiser UB, Chen GL, Manson JE, Goldstein JM. Sex and gender differences research design for basic, clinical, and population etudies: essentials for investigators. *Endocr Rev.* 2018;39:424–439.