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Impact of pre-angioplasty antithrombotic therapy administration on coronary reperfusion in ST-segment elevation myocardial infarction: Does time matter?

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ABSTRACT

Background: Optimal timing of antithrombotic therapy for patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI) is unclear. We analyzed the impact of pre-angioplasty administration of unfractionated heparin (UFH) on infarct-related artery (IRA) patency and mortality.

Method: Multicenter prospective observational study of 3520 STEMI patients treated with PPCI from 2016 to 2018. Subjects were divided into four groups according to the elapsed time from heparin administration to PPCI: Group 1: Upon arrival at catheterization laboratory or ≤ 30 min ($n = 800$; 22.7%); Group 2: 31 to 60 min ($n = 994$; 28.2%); Group 3: 61 to 90 min ($n = 1091$; 31%); Group 4: >90 min ($n = 635$; 18%). IRA patency was defined as thrombolysis in myocardial infarction (TIMI) flow grade 2–3. Multivariate analyses assessed factors associated with IRA patency and both 30-day and 1-year mortality.

Results: UFH administration at STEMI diagnosis was an independent predictor of IRA patency especially when administered more than 60 min before the PPCI (OR 1.43; 95% CI 1.14–1.81), either an independent predictor of 30-day (HR 0.63; 95% CI 0.42–0.94) and 1-year (HR 0.57; 95% CI 0.41–0.80) mortality. The effect of UFH on IRA patency was higher when administered earlier from the symptom onset.

Conclusion: UFH administration at STEMI diagnosis improves coronary reperfusion prior to PPCI and this benefit seems associated with superior clinical outcomes. The presented results highlight a time-dependent effectiveness of UFH, since its reported effect is greater the sooner UFH is administered after symptom onset.

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1. Introduction

ST-segment elevation myocardial infarction (STEMI) remains one of the leading causes of mortality and morbidity worldwide [1]. Primary percutaneous coronary intervention (PPCI) is the preferred reperfusion strategy in STEMI patients, especially when performed within the first 120 min after the diagnosis. However, although PPCI has been related to higher rates of reperfusion and better prognosis [2–4], a delay

Abbreviations: IRA, Infarct-related artery; PPCI, Primary percutaneous coronary intervention; PCI, Percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in myocardial infarction; UFH, Unfractionated heparin..

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between the onset of symptoms and reperfusion of the infarct-related artery (IRA) has been related to worse outcomes [5].

In order to improve STEMI patient care, regional networks have been created around the world [6–8] with the aim of shortening delays in restoring IRA blood flow and increasing rates of IRA reperfusion. In June 2009, the Acute Myocardial Infarction Code network (AMI Code) was created in Catalonia (Spain) [9,10]. However, even with the establishment of regional networks, some delays in patient transfer to the catheterization laboratory (Cath Lab) still exist. Any treatment administered during such a delay that could improve IRA patency prior to PPCI would be extremely useful, particularly in those patients who will be subjected to longer delays. A higher initial thrombolysis in myocardial infarction (TIMI) flow grade at the IRA has been related to a better post-PCI TIMI flow grade and to better prognosis [11,12].

Effective antiplatelet therapy in combination with anticoagulants has been recommended for STEMI patients who are candidates for PPCI [2–4].There is limited evidence about the need and timing of anticoagulation therapy with unfractionated heparin (UFH). Moreover, it is not clear if higher IRA patency rates could be achieved with a combination of UFH with the novel, more powerful P2Y12 inhibitors, such as ticagrelor or prasugrel, which are increasingly being used in STEMI patients [13,14].

We have performed an observational prospective multicenter study to explore the impact of early pre-angioplasty UFH administration on initial IRA patency and on the short- and long-term prognosis of real-world STEMI patients. We also investigated the potential effect of the addition of novel antiplatelet agents to UFH.

2. Methods

2.1. Patient population

This was an observational, multicenter study based on prospectively collected data from real-world patients treated within the Catalan AMI Code network from January 2016 to December 2018.

The AMI Code network was created in June 2009 in Catalonia, an autonomous region of Spain with approximately 7.6 million inhabitants. Its aim was to establish a treatment network for reperfusion therapy in patients with STEMI. It prioritizes PPCI as the first-choice reperfusion treatment, provided that it is performed within 120 min from first medical contact. The operating protocol was based on the division of Catalonia into different sectors arranged around ten centers with catheterization facilities operating on a 24-h basis. The Emergency Medical System (EMS) connects all patients attended in non-capable centers or with first attendance by the EMS to one of these ten capable centers [9,10]. Patients also can self-present to the emergency room of a PCI-capable center, from which they are directly transferred to the Cath Lab after STEMI diagnosis.

The AMI Code network is controlled by a single Emergency System Coordinating Center, which has all the information relevant to the STEMI network, including Cath Lab availability, number and location of available EMS units, and transfer time depending on traffic. After PPCI, patients are transferred back to coronary units closer to their home. Moreover, an on-line data registry, the AMI Code Registry, of all patients treated within the AMI Code network was established and includes demographic, clinical, care, therapeutic and discharge data. It is mandatory to introduce all patient data into the Registry, which is controlled by the AMI Code network office. The PCI-capable centers are responsible for recording this information. Patient data are initially registered by the first physician who attends the patient. Once at Cath Lab, the PCI operator verifies all the information recorded, especially data on timing and antithrombotic drugs administered, and also completes data regarding PPCI. Follow-up during the PCI index admission is performed by the person responsible for this at the PCI-capable center, who enters all the information in the on-line AMI Code Registry. Bleeding was only included in the registry when the patient required transfusion. Later, at the AMI Code network office, all this information is controlled and maintained. Moreover, the data included in the Registry is verified every three to six months by internal audits at the AMI Code network office and every three years by an external audit.

Catalonia has a huge geographical variability, ranging from plains and coastal areas with populous cities to a very dispersed population in mountainous areas, which increases the difficulty of coordination among centers.

We included patients who presented with STEMI <12 h from onset of symptoms and who were treated with PPCI regardless of the location of the first medical contact. Patients without complete data in the AMI Code Registry on UFH administration were excluded. The definition of STEMI and indications for PPCI followed the current STEMI Guidelines [2]: all patients with chest pain and ECG showing ST-segment elevation in two or more contiguous leads, with a minimum of 0.1 mV in frontal leads and 0.2 mV in precordial leads, or with a left bundle branch block (new onset or indeterminate chronology), or with persistent ischemic symptoms in the presence of right bundle branch block.

All patient information was acquired in accordance with ethical and legal requirements for research purposes from a database, the AMI Code Registry, belonging to the Catalan Health Department. Data on 30-day and 1-year mortality were based on the National Death Registry from the Spanish government, a data system that contains personal information on every single death that has been registered in the Civil Registries of Spain. These data are transferred to the Catalan Department of Health and linked with the STEMI patients included at AMI Code Network database to mortality follow up. Foreign patients for whom mortality data could not be acquired from the Registry were excluded from the study. All study procedures were in accordance with Guidelines for Good Clinical Practice and with the ethical standards outlined in the Declaration of Helsinki and were approved by the Ethics and Clinical Research Committee (no.2019/8704).

2.2. Pre-PCI medical treatment and IRA patency

The initial pre-PCI medical treatment was administered according to the criteria of the first attending physician – either at the non-capable center, at the capable center or by the EMS crew – following the recommendations of the Catalan Society of Cardiology [15], and consisted of aspirin (250 or 300 mg), a P2Y12 inhibitor (600 mg of clopidogrel, 180 mg of ticagrelor, or 60 mg of prasugrel), and a bolus of UFH (70–100 UI/Kg with a maximum of 5000 UI). Glycoprotein IIb/IIIA inhibitors were not recommended as pre-treatment. For patients who did not receive pre-treatment before their arrival at Cath Lab, it was administered just upon their arrival, before PPCI.

Patients who received enoxaparin or bivalirudin as anticoagulation therapy at the first medical contact were excluded from the study in order to have a more homogeneous sample.

Patients were classified into four groups according to the time between UFH administration and coronary angiography. In Group 1, UFH was administered upon arrival at the Cath Lab or ≤ 30 min before coronary angiography. In Group 2, UFH was administered 31–60 min before coronary angiography. In Group 3, UFH was administered 61–90 min before coronary angiography. In Group 4, UFH was administered >90 min before coronary angiography.

TIMI flow grade at the initial coronary angiography was assessed by the PCI operator and patients were classified according to the TIMI Study Group [16,17] TIMI flow grade 0–1 and TIMI flow grade 2–3. Initial IRA patency was defined as TIMI flow grade 2–3 on the initial angiogram. The revascularization strategy during PCI and the administration of glycoprotein IIb/IIIA inhibitors were decided by the interventional cardiologist and the cardiologist who treated the patient at the Cath Lab after coronary anatomy and thrombus burden assessment. The ischemia time was defined as time between onset of symptoms and wire cross.

2.3. Study endpoints

The primary endpoints of the present study were the initial IRA patency based on the time between UFH administration and coronary angiography and the association with 30-day and 1-year mortality from any cause.

The secondary endpoint was the impact on initial IRA patency and on 30-day and 1-year mortality of the addition of novel P2Y12 antiplatelet agents (ticagrelor or prasugrel) to UFH.

2.4. Statistical analyses

Categorical variables were expressed as proportions (percentages) and were analyzed using the Chi-square test. Continuous variables were expressed as mean (±standard deviation [SD]) and were analyzed using Student's *t*-test. Time variables were expressed as median plus interquartile range (IQR) and were analyzed using the non-parametric Kruskal-Wallis test. The relationship between qualitative and quantitative variables was analyzed using Student's t-test for independent samples and ANOVA. *P*-values were corrected using Tukey's test for multiple comparisons. Variables without normal distributions were analyzed using the Mann-Whitney U and Kruskall-Wallis tests.

A multivariate logistic regression analysis to determine independent predictors of initial IRA patency was performed including the target variable and all available covariates suggested by literature as predictors of the outcome. We included the following covariates: age, sex, diabetes, current smoking, weight, Killip-Kimball Class, anterior wall myocardial infarction, left main coronary artery disease, multivessel disease, ischemia time, aspirin, clopidogrel, ticagrelor and prasugrel administered at first medical contact (FMC), symptoms onset -UFH administration and UFH-to-coronary angiography (31–60 min vs 61–90 min vs >90 min). Two additional multivariate logistic regression analyses were performed: one including the interaction between UFH administration and symptom onset in order to study a possible time-dependent effect between UFH administration and symptom onset and the other including the addition of prasugrel or ticagrelor to UFH administration.

Multivariate Cox regression analyses of 30-day and one-year mortality were performed including the target variable, PCI-center as strata and all available covariates previously suggested as predictors of outcome. The following covariates were included: age, sex, weight, Killip-Kimball Class III-IV, anterior wall myocardial infarction, left main coronary artery disease, ischemia time, pre-PCI TIMI flow grade, post-PCI TIMI flow grade, PCI-capable center, ventricular fibrillation, and UFH-to-coronary angiography (31–60 min vs 61–90 min vs >90 min). Additional multivariate Cox regression analyses of 30-day and 1-year mortality were performed including the addition of prasugrel or ticagrelor to UFH administration.

We further performed a sub-analysis redefining IRA patency as pre-procedural TIMI 3 flow with the same models previously described.

All analyses were carried out using R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as a two-sided *p*-value ≤0.05.

3. Results

3.1. Patient population

A total of 4180 STEMI patients treated with PPCI were included in the AMI Code registry with available pre-PPCI antithrombotic treatment information, from January 2016 to December 2018. Patients with missing data ($n = 223$), foreigners with unavailable follow-up ($n = 310$), and those receiving enoxaparin or bivalirudin ($n = 127$) were excluded from the study. The remaining 3520 patients were classified into the four groups according to the time elapsed between UFH and coronary angiography: 800 (22.7%) patients in Group 1 (upon arrival at Cath Lab or ≤ 30 min); 994 (28.2%) patients in Group 2 (31–60 min); 1091 (31%) patients in Group 3 (61–90 min) and 635 (18%) patients in Group 4 (>90 min).

Clinical characteristics and procedural data are summarized in Table 1.

Mean age was 63.5 (±13.2) years, and 78.8% of the patients were males, with some differences across the groups in the distribution of hypertension and smoking habits. Previous stroke ($p = 0.023$) was more frequent in Group 1. There were no differences across groups in STEMI location, but Killip-Kimball III-IV class was more frequent in Groups 1 and 4 ($p < 0.001$). Antiplatelet therapy was administered less frequently in Group 1, while overall, clopidogrel was given more frequently than ticagrelor or prasugrel (70% vs 21.9%; $p = 0.025$). The 81.5% of patients received UFH at first medical contact when the STEMI diagnosis was performed.

Overall median time between UFH administration and coronary angiography was 67 (IQR 51–88) minutes. We observed differences in the administration of UFH depending on the PCI-capable center where the patient was attended (either at first medical contact or transferred), ranging from 73.3% to 92.4% ($p < 0.001$). We also found differences in the median time between first medical contact and coronary angiography depending on the PCI-capable center where the patient was attended (either at first medical contact or transferred), ranging from 91 (IQR 74–124) to 118 (IQR 90.8–153) minutes ($p < 0.001$). There were no differences in the severity of coronary artery disease or post-PCI TIMI flow grade 2–3 between groups. The incidence of bleeding requiring transfusion, was very low (0.6%) without differences among groups.

3.2. IRA patency at initial angiography

Initial pre-PCI TIMI flow grade was 2–3 in 923 (26.2%) patients, 23.7% in Group 1, 23.9% in Group 2, 29.6% in Group 3 and 27.4% in Group 4 ($p = 0.006$). Online supplementary Table 1 shows clinical and procedural characteristics according to TIMI flow grade (0–1 vs 2–3).

The multivariate analysis identified UFH administration 61–90 min before PPCI as an independent predictor of pre-PCI TIMI flow grade 2–3 (odds ratio [OR] 1.43; 95% CI 1.14–1.81; $p = 0.002$). UFH administration >90 min before the PPCI also emerged as an independent predictor of pre-PCI TIMI flow grade 2–3 (OR 1.34; 95% CI 1.03–1.74; $p = 0.03$) (Table 2).

3.3. IRA patency according to the elapsed time between symptom onset and UFH administration

As shown in Fig. 1, the impact of UFH administration on TIMI flow grade 2–3 was time-dependent, with a higher effect when administered earlier from symptom onset.

3.4. Impact of pre-angioplasty UFH administration on 30-day and 1-year mortality

For the entire study cohort, all-cause mortality was 5.8% at 30-day and 9.03% at 1-year. Compared to Group 1, the other three Groups had lower mortality rates both at 30 days (Group 2 vs 1: 3.62% vs 9.88%, $p < 0.001$; Group 3 vs 1: 4.22% vs 9.88%, $p < 0.001$; Group 4 vs 1: 6.77% vs 9.88%, $p = 0.05$) and at 1 year (Group 2 vs 1: 6.44% vs 15.2%, $p < 0.001$; Group 3 vs 1: 6.23% vs 15.2%, $p < 0.001$; Group 4 vs 1: 10.1% vs 15.2%, $p = 0.008$).

The multivariate Cox regression analyses found that UFH administration before PPCI was an independent protective factor for both 30-day (HR 0.57, 95% CI 0.37–0.88, $p = 0.012$ (Group 2); HR 0.63, 95% CI 0.42–0.94, $p = 0.025$ (Group 3)) and 1-year mortality (HR 0.6, 95% CI 0.43–0.83, $p = 0.002$ (Group 2); HR 0.57, 95% CI 0.41–0.8; $p < 0.001$) (Group 3) when administered 31 to 90 min before the PPCI (Groups 2 and 3). The administration of UFH >90 min before PPCI (Group

Table 1
Baseline patient characteristics and clinical procedures of the four study groups.

	All Patients $n = 3520$	Group 1 (< 30 min) $n = 800$ (22.7%)	Group 2 (31–60 min) $n = 994$ (28.2%)	Group 3 (61–90 min) $n = 1091$ (31%)	Group 4 (>90 min) $n = 635$ (18%)	p-value*
Patient characteristics						
Male sex, n (%)	2773 (78.8)	600 (75)	804 (80.9)	888 (81.4)	481 (75.7)	0.001
Age, yrs – mean (±SD)	63.5 (13.2)	65.4 (14)	62.6 (12.8)	62.3 (12.8)	64.4 (13.4)	<0.001
Current smoker, n (%)	1471 (41.8)	281 (35.1)	462 (46.5)	494 (45.3)	234 (36.9)	<0.001
Hypertension, n (%)	1878 (53.4)	461 (57.6)	511 (51.4)	555 (50.9)	351 (55.3)	0.012
Dyslipidemia, n (%)	1575 (44.7)	356 (44.5)	457 (46)	484 (44.4)	278 (43.8)	0.818
Diabetes, n (%)	614 (17.4)	150 (18.8)	158 (15.9)	180 (16.5)	126 (19.8)	0.121
Previous stroke, n (%)	153 (4.4)	48 (6)	41 (4.1)	34 (3.1)	30 (4.7)	0.023
Previous MI, n (%)	331 (9.4)	91 (11.4)	85 (8.5)	97 (8.9)	58 (9.1)	0.180
Previous anticoagulant therapy, n (%)	111 (3.2)	65 (8.1)	17 (1.7)	14 (1.3)	15 (2.4)	<0.001
STEMI anterior location, n (%)	1504 (42.7)	355 (44.4)	423 (42.6)	445 (40.8)	281 (44.3)	0.365
Initial Killip-Kimball class, n (%)						<0.001
K-K I	2879 (82.8)	636 (79.8)	842 (85.9)	913 (84.8)	488 (78.1)	
K-K II	277 (8)	59 (7.4)	77 (7.9)	81 (7.5)	60 (9.6)	
K-K III	83 (2.4)	22 (2.8)	18 (1.8)	18 (1.7)	25 (4)	
K-K IV	240 (6.9)	80 (10)	43 (4.4)	65 (6)	52 (8.3)	
Ventricular fibrillation, n (%)	303 (8.61)	81 (10.1)	79 (7.95)	87 (7.97)	56 (8.82)	0.323
Asystolia, n (%)	79 (2.24)	29 (3.62)	16 (1.61)	17 (1.56)	17 (2.68)	0.009
Complete atrioventricular block, n (%)	231 (6.56)	59 (7.38)	56 (5.63)	70 (6.42)	46 (7.24)	0.427
Antiplatelet therapy at FMC, n (%)						
Aspirin (250-300 mg)	3303 (93.8)	655 (81.9)	965 (97.1)	1066 (97.7)	617 (97.2)	<0.001
Clopidogrel (600 mg)	2465 (70)	492 (61.5)	717 (72.1)	789 (72.3)	467 (73.5)	< 0.001
Ticagrelor or prasugrel	771 (21.9)	117 (14.6)	241 (24.2)	269 (24.7)	144 (22.7)	< 0.001
Initial TIMI flow grade, n (%)						0.006
0–1	2597 (73.8)	611 (76.3)	757 (76.1)	768 (70.4)	461 (72.6)	
2–3	923 (26.2)	189 (23.7)	237 (23.9)	323 (29.6)	174 (27.4)	
Centre of FMC, n (%)						<0.001
PCI-capable center	464 (13.2)	189 (23.6)	171 (17.2)	71 (6.5)	31 (4.8)	
Non-PCI capable center	1766 (50,2)	342 (42.8)	371 (37,3)	601 (55,1)	454 (71.6)	
EMS	1290 (36.6)	269 (33.6)	452(45.5)	419 (38.4)	150 (23.6)	
Time intervals, mins – median (IQR)						
Therapeutic decision to wire-cross	66.0 (52.0–86.0)	63.0 (46.0–89.0)	52.0 (44.0–60.0)	70.0 (61.8–80.0)	100 (82.0–117)	<0.001
Ischemia time	192 (137–305)	198 (134–336)	164 (116–252)	187 (138–287)	244 (181–395)	<0.001
FMC to wire-cross	104 (81.0;140)	109 (78.0;161)	82.0 (68.0;103)	101 (88.0;122)	140 (121;175)	<0.001
SO to UFH administration	128 (75.0–240)	175 (112–315)	115 (70.0–205)	110 (65.0–210)	120 (69.0–260)	<0.001
SO to FMC	72 (35–158)	65 (29–150)	69 (36–141)	74 (36–158)	84 (40–188)	<0.001
PCI characteristics, n (%)						
Single vessel disease, n (%)	1887 (54.5)	410 (52.4)	555 (56.6)	600 (55.8)	322 (51.6)	0.161
PCI, n (%)						0.340
Complete revascularization	2019 (58.6)	444 (57.2)	592 (60.7)	634 (59)	349 (56.4)	
Non-complete revascularization	1427 (41.4)	332 (42.8)	384 (39.3)	441 (41)	270 (43.6)	
Glycoprotein IIb/IIIa inhibitors, n (%)	619 (18.68)	121 (16.5)	184 (20.3)	211 (20.1)	103 (16.8)	0.049
DES use, n (%)	989 (72.8)	204 (60)	265 (79.8)	308 (75.7)	212 (75.7)	<0.001
Bleeding requiring transfusion, n (%)	21 (0.60)	9 (1.12)	6 (0.60)	5 (0.46)	1 (0.16)	0.093
Post-PCI TIMI flow grade 2–3, n (%)	3460 (98.5)	783 (98.1)	982 (98.9)	1074 (98.7)	621 (98.3)	0.491

DES, Drug eluting stent; EMS, Emergency medical system; FMC, first medical contact; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention; SO, symptom onset; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; UFH, unfractionated heparin;

* p-value test differences for all four patient groups.Fig. 2

4) remained as an independent protective factor for 1-year mortality (HR 0.68, 95% CI 0.49–0.94; p = 0.02) (Table 3).

In addition, pre-PPCI TIMI 2–3 flow emerged as an independent predictor factor for both 30-day mortality (HR 0.68, 95% CI 0.47–0.99, $p = 0.04$) and 1-year mortality (HR 0.72, 0.55–0.96, $p = 0.03$).

Online supplementary Fig. 2 shows the Kaplan-Meier survival curves of all-cause 30-day mortality from the first medical contact and for the period from day 30 to 1 year, among 30-day survivors in the four study groups.

3.5. Impact of the addition of ticagrelor or prasugrel to UFH on IRA patency and on 30-day and 1-year mortality

A total of 688 patients (19.5%) were pre-treated with ticagrelor or prasugrel added to UFH: 34 (4.25%) in Group 1, 241 (24.2%) in Group 2, 269 (24.7%) in Group 3, and 144 (22.7%) in Group 4 ($p < 0.001$). Median time from ticagrelor or prasugrel administration to coronary angiography was 69 min (IQR 50–95). The administration of ticagrelor or prasugrel with UFH was not associated with a higher probability of

Table 2
Multivariate logistic regression analysis of pre-procedural IRA patency, defined as TIMI flow grade 2–3, adjusted for weight, age, male sex, Killip-Kimball class III-IV, anterior wall infarction, left main coronary artery disease, multivessel disease, diabetes, current smoker, ischemia time, AAS, clopidogrel, ticagrelor and prasugrel administered at FMC and time from SO to UFH administration.

Factor	Odds Ratio	95% CI	p-value
31–60 min from UFH administration to coronary angiography (Group 2)	1.01	0.80–1.23	0.902
61–90 min from UFH administration to coronary angiography (Group 3)	1.43	1.14–1.81	0.002
>90 min from UFH administration to coronary angiography (Group 4)	1.34	1.03–1.74	0.030

CI, confidence interval; IRA, infarct-related artery; FMC, first medical contact; SO, symptom onset; TIMI, thrombolysis in myocardial infarction; UFH, unfractionated heparin;

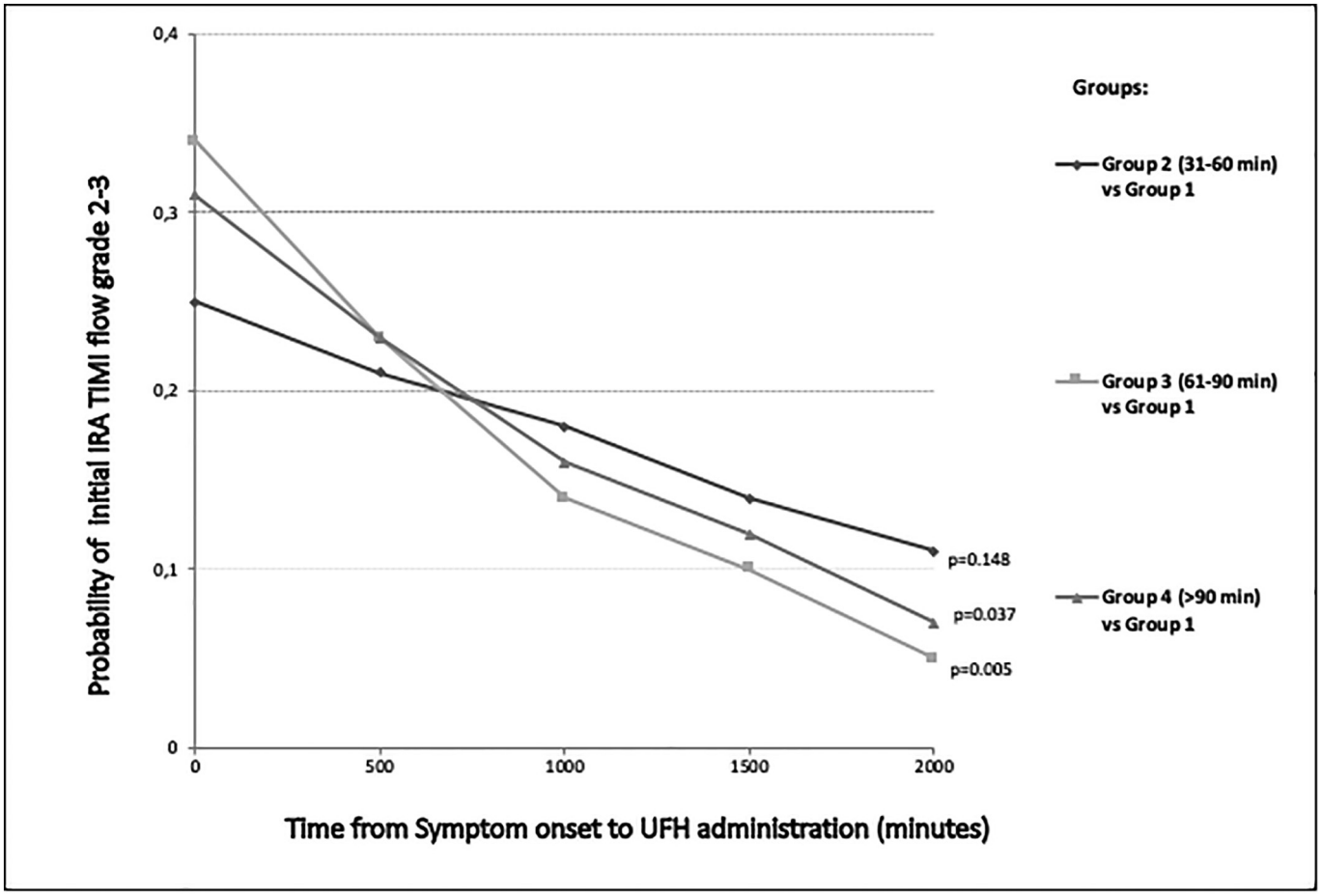

Fig. 1. Probability of pre-PPCI IRA TIMI 2–3 flow according to the elapsed time between symptom onset an UFH administration.

Table 3
Multivariate Cox regression analyses for 30-day and 1-year mortality adjusted for age, male sex, weight, Killip-Kimball class III-IV, anterior wall infarction, left main coronary artery disease, pre-procedural TIMI flow grade 2–3, post-procedural TIMI flow grade 2–3, ischemia time, ventricular fibrillation, PCI capable center and including PCI - capable center as strata.

Factor	30-day Mortality			1-year Mortality		
	HR	95% CI	p-value	HR	95% CI	p-value
31–60 min from UFH administration to coronary angiography (Group 2)	0.57	0.37–0.88	0.012	0.60	0.43–0.83	0.002
61–90 min from UFH administration to coronary angiography (Group 3)	0.63	0.42–0.94	0.025	0.57	0.41–0.80	<0.001
>90 min from UFH administration to coronary angiography (Group 4)	0.71	0.48–1.07	0.103	0.68	0.49–0.94	0.021

CI, confidence interval; FMC, first medical contact, HR, hazard ratio; PCI, percutaneous coronary interventionism; TIMI, thrombolysis in myocardial infarction; UFH, unfractionated heparin;

IRA patency. Only a slight trend towards a higher probability of IRA patency was observed when ticagrelor or prasugrel and UFH were administered >90 min before PPCI (OR 3.33, 95% CI 0.97–15.5; $p = 0.079$). In the multivariate analysis, no impact of ticagrelor or prasugrel on 30-day or 1-year mortality was found.

After additional sub-analysis redefining IRA patency as pre-procedural TIMI 3 blood flow, similar results were obtained (Tables 2 and 3, supplementary material).

4. Discussion

The present study of a large regionwide cohort of STEMI patients shows that pre-angioplasty treatment with UFH improves IRA reperfusion, especially when the time between UFH administration and PPCI is longer than 60 min. Our results also demonstrate that the benefit of UFH administration is time-dependent, with a higher probability of IRA patency when UFH is administered promptly after symptom onset. This beneficial effect on earlier coronary reperfusion seems associated with superior clinical outcomes such a lower mortality both at 30 days and at one year.

Achieving rapid IRA reperfusion is the most important goal in STEMI patients. Currently, PPCI is the preferred reperfusion strategy when performed less than 120 min after the patient's first medical contact [2,3]. It is known, however, that transfers from non-PCI-capable hospitals or emergency medical services can mean longer delays in reperfusion that are associated with worse outcome [18,19]. Current clinical practice guidelines recommend adjunctive antithrombotic therapy with antiplatelet and anticoagulant therapy in STEMI patients before PPCI, but the optimal timing for administration remains controversial [2,3].

Over the years, different adjunctive therapies have been tested with the aim of improving IRA patency before PPCI and reducing ischemia time. Some studies have analyzed the impact of UFH administration in STEMI patients prior to PPCI. The HEAP pilot study [20] treated 108 STEMI patients with a single intravenous high-dose bolus of 300 U/kg

of heparin plus aspirin (160 mg chewed) in the emergency room and compared their results with those in a data base of matched patients receiving only aspirin without heparin. Median time between UFH administration and angiography was 85 min, and they reported 51% IRA patency with early administration of heparin, especially at less than two hours from the onset of symptoms. However, this benefit was not confirmed in the HEAP randomized trial [21], which compared high-dose (300 IU/kg) vs no/low dose (0/5000 IU) of UFH in 584 patients with myocardial infarction scheduled for PPCI. Median time from UFH administration to balloon was 71 min and no difference in initial IRA patency between groups was found. Despite this lack of statistically significant differences, it is remarkable that one quarter of patients in the group of no/low dose received 5000 IU of heparin that could mitigate differences between the two groups. A later non-randomized study by the same group included 1702 patients and found that pre-hospitalization administration of UFH (5000 IU) plus aspirin at a median of 81 (±43) minutes before PPCI improved IRA reperfusion compared to the administration of the same medication in the emergency room of a PCI-capable center at a median of 26 (±39) minutes before PCI [22].

These studies were carried out two decades ago, at a time when regional networks had not been established. More recent observational studies [23–25] support the role of pre-PCI UFH administration to improve pre-procedural IRA patency. In line with the present study, a single-center study performed by our group [26] assessed the effect of early administration of a fixed dose of 5000 UI of UFH on IRA recanalization in 1326 consecutive STEMI patients transferred to a PCI-capable center. Pre-transfer UFH administration was associated with higher rates of IRA patency (30.3% TIMI flow grade 2–3 in the pre-transfer group vs 21.2% in the post-transfer group [at the Cath Lab]; $p < 0.001$). Moreover, early UFH administration was associated with lower rates of 1-year mortality (HR 0.51; $p = 0.02$) with no increase in bleeding risk (1.5% vs 1.1%; $p = 0.5$).

To the best of our knowledge, this is the first study to analyze the effect of UFH administration on a sliding time scale. We have found that UFH administration longer than 60 min prior to PPCI was related to improved rates of pre-procedural IRA patency. Heparin antithrombotic activity starts immediately after its administration but it has been reported that the fibrinolysis-enhancing property of 5000 UI of UFH starts 60 min after infusion, when t-PA levels increase [27] and is subject to inter and intra-individual variability.

Our findings both in the present study and in the previous study by our group [26] lead us to speculate that the optimal time for UFH administration is at STEMI diagnosis, as soon as possible after the onset of symptoms, especially when a delay to PPCI of more than 60 min is expected. The sooner UFH is administered, the more likely it is that reperfusion will be achieved because fresh and unorganized clots will be more accessible for heparin.

It is well known, that an occluded IRA at initial PPCI is related to worse outcomes and higher mortality rates [28–30]. In our study we found that administration of UFH longer than 30 min before PPCI was an independent predictor of improved 30-day and 1-year survival. These results of this observational study could suggest that early UFH administration at STEMI diagnosis could play a role reducing mortality rates in STEMI patients due to an earlier restoration of blood flow at the IRA. However, the mortality outcomes should be interpreted with caution due to the possibility of undetected residual confounding.

We have observed no differences in the initial IRA TIMI flow grade according to the addition of novel P2Y12 to UFH administration in comparison to clopidogrel combined with UFH. Previous studies analyzing the effect of early administration of ticagrelor or prasugrel compared to clopidogrel in STEMI patients treated with PPCI have yielded conflicting results [13,14,31–33]. In our study, we were able to specifically test the early co-administration of the novel, more powerful antiplatelet drugs that are now available. However, we observed no differences if patients received ticagrelor or prasugrel instead of clopidogrel either in initial IRA patency or clinical outcomes, probably because median time between administration and coronary angiography was too short. It has been reported that the antiplatelet action of ticagrelor starts 90–120 min after administration, while that of prasugrel starts 30 min to 4 h after administration and also depends on oral absorption variability [14,34,35]. Moreover, despite not reaching statistical significance, we observed a tendency towards improved IRA patency when administration took place >90 min before PPCI. Nonetheless, only 21.9% of patients were pretreated with ticagrelor or prasugrel, which is a sample that is probably not powerful enough to detect differences between groups.

In addition, the incidence of bleeding requiring transfusion in our study was very low, with no differences between groups, indicating its safe use in this setting. However, it was slightly lower than those reported in previous studies [23,36], which was already very low. This could be explained by the spread use of radial approach for PPCI in our region [9,36].

It is important to highlight the wide geographical variability of the region covered by the Catalan AMI Code network. This variability can lead to large differences in time elapsed from first medical contact to PPCI, which can range from 91 to 118 min ($p < 0.001$). Moreover, we have observed significant differences in the percentage of patients treated with UFH depending on the PCI-capable center where the patient was first attended to or later transferred. In our study, the median time between UFH administration and angiography was 67 min, and the maximum benefit was observed when UFH was administered longer than 60 min before PPCI. Our results will hopefully encourage a more homogeneous use of UFH, especially for STEMI patients who can expect a delay longer than 60 min before a definitive revascularization with PPCI.

Our study has several limitations, primarily its observational nature. Since this was a non-randomized study, results may be influenced by some confounding factors not considered in our multivariable analyses. For example, we lacked data on left ventricular ejection fraction, although we were able to include other related data, such as anterior wall infarction, left main coronary artery disease, and Killip-Kimball class in our multivariate analyses to assess the impact of UFH administration at STEMI diagnosis on long term mortality. Infarct size studied by c-MRI would have helped to support our mortality results, but these data were not available in our study. Furthermore, survivor bias could explain some of the differences, since among patients with longer delays, those who die before PPCI may leave the remaining cohort with better prognosis and IRA patency. However, the fact that UFH was administered equally regardless of the severity of the STEMI and longer delays in access to PPCI (Group 4) did not compromise the therapeutic benefit of UFH, would indicate that any possible differences due to survivor bias would be quite small. Finally, information regarding the use of dual antiplatelet therapy at long-term follow-up was not available for our study. Nevertheless, the fact that we had access to a large multicenter registry with a large sample size confers external validity to our data. A randomized multicenter clinical trial is warranted to prospectively validate our results.

In summary, in this large multicenter real-life observational prospective registry, we have found that UFH administration at STEMI diagnosis improves coronary reperfusion prior to PPCI and this benefit could be associated with superior clinical outcomes, such a reduced associated mortality at 30 days and one year. This effect is time-dependent, as the sooner after symptom onset the UFH is administered, the higher the probability of IRA patency. In contrast, we found no association with either a higher probability of IRA patency or lower mortality for the co-administration of the novel antiplatelets ticagrelor or prasugrel.

Even though considered within an observational study nature, the results of the present investigation could be of notable importance in routine initial management of STEMI patients, especially when a delay of more than 60 min is envisaged before PPCI. Further clinical trials on this topic would be mandatory in order to fully elucidate such interesting real-life findings.

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Declaration of Competing Interest

None.

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