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Clinical paper

The balance of thrombosis and hemorrhage in STEMI patients with or without associated cardiac arrest: An observational study

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Abstract

Background: Data is scarce on hemorrhagic and thrombotic complications in patients with ST-elevation myocardial infarction (STEMI) associated with out-of-hospital cardiac arrest (OHCA).

Methods: This is a monocentric, retrospective study conducted from January 2012 to December 2017 in a tertiary university hospital, which serves as a cardiac arrest center for a large urban area. Over the study period, all consecutive patients who were treated with stent implantation for STEMI with or without OHCA were included. Baseline characteristics, treatments, hemorrhagic and thrombotic events were compared between STEMI patients with and without OHCA. Univariate and multivariate analysis were performed in order to identify predictors of 30-day mortality, occurrence of major bleeding (MB), and early stent thrombosis (ST).

Results: A total of 549 patients treated for STEMI without OHCA and 146 patients for STEMI with OHCA were included. The incidence of definite ST and MB after coronary angioplasty was significantly higher in patients with OHCA (2.6% vs. 7.5%, $p = 0.004$ and 3.3% vs. 19.2%, $p < 0.001$, respectively). Independent predictors of MB in OHCA patients were anticoagulation therapy (HR = 3.11, 95%CI [1.22−7.98], $p = 0.02$) and the use of glycoprotein IIb/IIIa inhibitors (HR = 4.16, 95%CI [1.61−10.79], $p = 0.003$). Independent predictors of mortality in OHCA patients were age (HR = 1.05, 95%CI [1.02−1.09], $p = 0.004$) and ST (HR = 5.62, 95%CI [1.61−19.65], $p = 0.007$, with a protective effect of new anti-P2Y12 treatments (HR = 0.20, 95%CI [0.08-0.46], $p < 0.001$).

Conclusion: Patients treated for STEMI associated with OHCA are at higher-risk of ST and MB than those who did not experience cardiac arrest. In this subset of patients, prospective studies are needed to better evaluate the balance of thrombosis and hemorrhage.

Keywords: Cardiac-arrest, Acute coronary syndrome, Bleeding, Stent thrombosis

Abbreviations: ACS, Acute coronary syndrome; PCI, Percutaneous coronary intervention; OHCA, Out-of-hospital cardiac arrest; STEMI, ST-elevation myocardial infarction; ST, Stent thrombosis; BARC, Bleeding Academic Research Consortium; GUSTO, Global Utilization Of Streptokinase And Tpa For Occluded Arteries; TIMI, Thrombolysis in Myocardial Infarction; ORs, Odds ratios; CI, Confidence interval.

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Introduction

Acute coronary syndromes (ACS) are the leading cause of sudden cardiac arrest in adults.[1] European guidelines recommend urgent coronary angiography in a view for primary percutaneous coronary intervention (PCI) in survivors of out-of-hospital cardiac arrest (OHCA).[1,2] This primary PCI strategy is particularly recommended in patients with resuscitated cardiac arrest and an ECG consistent with ST segment elevation myocardial infarction (STEMI) (Class I), but urgent angiography (and PCI if indicated) should also be considered in those without diagnostic ST-segment elevation but with a high suspicion of ongoing myocardial ischemia (Class IIa).[3] Data concerning thrombotic events in these OHCA patients are controversial. Shock, hypothermia and changes in antiplatelet pharmacokinetic have been pointed at as potential promoters of stent thrombosis (ST). Indeed, hypothermia used to prevent ischemia-related organ damage has been showed to be associated with pro-thrombotic side effects in pre-clinical studies. Different mechanisms such as increased expression of platelet activation marker P-selectin, platelet-leukocyte aggregate formation, and thrombocytopenia were described.[4] When comparing ST in patients with acute myocardial infarction and OHCA, Joffre et al. found a significantly higher incidence of confirmed acute or subacute ST in the cardiac-arrest group treated with cooling than in the control group (10.9% vs. 2.0%, $p = 0.01$).[5] On the other side, OHCA patients are also at higher risk of bleeding events, that may be promoted by cardio-pulmonary resuscitation maneuvers and subsequent trauma induced by chest compressions used for resuscitation, by antithrombotic therapies associated with coronary angiography and subsequent angioplasty (i.e., antiplatelet therapy, heparin, and Glycoprotein IIb/IIa-inhibitors), by the need of arterial and venous lines insertion at the initial phase of intensive care, and by potential need of large mechanical support devices such as Impella or Extra-corporeal membrane oxygenation.[6] There is an activation of the inflammatory reaction associated with clinical features that are very similar to those observed during severe sepsis. Coagulation abnormalities have been identified, involving a significant activation of coagulation factors, whereas endogenous anticoagulants (anti-thrombin, protein S and C) are decreased. This intravascular coagulation can be implicated in the genesis of microvascular abnormalities, which in turn lead to more visceral lesions. Of note these coagulation abnormalities are particularly common in patients who die quickly from a post-resuscitation shock.[7] Lastly, cardiac arrest patients treated with hypothermia experience increased platelet aggregation and strengthened clot formation over time. In addition, in patients on oral dual platelet inhibition, the effect of ticagrelor is delayed, probably due to slow gastric emptying,[8] Indeed, the effect of platelet inhibition with the P2Y12-antagonist pro-drug clopidogrel may vary secondary to differences in intestinal absorption, variations in liver cytochrome activities, drug interactions, and platelet receptor polymorphisms.[9] Although thrombotic/hemorrhagic balance is starting to be well documented in ACS without cardiac arrest,[10] data is scarce concerning patients presenting STEMI associated with OHCA, two populations that share the same trigger but seem to be fundamentally different in regard of thrombotic/hemorrhagic balance. Therefore, using an observational retrospective study we sought to evaluate the thrombotic/hemorrhagic balance in patients with STEMI associated or not with OHCA.

Methods

Study design and population

This was an observational, single-center, retrospective study of consecutive patients treated for STEMI associated with OHCA between January 2012 and December 2017, that was conducted at Cochin Hospital, an academic tertiary center. In this analysis, all consecutive patients presenting with STEMI associated with OHCA during the study period were included. STEMI diagnosis was defined by chest pain or cardiac arrest associated with ST-elevation or left bundle branch block on the electrocardiogram and elevated troponin, at least 3 times of the normal range. For OHCA patients, restoration of spontaneous circulation after initial cardio-pulmonary resuscitation was mandatory for inclusion in the present study. Patients were followed-up at 30 days after hospital admission. Baseline demographics, medical history, cardiac catheterization data and in-hospital outcomes were abstracted from medical charts. The study was conducted according to the Declaration of Helsinki. As this was a retrospective analysis conducted per institutional guidelines for data security and privacy, a waiver of consent was granted. Data were anonymized by authors prior to analysis.

Clinical endpoints and definitions

The primary endpoints were the occurrence of in-hospital acute ST and the incidence of in-hospital bleeding events. ST was defined according to the Academic Research Consortium for trials involving stent.[11] A ST was *definite* when ACS with angiographic or pathological confirmation of thrombus was provided, *probable* when unexplained death within 30 days or MI involving target vessel territory without angiographic confirmation was diagnosed. In cardiac arrest patients, *probable* stent thrombosis was determined using serial troponin measurements, serial 12-lead ECGs and unexplained hemodynamic deterioration without other clear cause for cardiac arrest patients and without angiographic confirmation of stent thrombosis. Repeated coronary angiography was usually performed in the department in case of recurrent ST-segment elevation, abnormal troponin rise after the acute phase or hemodynamic degradation associated with ECG modifications. Bleedings complications were defined using the Bleeding Academic Research Consortium (BARC).[12] Type 3 and 5 of BARC classification were considered as major bleedings. Type 3 encompassed: 3a: Overt bleeding plus hemoglobin drop of 3 to <5 g/dL or any transfusion with overt bleeding; 3b: overt bleeding plus hemoglobin drop ≥ 5 g/dL or cardiac tamponade or bleeding requiring surgical intervention for control or bleeding requiring intravenous vasoactive agents and 3c: Intracranial hemorrhage, subcategories confirmed by autopsy or imaging or lumbar puncture or intraocular bleed compromising vision. Type 5 included fatal bleeding, ie. 5a: probable fatal bleeding, no autopsy or imaging confirmation but clinically suspicious; 5b: Definite fatal bleeding overt bleeding or autopsy or imaging confirmation. Additional GUSTO (*Global Utilization Of Streptokinase And Tpa For Occluded Arteries*) and TIMI (*Thrombolysis in Myocardial Infarction*) bleeding classifications are reported in the present analysis.[12] All-cause death and hospitalization duration are also reported.

Statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation when normally distributed and as median [inter-quartile range]

otherwise. Categorical variables were expressed as count and percentage. The associations between categorical variables were assessed using a chi-square test (or Fisher exact test when appropriate) and continuous variables compared with Student t-test. Univariate and multivariable logistical regression were developed to assess the association between baseline characteristics and the association with the occurrence of major bleeding, ST and death with pre-specified patient, lesion and procedural variables. Candidate covariates that showed marginal associations to outcome on univariate testing ($p \leq 0.20$), were included in our multivariate analysis for major bleeding and death. Odds ratios (ORs) are presented with 95% confidence interval (CI). Statistical significance was defined at a level of $\alpha \leq 0.05$. Statistical analyses were carried out using SPSS package v23.0 (Chicago, IL, USA).

Results

Population clinical and biological characteristics

Between January 2012 and December 2017, 549 patients were treated for STEMI without OHCA and 146 for STEMI with OHCA. Their clinical and biological characteristics are reported in Table 1. Briefly, sex and age were similar in the two groups with male sex predominance (80.5% in the STEMI group vs. 84.9% in the STEMI with OHCA group, $p = 0.22$; and mean age of 61 ± 12.4 vs. 61.3 ± 12.8 years, $p = 0.78$; respectively). Patients without OHCA had higher cardiovascular risk factors, except for smoking status, likely due to the difficulty of past medical history collection in OHCA patients. Left ventricular ejection fraction was lower in the OHCA group (34.2% vs. 48.3%; $p < 0.0001$) with higher use of mechanical support devices. Biologically, white blood cells count was higher in the OHCA group (18.6 ± 7.3 vs. $11.9 \pm 4.5 \times 10^3/mm^3$, $p < 0.0001$), as well as creatinine level (105.6 ± 50.7 vs. 83.1 ± 43.1 mmol/L, $p < 0.0001$). Platelets count was similar in both groups (227 ± 87 vs. $229 \pm 79 \times 10^3/mm^3$, $p = 0.83$) whereas hemoglobin was slightly lower in the OHCA group, although in the normal range in both groups (13.1 ± 2.0 vs. 13.9 ± 5.6 g/dL, $p = 0.007$). Ultrasensitive troponin peak was similar in both groups (5692 ± 9187 vs. 5239 ± 7908 ng/L, $p = 0.60$).

Angiographic baseline characteristics

Left anterior descending artery was more frequently the culprit lesion in patients with OHCA (60.3% vs. 47.7%, $p = 0.007$) whereas right coronary artery was less frequently the culprit lesions in patients with OHCA (19.2% vs 37.9%, $p < 0.0001$). Mean total stent length was similar in both groups (28.5 ± 18.3 mm vs. 25.6 ± 13.2 mm, $p = 0.10$) as well as stent diameter (3.03 ± 0.43 mm vs. 3.11 ± 0.45 mm, $p = 0.07$). Bare-metal stents were more frequently used in patients with OHCA (46.5% vs. 22.1%, $p < 0.0001$). There was no difference on final TIMI flow whereas no-reflow was more frequently observed in

Table 1 – Baseline clinical and biological characteristics of STEMI patients with or without associated OHCA.

	STEMI (n: 549)	STEMI with OHCA (n: 146)	*p* Value
Age, years, mean ± SD	61 (±12.4)	61.3 (±12.8)	0.78
Male, % (n)	80.5% (442)	84.9 % (124)	0.22
Smoking, % (n)	45.2 % (248)	48.6 % (71)	0.46
Hypertension, % (n)	39.7% (218)	26.0 % (38)	**0.002**
Diabetes mellitus, % (n)	26.8% (147)	13.0 % (19)	**0.0005**
Hypercholesterolemia, % (n)	36.2% (199)	19.2 % (28)	**<0.0001**
Family history of coronary artery disease, % (n)	20.9 % (115)	2.0 % (3)	**<0.0001**
ECMO, % (n)	0.9 % (5)	4.1% (6)	**0.006**
IABP, % (n)	4.3 % (24)	9.6% (14)	0.01
Impella, % (n)	0.1 % (1)	0% (0)	0.61
Shockable rhythm, % (n)	N/A	59.6% (87)	N/A
Therapeutic temperature management, % (n)	N/A	72.6% (106)	N/A
Public location of cardiac arrest, % (n)	N/A	41.8% (61)	N/A
Present witness of cardiac arrest, % (n)	N/A	89 % (130)	N/A
Resuscitation by the witness, % (n)	N/A	56% (93)	N/A
No Flow time, mean ± SD	N/A	3.5 (±4.5)	N/A
Low Flow time, min, mean ± SD	N/A	21.7 (±17.1)	N/A
LVEF, %, mean ± SD	48.3 (±11.2)	34.2 (±14.6)	**< 0.0001**
WBC, ×10*3/mm3, mean ± SD	11.9 (±4.5)	18.6 (±7.3)	**< 0.0001**
Hemoglobin, g/dL, mean ± SD	13.9 (±5.6)	13.1 (±2.0)	**0.007**
Platelets, ×10*3/mm3, mean ± SD	229 (±79)	227 (±87)	0.83
Creatinine, µmol/, mean ± SD	83.1 (±43.1)	105.6 (±0.7)	**<0.0001**
Troponin peak, ng/l, mean ± SD	5239 (±7908)	5692 (±9187)	0.60
Creatine kinase, IU/l, mean ± SD	1957 (±4615)	2307 (±2986)	0.39
AST, mmol/l, mean ± SD	202 (±546)	352 (±402)	**0.0004**
ALT, mmol/l, mean ± SD	71 (±306)	199 (±230)	**<0.0001**
aPTT ratio, mean ± SD	4.1 (±2.6)	3.3 (±2.4)	**0.001**
Prothrombin time, %, mean ± SD	79.3 (±17.3)	64.6 (±17.8)	**<0.0001**
pH, mean ± SD	N/A	7.21 (±0.15)	N/A
Lactates, mmol/L, mean ± SD	N/A	4.9 (4.5)	N/A

Abbreviations: ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; LVEF: left ventricular ejection fraction; WBC: white blood cells; AST: aspartate aminotransferase; ALT: alanine aminotransferase; aPTT: activated partial thromboplastin time.

patients without OHCA (11.7% vs. 5.5%, p = 0.03). All angiographic characteristics are reported in Table 2.

Antithrombotic therapies

All patients admitted received aspirin loading dose and heparin loading dose by pre-hospital medicalized emergency unit. There was no difference in patients receiving an initial loading dose of clopidogrel (27.7% in the STEMI group vs. 16.4% in the STEMI-OHCA group, p = 0.06) or more potent antiplatelet therapy (ticagrelor or prasugrel) (71.2% vs. 67.1%, p = 0.06). Nevertheless, more patients in the OHCA group did not receive any second oral antiplatelet therapy (16.4% vs. 1.1%, p > 0.0001). A modification in the therapeutic strategy was observed less frequently in the OHCA group (4.1% vs 9.3%, p = 0.04). In addition, anticoagulation therapy was more frequently prescribed in OHCA patients (30.8% vs.9.4%, p = 0.0001). Glycoprotein IIb/IIIa inhibitors were similarly used in both groups (38.3% vs 40.6%, p = 0.62). Antithrombotic therapies used are reported in Table 2.

Thirty-days clinical outcomes

Thirty-days mortality was 3.1% in the STEMI group vs 47.9% in the STEMI-OHCA group, p < 0.0001. The occurrence of any bleeding according to BARC classification was more frequent in the STEMI-OHCA group (29.5% vs 8.6%, p < 0.0001), as well as BARC 3–5 bleedings (19.2% vs 3.3%, p < 0.0001). When using GUSTO and TIMI major classifications, the occurrence of GUSTO severe or TIMI major bleedings were also higher in the OHCA group. The occurrence of ST was also more frequent in the OHCA group (12.3% vs 3.1%, p < 0.0001), as well as definite ST (7.5% vs 2.6%, p = 0.004). All clinical outcomes are summarized in Table 3. Major (BARC 3–5) bleeding types are summarized in Fig. 1. In the OHCA group, the most common BARC 3–5 bleeding type was from other causes than vascular, cardiac, gastro-intestinal or intra-cranial bleeding. Other causes included 4 bleedings that could be related to cardio-pulmonary resuscitation (3 hemothorax and 1 internal bleeding related to hepatic fracture).

Factors associated with ST, major bleeding and mortality in STEMI patients with OHCA

Univariate factors associated with ST in STEMI patients with OHCA were the use of drug-eluting stent (HR = 2.826; IC95% 1.066–7.489; p = 0.037) and post-PCI anticoagulation therapy (HR = 2.496; IC95% 1.059–5.88; p = 0.037) (Supplemental Table 1).

Univariate factors associated with major bleeding (BARC 3–5) in STEMI patients with OHCA were the use of post-PCI anticoagulation therapy (HR = 2.496; IC95% 1.059–5.88; p = 0.037) and Glycoprotein IIb/IIIa inhibitors (HR = 3,091; IC95% 1,106–2,269; p = 0,009). Using

Table 2 – Baseline procedural characteristics and treatment of STEMI patients with or without associated OHCA.

	STEMI (n: 549)	STEMI with OHCA (n: 146)	*p* Value
Number of coronary arteries with significant lesion, % (n)			0.47
1, % (n)	43.7% (240)	40.4% (59)	
>1, % (n)	56.3% (309)	59.6% (87)	
Culprit coronary artery, % (n)			**<0.0001**
LAD	47.7% (262)	60.3% (88)	
LCX	13.1% (72)	17.1 % (25)	
RCA	37.9% (208)	19.2% (28)	
LMCA	1.3% (7)	3.4% (5)	
No reflow, % (n)	11.7 % (64)	5.5% (8)	**0.03**
Final TIMI flow, mean ± (SD)	2.9 (±0.5)	2.8 (±0.7)	0.07
Stent implantation, % (n)	91% (502)	88.3% (129)	0.25
Bare-metal stent, % (n)	22.1% (111)	46.5% (68)	**<0.0001**
Drug-eluting stent, % (n)	71% (391)	41.8% (61)	**<0.0001**
Total length of implanted stent, mm, mean ± (SD)	25.6 (±13.2)	28.5 (±18.3)	0.10
Stent diameter, mm, mean ± (SD)	3.11 (±0.45)	3.03 (±0.43)	0.07
Thromboaspiration use, % (n)	36.6 % (201)	34.9% (51)	0.71
Total DAP, Gy.cm^2, mean ± (SD)	7498 (±7279)	8315 (±9561)	0.36
Angioscopy duration, min, mean ± (SD)	11.58 (±8.5)	13.11 (±8.7)	0.07
Antiplatelet treatment characteristics			
Aspirin, % (n)	100 % (549)	100 % (146)	0.61
P2Y12 inhibitors	98.9% (543)	83.6% (122)	**<0.0001**
Clopidogrel, % (n)	27.7% (152)	16.4% (24)	0.06
Ticagrelor or Prasugrel, % (n)	71.2% (391)	67.1 % (98)	0.06
None, % (n)	1.1 % (6)	16.4% (24)	**<0.0001**
Switch of P2Y12 inhibitors therapy during hospitalization, % (n)			
Clopidogrel to Ticagrelor or Prasugrel, % (n)	2.7% (15)	0.7% (1)	0.14
Ticagrelor or Prasugrel to Clopidogrel, % (n)	5.6% (31)	0.7% (1)	**0.01**
Anti-P2Y12 interruption, % (n)	0.4% (2)	2.7% (4)	**0.006**
Glycoprotein IIbIIIa inhibitors, % (n)	40.6% (223)	38.3% (56)	0.62
Post-PCI anticoagulation therapy, % (n)	9.4 % (52)	30.8% (45)	**<0.0001**
Thrombolysis therapy prior-PCI, % (n)	0 % (0)	3.4 % (5)	**<0.0001**
Shock needing vasoactive therapies	3% (17)	65.0% (95)	**<0.0001**

Abbreviations: LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery; LMCA: left main coronary artery; TIMI: thrombolysis in myocardial infarction; DAP: dose area product; PCI: percutaneous coronary intervention.

Table 3 – Thirty-days clinical outcomes of STEMI patients with or without associated OHCA.

	STEMI (n : 549)	STEMI with OHCA (n : 146)	*p* value
All-cause death, % (n)	3.1 % (17)	47.9% (70)	<**0.0001**
Any bleeding, % (n)	8.6 % (47)	29.5% (43)	<**0.0001**
BARC 3–5 bleeding, % (n)	3.3 % (18)	19.2% (28)	<**0.0001**
BARC 1–2 bleeding, % (n)	5.3% (29)	10.3% (15)	**0.03**
GUSTO « severe » bleeding, % (n)	1.5 % (8)	9.6% (14)	<**0.0001**
GUSTO «mild» or «moderate» bleeding, % (n)	7.1% (39)	19.9% (29)	<**0.0001**
TIMI «major» bleeding, % (n)	1.8% (10)	11.6% (17)	<**0.0001**
TIMI «minor» bleeding, % (n)	6.2% (34)	17.1% (25)	<**0.0001**
Stent thrombosis, % (n)	3.1% (17)	12.3% (18)	<**0.0001**
Definite, % (n)	2.6% (14)	7.5% (11)	**0.004**
Probable, % (n)	0.5 % (3)	4.8% (7)	<**0.0001**
Hospitalization duration, days, mean ± (SD)	5.6 (±5.0)	12.6 (±13.4)	<**0.0001**

Abbreviations: BARC: Bleeding Academic Research Consortium; GUSTO: Global Utilization Of Streptokinase And Tpa For Occluded Arteries; TIMI: Thrombolysis in Myocardial Infarction.

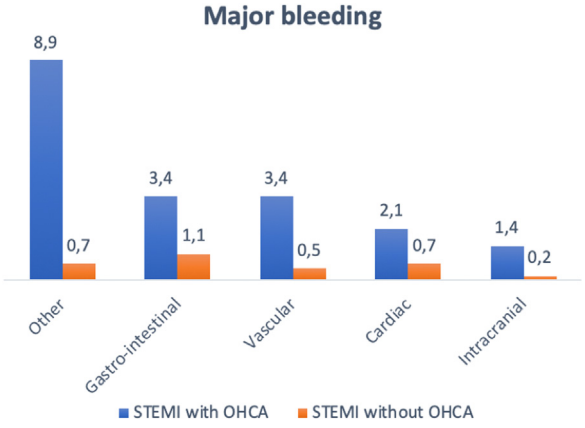

Fig. 1 – Bleeding types among major (BARC 3–5) bleedings in STEMI patients with or without associated OHCA, expressed in percentage. Abbreviations: BARC: Bleeding Academic Research Consortium; STEMI: ST-segment elevation myocardial infarction; OHCA: out-of-hospital cardiac arrest.

multivariate analysis, these two factors remained significantly associated with major bleeding (respectively, HR = 3.11; IC95% 1.22–7.98; p = 0.02 and HR = 4.16; IC95% 1.61–10.79; p = 0.003) (Table 4).

Univariate factors associated with all-cause death in STEMI patients with OHCA were the age (HR = 1.050; IC95% 1.021–1,080; p < 0.001) and the occurrence of ST (HR = 3,193; IC95% 1.075 –9.488; p = 0,037). The use of ticagrelor or prasugrel was associated with lower all-cause mortality in univariate analysis (HR = 0.198; IC95% 0.093–0.423; p < 0.001). All three factors remained significant after multivariate analysis (respectively, HR = 1.05; IC95% 1.02 –1.09; p = 0.004, HR = 5.62; IC95% 1.61–19.65; p = 0.007, and HR = 0.20; IC95% 0.08-0.46; p < 0.001) (Table 5).

Discussion

This retrospective study of 695 STEMI patients including 146 patients with associated OHCA reports thirty-days clinical outcomes and evaluates predictors of all-cause mortality, ST and major bleeding in OHCA patients. The main findings of our study are threefold. First, the occurrence of definite ST was higher in patients with associated OHCA (12.3% vs 2.7%, p = 0.04). Second, the rate of major bleedings (BARC 3–5) were also higher in OHCA patients (19.2% vs 3.3%, p < 0.001). Last, using multivariate analysis, age (HR = 1.05; IC95% 1.02–1.09 ; p = 0.004) and the occurrence of ST (HR = 5.62; IC95% 1.61–19.65 ; p = 0.007) were predictive of all-cause mortality at thirty-days in OHCA patients, whereas the use of potent antiplatelet therapy (ticagrelor or prasugrel) was associated with lower all-cause mortality

Table 4 – Univariate and multivariate analysis of factors associated with BARC 3–5 bleeding in STEMI patients with OHCA.

Univariate analysis	Odds ratio	95% CI	p
Age	0.996	0.964–1.029	0.791
Diabetes	1.615	0.529–4.932	0.400
Dyslipidemia	0.653	0.207–2.061	0.467
Smoker	1.070	0.469–2.440	0.872
Hypertension	0.935	0.362–2.415	0.890
LVEF	0.972	0.943–1.002	0.072
P2Y12 inhibitors therapy	0.349	0.077–1.585	0.173
Clopidogrel	2.395	0.907–6.327	0.078
Ticagrelor or prasugrel	0.889	0.375–2.106	0.789
Post-PCI anticoagulation therapy	2.496	1.059–5.88	0.037
Glycoprotein IIbIIIa inhibitors use	3.091	1.321–7.234	0.009
Stent thrombosis	0.490	0.106–2.269	0.362
Thromboaspiration	1.802	0.780–4.163	0.168
Bare-metal stent	0.747	0.502–2.612	0.747
Drug-eluting stent	0.717	0.310–1.655	0.435
Hemoglobin	0.725	0.228–2.311	0.587
WBC	0.946	0.817–1.094	0.453
Platelets	0.997	0.992–1.003	0.343
Creatinine level	0.994	0.983–1.005	0.291
Multivariate analysis	**Odds ratio**	**95% CI**	**P**
Clopidogrel	0.249	0.05–1.24	0.09
Post-PCI anticoagulation therapy	3.11	1.22–7.98	**0.02**
Glycoprotein IIbIIIa inhibitors use	4.16	1.61–10.79	**0.003**
Thromboaspiration	1.51	0.61–3.78	0.38

Abbreviations: same as Tables 1–3. Bold values represent significant variables.

Table 5 – Univariate and multivariate analysis of factors associated with all-cause death in STEMI patients with OHCA.

Univariate analysis	Odds ratio	95% CI	P
Age	1.050	1.021–1.080	**<0.001**
LVEF	0.978	0.954–1.001	0.061
Any bleeding	0.904	0.443–1.847	0.783
BARC 3–5 bleeding	1.301	0.569–2.973	0.533
P2Y12 inhibitors therapy			
Clopidogrel	1.6	0.659–3.885	0.299
Ticagrelor or prasugrel	0.198	0.093–0.423	**<0.001**
Post-PCI anticoagulation therapy	1.205	0.595–2.439	0.605
Glycoprotein IIbIIIa inhibitors use	0.701	0.358–1.374	0.301
Stent thrombosis	3.193	1.075–9.488	**0.037**
Total stent length	0.997	0.969–1.026	0.861
Thromboaspiration	0.579	0.289–1.160	0.123
Bare-metal stent	1.273	0.662–2.447	0.470
Drug-eluting stent	0.618	0.322–1.184	0.147
Hemoglobin	1.284	0.644–2.560	0.478
WBC	1.046	0.922–1.186	0.487

Multivariate analysis	Odds ratio	95% CI	P
Age	1.05	1.02–1,09	0,004
LVEF	1.00	0.97–1.02	0.72
Ticagrelor or Prasugrel	0.20	0.08–0.46	**<0.001**
Stent thrombosis	5.62	1.61–19.65	**0.007**
Thromboaspiration	0.54	0.24–1.23	0.12
Drug-eluting stent	0.49	0.23–1.06	0.07

Abbreviations: same as Tables 1–3. Bold values represent significant variables.

(HR = 0.20; IC95% 0.08–0.46 ; $p < 0.001$). To our knowledge, the present study is one of the more recent and largest observational study that evaluates the thrombotic/hemorrhagic balance in STEMI patients associated or not with OHCA. Recent large-scale registries showed that with contemporary antithrombotic therapies and modern generation drug-eluting stents, the rate of early ST is around 1%.[13] Our study demonstrated a relatively higher rate of definite ST (2.7%) in STEMI patients without OHCA. Nevertheless, the interesting part is that the rate of ST was four times higher in OHCA patients. Indeed, studies in OHCA STEMI patients are scarce. In this subset of patients, in-hospital ST rates range from 1.1%[14] to 45.5%,[15] with large variations between studies.[13–16] Some predictive factors of ST in OHCA patients were previously reported to be age>80 years-old, the occurrence of cardiogenic shock, an hemodynamic support use, the use of multiple stents to treat the culprit lesion, and the occurrence of vascular complications.[16] In our study, the use of drug-eluting stent and anticoagulation post-PCI were predictive of stent-thrombosis in univariate analysis. Nevertheless, due to the heterogeneity of the drug-eluting stent used, it is difficult to draw any conclusion from these findings. As anticoagulation therapy post-PCI was associated with major bleeding, one can hypothesized that major bleeding is usually associated with withdrawal of aggressive antithrombotic therapies and could therefore result in stent thrombosis. Indeed, as for STEMI not associated with OHCA, post-procedural anticoagulation has been described as deleterious with increased bleedings without any impact on ischemic events.[17] In addition, multivariate analysis could not be performed due to the small number of such event, in order to prevent from overfitting. Nevertheless, ST was an independent risk factor of all-cause mortality at thirty-days and more potent platelet therapy use, such as ticagrelor or prasugrel, preventive from all-cause mortality. Therefore, in OHCA STEMI patients, we should focus to reduce any potential ST trigger, first by appropriate stenting technique, with the help, if needed of intravascular imaging; and second by appropriate antiplatelet therapy. The limits of pharmacodynamics of all oral P2Y12 inhibitors have been previously described, with reduced antiplatelet response of clopidogrel[18] and discordant findings on ticagrelor.[19,20] In such setting, the use of cangrelor could be of particular interest.[21,22]

On the other hand, the rate of major bleeding in OHCA STEMI patients in our study was also five times higher than in patients who did not experience cardiac arrest. This rate ranges from 7.5%[23] to 22.2%[24] in previous reports, with large variations between studies that reported bleeding rates in OHCA patients.[14,25] Nevertheless, there was a large variation between the definitions of major bleeding across studies. In our study, the predictors of major bleeding in OHCA STEMI patients were the use of Glycoprotein IIb/IIIa inhibitors and post-PCI anticoagulation therapy. Despite the strong association, one limitation of this observation is the lack of accurate data on the dose of Glycoprotein IIb/IIIa inhibitors and heparin used in our patients. Nevertheless, other studies reported that the use of Glycoprotein IIb/IIIa inhibitors in such patients was associated with an increased bleeding risk without reduction of thrombotic events.[26] Post-resuscitation increased bleeding risk can be due to multiple factors such as traumatic resuscitation maneuvers, post-resuscitation syndrome associated with shock, coagulation disturbances and requirement for invasive therapeutics including invasive monitoring, renal-replacement therapy, hemodynamic support devices with their inherent risks of vascular complications. This should be kept in mind when treating these high bleeding-risk patients.

Our study has several limitations that need to be acknowledged. The results must be interpreted with caution, as this is a single-center non-randomized study with a relatively small sample size. Due to the retrospective nature of our observational study, we cannot assess whether there was a change of practice between the beginning and the end of the study period. Nevertheless, it would have impacted both arms of the study. The abstracted data did not show details on the total dose of heparin received both during and after PCI. Nevertheless, as activated partial thromboplastin time was higher in the OHCA group, it could not have lowered the rates of bleedings in the OHCA arm. Indeed, some baseline characteristics could be missing in OHCA patients due to the retrospective nature of the study, especially in patients who died early after admission. In addition, coagulation factor activities, protein C/S concentrations and platelet aggregometry were not routinely performed. Also minor bleedings are frequently missing in such studies as they are not always mentioned in the charts. Nevertheless, our study highlights the fact that STEMI patients and STEMI patients who experienced cardiac arrest should be considered as different populations as they are at higher risk of both thrombotic and hemorrhagic complications. Clinical studies should be performed to address the best antithrombotic therapy in order to prevent ST but also reduce major bleedings.

Conclusion

In this study, patients treated for STEMI associated with OHCA are at higher risk of ST and major bleeding than those who did not. The use of anticoagulation therapy and glycoprotein IIb/IIIa inhibitors contributes

to increase bleeding complications and should be used with caution. A strategy favoring new anti-P2Y12 could improve the prognosis of these patients. Randomized controlled studies are needed to confirm these findings and better evaluate thrombotic and hemorrhagic balance in STEMI patients associated with OHCA.

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Conflict of interest

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.10.022.

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