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Out-of-hospital cardiac arrest and stent thrombosis: Ticagrelor versus clopidogrel in patients with primary percutaneous coronary intervention under mild therapeutic hypothermia☆

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ABSTRACT

Background: Out-of-Hospital Cardiac Arrest (OHCA) and mild therapeutic hypothermia (MTH) have been linked to increased risk of Stent Thrombosis (ST) in comatose survivors who undergo percutaneous coronary intervention (PCI). In this sense, there is no formal recommendation about which antiplatelet regimen should be used in patients with acute coronary syndromes (ACS) after OHCA.
Aims: To compare the incidence of probable/definite ST and bleeding events between ticagrelor and clopidogrel, in patients with ACS under MTH after an OHCA.
Methods and results: From January 2010 to August 2016, 144 patients underwent MTH after an OHCA. Overall, 114 had an ACS (79%) and 98 (67,3%) were treated with primary PCI and stent implantation. Among them, 61 (62,2%) were treated with clopidogrel, and 32 (32,6%) with ticagrelor. During hospitalization, the incidence of probable or definite ST was significantly higher in patients receiving clopidogrel compared to ticagrelor (11,4% vs. 0%; p: 0.04), and no significant differences in any (28,6% vs. 25%; p: 0.645) or major bleeding (BARC 3 or 5) (11,4% vs. 12,5%; p: 0.685) were found. Hospital mortality did not differ between groups (26,2% vs. 25%; p: 0.862).
Conclusions: In this study, as compared to clopidogrel, ticagrelor was associated with a lower rate of ST, without differences in haemorrhagic events in patients with OHCA for an ACS under MTH. Similarly to other settings, ticagrelor might be a valid alternative to clopidogrel in these patients.

Introduction

Acute coronary syndromes (ACS) are the commonest cause of malignant arrhythmias leading to sudden cardiac death.[1] Mild therapeutic hypothermia (MTH) and emergent coronary angiography with primary percutaneous coronary intervention (PCI) improves outcomes in the setting of Out-of-Hospital Cardiac Arrest (OHCA) after a coronary event.[2,3] MTH has been proposed to preserve neurological status in these patients.[4]

MTH has been associated with haemostasis and coagulopathy disorders.[5,6] The relationship between a higher risk of stent thrombosis (ST) and OHCA is however very controversial. Whereas several studies have reported a higher risk of stent thrombosis (ST) after primary PCI in OHCA patients,[7–12] some other studies did not find this association.[13,14] A recent study suggested that just the fact of having suffered an OHCA by itself increases the risk of ST regardless the use of MTH.[12] Alterations in platelet reactivity and pharmacokinetics of antiplatelet agents with MTH may pre-dispose to ST in these patients.[9–11]

Dual antiplatelet therapy (DAPT) with aspirin and P2Y12 inhibitor are the standard of care for patients after PCI.[15] Accordingly, DAPT has been integrated into management of patients after OHCA who undergo PCI and subsequently are treated with MTH.

Abbreviations: ACS, acute coronary syndrome; BARC, bleeding academic research consortium; BMS, bare metal stent; DAPT, dual antiplatelet therapy; DES, drug eluting stent; GP IIb-IIIa, glycoprotein IIb-IIIa receptors; ICU, intensive cardiac unit; LVEF, left ventricle ejection fraction; MTH, mild therapeutic hypothermia; OHCA, out-of-hospital cardiac arrest; PCI, percutaneous coronary intervention; ST, stent thrombosis.

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Nonetheless there is no formal recommendations about which antiplatelet regimen should be used in patients with ACS and OHCA.[1] In the PLATelet inhibition and patient outcomes (PLATO) trial, ticagrelor was associated with a significant reduction of cardiovascular events, cardiovascular mortality, all cause mortality and ST in patients with ACS compared to clopidogrel,[16] In this regard, Tilemann et al. reported that the administration of crushed ticagrelor via nasogastric tube reliably inhibited platelet function regardless of the presence of hypothermia in ACS patients,[17] and other studies confirmed these findings.[18–20]

Previous reports showing increased ST in OHCA patients with MTH did not focus in antiplatelet treatment until, although surprisingly, Gouffran et al. observed an increase of ST in patients treated with new P2Y12 inhibitors receptors (ticagrelor or prasugrel) compared to clopidogrel in a cohort of 101 OHCAs treated with PCI and MTH.[10] Thus, the aim of the study was to compare the incidence of ST and bleedings events between ticagrelor or clopidogrel in patients with ACS undergoing PCI after OHCA under MTH.

Methods

Patients

This was a single centre observational study. We retrospectively screened consecutive patients admitted to our Hospital between January 2010 and August 2016 with ACS and OHCA undergoing primary PCI under MTH. Exclusion criteria included patients with ACS without stent implantation, and patients who died before the index procedure. Although patients who received prasugrel were included in the main cohort, the small number of subjects in this group precluded any specific comparison with ticagrelor or clopidogrel. The study was approved by Ethics Committee of our centre (approval reference number 2013/8596) and complies with principles laid down in the Declaration of Helsinki.

Procedural characteristics

All surviving OHCA patients admitted to our centre without an evident extra cardiac cause were admitted immediately to the cardiac catheterization laboratory regardless of the clinical and ECG findings. If there was a high suspicion of ACS defined by ECG changes, initial shockable rhythm or previous chest pain, antithrombotic treatment with aspirin and heparin was initiated by emergency team prior to admission. Primary PCI was attempted if there was an acute coronary atherothrombotic lesion. The use of glycoprotein IIb-IIIa receptors inhibitors (GPI IIb-IIIa) and manual thrombus aspiration were left to the operator preference. The length, diameter and type of stent Drug Eluting Stent (DES) or Bare Metal Stent (BMS), were also decided by the operator. After PCI all patients were transferred to the Intensive Cardiac Unit (ICU).

In order to reduce delays, most of the patients arrived without nasogastric tubing at the cardiac catheterization laboratory. Nasogastric tubing was therefore placed in the cath lab just after PCI, so the loading dose of P2Y12 inhibitors was crushed, dissolved and administered right after the PCI. Unfortunately, there was no accurate estimation of the time delay between PCI and P2Y12 inhibitors administration. P2Y12 inhibitors were however always administered within the 30 min after PCI and prior to the ICU transfer. Although small, this variable delay in drug administration may have contribute to the final results, as ticagrelor has a faster mechanism of action compared to clopidogrel.

The loading dose was followed by maintenance dose (clopidogrel 75 per day, prasugrel 10 mg per day, ticagrelor 90 mg bid.)

All patients received MTH according to the local ICU protocol. All patients reached 33 °C fewer than 8 h from cardiac arrest, and this temperature was maintained for 24 h. Warming took place gradually in 24–30 h, with a rate of 0.10–0.15 °C/h. This protocol has been comprehensively described somewhere else.[7] In the ICU, patients received standard treatment that included mechanical ventilation and correction of cardiovascular instability.

Data analysis

The baseline and procedural data of patients were systematically collected in a dedicated database. The primary endpoint was the occurrence of definite and probable stent thrombosis (ST),[21] during hospitalization according to the Academic Research Consortium definitions, as well as the incidence of bleeding events according to the BARC criteria.[22]

A routine angiography was not compulsory after baseline PCI and was only performed in case of a clinical event, ECG or echocardiography changes or severe hemodynamic instability.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and non-normally distributed variables were expressed as median [inter-quartile range]. Categorical variables were expressed as count and percentage. Baseline characteristics between groups were compared using *t* test for continuous variables and chi-square test for categorical variables. Results were considered statistically significant at a p-value <0.05. Statistical analyses were carried out using SPSS package v20.0 (Chicago, IL, USA).

Results

From January 2010 to August 2016, 144 patients were treated with MTH after an OHCA. Overall, 114 had an ACS (79%) and 98 (67,3%) underwent primary PCI with stent implantation. Among them, 61 (62,2%) were treated with clopidogrel, (clopidogrel group), 32 (32,6%) with ticagrelor (ticagrelor group) and 5 (5,1%) with prasugrel.

As shown in Table 1, baseline characteristics were similar among groups. Of note, most of the patients presented cardiac arrest secondary to STEMI. Post-resuscitation shock was similar in both groups (65.5% in the clopidogrel group vs. 71.8% in the ticagrelor group; p = 0.67). As shown in Table 2, procedural data revealed no significant differences in the use of GP IIb-IIIa inhibitors or thromboaspiration, but a significant higher use of DES in the ticagrelor group.

Clinical outcomes

During hospitalization, 7 (7.1%) patients presented definite or probable ST, 7 (11,4%) in the clopidogrel group and none (0%) in the ticagrelor group (p:0,04). None of five patients with prasugrel presented ST (Table 3). Stent thrombosis was classified as acute in 2 patients and sub acute in the other 5 patients. Two patients with DES and 5 with BMS presented definite ST.

DES were implanted in 33 patients (16 in the clopidogrel and 17 in the ticagrelor group). Only 2 patients in the clopidogrel group (12.5%) presented ST and there were no significant differences among groups (12.5% vs. 0%, p = 0.13). An individual and more comprehensive description of ST is provided in Table 4.

There were no significant differences in any bleeding (28,6% with clopidogrel vs. 25% with ticagrelor; p:0,645) and major bleeding (BARC 3 or 5) (11,4% vs. 12,5; p = 0,685) among groups (Table 3).

Sixteen (26,2%) patients in the clopidogrel group and 8 (25.0%) in the ticagrelor group died during hospitalization without significant differences between groups. Among them, 2 patients who

Table 1
Baseline clinical characteristics.

	Clopidogrel (n:61)	Ticagrelor (n:32)	p:value
Age, years, mean ± SD	57, 4 ± 12	56, 5 ± 9,8	0.759
Male, n (%)	52 (85,2)	28 (87,5)	0.766
Smoking, n (%)	32 (52,4)	13 (40,6)	0.630
Hypertension, n (%)	26 (42,6)	11 (34,3)	0.308
Diabetes Mellitus, n (%)	10 (16,3)	6 (18,7)	0.359
Hypercholesterolemia, n (%)	30 (49,1)	12 (37,5)	0.243
Previous myocardial infarction, n (%)	11 (18)	6 (18,7)	0.139
Renal failure, n (%)	5 (8,1)	1 (3,1)	0.252
Initial shockable rhythm, n (%)	49 (80,3)	26 (81,2)	0.121
Total ischemic time, min. (mean ± SD)[a]	125, 4 ± 72,0	141, 3 ± 52,1	0.338
Time from cardiac arrest to return of spontaneous circulation, min. (mean ± SD)	30, 1 ± 16,9	26, 1 ± 10,6	0.292
ST- segment elevation myocardial infarction, n (%)	54 (88,5)	45 27 (87)	0.675
Post-resuscitation shock, n (%)	40 (65,5)	32 23 (71,8)	0.400
LVEF mean ± SD	40, 3 ± 16,3	41, 9 ± 12,8	0.685

LVEF: left ventricular ejection fraction.
[a] Time from symptom onset to coronary flow restoration.

Table 2
Procedural characteristics.

	Clopidogrel (n:61)	Ticagrelor (n:32)	p:value
Culprit coronary artery, n (%)			0.197
LAD	27 (44,2)	17 (53,2)	
LCX	13 (21,3)	6 (18,7)	
RCA	19 (31,2)	8 (25)	
TIMI flow 0 or 1 before PCI, n (%)	34 (55,7)	16 (50)	0.537
Thromboaspiration, n (%)	33 (54)	14 (43,7)	0.343
Glycoprotein IIb-IIIa receptors inhibitors used, n (%)	13 (21,3)	6 (18,7)	0.771
TIMI flow 3 after PCI, n (%)	52 (85,2)	30 (93,7)	0.644
Number of implanted stents (mean ± SD)	1,28 ± 0,68	1,26 ± 0,44	0.888
Patients treated with DES, n (%)	16 (26,2)	17 (53,1)	**0.01**
Mean diameter stent, mm, (mean ± SD)	3,10 ± 0,65	3,33 ± 0,72	0.181
Total stent length, mm, (mean ± SD)	23,4 ± 13,2	21,9 ± 8,8	0.608
Bifurcation lesions, n (%)	8 (13,1)	8 (25)	0.149
No reflow, n (%)	7 (11,4)	3 (9,3)	0.555
IABP, n (%)	12 (19,6)	3 (9,3)	0.200

LAD: Left Anterior Descending; LCX: Left Circumflex; RCA: Right Coronary Artery; PCI: Percutaneous Coronary Intervention; DES: Drug Eluting Stent; IABP: Intra-Aortic Balloon Pump.
The values in bold mean that there are statistically significant differences in these variables.

Table 3
Patient Outcomes.

	Clopidogrel (n: 61)	Ticagrelor (n: 32)	p:
Definite stent thrombosis n (%)	7 (11.4)	0 (0)	**0.046**
Probable stent thrombosis	0 (0)	0 (0)	
Any bleeding, n (%)	18 (28,6)	8 (25)	0.645
BARC type 3 or 5, n(%)	7 (11,4)	4 (12,5)	0.685
Mortality, (%)	16 (26,2)	8 (25.0)	0.862

BARC (bleeding academic research consortium).
The values in bold mean that there are statistically significant differences in these variables.

Table 4
Patients with stent thrombosis.

	Artery	No. of stents	Pre-treatment	PCI	Post-procedure treatment	Day of ST	Death
1	RCA	1	ASA, Heparin	BMS 3 × 18 mm	Clopidogrel, abciximab	3	No
2	LAD/LCX	2	ASA, Heparin	DES 2.5 × 33, 3 × 33 mm	Clopidogrel, abciximab	4	No
3	LAD	1	ASA, Heparin,	BMS 2,5 × 14 mm	Clopidogrel, abciximab	2	No
4	LAD	1	ASA, Heparin, Tenecteplase	BMS 2,5 × 19 mm	Clopidogrel	3	Yes
5	LAD	4	ASA, Heparin	BMS 3 × 18, 3.5 × 8, 2,5 × 13, 2.25 × 13	Clopidogrel, abciximab	1	Yes
6	LCX	1	ASA, Heparin	DES 2.5 × 18	Clopidogrel	2	No
7	RCA	1	ASA, Heparin	BMS 3 × 23	Clopidogrel	1	No

ASA: aspirin; BMS: bare metal stent; DES: drug eluting stent, LAD: left anterior descending; LCX: left circumflex, PCI: percutaneous coronary intervention; RCA: right coronary artery; ST: stent thrombosis.

presented ST died (28.5% of them), both in the clopidogrel group The cause of mortality in these two patients was severe neurologic damage and cardiogenic shock with end-organ failure respectively.

Discussion

The main finding of the present study was that the use of ticagrelor in patients undergoing PCI under MTH after OHCA was associated with a lower incidence of ST without differences in haemorrhagic events compared to clopidogrel.

The present study shows a high incidence of ST (7,1% overall). Our group already reported a higher rate of ST in OHCA survivors treated with primary PCI under MTH.[7] Accordingly, other studies confirmed the higher incidence of ST in OHCA survivors[8–12], although other studies did not confirm these findings.[13,14]

The impact of MTH on ST is however not clear. In fact, Shan et al. reported high rates of ST in OHCA patients after PCI (4,7%) without differences in patients undergoing MTH or not (3,9% vs. 4,7%).[12] Gouffran et al. reported a high incidence of ST (10.9%) in a cohort 101 OHCA survivors treated with PCI and MTH. Surprisingly, more patients presented ST with the use of new P2Y12 inhibitors than those receiving clopidogrel. The authors suggest that this finding might be explained by the fact that ADP pathway may not be the only target for antiplatelet strategies after OHCA.[10] In contrast, Tilemann et al. reported no ST in 27 patients undergoing MTH with PCI treated with crushed ticagrelor.[17]

The mechanisms explaining why there is an increased risk of ST in patients with OHCA and MTH are not well established yet. All these mechanisms would create a prothrombotic environment leading to a higher incidence of thrombotic events.[18–20] (a) Activation of platelet aggregation by cold, (b) antiplatelet absorption disorders through the digestive tract; (c) drug metabolism slowing-down; and (d) probable endothelial dysfunction have been proposed as these potential mechanisms among others. Since platelet adenosine diphosphate receptor P2Y12 is a pivotal target for antiplatelet treatment in ACS, particularly in patients with implanted stent, and MTH might interfere with the action of these agents, the use of conventional DAPT with aspirin and clopidogrel may be inefficient after OHCA and hypothermic conditions.[17–20] In this sense, ticagrelor may represent a valid alternative to reduce thrombotic events in patients under MTH as it provides a more rapid and intense inhibition of platelet reactivity. Ticagrelor is a direct inhibitor of the P2Y12 receptor and does not require metabolic transformation. Additionally, it has been associated with a superior pharmacodynamic profile compared to clopidogrel in patients undergoing PCI.[18–20,23] In fact, Steblovik et al. reported a faster and stronger platelet inhibition with ticagrelor as compared to clopidogrel in 37 comatose survivors of OHCA undergoing PCI and MTH before and after PCI[23]

Bednar et al. measured platelet inhibition by VASP (vasodilator-stimulated phosphoprotein) in 40 patients with ACS and OHCA treated with MTH who received one P2Y12 inhibitor (clopidogrel, prasugrel or ticagrelor) and observed that the proportion of patients with ineffective platelet inhibition after clopidogrel, prasugrel and ticagrelor was (77% vs. 19% vs. 1%) on day 1, (77 vs. 17 vs. 0%) 2 (85 vs. 6 vs. 0%) and 3 ($p < 0{,}001$).[18] Moudgil et al. reported a more rapid (within 4 h) and sustained reduction (6 days) in platelet reactivity with ticagrelor compared to clopidogrel in 15 patients with ACS after an OHCA treated with MTH.[19] Rosencher et al. reported, in a cohort of 20 OHCA patients, a higher residual platelet activity with clopidogrel than ticagrelor 4 h after the loading dose, not only during MTH, but also after MTH up to day 7.[20]

There are currently no specific recommendations for antithrombotic therapy in patients with OHCA caused by ACS.[1] In this regard, conversely to Gouffran et al., our series showed a reduction of ST in patients treated with ticagrelor without differences in haemorrhagic events compared to clopidogrel. These findings would support the clinical benefits of ticagrelor over clopidogrel that were already observed in pharmacodynamics and pharmacokinetics studies in OHCA patients.

In the present study, there were no significant differences in classic risk factors for ST namely number, length and diameter of the implanted stents, diabetes, renal failure, bifurcated lesions, no reflow and cardiogenic shock. In the ticagrelor group, patients were treated more frequently with DES compared to clopidogrel. This may have helped to reduce the rate of ST in the ticagrelor group.[24]

Although the incidence of any or major haemorrhagic events was high, no significant differences among groups were found. The absence of differences between groups might be related to the fact that post-resuscitation syndrome and MTH may produce alterations in haemostasis and coagulopathy. Hypothermia below 33° affects the synthesis and kinetics of clotting enzymes, thrombin generation, and plasminogen activator inhibitors and is related to platelet dysfunction, and this may be associated with an increased risk of haemorrhagic events[25,26] regardless of the treatment with P2Y12 inhibitors.

Our group has already reported a very high incidence of major bleedings (64,7% with BARC 3 o 5) without reduction of thrombotic events in OHCA patients undergoing primary PCI and MTH treated with GPI IIb-IIIa. The use of GP IIb-IIIa inhibitors might be seen as a valid alternative to reduce thrombotic events for the immediate action and the intravenous administration in patients who cannot swallow. Nonetheless, the absence of differences in thrombotic events in patients with and without GP IIb-IIIa inhibitors and the higher incidence of haemorrhagic events do not seem to support this option.[27]

Stent thrombosis is a multifactorial phenomenon, which is clearly not only driven by the lack of clopidogrel efficacy during MTH. However, in such a prothrombotic environment, it seems logical that these patients should be treated like high-risk patients with the more effective and safe antiplatelet strategy. New intra-venous P2Y12 inhibitors, like cangrelor could also play and important a role in this setting. Further clinical studies are required in this context.[28]

The present study has several limitations. The results must be interpreted with caution, as this is a single-centre non-randomized and retrospective study with a relatively small sample size. The study includes patients that were treated in a long period (6 years) with most of them receiving clopidogrel. Ticagrelor was however used more often during the last years of the study and the observed result may have been affected, at least in part, by improvements in treatment over time. The limited number of patients precluded any further solid analysis of subgroups analysing classical ST risk factors other than the use of DES. The number of patients receiving prasugrel in this setting was very small and therefore not included in the analysis.

Conclusion

In this study, as compared to clopidogrel, ticagrelor was associated with a lower rate of ST, without differences in haemorrhagic events in patients with ACS under MTH. Similarly to other settings, ticagrelor might be a very valid alternative to clopidogrel in MTH. The results of the study are hypothesis generating and further randomized data will be needed.

Conflict of interest statement

There is no conflict of interest and relationship with the industry by any authors.

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