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Ticagrelor effectively inhibits platelet aggregation in comatose survivors of cardiac arrest undergoing primary percutaneous coronary intervention treated with mild therapeutic hypothermia

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Abstract

Background: *Mild therapeutic hypothermia (MTH) is believed to reduce the effectiveness of antiplatelet drugs. Effective dual-antiplatelet therapy after percutaneous coronary intervention (PCI) is mandatory to avoid acute stent thrombosis. The effectiveness of ticagrelor in MTH-treated out-of-hospital cardiac arrest (OHCA) survivors is still a matter of debate. The aim of the study was to evaluate the impact of MTH on the platelet-inhibitory effect of ticagrelor in comatose survivors of OHCA treated with primary PCI.*

Methods: *Eighteen comatose survivors of OHCA with acute coronary syndrome undergoing immediate PCI treated with MTH were compared with 14 patients with uncomplicated primary myocardial infarction after PCI, matched for gender and age, in a prospective, single-center, observational study. Platelet aggregation was evaluated using VerifyNow P_2Y_{12} point-of-care testing at 3 time points: admission (T_0), during MTH (T_1), and 48–72 h after rewarming (T_2).*

Results: *Ticagrelor effectively inhibits platelet aggregation in OHCA patients subjected to MTH and in all patients in the control group. The effectiveness of ticagrelor did not differ between the MTH group and the control group ($p = 0.581$). In 2 cases in the MTH population, the platelet response to ticagrelor was inadequate, and in one of them it remained insufficient during the re-warming phase. There was no stent thrombosis in these patients.*

Conclusions: *The present study confirmed the effectiveness of ticagrelor to inhibit platelets in myocardial infarction patients after OHCA treated with primary PCI undergoing hypothermia. The use of cooling was not associated with an increased risk of stent thrombosis.* (Cardiol J)

Key words: out-of-hospital cardiac arrest, platelet function, primary percutaneous coronary intervention, ticagrelor, VerifyNow

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Introduction

The leading cause of out-of-hospital cardiac arrest (OHCA) is myocardial infarction (MI) [1, 2]. Patients who survive cardiac arrest (CA) due to acute coronary syndrome should therefore undergo emergency coronary angiography, because 30–40% of them either have a totally occluded infarct-related artery or an unstable coronary lesion [2–4]. Aggressive post-CA care, such as coronary artery reperfusion and mild therapeutic hypothermia (MTH), doubles the number of patients that survive to hospital discharge [5]. Effective dual-antiplatelet therapy (DAPT) including acetylsalicylic acid (ASA) and a P_2Y_{12} receptor inhibitor following a percutaneous coronary intervention (PCI) is mandatory to avoid acute stent thrombosis (ST). Whole-body ischemia caused by CA as a result of reperfusion injury following resuscitation often causes systemic inflammatory response syndrome, which disrupts the coagulation system and platelet function. Moreover, post-resuscitation myocardial dysfunction results in a decreased stroke volume, which, by reducing intestinal blood flow, may lead to an impaired absorption of antiplatelet drugs. MTH (32–34°C) has become the standard therapeutic option for improving neurological outcomes, and thus survival rates, after OHCA [3]. MTH inhibits the activation of the coagulation system while activating platelet aggregation [6, 7]. Cooling has been shown to augment adenosine diphosphate (ADP)-induced platelet aggregation, resulting in the reduced effectiveness of antiplatelet drugs [8]. Some previous studies have suggested that patients undergoing PCI and MTH after OHCA are at a higher risk of acute ST [9–12]. Other studies, however, including some meta-analyses, indicate that this risk is not actually increased in such patients [13–16]. Therefore, it is particularly important to assess the effectiveness of antiplatelet therapy in patients undergoing MTH after PCI. In this setting, ticagrelor should be the drug of choice before clopidogrel due to its better absorption, faster metabolism, quicker onset of action, and its lack of requirement for metabolic activation [17–21]. The VerifyNow-P_2Y_{12} (VN-P_2Y_{12}) test we used measures the extent of platelet aggregation in the presence of ticagrelor; its reliability in platelet aggregation assessment in patients with MTH has been previously established [19]. We therefore aimed to test platelet function following administration of ticagrelor in OHCA patients undergoing PCI, who were subjected to MTH for 24 h, and compare the results to a matched patient group with MI without MTH. The aim of the study was to evaluate the impact of MTH on the platelet-inhibiting effect of ticagrelor in comatose survivors of OHCA who underwent primary PCI.

Methods

We conducted a prospective, single-center observational study. The protocol was approved by the Jagiellonian University Ethics Committee in Krakow. Written informed consent was obtained from patients regaining consciousness after CA and conscious patients with acute coronary syndrome. Therapeutic hypothermia was achieved by using an endovascular cooling device (Zoll Medical Corporation Chelmsford, MA) to a target temperature of 32.0°C maintained for 24 h. Subsequently, rewarming was performed at a rate of 0.2°C/h.

The inclusion criteria for this study were patients aged 18 years or older, who had OHCA from an MI with return of spontaneous circulation, who survived 24 h after admission and were treated with DAPT. The exclusion criteria included known coagulopathy, anticoagulation with a vitamin K antagonist (international normalized ratio within the therapeutic range), intake of a direct oral anticoagulant, effective inhibition of platelet function on admission, MTH pre-hospital, periprocedural use of glycoprotein IIb/IIIa receptor inhibitor, or those who were already taking clopidogrel, prasugrel, or ticagrelor. Patients were enrolled in the MTH group between January 2014 and January 2016. The control group consisted of gender- and age-matched patients with uncomplicated MI after undergoing a primary PCI and were admitted between December 2015 and August 2017. During MTH, all patients received an IV injection of analgesic opioid and sedation drugs. Neuromuscular blockade was often used according to the protocol of MTH. A loading dose (LD) of 300 mg ASA and 180 mg ticagrelor were administered via a nasogastric tube on admission, followed by 75 mg ASA once daily and 90 mg ticagrelor twice daily. The control group patients were administered ASA and ticagrelor orally according to the same protocol. The mean time between the first maintenance dose of ticagrelor (270 mg) and blood sampling in the MTH group was 495 ± 219 min. Prior to the procedure, platelet function was assessed using VN-P_2Y_{12} point-of-care testing (Accumetrics Ltd., San Diego, CA, USA). A cut-off value below 194 platelet reactivity units (PRU) was adopted as evidence of a P_2Y_{12} effective platelet function inhibition [22, 23]. Platelet aggregation was evaluated at 3 timepoints: when

Table 1. Clinical characteristics.

Variable	MTH group (n = 18)	Control group (n = 14)	P
Males	14 (78%)	12 (86%)	0.909
Age	68 ± 10	66 ± 9	0.742
History of MI	1 (6%)	2 (14%)	0.819
History of revascularization	2 (11%)	2 (14%)	0.788
Arterial hypertension	13 (72%)	10 (71%)	0.729
Diabetes mellitus type 2	5 (28%)	3 (21%)	1
Obesity	8 (44%)	2 (14%)	0.149
Stroke	1 (6%)	0 (0%)	0.898
Dyslipidemia	9 (50%)	6 (43%)	0.964
Tobacco smoking	5 (28%)	2 (14%)	0.628
Peripheral artery disease	1 (6%)	2 (14%)	0.819

Values are shown as mean ± standard deviation (SD) or number (percentage); MI — myocardial infarction; MTH — mild therapeutic hypothermia

baseline blood samples were taken prior to LD (T_0), when samples were drawn during MTH 12–24 h after LD (T_1), and 48–72 h after re-warming (T_2). All patients in the MTH group reached the target temperature (32°C) during sampling. The average core temperature between groups of patients after CA and control at the 3 timepoints were 35.3 ± ± 0.6°C vs. 36.3 ± 0.5°C at T_0, 32.2 ± 0.1°C vs. 36.7 ± 0.4°C at T_1, and 36.7 ± 0.1°C vs. 36.6 ± 0.4°C at T_3, respectively. The key outcome variable was the level of effective platelet inhibition after ticagrelor administration, as assessed by VN-P_2Y_{12}, which was measured at the timepoints specified above. We also monitored the presence of ST [24] and the occurrence of major bleeding as defined by the Bleeding Academic Research Consortium (BARC) for bleeding classification [25]. The VN-P_2Y_{12} assay we used in our study was a point-of--care test, which is widely used to assess residual platelet reactivity in patients with MTH [26–29].

Statistical analysis

All statistical analyses were carried out using SAS software (version 4.0, SAS Institute Inc.). Categorical variables were presented as numbers of subjects and percentages. Continuous variables were analyzed for normal distribution using the Shapiro-Wilk test and were presented as mean ± standard deviation for normal distribution and as median values with lower and upper quartiles for non-normal distribution. Differences for continuous variables between groups (MTH vs. control) were analyzed using a parametric Student's test or Mann-Whitney U-test, as appropriate. Categorical data were compared using the χ^2 test or χ^2 test with Yates' correction. P values less than 0.05 were considered significant

Sample size calculation

Based on previously published data involving patients with ST-segment elevation MI [30] and our own database [7] and considering values of PRU Mi1 = 46 and PRU Mi2 = 105 for both groups, respectively, we estimated that at least 17 patients were required to reach statistical significance using a power of 80% and a 2-sided α-level of 0.05, $\delta = 60$.

Results

Patient characteristics

We prospectively included 18 patients who were admitted for an acute MI after OHCA and subsequently underwent primary PCI and were subjected to MTH for 24 h. They were compared to 14 matched patients who were admitted to the hospital due to MI and were undergoing PCI but were not in CA (control group). There was no difference in demographics, medical history, or periprocedural details between the groups. No patient in the control group was treated with opiates during transport or during hospitalization. The baseline clinical characteristics are shown in Table 1, the characteristics of the MTH group are shown in Table 2, and hospitalization details are depicted in Table 3.

Platelet count in patients in the MTH group decreased significantly after implementing MTH from 194 ± 52 [$10^{-3}/\mu$L] (T_0) to 149 ± 38 [$10^{-3}/\mu$L] (T_1) ($p < 0.001$). This phenomenon persisted

Table 2. Characteristics of mild therapeutic hypothermia (MTH) group (n = 18).

Cardiac arrest data	
Initial cardiac arrest rhythm:	
VF/VT	15 (83%)
Asystole	1 (6%)
Pulseless electrical activity	2 (11%)
Time to ROSC [min]	21 ± 15
Witness	18 (100%)
Bystander CPR	11 (61%)
Condition at admission to hospital	
GCS score (3–4)	10 (56%)
GCS score (5–6)	8 (44%)
Cardiogenic shock	3 (17%)
Circumstances and details of MTH	
Time to MTH [min]	129 ± 51
Total time of MTH [min]	1480 ± 149
Neurological outcome	
Good neurological outcome at discharge	12 (67%)
Death during hospitalization	1 (6%)

Values are shown as mean ± standard deviation or number (percentage); CPR — cardiopulmonary resuscitation; GCS — Glasgow Coma Scale; ROSC — return of spontaneous circulation; VT/VF — ventricular tachycardia/ventricular fibrillation

after the re-warming phase with a platelet count of 141 ± 45 [$10^{-3}/\mu L$] (T_2), (Table 4).

Antiplatelet results using VN-P_2Y_{12}

Platelet reactivity unit values did not differ significantly between the MTH group and the control group in any of the evaluated timepoints. In the MTH population, the average PRU after a LD of ticagrelor fell from 265 ± 41 at the baseline (T_0), to 87 ± 89 at T_1 (p = 0.44). There was an increase in the percentage of mean platelet inhibition from 0.2 ± 0.9 (T_0) to 67 ± 3 (T_1) (p = 0.856) and at T_1, 2 out of 18 (11%) patients had inadequate platelet inhibition (p = 0.851). After re-warming, we recorded sustained antiplatelet effect of ticagrelor with a PRU value of 64 ± 53 (T_2) and mean platelet inhibition percentage of 75 ± 19 (T_2). All patients except 1 (5.5%) in T_2 demonstrated effective inhibition of platelets with ticagrelor (Figs. 1–3). Similar results were observed in the control group (Table 5).

Stent thrombosis and bleeding

No cases of ST occurred during hospitalization in either group. In the MTH group, 6 (34%) patients experienced BARC 3a bleeding vs. none in the control group (p = 0.052; Table 3). In 2 subjects, the bleeding affected the upper gastro-

Table 3. Hospitalization details.

Variable	MTH group (n = 18)	Control group (n = 14)	P
Cardiogenic shock at admission	3 (17%)	0 (0%)	0.321
STEMI	9 (50%)	8 (57%)	0.964
Acute coronary occlusion	10 (56%)	9 (50%)	0.892
MVD (2 or 3)	9 (50%)	7 (50%)	0.722
PCI success	17 (94%)	14 (100%)	0.898
Cardiogenic shock during hospitalization	8 (44%)	0 (0%)	0.014
Stent thrombosis	0 (0%)	0 (0%)	–
Pneumonia	12 (67%)	0 (0%)	0.001
Bleeding BARC 3a	3 (17%)	0 (0%)	0.321
Bleeding BARC 3b	3 (17%)	0 (0%)	0.321
Major bleeding	6 (33%)	0 (0%)	0.052
Renal failure	13 (72%)	1 (7%)	0.001
GFR	54 ± 22	78 ± 16	0.009
Stroke	2 (11%)	0 (0%)	0.492

Values are shown as mean ± standard deviation or number (percentage); BARC — Bleeding Academic Research Consortium; GFR — glomerular filtration rate; MTH — mild therapeutic hypothermia; MVD — multi-vessel disease; PCI — percutaneous coronary intervention; STEMI — ST--segment elevation myocardial infarction

Table 4. Platelet count.

Platelet count [$10^{-3}/\mu L$]	MTH group (n = 18)	Control group (n = 14)	P
Basal (T_0)	194 ± 52	232 ± 52	0.166
MTH (T_1)	149 ± 38	223 ± 50	0.004
NT (T_2)	141 ± 45	208 ± 38	0.004

Values are shown as mean ± standard deviation; MTH — mild therapeutic hypothermia; NT — normothermia; T_0 — after admission; T_1 — 12–24 h after percutaneous coronary intervention; T_2 — 48–72 h after percutaneous coronary intervention

Table 5. Sample collection and results of VerifyNow-P_2Y_{12} test in mild therapeutic hypothermia (MTH) group versus control group.

Variable	T_0			T_1			T_2		
	MTH (n = 18)	Control (n = 14)	P	MTH (n = 18)	Control (n = 14)	P	MTH (n = 18)	Control (n = 14)	P
PRU	265 ± 41	251 ± 42	0.44	87 ± 89	31 ± 38	0.110	64 ± 53	41 ± 28	0.081
Percentage of platelet inhibition	0.2 ± 0.9	0.4 ± 1.3	0.856	67 ± 31	86 ± 16	0.202	75 ± 19	83 ± 12	0.169
Number of patients with satisfactory effect (PRU < 194)	–	–	–	16 (89%)	14 (100%)	0.581	17 (94%)	14 (100%)	0.898

Values are shown as mean ± standard deviation; number of patients with given score (%); PRU — platelet reactivity units; T_0 — after admission; T_1 — 12–24 h after percutaneous coronary intervention; T_2 — 48–72 h after percutaneous coronary intervention; PRU T_0 statistical power: 0.21 (Mi1 = 264.9; Mi2 = 246.1; δ = 44.9; α = 0.05); PRU T_1: statistical power: 0.51 (Mi1 = 86.7; Mi2 = 31.1; σ = 75.63; α = 0.05); PRU T_3 statistical power: 0.27 (Mi1 = 63.6; Mi2 = 41.3; δ = 44.7; α = 0.05)

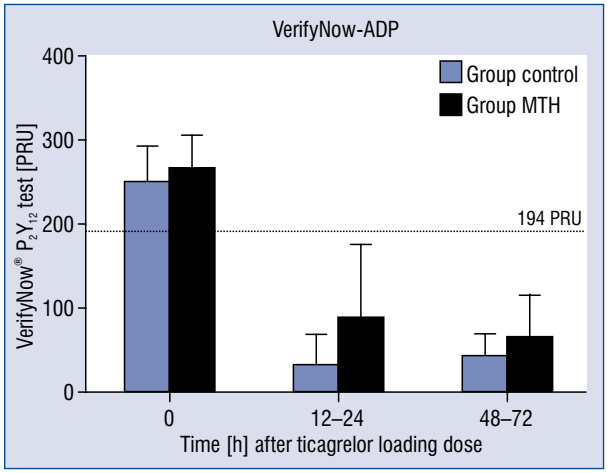

Figure 1. Data are presented as peak platelet reactivity units (PRUs) in the primary percutaneous coronary intervention-mild therapeutic hypothermia (PCI-MTH) group (black bars) and the control group (blue bars) at baseline, during hypothermia at T_1 (12–24 h), and after the rewarming phase at T_2 (48–72 h) after the ticagrelor loading dose. Thresholds at 194 PRU indicate high on-treatment reactivity. Mean ± standard deviation is shown. The statistical power calculations used at each time point are as follows: baseline: statistical power: 0.21 (Mi1 = 264.9; Mi2 = 246.1; δ = 44.9; α = 0.05), T_1 — statistical power: 0.51 (Mi1 = 86.7; Mi2 = 31.1; δ = 75.63; α = 0.05), T_2 — statistical power: 0.27 (Mi1 = = 63.6; Mi2 = 41.3; δ = 44.7; α = 0.05); p < 0.05; ADP — adenosine diphosphate.

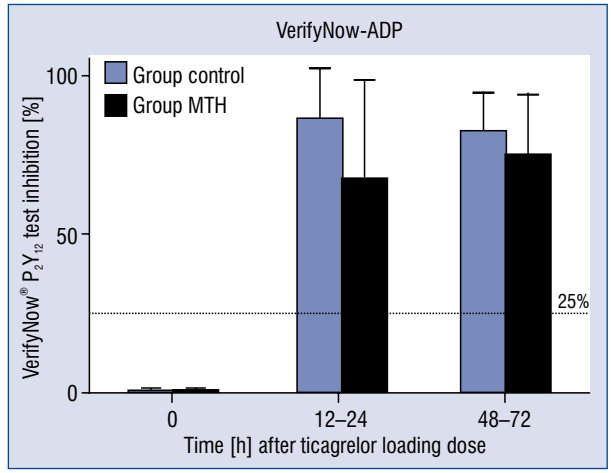

Figure 2. VerifyNow platelet reactivity in P_2Y_{12} assay (Accumetrics, Inc., San Diego, CA, USA). Data show a comparison of the antiplatelet effect between the primary percutaneous coronary intervention-mild therapeutic hypothermia (PCI-MTH) group (black bars) and the control group (blue bars) at baseline, T_1 (12–24 h), and T_2 (48–72 h) after a loading dose of ticagrelor. Platelet reactivity is expressed as the percentage of platelet inhibition. Mean ± standard deviation is shown, p < 0.05. The statistical power calculations used at each time point are as follows: baseline: statistical power: 0.05 (Mi1 = 0.22; Mi2 = 0.35; δ = 1.13; α = 0.05), T_1 — statistical power: 0.48 (Mi1 = 67.4; Mi2 = 86.4; δ = 26.9; α = 0.05), T_2 — statistical power: 0.25 (Mi1 = 74.7; Mi2 = 82.6; δ = 16.6; α = 0.05); p < 0.05; ADP — adenosine diphosphate.

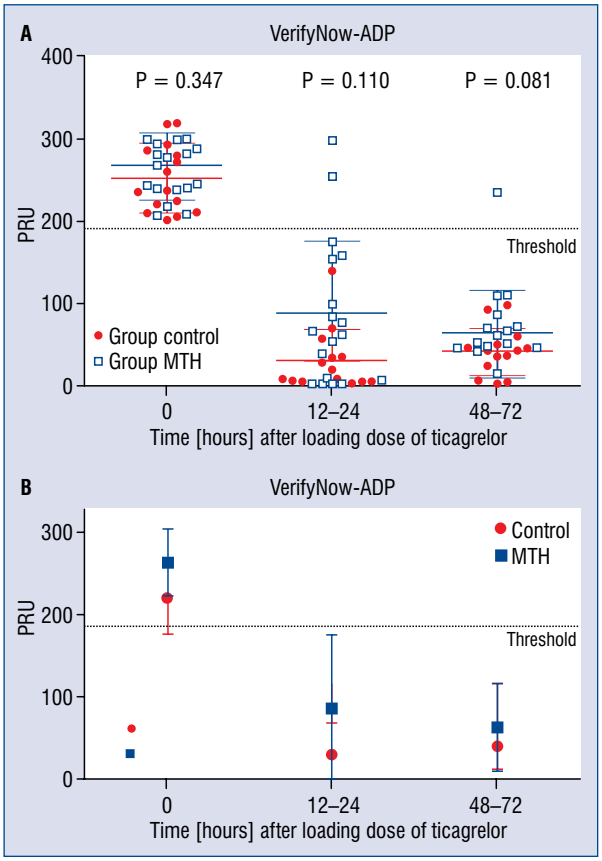

Figure 3. A. Platelet reactivity by treatment. VerifyNow P_2Y_{12} assay results: Individual results for the VerifyNow P_2Y_{12} assay (Accumetrics, Inc., San Diego, CA, USA) are expressed as P_2Y_{12} reaction units (platelet reactivity units [PRU]) at baseline (0 h) and each measured time point: T_1 (12–24 h) and T_2 (48–72 h) after ticagrelor loading dose. Platelet inhibition with 90 mg ticagrelor twice daily in n = 18 primary percutaneous coronary intervention-mild therapeutic hypothermia (PCI-MTH) patients (empty blue squares) is shown in comparison to n = 14 normothermic patients after primary PCI in the control group (red dots). Solid lines with error bars indicate the least-square means (95% confidence interval). The dashed line indicates a level of 194 PRU as a threshold for high platelet reactivity. There is no significant difference between the groups (all p > 0.01); ADP — adenosine diphosphate; **B.** Inhibition of platelet aggregation by VerifyNow P_2Y_{12} assay (Accumetrics, Inc., San Diego, CA, USA) at baseline (0 h), T_1 (12–24 h), and T_2 (48–72 h) after ticagrelor loading and maintenance therapy in n = 18 primary percutaneous coronary intervention--mild therapeutic hypothermia (PCI-MTH) patients (blue squares) and n = 14 control group (red dots). Solid lines with error bars indicate the least-square means (95% confidence interval). The dashed line indicates a level of 194 platelet reactivity units (PRU) as a threshold for high platelet reactivity; p > 0.01; ADP — adenosine diphosphate.

intestinal tract, and in 2 other cases, bleeding was related to arterial puncture site bleeding. In the last 2 cases, bleeding from the mucosa of the nostrils after insertion of a nasogastric tube and bronchial bleeding were observed.

Discussion

The main finding of the present study was that ticagrelor effectively inhibited platelet aggregation in a population of OHCA patients subjected to MTH for 24 h while undergoing primary PCI. The effectiveness of ticagrelor did not differ between either group, which is in line with previous reports [14, 19]. In 2 cases in the MTH population, platelet response to ticagrelor was inadequate, and in 1 of them it remained insufficient during the re-warming phase. In the first case, ticagrelor resistance may have been associated with impaired drug absorption secondary to reduced gastric and intestinal perfusion from decreased cardiac output in the course of cardiogenic shock [26]. In the second case, the resistance of platelets to ticagrelor during hypothermia which persisted in the re-warming phase may have been due to pre-activation of platelets caused by a higher baseline expression of activated glycoprotein IIb/IIIa in the course of advanced diabetes in a subject dialyzed for many years. This is in line with a previous publication that explicitly addressed the impact of renal impairment on residual platelet reactivity during DAPT in VN-P_2Y_{12} assessment [27, 28]. Of importance, according to previous pharmacodynamic and pharmacokinetic studies, ticagrelor can be safely used in patients with renal insufficiency, including those on dialysis [29].

To assess the potential impact of MTH on the antiplatelet effect of ticagrelor, we compared patients undergoing hypothermia after CA with the control group of patients with only MI. The degree of platelet inhibition 12–24 h after administration of ticagrelor in the MTH group was similar to that observed by the TICOMA investigators [18] and others, where sufficient platelet inhibition was achieved just after 3 h [18] and persisted during the 24–48 h period after the LD [18, 19]. Similar results were reported by Tileman et al. [15], who showed that the degree of platelet inhibition measured by impedance aggregometry 24 h after an LD of ticagrelor did not differ between 27 hypothermic and 10 normothermic patients with acute MI. Based on data from 9 OHCA patients who underwent PCI

and MTH and were given ticagrelor, the platelet reactivity index (PRI) value after 24 h was within the effective range in all cases in the assessment of PRI/vasodilator-stimulated phosphoprotein (VASP) [31]. Different observations were made by Ibrahim et al. [9], who found PRI/VASP values above 50% in 3 (33.33%) out of 10 PCI-MTH patients on ticagrelor treatment. Similarly, Kander et al. [33] recognized that in 7 (50%) out of 14 patients with dual-platelet inhibition, the effect of ticagrelor on platelets was still insufficient 12–24 h after induction of MTH and did not reach the target VASP PRI < 50 when measured by flow cytometry-based VASP. The authors of that study hypothesized that a probable cause of this phenomenon could be delayed gastric emptying in the MTH group [9, 32].

Our results confirm that a high rate of effective blocking of the P_2Y_{12} receptor by ticagrelor in the MTH group translated into a lack of ST, which is contrary to doubts raised by earlier researchers emphasizing the attenuated effect of P_2Y_{12} inhibitors caused by cooling [10, 11, 33]. In all patients included in our study, initiation of hypothermia was preceded by the administration of an LD of ASA and ticagrelor. The ATLANTIC trial highlights the importance of administering ticagrelor as early as possible to affect clinical endpoints [34]. In our study, we assessed platelet reactivity as a surrogate marker of thrombotic complication, because VN-P_2Y_{12} assessment has previously been used as a measure of platelet reactivity in response to MTH [19]. Overall, we did not observe ST or recurrent MI or unscheduled re-angiography in the MTH group. Similar results with 0% ST in OHCA patients undergoing MTH and PCI were observed by other researchers in groups of 27 [15], 33 [35], and 45 [36] patients, which was only slightly different from the 2.5% ST reported ST among 40 patients [37]. In all of the studies except one [36], subjects received pre-treatment with a full dose of heparin, ASA, and an LD of P_2Y_{12} inhibitor before cooling, which possibly minimized the risk for ST as described earlier [34]. Different results were presented in several other reports involving small groups of patients, indicating a relationship between the use of MTH and the occurrence of ST, the frequency of which varied from 10.9% to 49% [11, 33]. In a study by Ibrahim et al. [9], 4 (14.8%) patients from a group of 27 patients undergoing MTH and PCI after OHCA had ST. However, no subject from this group was given a LD of P_2Y_{12} antagonist as pretreatment [9]. Another study of a small cohort of patients treated with OHCA in conjunction with MTH where hypothermia was maintained for 24–48 h also observed a high occurrence of ST in 5 (45.5%) of 11 subjects. The average time from PCI to ST was 174 h, indicating that thrombotic incidents may have been associated with causes other than MTH [33].

A second important issue regarding prevention of acute and subacute ST risk in the MTH group is related to avoiding implantation of undersized stents, which may occur as a result of underestimating the diameter of an infarct-related artery secondary to coronary vasospasm in the course of cooling [38]. In 2014 and 2015, Joffre et al. [11] as well as Gouffran et al. [10] observed a 10.9% incidence of ST in the population they researched. Both studies were conducted retrospectively without comparative groups. In the first study, 46 (83.6%) out of 55 patients were in cardiogenic shock and required continuous vasopressor infusion [11]. This may have promoted coronary vasoconstriction and potentially impacted the operator's assessment of stent sizing, which may have led to length overestimation (average stent length of 26 mm) and stent diameter under-sizing with suboptimal expansion that could facilitate risk of ST. Hypothermia in this group was maintained for 24 h with a re-warming phase up to the next 24 h. The average delay for ST after baseline in this study was 3 ± 1.7 days, and in 2 (3.6%) out of 55 cases ST occurred within 24 h, while in the other 4 (7.2%) cases it occurred on the third day or later. Importantly, only 53% of OHCA patients in this study were pre-treated with ASA and 51% were pre-treated with heparin before stent implantation, and none of them had received DAPT [11]. In the second study [10], MTH with the re-warming phase was maintained for 24–36 h. The median time from PCI to ST was 2 days (mean time: 2.5 ± 2.3 days). Angiographically-confirmed ST during the first 48 h occurred in only 5 (4.9%) cases, while the remaining 3 (2.9%) were recognized only based on clinical suspicion [10] and, according to the BARC definition of ST [23], could be qualified only as a "possible event". A meta-analysis of 5 clinical trials involving a total of 290 patients who underwent PCI treatment with MTH showed an incidence of ST of 6%, which was higher than reported in non-hypothermia conditions. Importantly, the study mentioned above did not confirm significant differences between the frequency of ST between the groups treated with clopidogrel and those receiving newer agents (ticagrelor or prasugrel) [39].

The most compelling evidence regarding the relationship between the use of MTH and the risk of ST comes from a multicenter analysis by

Shah et al. [16], which included 49,109 patients who underwent a primary PCI, of whom 1,193 underwent MTH. There was no difference in ST incidence between the MTH and non-MTH groups (3.9% vs. 4.7%), which was further confirmed by propensity-matched analysis [16]. Furthermore, a meta-analysis of 9 trials including 744 patients with acute MI, who underwent PCI and were randomly assigned to either hypothermia or control treatment with target vessel revascularization, found no significant difference in the occurrence of ST between groups: ST incidence was 2.4% vs. 0.2%, respectively, with a relative risk of 3.55 [0.80; 15.87] ($p = 0.09$) [39].

The occurrence of serious bleeding (BARC 3a, 3b) in our study was limited to the group of MTH patients with a frequency of 6 (33%) patients, which is similar to reports from some previous studies [12, 40] and slightly more than others [15, 16]. Given the small cohort we examined, it is possible that our observations could be accidental. In previous reports, bleeding complications were more often observed in hypothermia-treated patients only in smaller studies [40, 41] similar to ours, as opposed to observations of larger populations [16, 42, 43]. One potential mechanism behind the increased risk of bleeding in MTH-treated patients could be a decreased platelet count in blood serum persisting after re-warming. This is consistent with prior studies involving cooling patients [44] as well as coagulation disorders and most likely results from impaired production of clotting enzymes at temperatures below 32°C, which was previously studied by our group and others [7, 8].

Limitations of the study

There are several limitations in our study. VN-P_2Y_{12} is a well-established and reliable method for evaluating response to P_2Y_{12} inhibitors. However, verification of our results by another test could be an added value, especially because there is no validation of the different testing systems in hypothermic patients. Unfortunately, in our study, we did not carry out serial tests of platelet function, which prevents us from determining the minimum time required to achieve effective platelet inhibition after administration of an LD of ticagrelor. We also lack sufficient data to evaluate both the early pharmacokinetic and pharmacodynamic effects of ticagrelor administered through a nasogastric tube. The lack of a control group consisting of patients after CA resulted from difficulties in recruiting such patients due to ethical reasons. Our study was conducted in 1 center, and its limited sample size had sufficient power to assess the effectiveness of platelet aggregation inhibition by ticagrelor but does not provide adequate statistical power to assess clinical endpoints.

Conclusions

The present study confirms the findings of the effectiveness of blocking platelets by ticagrelor in MI patients after OHCA treated with primary PCI undergoing hypothermia. The use of cooling was not associated with an increased risk of ST in patients in this very high-risk group, although it may be associated with a slightly increased risk of bleeding.

Conflict of interest: None declared

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