

Platelet reactivity and pharmacodynamic response to ticagrelor in patients undergoing extracorporeal cardiopulmonary resuscitation compared with conventionally resuscitated cardiac arrest patients

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Abstract

Background

Extracorporeal membrane oxygenation (ECMO) induces complex hemostatic disturbances, and the pharmacodynamic response to oral P2Y₁₂ inhibitors during extracorporeal cardiopulmonary resuscitation (ECPR) is poorly characterized. We compared platelet reactivity and ticagrelor response between ECPR and conventionally resuscitated cardiac arrest patients.

Methods

In this single-center analysis of two prospectively collected, non-contemporaneous cohorts, 16 adults undergoing ECPR and percutaneous coronary intervention (PCI) were compared with 20 conventionally resuscitated cardiac arrest patients undergoing PCI without ECMO. All received crushed ticagrelor via gastric tube. Platelet reactivity was measured before and 2–48 h after loading by Multiplate adenosine diphosphate (ADP) aggregometry and the VerifyNow P2Y₁₂ assay (P2Y₁₂ reaction units, PRU) and analyzed with linear mixed-effects models.

Results

Baseline PRU was lower in ECPR patients (median 220 vs. 246; $p = 0.020$), independently of platelet count. After loading, PRU declined more slowly with ECPR (group $\times$ time interaction $p < 0.001$) and was on average 95 PRU higher (95% CI 41–148; $p < 0.001$; adjusted for baseline and age); median PRU remained above the high on-treatment reactivity threshold for 4 h. Baseline Multiplate aggregation was lower with ECPR (22 vs. 60 U; $p = 0.033$), but not after adjustment for platelet count, and did not differ after loading. Major bleeding tended to be more frequent with ECPR (43.8% vs. 15.0%; $p = 0.073$).

Conclusions

Enteral ticagrelor provides delayed and attenuated P2Y₁₂ inhibition in ECPR patients, despite a bleeding tendency. Multiplate may underestimate this deficit when platelet counts are low. Rapid-onset, reversible intravenous P2Y₁₂ inhibition warrants evaluation.

Key points

In ECPR patients, P2Y₁₂ inhibition after crushed ticagrelor was delayed and attenuated, with PRU on average 95 units higher than in conventionally resuscitated cardiac arrest patients.

Median PRU in ECPR patients remained above the high on-treatment reactivity threshold during the first 4 h after loading.

Multiplate ADP aggregation did not differ after loading, and lower baseline aggregation in ECPR patients was largely explained by lower platelet counts.

ECPR patients undergoing PCI are therefore simultaneously exposed to a risk of early stent thrombosis and a risk of major bleeding.

Future studies should evaluate intravenous P2Y₁₂ inhibition and assay-guided antiplatelet strategies in ECPR patients undergoing PCI.

Introduction

Extracorporeal membrane oxygenation (ECMO) is a life-support therapy applied to the most compromised patients presenting with severe cardiopulmonary failure, such as extracorporeal cardiopulmonary resuscitation (ECPR) in the setting of cardiac arrest [1, 2]. While ECMO undoubtedly provides necessary hemodynamic support, it also introduces complex mechanisms of hemostatic disturbances, including thrombosis and bleeding, which complicates patient management [3, 4]. Achieving an optimal balance between anticoagulation and antiplatelet therapy is particularly difficult in this context.

Platelet function frequently becomes impaired in ECMO patients through various mechanisms, which include contact activation by the extracorporeal circuit, an increase in systemic inflammation, and various necessary pharmacologic therapies [5, 6]. In certain cases, especially coronary intervention, ECMO patients need dual antiplatelet therapy (DAPT), including P2Y₁₂ receptor inhibitors like clopidogrel, prasugrel or ticagrelor [7]. Nevertheless, the pharmacodynamic effect of these drugs in the context of ECMO support is not well characterized. Impaired drug absorption is described in previous reports of critically ill patients, particularly those receiving enteral medications with hypoperfusion following shock, vasopressor therapy and gastrointestinal dysfunction [8–10].

Stent thrombosis following primary percutaneous coronary intervention (PCI) is a risk that necessitates dual antiplatelet therapy with aspirin and P2Y₁₂ receptor inhibitors. Although used commonly, the efficacy of oral P2Y₁₂ inhibitors in ECPR patients is not well defined. Conventional platelet function tests, i.e. impedance aggregometry (Multiplate® ADP test) and optical aggregometry (VerifyNow® PRU test) give information on the antiplatelet response, however, they are not established in the setting of ECMO [5, 6].

The purpose of this study is to fill this knowledge gap by assessing platelet aggregation among adult ECPR patients treated with P2Y₁₂ inhibitors and comparing it with a cardiac arrest cohort not supported with ECMO. We hypothesized that ECPR patients would exhibit altered platelet reactivity together with reduced responsiveness to oral P2Y₁₂ inhibitors.

Methods

Study Design

This study is a single-center comparative analysis of two prospectively collected non-contemporaneous cohorts with longitudinal assessment of platelet function.

Study Population – ECPR Group

For the present analysis, we identified adult patients (18–70 years) who had undergone ECPR for cardiac arrest between February 2018 and August 2021 and who received P2Y₁₂ receptor inhibitor therapy during ECMO support after PCI. ECPR inclusion criteria were applied: age 18–70 years, initial shockable rhythm, witnessed arrest, bystander cardiopulmonary resuscitation and transport to the hospital within one hour of cardiac arrest. Ticagrelor was administered to patients as first-line P2Y₁₂ inhibitor, according to the guidelines [11]. We applied standard protocols of ECMO support, without any specific measures performed for this study. Patients receiving ECMO were excluded if they had thrombocytopenia (platelet count < 50 × 10⁹/L) on ECMO onset, if intravenous antiplatelet agents, such as eptifibatide, bivalirudin or cangrelor were used and if they had pre-ECMO chronic treatment with P2Y₁₂ inhibitors.

Control Group – Cardiac Arrest Cohort

The control group consisted of a prospective cohort of adult cardiac arrest patients (≥ 18 years) enrolled between August 2014 and April 2016 as part of a previously published randomized controlled trial conducted at the same institution [12]. All clinical and platelet function data in this cohort were collected prospectively according to a predefined study protocol. Patients underwent successful resuscitation and percutaneous coronary intervention (PCI) with ticagrelor treatment but did not receive ECMO support. The same platelet function sampling schedule and laboratory methods (VerifyNow® and Multiplate® testing) were used. Cardiac arrest cohort only excluded patients under 18 years of age. For this analysis, only patients who received the ticagrelor antiplatelet treatment were included.

Medical Management

Antiplatelet drug dosage was based on standard administration regimen according to manufacturer and contemporary international guidelines [11]. Aspirin (250–500 mg) was administered to the patients of both groups (ECPR and conventionally resuscitated cardiac arrest) at either pre-hospital location or on arrival, with maintenance doses of 100 mg per 24 h. Ticagrelor was started in the ICU. Tablets were crushed and administered through nasogastric or orogastric tube. The loading dose was 180 mg, with 90 mg every 12 hours afterwards.

ECMO Management

All patients were cannulated peripherally. Mean ECMO blood flow was 2.2 L/min.

A single i.v. bolus of 5,000 IU of unfractionated heparin was given at the time of ECMO insertion. Following cannulation, systemic anticoagulation was ensured by continuous administration of unfractionated heparin, which was adjusted to maintain an activated partial thromboplastin time (aPTT) value ranging between 50 to 70 seconds. The aPTT was checked at least three times daily. Well-trained intensive care physicians checked the ECMO circuit for the appearance of thrombi.

Clinical Data Collection

The following clinical data were prospectively collected: age and sex, comorbidities (arterial hypertension, diabetes, hyperlipidemia, smoking status, previous cerebrovascular insult, renal insufficiency, chronic heart failure and previous coronary artery disease), Simplified Acute Physiology Score (SAPS) II at ICU admission, platelet count before ECMO initiation, lowest platelet count during the ECMO run, need for platelet transfusion and bleeding events. In the ECPR cohort, bleeding was classified according to the Bleeding Academic Research Consortium (BARC) [13], and major bleeding was defined as BARC type 3–5. In the control cohort, bleeding had been prospectively recorded as bleeding requiring transfusion, which was considered major bleeding for the purpose of this analysis.

Blood Sampling and Laboratory Analysis

Blood samples were obtained in all patients for platelet function assessment. Blood samples were obtained before ticagrelor administration and subsequently at 2, 4, 12, 22 and 48 hours after administration in both cohorts. In ECPR patients, the baseline sample was obtained before ECMO implantation. Samples were drawn into two 0.11 M sodium citrate vacuum tubes and one lithium-heparin vacuum tube (Vacutube; Laboratorijska tehnika Burnik, Vodice, Slovenia).

Platelet function was assessed using the VerifyNow P2Y12 assay (Accumetrics, San Diego, CA, USA) and Multiplate impedance aggregometry (Roche Diagnostics International Ltd., Rotkreuz, Switzerland).

VerifyNow P2Y12 assay

This optical detection assay measures ADP-induced platelet agglutination on fibrinogen-coated beads in whole blood. The assay cartridge contains prostaglandin E1, which suppresses the P2Y1-mediated component of ADP signalling and thereby increases the specificity of the test for the P2Y12 receptor. Results are reported as P2Y12 reaction units (PRU). Testing was performed at 37°C within 20 minutes of sample collection.

Multiplate ADP test

This technique measures platelet aggregation by changes in electrical impedance, using ADP as the agonist. Adhesion of platelets to the sensor wires increases the electrical impedance, which is recorded in arbitrary aggregation units (AU) over time. The area under the curve (AUC) is expressed in units (U), where $1\text{ U} = 10\text{ AU} \times \text{min}$. Samples were analyzed within 1 h of collection.

Definition of high on-treatment platelet reactivity

High on-treatment platelet reactivity (HPR), indicating inadequate P2Y₁₂ inhibition, was defined according to published consensus cut-offs as PRU > 208 for the VerifyNow assay and > 46 U for the Multiplate ADP test [14].

Statistical Methods

Because platelet function was measured repeatedly and the number of samples decreased over time, the primary analysis was based on linear mixed-effects models with a random intercept for each patient, which use all available measurements. The overall difference in the time course between groups was tested with a likelihood-ratio test of the group $\times$ time interaction. The average between-group difference after ticagrelor loading (2–48 h) was estimated in a mixed model including group, time point, baseline value and age. Baseline differences were additionally adjusted for platelet count and age using linear regression, and the association between platelet count and baseline values was assessed with Spearman correlation.

Continuous variables are presented as mean $\pm$ standard deviation (SD) or median (interquartile range, IQR). Platelet function at individual time points was compared with the Mann–Whitney U test, and p values were adjusted for multiple comparisons within each assay using the Holm method. Age and platelet count were compared with Student's t test. Categorical variables are presented as counts and percentages and were compared with Fisher's exact test. Multiplate results of 0 U were considered technically invalid and treated as missing (six measurements). A two-sided p value < 0.05 was considered statistically significant. Analyses were performed in Python 3.12 using SciPy 1.17 and statsmodels. The analyses were conducted with the assistance of an AI tool (Claude, Anthropic) and independently verified by the authors.

Results

A total of 36 patients were analyzed, 16 in the ECPR group and 20 in the cardiac arrest control group. Baseline characteristics are summarized in Table 1. Patients in the ECPR group were significantly younger than controls (53 ± 8 vs. 61 ± 12 years, $p = 0.030$). No significant differences were observed between the groups regarding sex distribution and chronic comorbidities (hypertension, diabetes mellitus, hyperlipidemia and previous coronary artery disease). Initial platelet counts were numerically lower in the ECPR group than in the control group ($193 \pm 63 \times 10^9/\text{L}$ vs. $223 \pm 68 \times 10^9/\text{L}$), although the difference did not reach statistical significance ($p = 0.178$). There was a non-significant trend toward more frequent major bleeding in the ECPR group (43.8% vs. 15.0%, $p = 0.073$).

Table 1
Baseline patient characteristics

Age, years $\pm$ SD	ECPR (n = 16)	Cardiac arrest (n = 20)	p
	53 $\pm$ 8	61 $\pm$ 12	0.030
Male (n, %)	15 (93.8)	17 (85.0)	0.613
Hypertension (n, %)	9 (56.3)	10 (50.0)	0.749
Diabetes (n, %)	3 (18.8)	5 (25.0)	0.709
Hyperlipidemia (n, %)	3 (18.8)	3 (15.0)	1.000
Previous CAD (n, %)	1 (6.3)	1 (5.0)	1.000
Platelet count at baseline ($\times 10^9/L$)	193 $\pm$ 63	223 $\pm$ 68	0.178
Major bleeding (n, %)⊠	7 (43.8)	3 (15.0)	0.073

Data are presented as mean $\pm$ SD or n (%). SD standard deviation, CAD coronary artery disease, BARC Bleeding Academic Research Consortium. ⊠BARC type 3–5 in the ECPR group; bleeding requiring transfusion in the control group.

Multiplate: baseline ADP-induced aggregation was lower in ECPR patients than in controls (median 22 [IQR 6–48] vs. 60 [32–69] U; $p = 0.033$), but the difference did not persist after correction for multiple comparisons (Holm-adjusted $p = 0.196$). Baseline ADP aggregation correlated with platelet count (Spearman $\rho = 0.49$, $p = 0.008$), and after adjustment for platelet count and age the difference between groups was no longer significant (-11.7 U, 95% CI -33.4 to 10.0 ; $p = 0.28$). After ticagrelor loading, ADP aggregation was similar in both groups at all time points. The mixed model showed no difference in the time course (group $\times$ time interaction $p = 0.086$) or in post-loading aggregation (adjusted difference -0.8 U, 95% CI -8.5 to 6.8 ; $p = 0.84$) (Table 2, Fig. 1b).

VerifyNow: baseline PRU was lower in ECPR patients (median 220 [IQR 158–243] vs. 246 [221–300]; $p = 0.020$), and this difference persisted after adjustment for platelet count and age (-56.5 PRU, 95% CI -96.5 to -16.5 ; $p = 0.007$). After ticagrelor loading, however, PRU declined more slowly in the ECPR group (group $\times$ time interaction $p < 0.001$). Over the 2–48 h period, PRU was on average 95 units higher in ECPR patients than in controls after adjustment for baseline PRU and age (95% CI 41–148; $p < 0.001$). At 2 and 4 h, median PRU in ECPR patients remained above the HPR threshold (244 [186–311] and 228 [192–317]), whereas in controls it had already fallen below it (205 [163–227] and 164 [115–222]). At 12 h, HPR persisted in 5 of 12 ECPR patients (42%) compared with 2 of 19 controls (11%; $p = 0.078$). Differences at individual time points did not remain significant after correction for multiple comparisons. The number of evaluable ECPR patients decreased from 16 at baseline to 7 at 48 h (Table 2, Fig. 1a).

Table 2

Platelet reactivity assessed by Multiplate ADP impedance aggregometry and the VerifyNow P2Y12 assay in the ECPR group and the conventionally resuscitated cardiac arrest control group

ADP0	ECPR (n = 16)	Cardiac arrest (n = 20)	p (Holm-adjusted p)
	22 (6–48); 11	60 (32–69); 18	0.033 (0.196)
ADP2	22 (13–32); 13	23 (18–42); 20	0.407 (1.000)
ADP4	24 (10–35); 13	22 (15–34); 20	0.796 (1.000)
ADP12	12 (9–16); 13	12 (7–21); 18	0.718 (1.000)
ADP22	12 (10–12); 9	12 (9–16); 18	0.569 (1.000)
ADP48	14 (12–14); 3	18 (15–24); 12	0.128 (0.638)
PRU0	220 (158–243); 16	246 (221–300); 19	0.020 (0.102)
PRU2	244 (186–311); 12	205 (163–227); 20	0.134 (0.277)
PRU4	228 (192–317); 12	164 (115–222); 20	0.023 (0.102)
PRU12	142 (81–259); 12	133 (26–147); 19	0.092 (0.277)
PRU22	109 (96–161); 9	95 (54–137); 18	0.181 (0.277)
PRU48	131 (98–133); 7	56 (36–79); 14	0.015 (0.092)
Data are presented as median (IQR); number of evaluable patients. p values are from the Mann–Whitney U test; Holm-adjusted p values within each assay are shown in parentheses. ADP0–ADP48 and PRU0–PRU48 denote values at baseline and 2, 4, 12, 22 and 48 h after the ticagrelor loading dose. ADP Multiplate ADP test (U), PRU P2Y12 reaction units, IQR interquartile range			

Discussion

Our findings indicate that ECPR patients respond to enteral ticagrelor with delayed and attenuated P2Y12 inhibition. Compared with conventionally resuscitated cardiac arrest patients, PRU values after loading were on average almost 100 units higher, and a substantial proportion of ECPR patients remained above the HPR threshold for at least 12 h. In contrast, Multiplate ADP aggregation after loading was similar in both groups.

The two main findings of our study are, first, that baseline P2Y12 reactivity measured by VerifyNow was lower in ECPR patients than in conventionally resuscitated cardiac arrest patients, independently of platelet count, whereas the lower baseline Multiplate aggregation was largely explained by lower platelet counts. Second, ECPR patients demonstrated a delayed and attenuated pharmacodynamic response to ticagrelor, resulting in a prolonged period of inadequate P2Y12 inhibition after drug administration.

Reduced platelet reactivity after cardiac arrest has been reported previously [15], whereas other investigators have described platelet hyperfunction after restoration of spontaneous circulation [16]. The

lower baseline PRU in our ECPR patients, who were sampled before ECMO implantation after refractory cardiac arrest, may reflect platelet consumption and exhaustion during prolonged resuscitation. Despite this lower starting point, VerifyNow demonstrated higher residual platelet reactivity after ticagrelor administration than in controls. The mechanisms underlying this finding are likely multifactorial and may include extracorporeal circuit-induced platelet activation, systemic inflammatory response, ischemia–reperfusion injury, and altered drug absorption and distribution [5, 8, 16].

In ECPR patients, we observed delayed P2Y₁₂ inhibition compared with conventionally resuscitated cardiac arrest patients: median PRU remained above the HPR threshold during the first 4 h after loading, and PRU values decreased more slowly throughout the 48-hour observation period. These findings suggest a delayed and attenuated pharmacodynamic response to oral ticagrelor in the setting of ECPR.

Delayed P2Y₁₂ inhibition in ECPR patients can likely be attributed to several factors. Drug absorption may be impaired due to paralytic ileus, gastrointestinal hypoperfusion, or altered splanchnic circulation. Although we crushed ticagrelor and administered it via nasogastric or orogastric tube to improve bioavailability, this method may still result in delayed or incomplete absorption in critically ill ECMO patients [8–10]. In addition, systemic inflammation and ECMO circuit-related platelet activation and consumption may independently influence both baseline platelet reactivity and pharmacodynamic response to antiplatelet therapy [17, 18]. Delayed and insufficient P2Y₁₂ inhibition after enteral loading has previously been described in resuscitated patients treated with therapeutic hypothermia, with high rates of non-response to ticagrelor and prasugrel [19], whereas other investigators found adequate inhibition 24 h after crushed ticagrelor [10]. This time course is consistent with our observations, in which inadequate P2Y₁₂ inhibition in ECPR patients was already evident during the first hours after loading.

Multiplate and VerifyNow showed discordant results after ticagrelor loading: VerifyNow detected markedly weaker P2Y₁₂ inhibition in ECPR patients, whereas Multiplate aggregation did not differ between groups. Poor agreement between these methods has been reported previously [20]. The two assays evaluate different aspects of platelet function. VerifyNow, which contains prostaglandin E₁, more specifically reflects the P2Y₁₂ receptor pathway, whereas Multiplate measures global ADP-induced aggregation in whole blood and is strongly dependent on platelet count. In our cohort, baseline Multiplate values correlated with platelet count, and the lower baseline aggregation in ECPR patients was no longer significant after adjustment. Low Multiplate values in ECMO patients with reduced platelet counts may therefore mask inadequate receptor-level inhibition, and VerifyNow may be the more informative assay for monitoring P2Y₁₂ inhibitor therapy in this setting. Reliance on a single assay may thus lead to an overestimation of the antiplatelet effect in ECPR patients, who are simultaneously exposed to thrombotic complications, including stent thrombosis, and bleeding complications.

ECPR patients who undergo primary PCI and coronary stenting may be at an even higher risk of early stent thrombosis, as longer resuscitation times have been shown to significantly increase this risk [21]. The early post-PCI period in ECPR patients thus combines attenuated P2Y₁₂ inhibition with circuit-

related platelet activation, which may create a particularly vulnerable prothrombotic window. At the same time, the trend toward more frequent major bleeding in our ECPR cohort, occurring in the setting of systemic heparinization, large-bore cannulation and ECMO-associated platelet dysfunction, illustrates the opposite side of the hemostatic balance. Antiplatelet strategies in these patients should therefore aim for rapid and predictable, yet readily reversible, P2Y12 inhibition, a profile that intravenous agents may provide more reliably than crushed oral tablets.

Limitations

This study has several limitations. It is a single-center study, and the small sample size may limit the generalizability of the results.

The comparison was conducted between two prospectively collected cohorts enrolled during different study periods. Although both cohorts were enrolled at the same institution and underwent identical platelet function testing protocols, using a control group from a different time period introduces the possibility of residual confounding and temporal bias. In addition, baseline platelet reactivity measured by VerifyNow differed between groups before ticagrelor administration. Therefore, subsequent differences in platelet function measurements cannot be attributed solely to ECMO support and may partially reflect differences in illness severity, duration of cardiac arrest, and the underlying pathophysiology of patients selected for ECPR.

Furthermore, the number of evaluable samples in the ECPR group decreased over time, from 16 patients at baseline to 7 PRU measurements at 48 h, and this dropout was probably not random but related to disease severity. Mixed-effects models make use of all available measurements, but results at later time points should be interpreted with caution. Six Multiplate measurements of 0 U were considered technically invalid and excluded. Finally, bleeding was classified according to BARC in the ECPR cohort, whereas in the historical control cohort it had been recorded as bleeding requiring transfusion. Although overt bleeding requiring transfusion corresponds to at least BARC type 3a, the comparison of bleeding rates should be regarded as exploratory.

Plasma concentrations of ticagrelor and its active metabolites were not measured, so no pharmacokinetic data could be directly correlated with platelet function findings. Platelet reactivity was assessed using two validated assays (Multiplate® and VerifyNow®), which evaluate different aspects of platelet biology and demonstrated discordant findings in the present study. Variability in assay characteristics and the absence of a definitive reference standard may have influenced the observed results.

Despite these limitations, our observations provide important insight into the complexity of antiplatelet treatment in ECMO patients and highlight the need for prospective multicenter trials to guide future practice.

Conclusions

To our knowledge, this is the first study to characterize platelet reactivity and the pharmacodynamic response to oral P2Y12 inhibitors in patients undergoing ECPR after refractory cardiac arrest. Compared with conventionally resuscitated cardiac arrest patients, ECPR patients demonstrated delayed and attenuated P2Y12 inhibition after crushed ticagrelor, with higher residual platelet reactivity by VerifyNow testing, whereas Multiplate aggregation after loading did not differ and baseline Multiplate values were largely determined by platelet count. These findings suggest a prolonged period of inadequate platelet inhibition after ticagrelor administration. In selected ECPR patients at high risk of early stent thrombosis, alternative antiplatelet strategies, including intravenous P2Y12 inhibitors, should be considered. Further studies are needed to better define and balance the competing thrombotic and bleeding risks in this high-risk population.

Declarations

Funding

The authors received no specific funding for this work.

Competing interests

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics approval

The study was performed in line with the principles of the Declaration of Helsinki. The analysis of the ECPR cohort was approved by the National Medical Ethics Committee of the Republic of Slovenia (protocol number 0120-377/2020/6). The control cohort was enrolled in a randomized trial approved by the National Medical Ethics Committee of the Republic of Slovenia (0120-61/2019/8).

Consent to participate

Written informed consent was waived by the ethics committee because all patients were treated according to institutional ECMO protocols and no study-related interventions were performed.

Data availability

The datasets generated and analyzed during the current study are not publicly available due to patient privacy and ethical restrictions but are available from the corresponding author on reasonable request.

Author contributions

U.M. contributed to the study design, patient recruitment, data collection, data interpretation, and drafted the manuscript. J.B. performed the statistical analysis. P.K contributed to the study design and data interpretation, K.S. shared his cardiac arrest data and contributed to the study design M.B.M. performed the laboratory analyses. T.G. and M.N. contributed to the study design, interpretation of the results, and

scientific supervision. All authors critically revised the manuscript, approved the final version, and agree to be accountable for the work.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the authors used Claude, Anthropic for statistical analyses. The authors reviewed and edited the output as needed and take full responsibility for the content of the published article.

References

1. Abrams D, Combes A, Brodie D (2014) Extracorporeal membrane oxygenation in cardiopulmonary disease in adults. *J Am Coll Cardiol* 63:2769–2778. <https://doi.org/10.1016/j.jacc.2014.03.046>
2. Richardson AS, Schmidt M, Bailey M, Pellegrino VA, Rycus PT, Pilcher DV (2017) ECMO cardiopulmonary resuscitation (ECPR), trends in survival from an international multicentre cohort study over 12-years. *Resuscitation* 112:34–40. <https://doi.org/10.1016/j.resuscitation.2016.12.009>
3. Aubron C, Cheng AC, Pilcher D et al (2013) Factors associated with outcomes of patients on extracorporeal membrane oxygenation support: a 5-year cohort study. *Crit Care* 17:R73. <https://doi.org/10.1186/cc12681>
4. Oliver WC (2009) Anticoagulation and coagulation management for ECMO. *Semin Cardiothorac Vasc Anesth* 13:154–175. <https://doi.org/10.1177/1089253209347384>
5. Balle CM, Jeppesen AN, Christensen S, Hvas AM (2018) Platelet function during extracorporeal membrane oxygenation in adult patients: a systematic review. *Front Cardiovasc Med* 5:157. <https://doi.org/10.3389/fcvm.2018.00157>
6. Balle CM, Jeppesen AN, Christensen S, Hvas AM (2019) Platelet function during extracorporeal membrane oxygenation in adult patients. *Front Cardiovasc Med* 6:114. <https://doi.org/10.3389/fcvm.2019.00114>
7. Orban M, Kleeberger J, Ouarrak T et al (2021) Clopidogrel vs. prasugrel vs. ticagrelor in patients with acute myocardial infarction complicated by cardiogenic shock: a pooled IABP-SHOCK II and CULPRIT-SHOCK trial sub-analysis. *Clin Res Cardiol* 110:1493–1503
8. Forsberg J, Bedard E, Mahmoud SH (2023) Bioavailability of orally administered drugs in critically ill patients. *J Pharm Pract* 36:967–979. <https://doi.org/10.1177/08971900221100205>
9. Umińska JM, Ratajczak J, Buszko K et al (2020) Impact of mild therapeutic hypothermia on bioavailability of ticagrelor in patients with acute myocardial infarction after out-of-hospital cardiac arrest. *Cardiol J* 27:780–788. <https://doi.org/10.5603/CJ.a2019.0024>
10. Tilemann LM, Stiepak J, Zelniker T et al (2016) Efficacy of enteral ticagrelor in hypothermic patients after out-of-hospital cardiac arrest. *Clin Res Cardiol* 105:332–340. <https://doi.org/10.1007/s00392-015-0925-1>

11. Ibanez B, James S, Agewall S, et al et al (2018) 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 39:119–177.
<https://doi.org/10.1093/eurheartj/ehx393>
12. Steblovnik K, Blinc A, Mijovski MB, Fister M, Mikuz U, Noc M (2016) Ticagrelor versus clopidogrel in comatose survivors of out-of-hospital cardiac arrest undergoing percutaneous coronary intervention and hypothermia: a randomized study. *Circulation* 134:2128–2130.
<https://doi.org/10.1161/CIRCULATIONAHA.116.024872>
13. Mehran R, Rao SV, Bhatt DL et al (2011) Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 123:2736–2747. <https://doi.org/10.1161/CIRCULATIONAHA.110.009449>
14. Tantry US, Bonello L, Aradi D et al (2013) Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. *J Am Coll Cardiol* 62:2261–2273. <https://doi.org/10.1016/j.jacc.2013.07.101>
15. Steblovnik K, Blinc A, Bozic-Mijovski M, Kranjec I, Melkic E, Noc M (2015) Platelet reactivity in comatose survivors of cardiac arrest undergoing percutaneous coronary intervention and hypothermia. *EuroIntervention* 10:1418–1424. https://doi.org/10.4244/EIJY14M05_02
16. Spiel AO, Frossard M, Mayr FB et al (2009) Pronounced platelet hyperfunction in patients with cardiac arrest achieving restoration of spontaneous circulation. *Crit Care Med* 37:975–979.
<https://doi.org/10.1097/CCM.0b013e3181962cb9>
17. Panigada M, Artoni A, Passamonti SM et al (2016) Hemostasis changes during veno-venous extracorporeal membrane oxygenation for respiratory support in adults. *Minerva Anesthesiol* 82:170–179
18. Malfertheiner MV, Philipp A, Lubnow M et al (2016) Hemostatic changes during extracorporeal membrane oxygenation: a prospective randomized clinical trial comparing three different extracorporeal membrane oxygenation systems. *Crit Care Med* 44:747–754
19. Ibrahim K, Christoph M, Schmeinck S et al (2014) High rates of prasugrel and ticagrelor non-responder in patients treated with therapeutic hypothermia after cardiac arrest. *Resuscitation* 85:649–656
20. Vries MJ, Bouman HJ, Olie RH et al (2017) Determinants of agreement between proposed therapeutic windows of platelet function tests in vulnerable patients. *Eur Heart J Cardiovasc Pharmacother* 3:11–17
21. Rauber M, Nicol P, Sabic E, Joner M, Noc M (2022) Timing and predictors of definite stent thrombosis in comatose survivors of out-of-hospital cardiac arrest undergoing percutaneous coronary intervention and therapeutic hypothermia (ST-OHCA study). *EuroIntervention* 18:740–748.
<https://doi.org/10.4244/EIJ-D-22-00336>

Figures

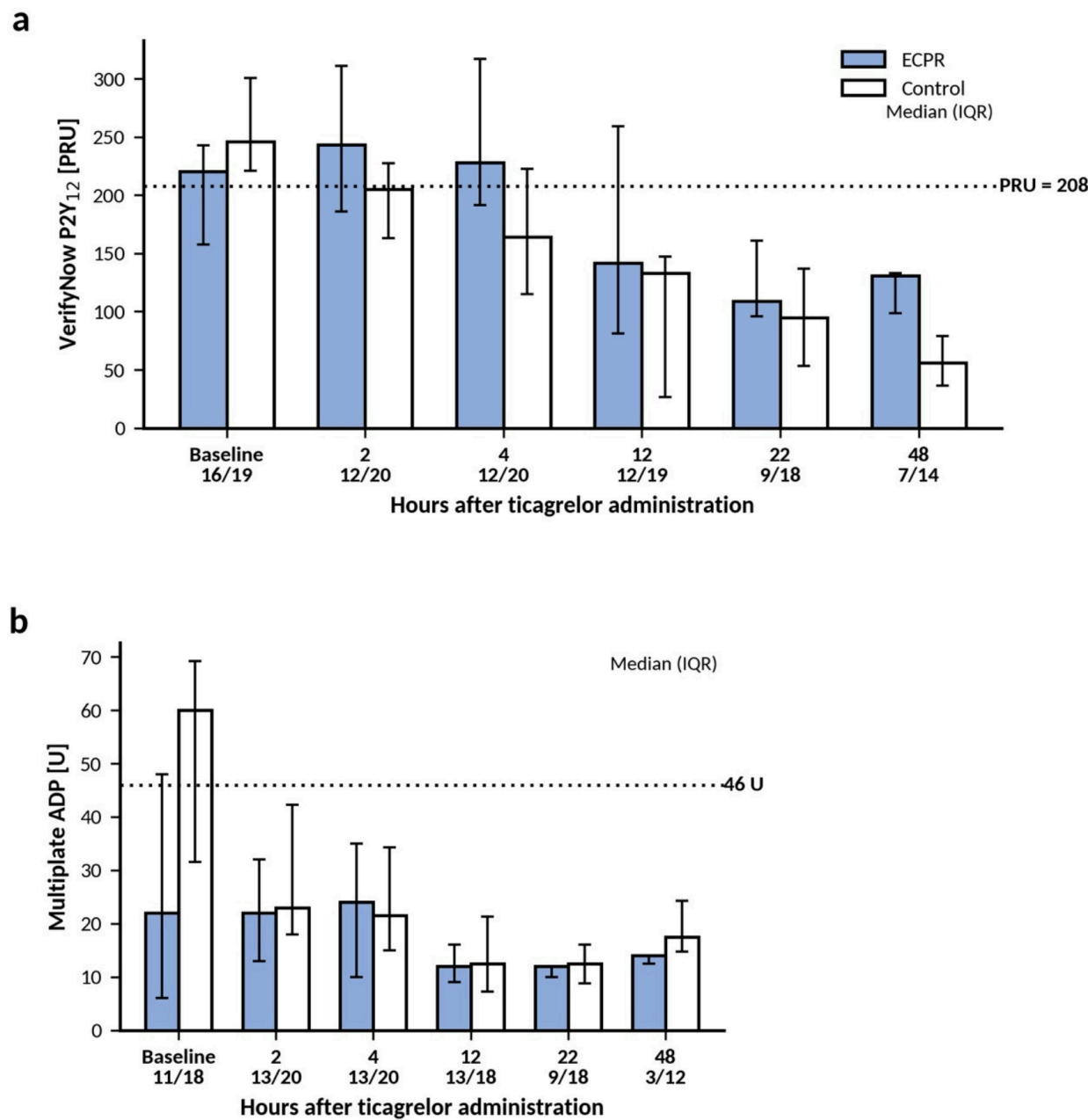


Figure 1

Platelet reactivity in ECPR patients and conventionally resuscitated cardiac arrest patients (control), measured with the VerifyNow P2Y₁₂ assay (a) and Multiplate ADP impedance aggregometry (b). Bars show medians and error bars interquartile ranges; numbers below the time points indicate evaluable patients (ECPR/control). Dashed lines indicate published thresholds for high on-treatment platelet reactivity (PRU > 208 and > 46 U). Group × time interaction in linear mixed-effects models: $p < 0.001$ for

VerifyNow and $p = 0.086$ for Multiplate. PRU P2Y12 reaction units, U aggregation units, IQR interquartile range