Factors Affecting Platelet Reactivity 2 Hours After P2Y₁₂ Receptor Antagonist Loading in Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction

– Impact of Pain-to-Loading Time –

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Background: Delay in the onset of antiplatelet action occurs in patients with ST-elevation myocardial infarction (STEMI) and is likely due to disturbed absorption. We hypothesized that patients presenting relatively late after the onset of symptoms would have faster antiplatelet action.

Methods and Results: We analyzed patient-level data from 5 studies of 207 P2Y₁₂ receptor antagonist-naïve patients with STEMI undergoing primary percutaneous coronary intervention (PCI). All patients had available platelet reactivity (PR) assessment with the VerifyNow assay (in P2Y₁₂ reaction units; PRU) prior to and 2 h after loading. High PR (HPR) was defined as ≥ 208 PRU. Pain-to-antiplatelet loading time independently predicted PR at 2 h after loading: every 1-h increase in pain-to-antiplatelet loading time produced a 7% decrease in PR ($P=0.001$). Pretreatment PR, body mass index, morphine and novel P2Y₁₂ receptor antagonist also affected PR 2 h after loading. Novel P2Y₁₂ receptor antagonist use and per hour increase in pain-to-antiplatelet loading time were independently associated with lower probability for HPR with an OR (95% CI) of 0.145 (0.095–0.220) and 0.776 (0.689–0.873), $P<0.001$ for both (C-statistic, 0.752; 95% CI: 0.685–0.819).

Conclusions: In STEMI patients undergoing primary PCI, pain-to-antiplatelet loading interval is a newly described factor affecting PR shortly after P2Y₁₂ receptor antagonist loading, according to patient-level data pooled analysis. (*Circ J* 2016; **80**: 442–449)

Key Words: Antiplatelet; Myocardial infarction; Pharmacology

In the early phase of ST-segment elevation myocardial infarction (STEMI), platelets are highly activated and represent a main constituent of fresh thrombi.¹ Rapid, potent and consistent platelet inhibition is considered mandatory in order to achieve an optimal and sustained reperfusion result.^{2–4} A loading dose (LD) of oral antiplatelet agent should be given adjunctive to primary percutaneous coronary intervention (PCI) as early as possible or at the time of primary PCI according to practice guidelines.^{5–8} Delay in the onset of antiplatelet agent effects, however, has been recently described in the first several hours following oral clopidogrel, prasugrel or ticagrelor treatment.^{9–13} Several factors have been implicated,

with a dominant role attributed to an impaired intestinal drug absorption. This may have been caused by adrenergic activation, systemic vasoconstriction, opiates, abnormal muscular activity of the gastrointestinal tract, nausea or vomiting.^{9,13} In contrast, it is a common clinical perception that these conditions are very prevalent in the very early course of STEMI, while they tend to subside with time. We hypothesized that STEMI patients presenting for primary PCI relatively late after the onset of symptoms may have greater attenuation of conditions likely to impede absorption of oral antiplatelet agents, and therefore a more rapid onset of antiplatelet action might be expected with increasing onset of pain-to-antiplatelet

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Table 1. Studies Contributing to the Pooled Data

Study	n	Subjects	Study design	Treatment
Alexopoulos et al ¹²	52	Patients with STEMI undergoing primary PCI	Prospective, single-center, randomized, parallel	Ticagrelor 180 mg LD, Prasugrel 60 mg LD
Alexopoulos et al ¹⁴	36	Patients with STEMI undergoing primary PCI	Prospective, 4-center, non-randomized, sequential	Ticagrelor 360 mg LD†, Ticagrelor 180 mg LD
Alexopoulos et al ¹⁵	35	Patients with STEMI undergoing primary PCI	Prospective, 3-center, non-randomized, sequential	Prasugrel 100 mg LD†, Prasugrel 60 mg LD
Alexopoulos et al ¹⁶	10	Patients with STEMI undergoing primary PCI	Prospective, single-center, randomized, parallel	Ticagrelor 180 mg LD crushed†, Ticagrelor 180 mg LD whole pills
Alexopoulos et al ongoing study (ClinicalTrials.gov NCT01961856)	74	Patients with STEMI undergoing primary PCI	Prospective, 3-center, randomized, parallel	Ticagrelor 180 mg LD, Clopidogrel 600 mg LD

†Not included in the present analysis. LD, loading dose; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

LD time. To our knowledge, no previous study has explicitly analyzed the impact of this time interval on platelet reactivity changes after antiplatelet loading. In the present study, in STEMI patients admitted for primary PCI, we analyzed factors, including onset of pain-to-antiplatelet LD time, affecting the onset of antiplatelet action, as assessed on platelet reactivity 2 h after oral antiplatelet agent LD.

Methods

We analyzed platelet function in P2Y₁₂ receptor antagonist-naïve patients with STEMI undergoing primary PCI within 12 h from the onset of symptoms. We included all 207 patients treated with either clopidogrel 600 mg or prasugrel 60 mg or ticagrelor 180 mg LD with available platelet reactivity measurement prior to (hour 0) and at hour 2 after LD from 4 previously published^{12,14–16} and 1 ongoing study (ClinicalTrials.gov NCT02046486), in which detailed inclusion and exclusion criteria are reported (Table 1). Briefly, patients were excluded if they had a history of bleeding diathesis, chronic oral anticoagulation treatment, contraindications to antiplatelet therapy, platelet count <100,000/μl, hematocrit <30%, and creatinine clearance <25 ml/min. Moreover, patients with a history of stroke, weighing ≤60 kg, or >75 years of age were excluded from prasugrel treatment. In all cases, antiplatelet LD was administered after angiography and prior to primary PCI.

Peripheral venous blood samples were drawn with a loose tourniquet through a short venous catheter inserted into a forearm vein. The first 2–4 ml of blood was discarded to avoid spontaneous platelet activation, and blood was collected in 3.2% citrate (1.8 ml-draw plastic Vacuette tubes; Greiner, Monroe, NC, USA). Platelet-function testing was performed with the VerifyNow P2Y₁₂ assay (Accumetrics, San Diego, CA, USA). Platelet reactivity results are reported in P2Y₁₂ reaction units (PRU). High platelet reactivity (HPR) was defined as ≥208 PRU.¹⁷

Statistical Analysis

Categorical data are presented as frequencies and group percentages. Continuous data with normal and skewed distribution are presented as mean±SD and median (interquartile range – IQR), respectively. Kolmogorov-Smirnov test was used to examine data distribution normality. Jonckheere-Terpstra test was used to assess platelet reactivity across quartiles of pain-to-antiplatelet loading time. Given that distribution of platelet reactivity in >80% of patients in the integrated dataset was right-skewed, platelet reactivity in the overall population was

Table 2. Patient Demographic and Clinical Characteristics: Pooled Dataset

	Overall (n=207)
Male	180 (87.0)
Age (years)	59.4±11.1
BMI (kg/m ²)	28.6±4.5
Current smoker	135 (65.2)
Hyperlipidemia	93 (44.9)
Hypertension	98 (47.3)
Diabetes mellitus	34 (16.4)
Prior MI	8 (3.9)
Pain-to-loading time (h)	3.00 (2.00–4.67)
Loading-to-balloon time (min)	9.00 (5.00–12.00)
1-vessel disease	102 (49.3)
2-vessel disease	77 (37.2)
3-vessel disease	28 (13.5)
Culprit vessel	
LM	2 (1.0)
LAD	96 (46.4)
LCX	34 (16.4)
RCA	75 (36.2)
Bivalirudin	121 (58.5)
Morphine	33 (15.9)
Hematocrit (%)	42.1±4.1
PLT (×1,000/mm ³)	240.2±61.0
CrCl <60 ml/min†	19 (9.2)
PR at hour 0	232.9±50.6

Data given as mean±SD, median (IQR) or n (%). †Estimated using Cockcroft-Gault equation. BMI, body mass index; CrCl, creatinine clearance; IQR, interquartile range; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main; MI, myocardial infarction; PLT, platelets; PR, platelet reactivity; RCA, right coronary artery; SD, standard deviation.

analyzed with a generalized mixed model with gamma distribution and log link. To account for within-study correlation of participants, we modeled study as a random intercept and platelet reactivity at hour 0 as a covariate. Gender, smoking status, diabetes mellitus, bivalirudin use, morphine use, and novel P2Y₁₂ receptor antagonist use (vs. clopidogrel) were modeled as fixed categorical variables and age (in decades), creatinine clearance (per 30 ml/min), body mass index (BMI,

Figure 1. Distribution of platelet reactivity at hour 2 after antiplatelet loading dose in (A) the pooled population; and (B) ticagrelor, (C) prasugrel, (D) clopidogrel and (E) novel P2Y₁₂ receptor antagonist (ticagrelor and prasugrel)-treated patients. PRU, P2Y₁₂ reaction units.

Figure 2. Individual patient platelet reactivity (PR) at hour 2 vs. quartiles of pain-to-antiplatelet loading dose time. Horizontal lines, median; error bars, interquartile range. PRU, P2Y₁₂ reaction units.

per 5 kg/m²) and pain-to-antiplatelet LD time (h) as continuous variables. We also performed a stratified analysis of platelet reactivity according to P2Y₁₂ receptor antagonist used. To analyze platelet reactivity in clopidogrel-treated patients and in novel P2Y₁₂ receptor antagonist (ticagrelor and prasugrel)-treated patients, we performed generalized linear mixed (Gaussian distribution and link identity) and gamma-log modeling, respectively, adjusting for all the aforementioned variables except for type of P2Y₁₂ receptor antagonist used. All coefficients resulting from gamma-log and linear models are reported in non-exponential form. To assess potential predictive factors of HPR at hour 2, we fitted a logistic regression model in a backward elimination fashion ($P > 0.1$ for removal criterion), with study as a random intercept and platelet reactivity at hour 0 as a covariate. Gender, smoking status, diabetes mellitus, bivalirudin use, morphine use, and novel P2Y₁₂ receptor antagonist use (vs. clopidogrel) were modeled as fixed categorical variables and age (in decades), creatinine clearance (per 30 ml/min), BMI (per 5 kg/m²) and pain-to-antiplatelet LD time (in h) as continuous variables. The discriminative power of the final model was tested using the C-statistic.

All tests were 2-tailed and statistical significance was considered for $P < 0.05$. Analysis was performed using SPSS for Windows (version 20.0; SPSS, Chicago, IL, USA) and NCSS 8 (NCSS, Kaysville, UT, USA).

Each study protocol was approved by the hospital ethics committee and was conducted according to the principles of the Declaration of Helsinki. All patients provided written informed consent before enrollment.

Table 3. Multivariate Factors of PR in STEMI Patients 2 h After P2Y₁₂ Receptor Antagonist LD

	Coefficient (SE)	t	95% CI	P-value
Intercept	5.068 (0.531)	9.551	4.021 to 6.114	<0.001
PR at hour 0 (PRU)	0.002 (0.001)	3.509	0.001 to 0.003	0.001
Male gender	-0.179 (0.100)	-1.786	-0.378 to 0.019	0.076
Morphine use	0.334 (0.052)	6.407	0.231 to 0.437	<0.001
Bivalirudin use	0.123 (0.189)	0.650	-0.250 to 0.496	0.516
CrCl (per 30 ml/min) [†]	-0.078 (0.051)	-1.548	-0.178 to 0.021	0.123
Age (decades)	0.048 (0.028)	1.691	-0.008 to 0.103	0.092
BMI (per 5 kg/m ²)	0.137 (0.047)	2.897	0.044 to 0.230	0.004
Smoking	-0.036 (0.090)	-0.403	-0.213 to 0.140	0.687
DM	0.096 (0.063)	1.512	-0.029 to 0.221	0.132
Pain-to-loading time (h)	-0.073 (0.021)	-3.532	-0.113 to -0.032	0.001
Novel P2Y ₁₂ receptor antagonist (vs. clopidogrel)	-0.580 (0.037)	-15.515	-0.654 to -0.507	<0.001

[†]Calculated using the Cockcroft-Gault formula. PRU, P2Y₁₂ reaction units; SE, standard error. Other abbreviations as in Tables 1,2.

Table 4. Multivariate Factors of PR in Clopidogrel-Treated STEMI Patients 2 h After LD

	Coefficient (SE)	t	95% CI	P-value
Intercept	205.5 (56.4)	3.642	91.2 to 319.8	0.001
PR at hour 0 (PRU)	0.3 (0.1)	2.3	0.04 to 0.6	0.03
Male gender	9.6 (34.5)	0.3	-60.4 to 79.6	0.8
Morphine use	-8.5 (22.0)	-0.4	-53.1 to 36.0	0.7
Bivalirudin use	-6.0 (13.6)	-0.4	-33.5 to 21.5	0.7
CrCl (per 30 ml/min) [†]	-2.5 (8.4)	-0.3	-19.5 to 14.5	0.8
Age (decades)	4.8 (8.6)	0.6	-12.7 to 22.3	0.6
BMI (per 5 kg/m ²)	2.9 (9.1)	0.3	-15.6 to 21.3	0.8
Smoking	-32.8 (14.1)	-2.3	-61.4 to -4.2	0.03
DM	42.4 (15.5)	2.7	10.9 to 73.7	0.009
Pain-to-loading time (h)	-12.8 (3.8)	-3.4	-20.4 to -5.2	0.002

[†]Calculated using the Cockcroft-Gault formula. Abbreviations as in Tables 1–3.

Results

In total, pooled patient-level data of 207 patients from 5 studies were used for analysis (Table 1). Patient demographic and clinical characteristics listed in Table 2. Distribution of platelet reactivity at hour 2 after LD in the pooled population seems to have a bimodal pattern, being a mixture of right-skewed and Gaussian distribution (Figure 1A). Ticagrelor (52.7% of patients in the pooled population) produced a highly right-skewed distribution; prasugrel (29.4% of patients), a less right-skewed and more uniform distribution; and clopidogrel (17.9% of patients), a Gaussian distribution (Figures 1B–D). Platelet reactivity in the subgroup of patients treated with novel agents (ticagrelor and prasugrel, 82.1% of patients in the pooled population) also had a right-skewed distribution (Figure 1E). There was a trend (that did not achieve statistical significance) towards decrease in platelet reactivity at hour 2 across quartiles of pain-to-antiplatelet LD time (Figure 2).

Variables affecting platelet reactivity at hour 2 after LD are listed in Table 3. Pain-to-antiplatelet LD time emerged as a factor with significant impact on platelet reactivity at hour 2 after LD. With every 1-h increase in pain-to-antiplatelet LD time, log of platelet reactivity was decreased by 0.073, corresponding to a 7% decrease in platelet reactivity (P=0.001).

Additional factors affecting platelet reactivity at hour 2 after LD in the overall population were also identified: Platelet reactivity at hour 0 had a significant influence, although with a very low effect size. BMI and morphine use had a positive effect on platelet reactivity. In particular, every 5-unit increase in BMI and morphine use resulted in a 0.137 and 0.334 increase in the log of expected platelet reactivity, respectively, corresponding to approximately a 15% and 40% increase in platelet reactivity (P=0.004 and P<0.001, respectively). Treatment with novel P2Y₁₂ receptor antagonist had a negative effect on platelet reactivity: compared with clopidogrel-treated patients, log of platelet reactivity was decreased by 0.580, corresponding to a 45% decrease in platelet reactivity in novel P2Y₁₂ receptor antagonist-treated patients (P<0.001).

In the subgroup of clopidogrel-treated patients (Table 4), pain-to-antiplatelet LD time remained a factor that significantly affected platelet reactivity: with every 1-h increase in pain-to-antiplatelet LD time, platelet reactivity decreased by 12.8 PRU (P=0.002). In the subgroup of novel P2Y₁₂-treated patients (Table 5), pain-to-antiplatelet LD time also preserved its impact on platelet reactivity at hour 2 after LD: with every 1-h increase in pain-to-antiplatelet LD time, log of platelet reactivity was decreased by 0.076, corresponding to a 7.3% decrease in platelet reactivity (P=0.001).

Table 5. Multivariate Factors of PR in Novel P2Y₁₂ Receptor Antagonist-Treated STEMI Patients 2 h After LD

	Coefficient (SE)	t	95% CI	P-value
Intercept	4.325 (0.491)	8.806	3.355 to 5.296	<0.001
PR at hour 0 (PRU)	0.002 (0.001)	3.886	0.001 to 0.003	<0.001
Male gender	-0.182 (0.116)	-1.566	-0.411 to 0.047	0.119
Morphine use	0.377 (0.089)	4.213	0.200 to 0.554	<0.001
Bivalirudin use	0.167 (0.204)	0.821	-0.235 to 0.570	0.413
CrCl (per 30 ml/min) [†]	-0.083 (0.070)	-1.185	-0.222 to 0.055	0.238
Age (in decades)	0.057 (0.025)	2.261	0.007 to 0.106	0.025
BMI (per 5 kg/m ²)	0.160 (0.051)	3.126	0.059 to 0.261	0.002
Smoking	-0.017 (0.094)	-0.177	-0.202 to 0.169	0.859
DM	0.100 (0.098)	1.019	-0.094 to 0.293	0.310
Pain-to-loading time (h)	-0.076 (0.022)	-3.477	-0.119 to -0.033	0.001

[†]Calculated using the Cockcroft-Gault formula. Abbreviations as in Tables 1–3.

Figure 3. Multivariate predictors of high platelet reactivity (HPR) at hour 2. PR, platelet reactivity; PRU, P2Y₁₂ reaction units.

HPR rate at hour 2 was 36.7% in the overall population. On multivariate analysis (**Figure 3**), novel P2Y₁₂ receptor antagonist use and per hour increase in pain-to-antiplatelet LD time were independently associated with lower probability for HPR, with an OR (95% CI) of 0.145 (0.095–0.220) and 0.776 (0.689–0.873), respectively ($P < 0.001$ for both in the final model, which had a good discriminative power; C-statistic, 0.752; 95% CI: 0.685–0.819). Pre-treatment platelet reactivity (at hour 0) was also identified as an independent predictor of HPR, although with low effect size. Moreover, increased age was associated with higher probability for HPR (OR, 1.279; 95% CI: 1.045–1.565; $P = 0.02$).

Discussion

In the highly prothrombotic state of patients presenting with STEMI, rapid and strong platelet inhibition is most desirable. Delay in the onset of antiplatelet action has been observed after P2Y₁₂ receptor antagonist loading, even when using the novel antiplatelet agents prasugrel and ticagrelor, proved to have faster onset of action than clopidogrel. Various methods

have been used to bridge the gap in antiplatelet activity, such as antiplatelet LD modification; prehospital treatment; cangrelor (i.v. P2Y₁₂ receptor antagonist) or glycoprotein IIb/IIIa inhibitor use.^{11,12,14–16,18–20} Identification of factors influencing the onset of antiplatelet action may facilitate better peri-interventional platelet inhibition and subsequently improved clinical outcome.²¹ The present study in a large cohort of STEMI patients confirms the influence of several previously reported factors such as intrinsic platelet reactivity, specific antiplatelet agent used, BMI and morphine use, on early (2 h after LD) platelet inhibition.^{22–30} Most importantly, onset of pain-to-antiplatelet LD time, was identified as (a newly recognized) independent factor significantly affecting platelet reactivity shortly after antiplatelet loading in STEMI patients undergoing primary PCI. A bimodal pattern of distribution of platelet reactivity at hour 2 after LD was observed. This may be attributed to the fact that patients in the pooled population were not treated with the same P2Y₁₂ receptor antagonist – a major determinant of platelet reactivity – but with 3 different agents, which differ in onset of action and antiplatelet potency. Of note, in stratified analysis according to P2Y₁₂ receptor

antagonist used, the effect of time remained constant across antiplatelet treatment (novel P2Y₁₂ receptor antagonists and clopidogrel).

Time from onset of symptoms to first medical contact and therefore potential loading with antiplatelet agents is frequently >4 h.^{1,31} This was the case in the present series as well. A more frequent occurrence of no-reflow phenomenon and a worse prognosis are well appreciated in late compared with early presenters following the onset of symptoms.^{32–34} In this higher risk cohort, however, we demonstrated a faster antiplatelet efficacy following a standard LD of oral P2Y₁₂ receptor antagonists. We assume that this earlier onset of antiplatelet action may have been caused by the diminution of conditions known to impede antiplatelet drug absorption. Increased sympathetic activation, nausea, vomiting, disturbed gastric motility and opiate use have increasingly been recognized as factors impeding oral drug absorption and contributing to delay of onset of action in relatively unstable patients. Following a high loading dose of clopidogrel, a significantly impaired bioavailability was first described by Heestermans et al in STEMI patients, as compared with healthy volunteers, and attributed to increased sympathetic drive, impaired gastric emptying, intestinal motility and absorption.⁹ Moreover, morphine, which is commonly used in STEMI patients, was found in a randomized, double-blind, placebo-controlled study to delay clopidogrel absorption, decrease plasma clopidogrel active metabolite, and retard and diminish its effects.²⁹ In a randomized comparison of prasugrel with ticagrelor in STEMI patients undergoing primary PCI, morphine use was first reported by Parodi et al to be associated with delayed activity of these agents.¹³ These results were further confirmed in a larger cohort.³⁰ Nevertheless, given that there is no pharmacokinetic confirmation, the basis of the potential interactions between the aforescribed mechanisms and the present findings remains speculative.

The exact significance of the present findings is not clear. Silvain et al have described a significant influence of ischemic time on thrombi composition, resulting in a positive and a negative correlation with intracoronary thrombus fibrin and platelet content, respectively.¹ An impact on the efficacy of drugs used for coronary reperfusion has been hypothesized, with a more mature thrombus likely being more resistant to antiplatelet treatment. Nevertheless, the faster action of antiplatelet agents described here may partially counteract this detrimental effect of changing thrombus composition in the early hours of STEMI. The slower onset of oral antiplatelet agent action in the very early hours may suggest a more prominent role for i.v. agents, either glycoprotein IIb/IIIa inhibitors or cangrelor, in the achievement of platelet inhibition. Moreover, the expected higher platelet inhibition 2 h after LD in patients presenting relatively late after the onset of symptoms raises the possibility for selection of slower acting but less potent clopidogrel in the case of concomitant high bleeding risk. This, however, should be balanced with the higher risk features of late presenters such as more frequent occurrence of no-reflow phenomenon and worst prognosis.^{32–34} Whether the described faster onset of antiplatelet action has any impact on bleeding frequency or severity is also unclear, given that – to our knowledge – no relationship between bleeding events and late presentation has been reported so far. The issue of the optimal timing of antiplatelet LD in STEMI patients has been recently investigated in the ATLANTIC trial, where, despite the negative primary endpoint result, the safety of pre-hospital use of ticagrelor was documented.¹⁹ Of note, morphine was the only one among the analyzed patient

characteristics that affected the co-primary endpoints, with a lower occurrence in the pre-hospital group in which morphine had not been used.

With regard to other factors identified in the present study as influencing platelet reactivity 2 h after LD, the role of baseline (prior to any P2Y₁₂ receptor antagonist treatment) platelet reactivity has been previously reported. In patients undergoing elective PCI, pretreatment platelet reactivity predicted platelet reactivity 6 h after treatment with thienopyridines.²² In 26 STEMI patients reported previously and included in this study, baseline platelet reactivity predicted platelet reactivity 2 h after ticagrelor LD, while in a large cohort of patients under ticagrelor maintenance dose, BASE (measured by VerifyNow), predicted platelet reactivity, although with a very low effect size.^{23,24} In line with the aforementioned reports, in an exclusively STEMI cohort described in the present study and treated with any of the 3 oral antiplatelet agents, pre-treatment platelet reactivity was positively associated with platelet reactivity 2 h after LD.

With increasing BMI, a higher platelet reactivity is anticipated from studies involving non-STEMI or STEMI patients beyond the acute phase.^{24–26} In the present analysis involving the early phase of STEMI, a similar positive association between increasing BMI and platelet reactivity 2 h after LD was identified. Morphine use was also positively associated with platelet reactivity 2 h after LD, in accordance with previous studies, most likely by delaying antiplatelet agent absorption.^{29,30} In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 platelet substudy, which established a higher platelet inhibition after 60 mg prasugrel vs. 300 mg clopidogrel at 1–2 h after-PCI (≥ 1 h after LD), only 12 STEMI patients had been included.²⁷ The Platelet Inhibition and Patient Outcomes (PLATO) PLATELET substudy, which also demonstrated a more potent platelet inhibition 2 h after ticagrelor 180 mg vs. clopidogrel 300–600 mg, involved only 10 STEMI patients.²⁸ In both studies, STEMI subgroups were not separately analyzed. In the present much larger analyzed cohort of STEMI patients, novel P2Y₁₂ receptor antagonist was identified as a strong predictor of lower platelet reactivity at 2 h after LD than clopidogrel. In line with this, in a double-blind randomized comparison in STEMI patients, lower platelet reactivity was recently reported following 60 mg prasugrel vs. 600 mg clopidogrel at 2 h after LD.³⁵ The described effect of age on HPR also is in accordance with a previous study on platelet reactivity in patients on ticagrelor maintenance dose.²⁴

Study Limitations

This was a retrospective analysis of the pooled data from different pharmacodynamic studies. Other factors not identified in the current analysis may be implicated, while a larger sample size may provide more precise estimates. Moreover, we cannot rule out residual bias due to overfitting. The present study design by default was not suitable or powered to reach any conclusions on clinical outcome. The lack of pharmacokinetic data does not allow elucidation of the exact mechanisms responsible for the impact of described factors, including symptom-to-antiplatelet LD time, on platelet reactivity. The HPR threshold used was obtained from receiver operating characteristic analysis in post-PCI studies involving stable or acute coronary syndrome patients, and it is not clear whether this threshold has any ability to predict upcoming events exclusively in STEMI patients undergoing primary PCI. Antiplatelet LD was not administered at first medical contact, as

suggested by the recent European Society of Cardiology Revascularization guidelines.³⁶ Such an approach would have posed logistic difficulties for baseline (prior to LD) blood sampling.

Conclusions

In a pooled patient-level analysis of STEMI patients undergoing primary PCI, the onset of pain-to-antiplatelet LD interval was identified as an independent determinant of platelet reactivity 2 h after P2Y₁₂ receptor antagonist loading, suggestive of a faster onset of antiplatelet action. This observation, which requires further confirmation and validation with clinical data, might improve antiplatelet treatment selection, particularly in patients for whom the balance between bleeding risk and ischemic complications is delicate.

Conflict of Interest

This study was supported by the Research Committee of the Patras University Medical School. D.A. has acted as a consultant for AstraZeneca, Boehringer Ingelheim, Bayer, and the Medicines Company, and has received remuneration from AstraZeneca.

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