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Pharmacodynamic Effects of Pre-Hospital Administered Crushed Prasugrel in Patients With ST-Segment Elevation Myocardial Infarction

Rosanne F. Vogel, MD,[a] Ronak Delewi, MD, PhD,[b] Dominick J. Angiolillo, MD, PhD,[c] Jeroen M. Wilschut, MD,[d] Miguel E. Lemmert, MD, PhD,[d,e] Roberto Diletti, MD, PhD,[d] Ria van Vliet,[f] Nancy W.P.L. van der Waarden, MSc,[g] Rutger-Jan Nuis, MD, PhD,[d] Valeria Paradies, MD,[f] Dimitrios Alexopoulos, MD, PhD,[h] Felix Zijlstra, MD, PhD,[d] Gilles Montalescot, MD, PhD,[i] Mitchell W. Krucoff, MD, PhD,[j] Nicolas M. van Mieghem, MD, PhD,[d] Pieter C. Smits, MD, PhD,[f] Georgios J. Vlachojannis, MD, PhD[a,f]

ABSTRACT

OBJECTIVES This study sought to compare the pharmacodynamic effects of pre-hospitally administered $P2Y_{12}$ inhibitor prasugrel in crushed versus integral tablet formulation in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (pPCI).

BACKGROUND Early dual antiplatelet therapy is recommended in STEMI patients. Yet, onset of oral $P2Y_{12}$ inhibitor effect is delayed and varies according to formulation administered.

METHODS The COMPARE CRUSH (Comparison of Pre-hospital Crushed Versus Uncrushed Prasugrel Tablets in Patients With STEMI Undergoing Primary Percutaneous Coronary Interventions) trial randomized patients with suspected STEMI to crushed or integral prasugrel 60-mg loading dose in the ambulance. Pharmacodynamic measurements were performed at 4 time points: before antiplatelet treatment, at the beginning and end of pPCI, and 4 h after study treatment onset. The primary endpoint was high platelet reactivity at the end of pPCI. The secondary endpoint was impact of platelet reactivity status on markers of coronary reperfusion.

RESULTS A total of 441 patients were included. In patients with crushed prasugrel, the occurrence of high platelet reactivity at the end of pPCI was reduced by almost one-half (crushed 34.7% vs. uncrushed 61.6%; odds ratio [OR] = 0.33; 95% confidence interval [CI] = 0.22 to 0.50; $p < 0.01$). Platelet reactivity <150 $P2Y_{12}$ reactivity units at the beginning of coronary angiography correlated with improved Thrombolysis In Myocardial Infarction flow grade 3 in the infarct artery pre-pPCI (OR: 1.78; 95% CI: 1.08 to 2.94; $p = 0.02$) but not ST-segment resolution (OR: 0.80; 95% CI: 0.48 to 1.34; $p = 0.40$).

CONCLUSIONS Oral administration of crushed compared with integral prasugrel significantly improves platelet inhibition during the acute phase in STEMI patients undergoing pPCI. However, a considerable number of patients still exhibit inadequate platelet inhibition at the end of pPCI, suggesting the need for alternative agents to bridge the gap in platelet inhibition. (J Am Coll Cardiol Intv 2021;14:1323–33) © 2021 by the American College of Cardiology Foundation.

From the [a]Department of Cardiology, University Medical Center Utrecht, Utrecht, the Netherlands; [b]Department of Cardiology, Amsterdam University Medical Center, Amsterdam, the Netherlands; [c]Department of Cardiology, University of Florida College of Medicine, Jacksonville, Florida, USA; [d]Department of Cardiology, Erasmus Medical Center, Rotterdam, the Netherlands; [e]Department of Cardiology, Isala Hospital, Zwolle, the Netherlands; [f]Department of Cardiology, Maasstad Hospital, Rotterdam, the Netherlands; [g]Emergency Medical Service, AmbulanceZorg Rotterdam-Rijnmond, Barendrecht, the Netherlands; [h]Department of Cardiology, National and Kapodistrian University of Athens Medical School, Attikon University Hospital, Athens, Greece; [i]Department of Cardiology, ACTION Group, Groupe Hospitalier Pitié-Salpêtrière Hospital (Assistance Publique-Hôpitaux de Paris), Sorbonne University, Paris, France; and the [j]Department of Cardiology, Duke University Medical Center, Durham, North Carolina, USA.
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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

HPR = high platelet reactivity

IQR = interquartile range

IRA = infarct-related artery

MACCE = major adverse cardiac and cerebrovascular event

PCI = percutaneous coronary intervention

PD = pharmacodynamic

pPCI = primary percutaneous coronary intervention

PRU = $P2Y_{12}$ reactivity units

STEMI = ST-segment elevation myocardial infarction

Patients with ST-segment elevation myocardial infarction (STEMI) exhibit an increased risk of thrombotic complications during and after primary percutaneous coronary intervention (pPCI), underscoring the importance of prompt and potent platelet inhibition (1–5). Unfortunately, a substantial number of STEMI patients experience inadequate platelet inhibition for a prolonged period of time after loading dose administration of an oral $P2Y_{12}$ inhibitor even when administered in a pre-hospital or early hospital setting (2,6–13). Such delayed onset of platelet inhibition in STEMI patients can be attributed, at least in part, to impaired gastrointestinal uptake reducing drug bioavailability of orally administered pharmacological agents (14,15). According to smaller pharmacokinetic and pharmacodynamic (PD) studies, a simple, yet effective way to accelerate gastrointestinal uptake in STEMI patients is to administer oral $P2Y_{12}$ inhibitors in a crushed tablet formulation (16–18). However, this strategy has not been tested in a pre-hospital setting and large randomized trials assessing clinical endpoints, including markers of early myocardial reperfusion, have been lacking. The present prespecified analysis of the COMPARE CRUSH (Comparison of Pre-hospital Crushed Versus Uncrushed Prasugrel Tablets in Patients With STEMI Undergoing Primary Percutaneous Coronary Interventions) trial was designed to assess the PD effects achieved by crushed prasugrel administration in a pre-hospital setting.

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METHODS

STUDY DESIGN AND PATIENT POPULATION. The COMPARE CRUSH (NCT03296540) trial was a multicenter, randomized study in patients presenting to the ambulance service with suspected STEMI and were planned to undergo pPCI (n = 727). The study design and enrollment criteria have been previously reported (19,20). In brief, patients with suspected STEMI were randomly allocated to receive either crushed or integral tablets of oral prasugrel 60-mg loading dose administered in the ambulance before transferal to the pPCI center. In the COMPARE CRUSH trial pre-hospital administration of crushed prasugrel tablets did not improve the primary efficacy endpoints represented by angio- and electrocardiographic markers of early reperfusion (i.e., Thrombolysis In Myocardial Infarction flow grade 3 in the infarct-related artery [IRA] pre-pPCI and complete ST-segment resolution 1 h post-pPCI) (20).

This pre-specified PD analysis included all patients with a final diagnosis of STEMI. Patients who: 1) were on maintenance clopidogrel or chronic anticoagulant therapy; 2) had 2 or more missing PD measurements out of the scheduled 4 measurements; 3) received glycoprotein IIb/IIIa inhibitor treatment during pPCI; or 4) had vomited after randomization were excluded from the PD analysis. The primary endpoint was the proportion of patients with high platelet reactivity (HPR), a marker of thrombotic risk, assessed at the end of pPCI. Platelet reactivity was analyzed using the VerifyNow system (Instrumentation Laboratory/Werfen, Barcelona, Spain) and expressed in $P2Y_{12}$ reactivity units (PRU). HPR was defined in line with expert consensus as a PRU ≥208 (21,22).

Other exploratory endpoints were HPR rates at the remaining measuring time points, predictors of HPR at the end of pPCI, predictors of early reperfusion markers (TIMI flow grade 3 in the IRA pre-pPCI and complete ST-segment resolution 1 h post-pPCI), and the incidence of major adverse cardiac and cerebrovascular events (MACCE) at 30 days. To assess adequate platelet inhibition levels as a predictor for early myocardial reperfusion, we chose an arbitrary determined cutoff for platelet reactivity (PRU ≤150). This cutoff was determined as the approximate median of the "optimal platelet reactivity" suggested by Aradi et al. (23). MACCE was defined as occurrence of any death, myocardial infarction, urgent revascularization, stent thrombosis, or stroke. All clinical events were adjudicated by a blinded, independent committee.

The trial was conducted in accordance with the Declaration of Helsinki (64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013), the Medicinal Research Involving Human Subjects Act, and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use-Good Clinical Practice. The local medical ethical committee approved the research protocol and all study procedures. Written informed consent was obtained from all participating patients.

BLOOD SAMPLE COLLECTION AND PD ASSESSMENTS. Blood samples for platelet reactivity assessment were collected in all COMPARE CRUSH trial participants. The 4 time points of sample collection for PD assessments were prespecified: 1) at first medical contact prior to prasugrel loading dose administration (baseline); 2) at the beginning of coronary

angiography directly after sheath placement; 3) at the end of pPCI just before sheath removal; and 4) 4 h after prasugrel loading dose administration.

Blood samples were collected using 2-ml blood containers (Vacutainer 9NC NaC 3.2%, Greiner Bio-One, Kremsmünster, Austria). During all blood sample collections, a dummy container was drawn prior to the formal blood sample to prevent error measurements due to hemolysis or possible interaction with pharmacological agents. The first blood sample was drawn directly after placing a Venflon (Becton Dickinson, Franklin Lakes, New Jersey) in the ambulance and before administration of any pharmacological agents. The blood samples at the beginning and end of coronary angiography or pPCI were drawn from the arterial sheath in the catheterization laboratory. The final blood sample was collected either from the Venflon or by a new venous puncture.

Platelet reactivity analysis was performed by trained personnel from the cardiac care units using the VerifyNow system and was conducted according to the manufacturer's instructions (10,24). All blood samples were analyzed within a time window of 15 min to 4 h after sample collection to reduce the risk of error measurements due to additional platelet activation during transportation, hemolysis, and coagulation. PRU measurements were designated as "missing" in the presence of a hemolyzed sample or when the analysis time window was violated.

STATISTICAL ANALYSIS. Categorical and continuous data were summarized as proportions and mean ± SD or median (interquartile range [IQR]). For comparison of descriptive data, the chi-square test, independent t test and Mann-Whitney *U* test were used, as appropriate. Reported odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using logistic regression. All p values < 0.05 were considered as statistically significant. Logistic regression was used to assess independent predictors of HPR, occurrence of TIMI flow grade 3 in the IRA pre-pPCI, and occurrence of complete ST-segment resolution 1 h after pPCI. Univariate variables with a statistical significance of $p \leq 0.10$ were included into a multivariable analysis. Both univariate and multivariable analyses were adjusted for individual baseline PRU values. The interaction between treatment effect and different subgroups (successful restoration of TIMI flow grade 3 pre-pPCI and complete ST-segment resolution 1 h post-pPCI) was investigated using logistic regression, and p values for interaction were reported. For statistical analysis the IBM SPSS Statistics 25.0.0.2 software package (IBM Corporation, Armonk, New York) was used. Illustrative graphics were composed using GraphPad Prism version 8.3 (GraphPad Software, San Diego, California) and Adobe Illustrator version 25.0.1 (Adobe, San Jose, California).

TABLE 1 Baseline Characteristics

	Crushed Prasugrel (n = 235)	Integral Prasugrel (n = 206)	p Value
Characteristics			
Age, yrs	61 ± 12	63 ± 12	0.10
Female	50 (21.3)	44 (21.4)	0.98
BMI, kg/m^2*	27 ± 4	27 ± 4	0.71
Cardiovascular risk factors			
Hypertension	86 (36.6)	77 (37.4)	0.91
Dyslipidemia†	45 (19.1)	53 (25.7)	0.14
Diabetes mellitus‡	42 (17.9)	24 (11.7)	0.07
Smoking§	113 (48.1)	80 (38.8)	0.02
Family history of CVD‖	88 (37.4)	79 (38.3)	0.81
Medical history			
Previous MI	15 (6.4)	19 (9.2)	0.27
Previous PCI	22 (9.4)	21 (10.2)	0.78
Medication history			
Aspirin	20 (8.5)	27 (13.1)	0.11
Beta-blocker	29 (12.3)	26 (12.6)	0.89
ACE inhibitor	18 (7.7)	18 (8.7)	0.67
ARB	17 (7.2)	17 (8.3)	0.68
Statins	32 (13.6)	39 (18.9)	0.11
Time symptom onset to FMC, min	55 (31–130)	56 (23–138)	0.63
Medication use ambulance			
Aspirin	234 (99.6)	204 (99.0)	0.49
Heparin	222 (94.5)	197 (95.6)	0.29
Procedural details			
pPCI	233 (99.1)	201 (97.6)	0.19
TIMI flow grade 3 IRA pre-pPCI	72 (30.6)	68 (33.0)	0.62
Thrombosuction	39 (16.6)	23 (11.2)	0.12
DES	228 (97.9)	197 (95.6)	0.44

Values are mean ± SD or n (%). Reported p values were calculated using the independent Student's *t*-test and the chi-square test. *Available in 158 versus 143 patients. †Available in 218 versus 198 patients. ‡Available in 218 versus 198 patients. §Available in 152 versus 131 patients. ||Available in 226 versus 197 patients.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; BMI = body mass index; CVD = cardiovascular disease; DES = drug eluting stent; FMC = first medical contact; IRA = infarct-related artery; MI = myocardial infarction; PCI = percutaneous coronary intervention; pPCI = primary percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

RESULTS

DEMOGRAPHIC AND PROCEDURAL DETAILS. The COMPARE CRUSH trial enrolled 633 patients with a final diagnosis of STEMI between November 2017 and March 2020. After excluding patients who were on chronic clopidogrel therapy (n = 13), on oral anticoagulant therapy (n = 6), and patients with ≥2 missing PD measurements or glycoprotein inhibitor use (n = 173), a total of 441 patients (crushed: n = 235; integral: n = 206) were included in the present analysis.

The baseline characteristics are shown in Table 1. The mean age was 62 ± 12 years, and 21% of the

TABLE 2 Pharmacodynamic Characteristics

	Crushed Prasugrel	Integral Prasugrel	OR (95% CI)	p Value
Baseline*				
PR, PRU	200 (174-228)	210 (177-237)	–	0.13
HPR	83 (44.6)	79 (51.6)	0.76 (0.49-1.16)	0.20
Beginning of coronary angiography†				
PR, PRU	189 (133-237)	227 (183-254)	–	<0.01
HPR	82 (40.0)	115 (63.9)	0.38 (0.25-0.57)	<0.01
Time since randomization, min	45 (36-58)	46 (34-57)	–	0.29
End of pPCI‡				
PR, PRU	168 (68-233)	226 (140-267)	–	<0.01
HPR	75 (34.7)	109 (61.6)	0.33 (0.22-0.50)	<0.01
Time since randomization, min	79 (63-104)	79 (65-93)	–	0.23
4 h after prasugrel administration§				
PR, PRU	7 (3-40)	9 (3-87)	–	0.04
HPR	4 (2.2)	11 (7.0)	0.31 (0.10-0.98)	0.05

Values are median (interquartile range) or n (%). Reported p values were calculated using the Mann-Whitney U test and the chi-square test. In case of rare events, Fisher exact test was used to compute the reported p values. HPR was defined as platelet reactivity ≥208 PRU. *Available in 186 versus 153 patients. †Available in 205 versus 180 patients. ‡Available in 216 versus 177 patients. §Available in 179 versus 158 patients.

CI = confidence interval; HPR = high platelet reactivity; OR = odds ratio; pPCI: primary percutaneous coronary intervention; PR = platelet reactivity; PRU = $P2Y_{12}$ reactivity unit.

patients were female. Patients had a mean body mass index (BMI) of 27 ± 4 kg/m^2, and 44% of the patients were active smokers at the time of randomization. Approximately 10% of the patients had a history of myocardial infarction or prior PCI. Medication use prior to enrollment did not differ between groups, with 11% of the patients on chronic aspirin therapy. Most patients (98%) were treated with pPCI, and 96% of the patients received a drug-eluting stent. A manual thrombus aspiration device was used in 14% of cases. Baseline characteristics between this cohort and the overall trial cohort were similar. Baseline and procedural characteristics of the crushed and integral groups were overall comparable, with the exception of a higher rate of active smokers in the crushed group (crushed 48.1% vs. integral 38.8%; p = 0.02).

PD ASSESSMENTS. Table 2 summarizes the results of the PD assessments. Median PRU values at baseline were similar between groups (crushed 200 [IQR: 174 to 228] vs. 210 [IQR: 177 to 237]; p = 0.13). At the beginning of coronary angiography, 45 min (IQR: 35 to 57 min) after prasugrel administration, the median PRU value was significantly lower in the crushed group compared with the integral group (189 [IQR: 133 to 237] vs. 227 [IQR: 183 to 254]; p < 0.01). This difference was even more pronounced at the end of pPCI 79 min (IQR: 63 to 95 min) after loading dose administration (crushed 168 [IQR: 68 to 233] vs. integral 226 [IQR: 140 to 267]; p < 0.01). Four hours after prasugrel loading dose administration, the absolute difference in platelet reactivity had diminished but was still significantly lower in the crushed formulation group (crushed 7 [IQR: 3 to 40] vs. integral 9 [IQR: 3 to 87]; p = 0.04). The individual PRU values at the 4 time points are visualized in Figure 1.

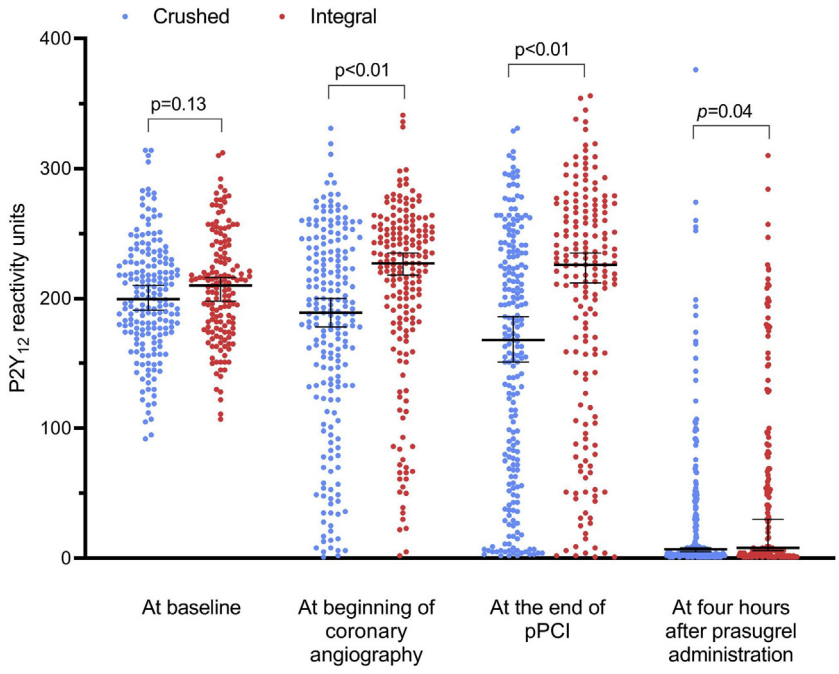
The primary endpoint of HPR at the end of pPCI occurred in 34.7% of the patients in the crushed group compared with 61.6% of the patients in the integral group (OR: 0.33; 95% CI: 0.22 to 0.50; p < 0.01) (Figure 2). HPR rates in the crushed group were already significantly lower compared with the integral group at the beginning of coronary angiography (40.0% vs. 63.9%; OR: 0.38; 95% CI: 0.25 to 0.57; p < 0.01). Four hours after prasugrel administration, HPR rates were low in both groups, with a borderline significant difference between crushed and integral prasugrel treatment (2.2% vs. 7.0%; OR: 0.31; 95% CI: 0.10 to 0.98; p = 0.05).

PREDICTORS OF HPR. Univariate analysis identified BMI per unit kg/m^2 (OR: 1.10; 95% CI: 1.02 to 1.18; p = 0.01), administration of integral prasugrel tablets (OR: 3.00; 95% CI: 1.86 to 4.85; p < 0.01), and opioid administration in the ambulance (OR: 2.98; 95% CI: 1.53 to 5.80; p < 0.01) as predictors of HPR as assessed at the end of pPCI (Table 3). Multivariable analysis identified administration of integral prasugrel tablets (OR: 2.94; 95% CI: 1.32 to 6.56; p < 0.01) as the only independent predictor of HPR assessed at the end of pPCI (Figure 3).

PREDICTORS OF MARKERS OF EARLY REPERFUSION. HPR assessed at the beginning of coronary angiography was identified as a significant predictor for absence of TIMI flow grade 3 in the IRA pre-pPCI (OR: 0.60; 95% CI: 0.38 to 0.94; p = 0.03) (Figure 4A, Supplemental Table 1A). Interestingly, patients with optimal to low platelet reactivity levels (≤150 PRU) at the beginning of coronary angiography had a 1.78 higher chance of having TIMI flow grade 3 in the IRA pre-pPCI (95% CI: 1.08 to 2.94; p = 0.02) compared with patients who had platelet reactivity levels >150 PRU. No significant predictors were identified regarding the occurrence of complete ST-segment resolution 1 h after pPCI (Figure 4B, Supplemental Table 1B). Of note, whether prasugrel was given crushed or in integral formulation did not have any additional impact on the observed correlation of HPR and TIMI flow grade 3 in the IRA pre-pPCI and complete ST-segment resolution at 1 h after pPCI (Supplemental Table 2).

CLINICAL EVENTS. Of the overall 633 STEMI patients, 30 (4.7%) had 1 or more MACCE within the first 30 days after pPCI. Fourteen (2.2%) patients experienced MACCE within the first 48 h, including 2 (0.3%)

FIGURE 1 Scatterplot of Individual $P2Y_{12}$ Reactivity Unit Measurements at Pre-Specified Time Points



Horizontal lines represent the median $P2Y_{12}$ reactivity unit value, and the **whiskers** represent the 25th to 75th percentile range.
pPCI = primary percutaneous coronary intervention.

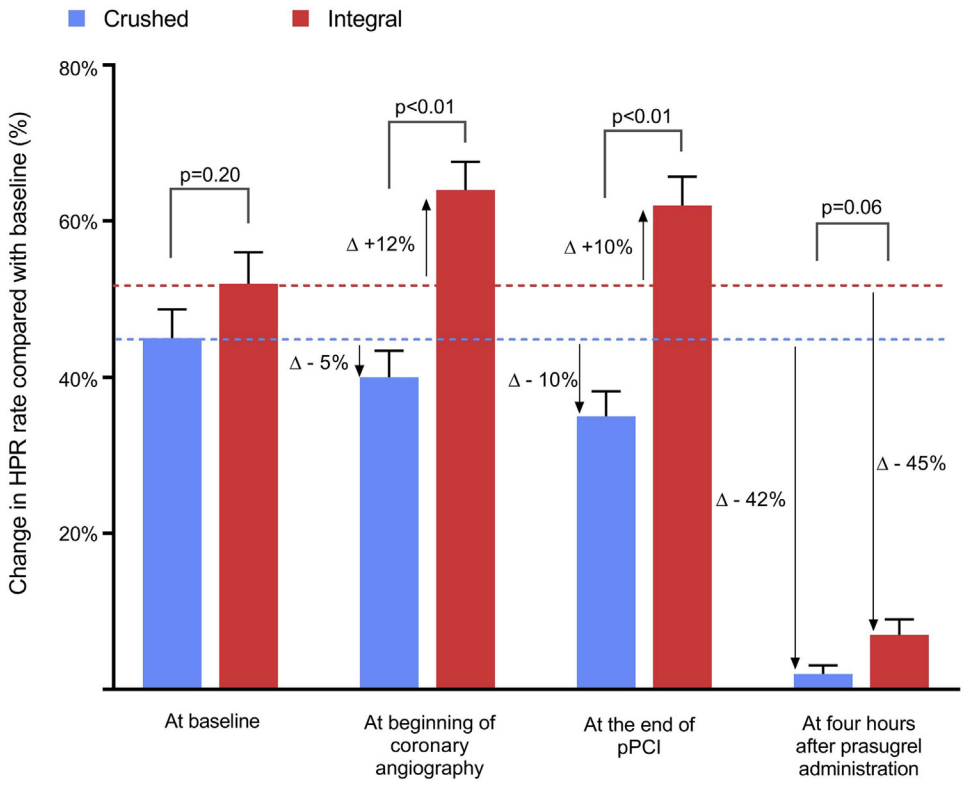
deaths (1 patient due to cardiogenic shock, 1 patient from hemorrhagic cerebrovascular accident). Acute or subacute stent thrombosis occurred in 4 (0.6%) patients. Of the 3 patients suffering of acute in-stent thrombosis, 2 were classified as definite and 1 was classified as probable. Both patients with definite stent thrombosis had HPR. Of note, no correlation was seen between the occurrence of MACCE during the first 48 h and HPR status.

DISCUSSION

The present study is—to the best of our knowledge—the largest PD analysis in STEMI patients assessing the efficacy of pre-hospital $P2Y_{12}$ inhibitor treatment with crushed prasugrel. We found that crushed prasugrel tablets led to faster and stronger platelet inhibition than integral tablets in the acute phase of STEMI (**Central Illustration**). Accordingly, HPR rates were significantly reduced during and after pPCI when using crushed prasugrel tablets. The present analysis from the randomized COMPARE CRUSH trial confirms previous reports showing that loading dose administration with crushed tablets improves the PD profile of oral $P2Y_{12}$ inhibitors in patients presenting with STEMI (16–18).

TIMI flow grade 3 in the IRA pre-pPCI has been previously identified as a strong independent predictor of survival and improved outcomes in STEMI patients (25,26). Even though the current analysis demonstrated that crushing $P2Y_{12}$ inhibitor tablets leads to significantly improved platelet inhibition in the acute phase, it did not significantly improve markers of early coronary reperfusion (20). However, the present analysis indicates that HPR at the beginning of coronary angiography correlates with a significantly lower occurrence of TIMI flow grade 3 in the IRA pre-pPCI. In line with this observation, patients who experienced enhanced platelet inhibition (PRU ≤150) had a 2-fold higher chance of having TIMI flow grade 3 in the IRA pre-pPCI, irrespective of the randomization allocation. Although a strong correlation between occurrence of TIMI flow grade 3 and platelet inhibition is observed, the causation remains to be proven. It is of interest to further investigate whether more potent platelet inhibition in a pretreatment setting can improve TIMI flow grade 3 in the IRA pre-pPCI. Of note, contrary to TIMI flow grade 3, there was no correlation identified between platelet inhibition level and complete ST-segment resolution in this present cohort. The differences observed between the association of on TIMI

FIGURE 2 Change in rates of HPR Compared With Baseline in the Crushed Versus the Integral Group



High platelet reactivity (HPR) was defined as platelet reactivity levels ≥208 $P2Y_{12}$ reactivity units. **Error bars** represent standard errors. pPCI = primary percutaneous coronary intervention.

flow grade 3 pre-PCI in the IRA and complete ST-segment resolution after PCI might be more reflective of the role of platelets on epicardial coronary thrombosis, while the level of platelet inhibition may have a less contributing role on preserving coronary microcirculatory obstruction and consequently ST-segment resolution.

Several clinical studies have investigated the effect of oral $P2Y_{12}$ inhibitors in the acute phase of STEMI on early coronary reperfusion with no clear benefit (6,27). The COMPARE CRUSH trial showed that even when combining pre-hospital administration and a crushed tablet formulation early markers of coronary reperfusion are not improved, and importantly a considerable number of STEMI patients persist with HPR during pPCI. These observations underscore the need for agents with more prompt and potent antiplatelet effects such as cangrelor or glycoprotein inhibitors, which are able overcome the gap in platelet inhibition attributed to oral $P2Y_{12}$ inhibitors (28,29). Whether earlier and more potent platelet inhibition can additionally facilitate optimal myocardial reperfusion in patients undergoing pPCI is still not clear, with only scarce evidence that timely application of glycoprotein inhibitors has the potential to influence early coronary reperfusion and clinical outcomes in STEMI (30,31). Whether targeting the $P2Y_{12}$ receptor with the only available parenteral drug cangrelor can achieve similar effect has yet to be investigated (32,33). New-generation subcutaneous and parenteral agents (i.e., selatogrel and the αIIbβ3 antagonist RUC-4) are currently under advanced clinical development and also represent attractive treatment options to achieve immediate and prompt platelet inhibition in STEMI patients (34–36).

CLINICAL IMPLICATIONS. HPR has been associated with thrombotic complications in patients undergoing pPCI, and a decrease in HPR rates may translate into improved outcomes during and after pPCI. Because administration of crushed

TABLE 3 Univariate Analysis of Predictive Factors of HPR at the End of pPCI

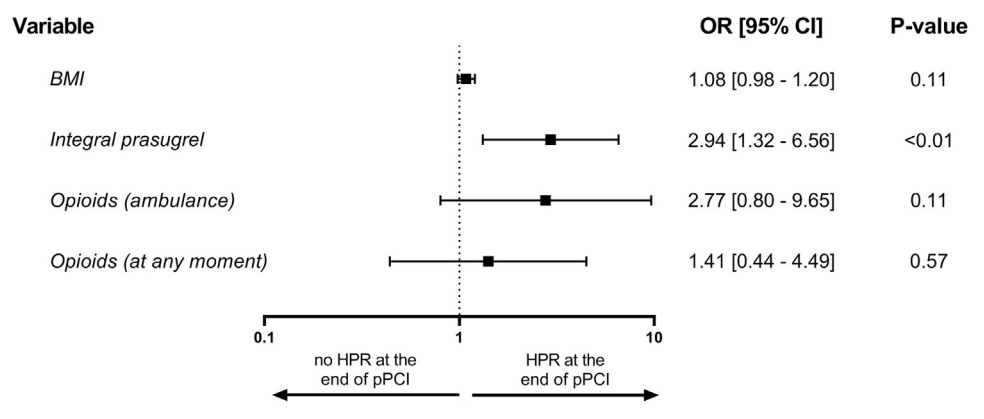
	HPR (n = 184)	No HPR (n = 209)	OR (95% CI)	p Value
Age, yrs*	61 ± 12	62 ± 13	0.92 (0.76–1.11)	0.37
Female	42 (22.8)	36 (17.2)	1.42 (0.86–2.34)	0.17
BMI, kg/m^2	28 ± 4	27 ± 4	1.10 (1.02–1.18)	0.01
Hypertension	73 (39.7)	70 (33.5)	1.32 (0.82–2.12)	0.26
Dyslipidemia	46 (25.0)	42 (20.1)	1.23 (0.71–2.12)	0.46
Diabetes mellitus	27 (14.7)	31 (14.8)	0.97 (0.56–1.70)	0.92
Smoking	78 (42.4)	98 (46.9)	0.87 (0.46–1.64)	0.66
History of				
MI	15 (8.2)	14 (6.7)	1.01 (0.43–2.37)	0.98
PCI	19 (10.3)	16 (7.7)	1.14 (0.52–2.52)	0.74
Maintenance medication				
Aspirin	21 (11.4)	21 (10.0)	1.20 (0.56–2.58)	0.64
Beta-blocker	27 (14.7)	23 (11.0)	1.26 (0.62–2.54)	0.53
ACE inhibitor	15 (8.2)	15 (7.2)	1.10 (0.48–2.52)	0.83
ARB	17 (9.2)	14 (6.7)	1.68 (0.76–3.76)	0.20
Statins	30 (16.3)	30 (14.4)	1.28 (0.69–2.38)	0.44
Calcium-channel blockers	14 (7.6)	20 (9.6)	0.75 (0.34–1.67)	0.48
Integral prasugrel	109 (59.2)	68 (32.5)	3.00 (1.86–4.85)	<0.01
Opioids administration				
In ambulance	48 (26.1)	27 (12.9)	2.98 (1.53–5.80)	<0.01
In hospital	30 (16.3)	32 (15.3)	1.25 (0.65–2.41)	0.51
At any moment	72 (39.1)	54 (25.8)	2.53 (1.45–4.41)	<0.01

Values are mean ± SD or n (%), unless otherwise indicated. HPR was defined as PRU >208. Reported ORs and p values were calculated using logistic regression. *OR per 10-U increase.

Abbreviations as in Tables 1 and 2.

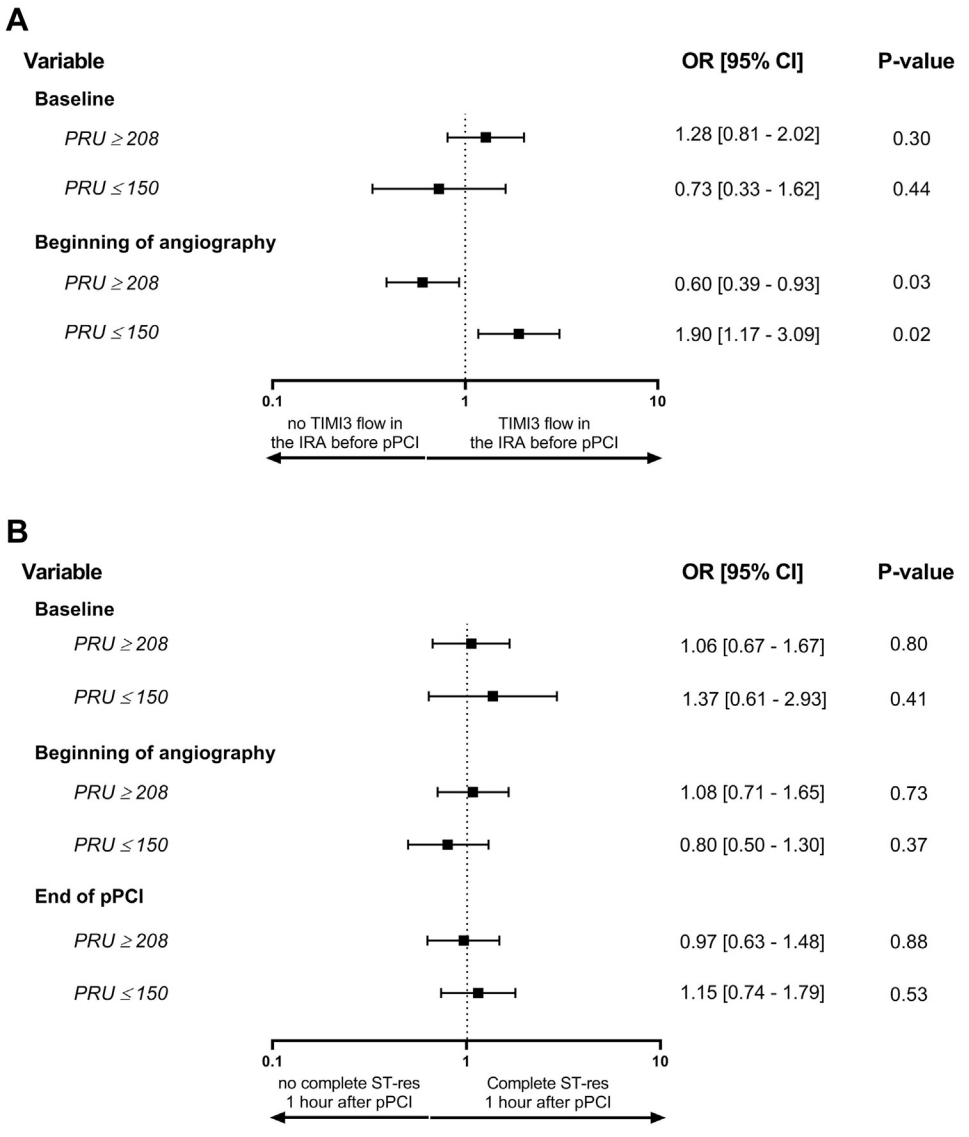
prasugrel tablets appears to be a safe (i.e., no increase in bleeding complications or other adverse events) and easy approach to accelerate the absorption of oral $P2Y_{12}$ inhibitors, it is a reasonable strategy to consider in STEMI patients. However, crushing tablets will not completely overcome the gap in platelet inhibition, which underscores the need to further investigate the benefits associated with earlier and more potent acting platelet inhibition. This latter note becomes even more important in view of the observed correlation of improved epicardial reperfusion in patients with enhanced platelet inhibition early in the acute phase of STEMI.

FIGURE 3 Predictors of HPR at the End of pPCI



Multivariable logistic regression assessing independent predictors of HPR. BMI = body mass index; CI = confidence interval; OR = odds ratio; other abbreviations as in Figure 2.

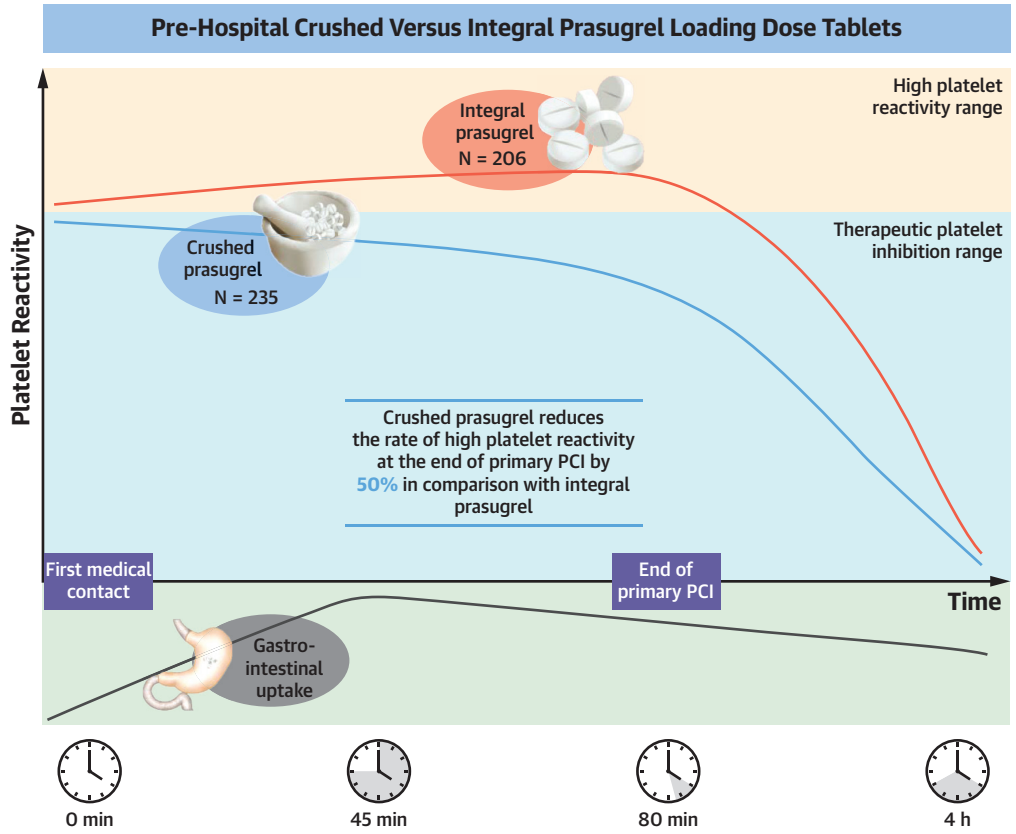
FIGURE 4 Platelet Reactivity Levels as Predictor of Early Coronary Myocardial Reperfusion



Univariate analysis of platelet reactivity status as predictor of **(A)** Thrombolysis In Myocardial Infarction flow grade 3 (TIMI3) in the infarct artery pre-pPCI and **(B)** complete ST-segment resolution 1 h post-pPCI. IRA = infarct-related artery; PRU = $P2Y_{12}$ reactivity units; ST-res = ST-segment resolution; other abbreviations as in Figures 2 and 3.

STUDY LIMITATIONS. The current study was not powered for clinical outcomes, nor was it powered to assess any correlations between platelet reactivity and clinical outcomes. Moreover, the short time between first medical contact and start of pPCI observed in our study could have limited the potential benefits of crushing prasugrel on HPR rates at the time of pPCI and the overall efficacy outcomes. Platelet reactivity measurements were performed using a single point-of-care platelet function test. Although our results indicate that opioid administration is an independent predictor for HPR, patients were not randomized for opioid administration, and thus we cannot exclude the possibility of a selection bias on our findings. Further, in order to assess a correlation between stronger platelet inhibition and markers of early myocardial reperfusion, we used an arbitrary selected cutoff of 150 PRU. Finally, our results cannot be

CENTRAL ILLUSTRATION **Pharmacodynamic Effects**



Vogel, R.F. et al. J Am Coll Cardiol Intv. 2021;14(12):1323–33.

Pre-hospital administration of prasugrel loading dose accelerates the onset of pharmacodynamic effects compared with integral tablets. Crushed prasugrel reduces the rate of high platelet reactivity (defined as >208 $P2Y_{12}$ reactivity U) at the end of primary percutaneous coronary intervention (PCI) by almost one-half compared with integral prasugrel.

extrapolated to patients with cardiogenic shock or patients who were unable to take in drugs orally (e.g., intubated patients requiring nasogastric tube), as these patients were excluded from our trial.

CONCLUSIONS

Pre-hospital administration of crushed tablets of prasugrel loading dose compared with integral tablets leads to more prompt and potent platelet inhibition in the acute phase of STEMI patients. However, despite faster platelet inhibition, approximately one-third of the patients still experience subtherapeutic platelet inhibition levels at the end of pPCI. Interestingly, low platelet activity at the beginning of coronary angiography is correlated with improved early epicardial reperfusion pre-pPCI. Future studies investigating antiplatelet therapies, which are able to achieve more prompt and potent platelet inhibitory effects, are needed to delineate the benefits of early platelet inhibition patients presenting with STEMI.

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ADDRESS FOR CORRESPONDENCE: Dr. Georgios J. Vlachojannis, Division Heart and Lungs, University Medical Center Utrecht, PO Box 85500-Internal postal address E 04.5.05, 3508 GA Utrecht, the Netherlands. E-mail: g.vlachojannis@umcutrecht.nl. Twitter: @GVlachojannis.

PERSPECTIVES

WHAT IS KNOWN? In patients with STEMI, the presence of inadequate platelet inhibition is associated with an increased risk of thrombotic complications.

WHAT IS NEW? Pre-hospital administration of prasugrel in a crushed formulation reduces the rate of HPR, a marker of thrombotic risk, compared with integral tablets by almost 50%. Nevertheless, a considerable number of STEMI patients experiences persisting high levels of platelet reactivity at the end of primary PCI.

WHAT IS NEXT? Treatment with oral $P2Y_{12}$ inhibitors seems unlikely to be able to bridge the gap in platelet inhibition in patients with STEMI planned to undergo pPCI, suggesting the need for alternative agents that can achieve faster and more potent antiplatelet effect.

REFERENCES

1. Aitmokhtar O, Paganelli F, Benamara S, et al. Impact of platelet inhibition level on subsequent no-reflow in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Arch Cardiovasc Dis 2017;110:626–33.

2. Beigel R, Fefer P, Rosenberg N, et al. Antiplatelet effect of thienopyridine (clopidogrel or prasugrel) pretreatment in patients undergoing primary percutaneous intervention for ST elevation myocardial infarction. Am J Cardiol 2013;112:1551–6.

3. Bonello L, Pansieri M, Mancini J, et al. High ontreatment platelet reactivity after prasugrel loading dose and cardiovascular events after percutaneous coronary intervention in acute coronary syndromes. J Am Coll Cardiol 2011;58:467–73.

4. Capodanno D, Alfonso F, Levine GN, Valgimigli M, Angiolillo DJ. ACC/AHA versus ESC guidelines on dual antiplatelet therapy: JACC Guideline Comparison. J Am Coll Cardiol 2018;72:2915–31.

5. Franchi F, Rollini F, Angiolillo DJ. Antithrombotic therapy for patients with STEMI undergoing primary PCI. Nat Rev Cardiol 2017;14:361–79.

6. Montalescot G, van 't Hof AW, Lapostolle F, et al. Prehospital ticagrelor in ST-segment elevation myocardial infarction. N Engl J Med 2014;371:1016–27.

7. Alexopoulos D, Gkizas V, Patsilinakos S, et al. Double versus standard loading dose of ticagrelor: onset of antiplatelet action in patients with STEMI undergoing primary PCI. J Am Coll Cardiol 2013;62:940–1.

8. Alexopoulos D, Makris G, Xanthopoulou I, et al. Onset of antiplatelet action with high (100 mg) versus standard (60 mg) loading dose of prasugrel in patients with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention: pharmacodynamic study. Circ Cardiovasc Interv 2014;7:233–9.

9. Tavenier AH, Hermanides RS, Ottervanger JP, et al. Impact of opioids on P2Y12-receptor inhibition in patients with ST-elevation myocardial infarction who are pre-treated with crushed ticagrelor: Opioids aNd crushed Ticagrelor In Myocardial infarction Evaluation (ON-TIME 3) trial. Eur Heart J Cardiovasc Pharmacother 2020 Jul 30 [E-pub ahead of print].

10. Franchi F, Rollini F, Cho JR, et al. Impact of escalating loading dose regimens of ticagrelor in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: results of a prospective randomized pharmacokinetic and pharmacodynamic investigation. J Am Coll Cardiol Intv 2015;8:1457–67.

11. Parodi G, Valenti R, Bellandi B, et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. J Am Coll Cardiol 2013;61:1601–6.

12. Alexopoulos D, Xanthopoulou I, Gkizas V, et al. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation myocardial infarction. Circ Cardiovasc Interv 2012;5:797–804.

13. Michelson AD, Frelinger AL 3rd, Braunwald E, et al. Pharmacodynamic assessment of platelet inhibition by prasugrel vs. clopidogrel in the TRITON-TIMI 38 trial. Eur Heart J 2009;30:1753–63.

14. Heestermans AA, van Werkum JW, Taubert D, et al. Impaired bioavailability of clopidogrel in patients with a ST-segment elevation myocardial infarction. Thromb Res 2008;122:776–81.

15. Ertl G, Gaudron P, Eilles C, Schorb W, Kochsiek K. Compensatory mechanisms for cardiac dysfunction in myocardial infarction. Basic Res Cardiol 1991;86 Suppl 3:159–65.

16. Parodi G, Xanthopoulou I, Bellandi B, et al. Ticagrelor crushed tablets administration in STEMI patients: the MOJITO study. J Am Coll Cardiol 2015;65:511–2.

17. Alexopoulos D, Barampoutis N, Gkizas V, et al. Crushed versus integral tablets of ticagrelor in ST-segment elevation myocardial infarction patients: a randomized pharmacokinetic/pharmacodynamic study. Clin Pharmacokinet 2016;55:359–67.

18. Rollini F, Franchi F, Hu J, et al. Crushed prasugrel tablets in patients with STEMI undergoing primary percutaneous coronary intervention: the CRUSH study. J Am Coll Cardiol 2016;67:1994–2004.

19. Vlachojannis GJ, Vogel RF, Wilschut JM, et al. COMPARison of pre-hospital CRUSHed vs. uncrushed Prasugrel tablets in patients with STEMI undergoing primary percutaneous coronary interventions: rationale and design of the COMPARE CRUSH trial. Am Heart J 2020;224:10–6.

20. Vlachojannis GJ, Wilschut JM, Vogel RF, et al. Effect of prehospital crushed prasugrel tablets in patients with ST-segment-elevation myocardial infarction planned for primary percutaneous coronary intervention: the randomized COMPARE CRUSH trial. Circulation 2020;142:2316–28.

21. Campo G, Fileti L, de Cesare N, et al. Long-term clinical outcome based on aspirin and clopidogrel responsiveness status after elective percutaneous coronary intervention: a 3T/2R (tailoring treatment with tirofiban in patients showing resistance to aspirin and/or resistance to clopidogrel) trial substudy. J Am Coll Cardiol 2010;56:1447–55.

22. Sibbing D, Aradi D, Alexopoulos D, et al. Updated expert consensus statement on platelet function and genetic testing for guiding P2Y(12) receptor inhibitor treatment in percutaneous coronary intervention. J Am Coll Cardiol Intv 2019;12:1521–37.

23. Aradi D, Kirtane A, Bonello L, et al. Bleeding and stent thrombosis on P2Y12-inhibitors: collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention. Eur Heart J 2015;36:1762–71.

24. Angiolillo DJ, Jakubowski JA, Ferreiro JL, et al. Impaired responsiveness to the platelet P2Y12 receptor antagonist clopidogrel in patients with type 2 diabetes and coronary artery disease. J Am Coll Cardiol 2014;64:1005–14.

25. Simes RJ, Topol EJ, Holmes DR Jr, et al. Link between the angiographic substudy and mortality outcomes in a large randomized trial of myocardial reperfusion. Importance of early and complete infarct artery reperfusion. GUSTO-I Investigators. Circulation 1995;91:1923–8.

26. Anderson JL, Karagounis LA, Califf RM. Meta-analysis of 5 reported studies on the relation of early coronary patency grades with mortality and outcomes after acute myocardial infarction. Am J Cardiol 1996;78:1–8.

27. Redfors B, Dworeck C, Haraldsson I, et al. Pretreatment with P2Y12 receptor antagonists in ST-elevation myocardial infarction: a report from the Swedish Coronary Angiography and Angioplasty Registry. Eur Heart J 2019;40:1202–10.

28. Franchi F, Rollini F, Rivas A, et al. Platelet inhibition with cangrelor and crushed ticagrelor in patients with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention. Circulation 2019;139:1661–70.

29. Gargiulo G, Esposito G, Avvedimento M, et al. Cangrelor, tirofiban, and chewed or standard prasugrel regimens in patients with ST-segment-elevation myocardial infarction: primary results of the FABOLUS-FASTER trial. Circulation 2020;142:441–54.

30. Montalescot G, Barragan P, Wittenberg O, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. N Engl J Med 2001;344:1895–903.

31. Van't Hof AW, Ten Berg J, Heestermans T, et al. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. Lancet 2008;372:537–46.

32. Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. N Engl J Med 2013;368:1303–13.

33. Angiolillo DJ, Schneider DJ, Bhatt DL, et al. Pharmacodynamic effects of cangrelor and clopidogrel: the platelet function substudy from the cangrelor versus standard therapy to achieve optimal management of platelet inhibition (CHAMPION) trials. J Thromb Thrombolysis 2012;34:44–55.

34. Li J, Vootukuri S, Shang Y, et al. RUC-4: a novel allbβ3 antagonist for prehospital therapy of myocardial infarction. Arterioscler Thromb Vasc Biol 2014;34:2321–9.

35. Sinnaeve P, Fahrni G, Schelfaut D, et al. Subcutaneous selatogrel inhibits platelet aggregation in patients with acute myocardial infarction. J Am Coll Cardiol 2020;75:2588–97.

36. Hulot JS, Montalescot G. Do we need a new P2Y12 receptor antagonist? Eur Heart J 2020;41:3141–3.

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APPENDIX For supplemental tables, please see the online version of this paper.