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Crushed Prasugrel Tablets in Patients With STEMI Undergoing Primary Percutaneous Coronary Intervention

The CRUSH Study

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ABSTRACT

BACKGROUND Platelet inhibitory effects induced by oral $P2Y_{12}$ receptor antagonists are delayed in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI), which may be attributed to impaired absorption affecting drug pharmacokinetics (PK) and pharmacodynamics (PD). Crushing tablets has been suggested to lead to more favorable PK/PD profiles. To date, no studies have investigated the PK/PD effects of crushing prasugrel.

OBJECTIVES This study sought to determine whether crushing prasugrel is associated with more favorable drug bioavailability and platelet inhibitory effects compared with whole tablets in STEMI patients undergoing PPCI.

METHODS Our prospective, randomized, open-label study assessed STEMI patients undergoing PPCI (n = 52) who were treated with a prasugrel 60-mg loading dose (LD) either as whole or crushed tablets. PK/PD analyses were performed at 7 time points. PD effects were measured as $P2Y_{12}$ reaction units and platelet reactivity index, and PK by plasma levels of prasugrel's active metabolite.

RESULTS Compared with whole tablets, crushed prasugrel led to reduced $P2Y_{12}$ reaction units by 30 min post-LD, which persisted at 1, 2 (164 vs. 95; least square mean difference = 68; 95% confidence interval: 10 to 126; primary endpoint), and 4 h post-LD. Significant differences were no longer present at 6 h post-LD. Parallel findings were shown with platelet reactivity index. Accordingly, high on-treatment platelet reactivity rates were reduced with crushed prasugrel. PK analyses showed a >3-fold faster absorption with crushed compared with whole prasugrel.

CONCLUSIONS In STEMI patients undergoing PPCI, crushed prasugrel leads to faster drug absorption, and consequently, more prompt and potent antiplatelet effects compared with whole tablet ingestion. (Pharmacological Effects of Crushing Prasugrel in STEMI Patients; NCT02212028) (J Am Coll Cardiol 2016;67:1994–2004)

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Prasugrel is an orally administered third-generation thienopyridine that irreversibly inhibits the platelet $P2Y_{12}$ receptor (1). Compared with clopidogrel, prasugrel has more prompt, potent, and predictable antiplatelet effects, which in turn leads to a greater reduction in atherothrombotic events in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) (2,3). Importantly, the benefits of prasugrel have shown to be consistent across several subgroups, including among patients with ST-segment elevation myocardial infarction (STEMI) (4,5). Over the past years, there has been a considerable increase in the use of prasugrel, particularly in STEMI patients undergoing primary percutaneous coronary intervention (PPCI) (6). Despite these therapeutic advancements, studies have demonstrated delayed antiplatelet effects of oral $P2Y_{12}$ inhibitors, including prasugrel, in STEMI patients undergoing PPCI, who demonstrate persistently elevated rates of high on-treatment platelet reactivity (HPR) for several hours after drug administration (7–10). Given the higher risk of periprocedural thrombotic events in STEMI patients undergoing PPCI, these observations underscore the need to achieve effective platelet inhibition more promptly (11).

SEE PAGE 2005

The delayed onset and attenuated antiplatelet effects, which have been consistently observed in STEMI patients treated with oral $P2Y_{12}$ receptor inhibitors, have been attributed to impaired drug absorption resulting in reduced drug bioavailability (10,12). Therefore, strategies to increase bioavailability of orally administered $P2Y_{12}$ receptor inhibitors have been advocated for STEMI patients, such as increasing the dosing regimen or crushing tablets (10,13–17). To date, there are no studies that have specifically assessed the pharmacokinetic (PK) and pharmacodynamic (PD) consequences of crushing prasugrel tablets. Therefore, the aim of this PK/PD study was to investigate whether crushing prasugrel is associated with more favorable drug bioavailability and platelet inhibitory effects compared with whole tablets in STEMI patients undergoing PPCI.

METHODS

STUDY DESIGN AND POPULATION. This was a prospective, randomized, open-label, parallel-design study investigating the PK and PD of a 60-mg loading dose (LD) of prasugrel administered as whole or crushed tablets in STEMI patients undergoing PPCI (NCT02212028). All consecutive patients presenting with STEMI at the University of Florida Health-Jacksonville were screened. Patients needed to meet all of the following inclusion criteria to be considered eligible for the study: 1) between 18 and 75 years of age; 2) present with STEMI and treated with PPCI; and 3) able to provide written informed consent. STEMI was defined as chest pain of <12 h duration and ST-segment elevation >0.1 mV in at least 2 contiguous leads. Patients were excluded if any of the following exclusion criteria were present: 1) age >75 years; 2) body weight <60 kg; 3) on treatment with any $P2Y_{12}$ receptor inhibitor in the previous 7 days; 4) known allergy to aspirin or prasugrel; 5) previous stroke or transient ischemic attack; 6) known blood dyscrasia or bleeding diathesis; 7) on treatment with an oral anticoagulant; 8) treatment with glycoprotein IIb/IIIa inhibitors (due to their interference with the VerifyNow P2Y12 assay [VN-P2Y12] [Accriva Diagnostics, San Diego, California]); 9) use of fibrinolytic agents <24 h; 10) active bleeding; 11) known platelet count $<80 \times 10^6$/ml; 12) known hemoglobin <10 g/dl; 13) hemodialysis or known creatinine clearance <30 ml/min; 14) known severe hepatic dysfunction; 15) patients requiring endotracheal intubation; and 16) pregnant or lactating females. The study complied with the Declaration of Helsinki and was approved by the Western Institutional Review Board, and all patients gave their written informed consent.

RANDOMIZATION AND STUDY PROCEDURES. Using a computer-based randomization system, patients were randomly assigned (1:1) in an open-label manner to receive a 60-mg LD of prasugrel (6 10-mg tablets) orally administered as either whole or crushed tablets. Investigators and patients were aware of treatment assignment. However, laboratory personnel performing PK and PD assessments were blinded.

Patients were treated as per local standard of care, which included 325 mg aspirin and 4,000 IU of unfractionated heparin at time of patient presentation. Access site, choice of anticoagulant, and procedural technique were at the discretion of the physician. As per institutional standards, the LD of prasugrel was administered immediately after the procedure, defined as removal of the guiding catheter from the body. This is in line with prior investigations, as it enables a more homogenous patient cohort with PK/PD profiles that would not be affected by procedural variables (i.e., length of the procedure) (10). Whole prasugrel tablets were swallowed with 50 ml of H2O. Crushed prasugrel was

ABBREVIATIONS AND ACRONYMS

HPR = high on-treatment platelet reactivity

PD = pharmacodynamic

PK = pharmacokinetic

PPCI = primary percutaneous coronary intervention

PRI = platelet reactivity index

PRU = $P2Y_{12}$ reaction units

STEMI = ST-segment elevation myocardial infarction

VASP = whole blood vasodilator-stimulated phosphoprotein

VN-P2Y12 = VerifyNow P2Y12 assay

prepared using a commercially available syringe crusher (Welcon, Fort Worth, Texas), which allows for preparation of crushed prasugrel in an average time of 2 to 3 min. After 5 rotations of the crushing mechanism, 25 ml of H2O was aspirated into the syringe and mixed by shaking the crushed pill contents for 30 sec. This suspension was then dispensed into a 165 ml dosing cup. The syringe crusher was rinsed using an additional 25 ml of H2O and added to the dosing cup for a total of 50 ml suspension, which was then administered orally. A maintenance dose regimen of prasugrel 10 mg once daily was started 24 h after the LD was administered. Patients were advised to continue this maintenance dose regimen for at least 12 months in addition to aspirin 81 mg daily for life.

Blood samples for PK and PD analysis were collected at a total of 7 time points: baseline (after arterial sheet insertion), 30 min, and 1, 2, 4, 6, and 24 h after administration of the randomized treatment. The 24-h blood sample was collected prior to the administration of the first 10-mg maintenance dose of prasugrel.

PK AND PD ASSESSMENTS. PK assessments included determination of plasma concentration of prasugrel's active metabolite (P-AM), as previously described (18). Time for the maximum plasma concentration (T_{max}), maximum observed plasma concentration (C_{max}), and the area under the plasma concentration versus time curve from time 0 to the last measurable concentration (AUC_{0-t}) were calculated. Moreover, to explore early exposure to P-AM, AUC from time 0 to 2 h (AUC_{0-2}) was also calculated. PD assessments included VN-P2Y12 and whole blood vasodilator-stimulated phosphoprotein (VASP), which were performed according to manufacturer's instructions, as previously described (10,19). In brief, the VN-P2Y12 assay (Accriva, San Diego, California) measures platelet-induced aggregation as an increase in light transmittance and reports results in $P2Y_{12}$ reaction units (PRU). VASP phosphorylation was measured by quantitative flow cytometry using commercially available labeled monoclonal antibodies according to standard protocols (Biocytex Inc., Marseille, France) and was used to determine the platelet reactivity index (PRI). HPR was defined as a PRU >208 or a PRI >50%, according to consensus definition (20). A complete description of PK and PD methodology is provided in the Online Appendix.

STUDY ENDPOINTS. The primary endpoint of the study was the comparison of PRU determined by VN-P2Y12 between whole and crushed prasugrel at 2 h post-LD administration. The primary endpoint was chosen at 2 h in line with previous investigations with prasugrel in PPCI and because it is the time point by which optimal platelet inhibition should be achieved in non-ST-segment elevation ACS patients following a 60-mg LD administration (9,21). Other endpoints included between-group comparisons of: 1) platelet reactivity, at each time point as well as over time; 2) rates of HPR; and 3) PK parameters. Given the described association between use of morphine and HPR in patients treated with PPCI (10,22), exploratory analyses were conducted within each group to evaluate any differences in PD and PK among patients receiving morphine. In-hospital adverse events, including ischemic and bleeding complications, defined according to previously reported criteria (3), were recorded.

STATISTICAL ANALYSIS. Assuming a 60 PRU difference at 2 h post-LD between the 2 arms after prasugrel administration with a common SD of 60 PRU and 15% rate of invalid results due to hemolysis or technical problems, we estimated that 52 patients needed to be randomized to obtain a 90% power and 2-sided alpha of 0.05. Because there are no published data on crushed prasugrel, the sample size of our study was arbitrarily determined on the basis of data of whole prasugrel in STEMI and in non-ST-segment elevation ACS settings (8,9,23).

The primary population was defined as patients who received the randomized treatment and had a valid primary endpoint value (PRU at 2 h). The primary population was considered for analysis of PK and PD endpoints. The treated population comprised all patients who received any dose of study medication and was considered for analysis of safety and adverse events. Patients vomiting within 30 min after study drug administration were excluded from the primary population.

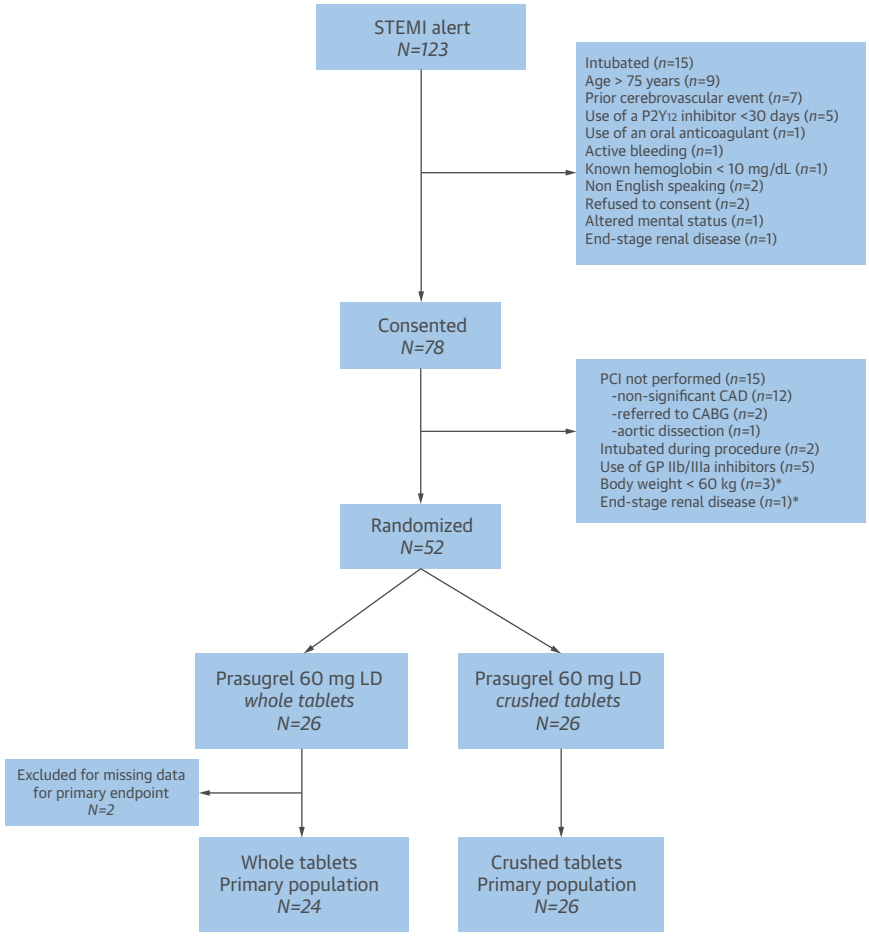
Conformity to the normal distribution was evaluated for continuous variables with the Kolmogorov-Smirnov test. For baseline characteristics, continuous variables are expressed as mean ± SD or median (interquartile range), and categorical variables are expressed as frequencies and percentages. The chi-square test or Fisher exact test was used to compare categorical variables between groups, whereas the Student *t* test or Mann-Whitney *U* test was used to compare continuous variables. Univariate analysis of variance (ANOVA) and analysis of covariance (ANCOVA) method with a general linear model, adjusted for baseline characteristics significantly different between groups, were used to evaluate the primary endpoint and all between-group comparisons. Mixed between within subjects, ANOVA and

ANCOVA with polynomial contrast, also adjusted for baseline characteristics significantly different between groups, were conducted with a general linear model to evaluate the overall difference between groups across time points. A repeated measures ANOVA model was used to evaluate intragroup comparisons, and the Bonferroni approach was used to correct for multiple comparisons. A sensitivity analysis was performed to evaluate differences in platelet reactivity between groups in the treated population. PK parameters were compared by the Mann-Whitney *U* test. A 2-tailed p value of <0.05 was considered to indicate a statistically significant difference for all the analyses performed. Results are reported as least-square means and 95% confidence interval (CI) for the previously detailed analyses. For PK parameters, T_{max} is reported as median (range) and C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}2}$ are reported as geometric mean (range). Statistical analysis was performed using SPSS version 22.0 software (SPSS Inc., Chicago, Illinois).

RESULTS

Between October 15, 2014, and August 12, 2015, there were a total of 123 patients presenting with STEMI at our institution. Of these, 45 patients did not meet study entry criteria, whereas 78 provided their written informed consent to participate in the study; of these, 52 were randomized (whole tablets, n = 26; crushed tablets, n = 26), representing the treated population. A total of 50 patients (whole tablets, n = 24; crushed tablets, n = 26) met criteria to be included in the primary population. No patients were excluded due to vomiting. There were no challenges with timely

FIGURE 1 Trial Profile



*Unknown at time of patient presentation. CABG = coronary artery by-pass graft; CAD = coronary artery disease; GP = glycoprotein; LD = loading dose; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

TABLE 1 Baseline Characteristics of the Primary Population

	Prasugrel 60-mg LD Crushed Tablets (n = 26)	Prasugrel 60-mg LD Whole Tablets (n = 24)	p Value
Age, yrs	57 ± 9	58 ± 10	0.800
Male	19 (73.1)	18 (75.0)	>0.999
Race			0.501
Caucasian	18 (69.2)	18 (75.0)	
African American	7 (26.9)	6 (25.0)	
Hispanic	1 (3.8)	0 (0.0)	
BMI, kg/m^2	30 ± 6	29.3 ± 8	0.764
DM	5 (19.2)	5 (20.8)	0.887
Smoking	14 (53.8)	10 (41.7)	0.389
Hypertension	18 (69.2)	11 (45.8)	0.094
Hyperlipidemia	10 (38.5)	9 (37.5)	0.994
PAD	0 (0.0)	1 (4.2)	0.293
Prior MI	1 (3.8)	4 (16.7)	0.131
Prior CABG	2 (7.7)	1 (4.2)	0.600
Creatinine, mg/dl	0.9 ± 0.2	0.9 ± 0.2	0.827
Platelet count, × 10^3/ml	246.8 ± 63	257.5 ± 63	0.567
Hematocrit, %	41.6 ± 5.3	41.4 ± 4.3	0.914
Hemoglobin, g/dl	14.2 ± 2	13.9 ± 1.7	0.600
Medications*			
Aspirin	26 (100.0)	24 (100.0)	>0.999
β-blockers	22 (84.6)	17 (73.9)	0.354
ACE-I	18 (69.2)	14 (58.3)	0.423
Nitrates	19 (73.1)	14 (58.3)	0.272
PPI	12 (46.2)	7 (29.2)	0.216
Insulin	5 (19.2)	5 (20.8)	0.887
Statins	24 (92.3)	23 (95.8)	0.600
CCB	3 (11.5)	3 (12.5)	0.917
Ondansetron	11 (42.3)	8 (33.3)	0.514
Morphine	22 (84.6)	16 (66.7)	0.138
Procedural anticoagulant			0.289
UFH only	3 (11.5)	7 (29.2)	
Bivalirudin	23 (88.5)	17 (70.8)	
Location of MI			<0.001
Anterior	11 (42.3)	2 (8.3)	
Inferior	10 (38.5)	22 (91.7)	
Lateral	5 (19.2)	0 (0.0)	
Radial access	9 (34.6)	13 (54.2)	0.164
TIMI flow pre-PCI			0.800
0	10 (38.5)	9 (37.5)	
1	10 (38.5)	7 (29.2)	
2	3 (11.5)	5 (20.8)	
3	3 (11.5)	3 (12.5)	
TIMI flow post-PCI			>0.999
3	26 (100.0)	24 (100.0)	

Values are mean ± SD or n (%). *Medications include home therapy and those administered during the index hospitalization.

ACE-I = angiotensin converting enzyme inhibitor; BMI = body mass index; CABG = coronary artery bypass graft; CCB = calcium-channel blockers; DM = diabetes mellitus; LD = loading dose; MI = myocardial infarction; PAD = peripheral artery disease; PPI = proton pump inhibitors; TIMI = Thrombolysis In Myocardial Infarction; UFH = unfractionated heparin.

preparation and administration of crushed prasugrel, which was well tolerated with the exception of patients reporting a bitter residual taste in 80% of cases. Patient disposition is summarized in Figure 1. Baseline characteristics are summarized in Table 1 and were well balanced between groups, with the exception of myocardial infarction (MI) location. In particular, more patients with inferior MI were randomized to whole tablets, whereas more patients with anterior MI were randomized to crushed tablets ($p < 0.001$). Although the use of morphine was numerically higher in the crushed group, this did not reach statistical significance.

Figure 2A illustrates the PD findings according to VN-P2Y12. Baseline PRU values were similar among patients randomized to crushed versus whole prasugrel tablets ($p > 0.1$). Although PRU levels significantly decreased over time in both groups ($p < 0.001$ for both), these declined more rapidly in patients treated with crushed prasugrel, who had platelet reactivity already reduced by 30 min. A significant reduction in PRU with crushed compared with whole tablets of prasugrel was observed at 2 h after LD administration (164 vs. 95; least-square means difference = 68; 95% CI: 10 to 126; $p = 0.022$; primary endpoint). Compared with whole prasugrel tablets, the crushed tablets led to reduced platelet reactivity, which was already evident at 30 min ($p = 0.053$) and 1 h ($p < 0.001$) after drug administration and persisted for up to 4 h ($p = 0.023$). Platelet reactivity continued to drop in both treatment arms, with PRU levels nonsignificantly lower with crushed prasugrel at 6 h ($p = 0.102$). At 24 h, platelet reactivity continued to decline in the whole tablet group but not in crushed tablet group, resulting in similar PRU levels at this time point ($p = 0.178$). During the overall 24-h study time course, PRU levels were significantly lower with crushed compared with whole prasugrel tablets (ANOVA $p = 0.008$). Crushed prasugrel was still significantly associated with reduced PRU levels at 2 h ($p = 0.022$) and during the overall 24-h study time course (ANCOVA $p = 0.048$) after adjusting for MI localization. Parallel findings were observed with VASP-PRI, with significant differences between groups already at 30 min, which persisted at 2 h ($p = 0.005$; adjusted $p = 0.014$) and during the overall study time course (ANOVA $p = 0.001$; adjusted $p = 0.004$) as shown in Figure 2B. Morphine was used in ~75% of the overall study population and was not associated with any significant difference on the primary endpoint as well as during the overall 24-h study time course (Online Figure 1), and there was no treatment effect by morphine interaction.

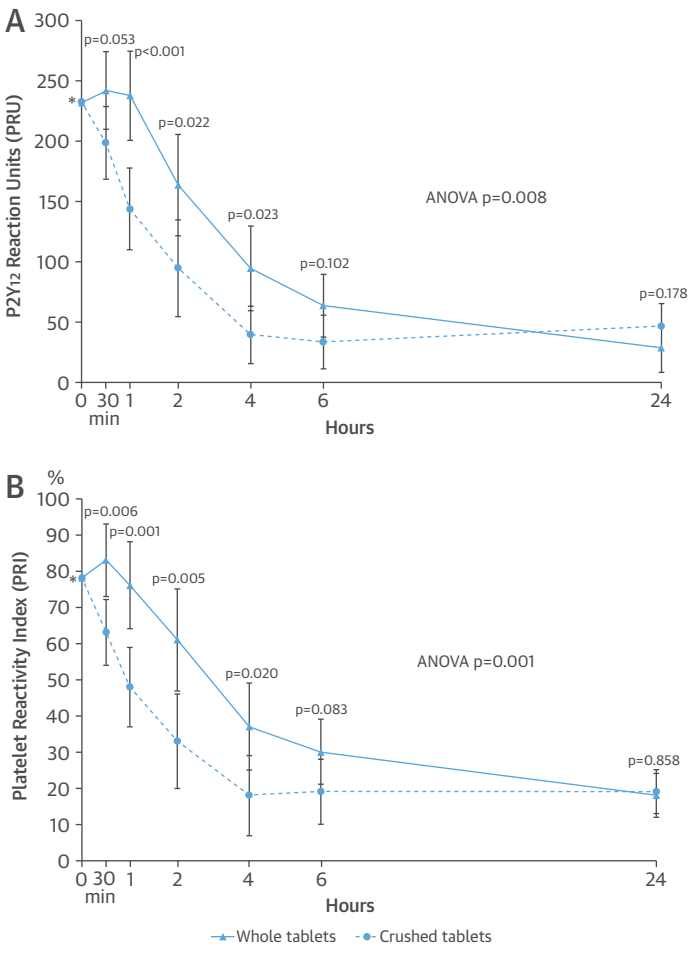
Rates of HPR as assessed by VN-P2Y12 were markedly reduced with crushed compared with whole tablet ingestion of prasugrel (Figure 3A). In particular, significantly reduced HPR rates were observed at 30 min, 1 h, and 2 h after drug administration.

Importantly, HPR was present in approximately one-half of the patient population treated with whole tablets at 2 h. HPR rates continued to decrease after 2 h in both treatment arms, being numerically lower at 4 h in the crushed arm; at 6 and 24 h, HPR rates were very low and similar between groups. HPR rates as assessed by VASP-PRI were overall higher but showed a similar trend compared with HPR defined by PRU (**Figure 3B**).

Compared with whole tablets, crushed prasugrel was associated with faster drug absorption, leading to higher plasma concentrations of P-AM at 30 min and 1 h and similar concentrations by 2 h (**Figure 4**). The T_{max} for P-AM was 0.8 h (0.5 to 4.0 h) and 3 h (0.5 to 24.0 h) in the crushed and whole tablets groups, respectively. Maximal P-AM plasma concentrations, measured as C_{max}, were increased by approximately 80% with crushed compared with whole prasugrel tablets (**Table 2**). Although exposure to P-AM during overall study time course (AUC_{0-t}) was similar between treatments, exposure to P-AM during the first 2 h after LD was ~3.5-fold higher with crushed prasugrel (**Table 2**). Morphine administration was associated with modestly reduced exposure to P-AM, but with very similar T_{max} and C_{max} (Online Table 1). A sensitivity analysis considering the treated population showed consistent results compared with those achieved in the primary population.

There was no major bleeding or other serious in-hospital adverse events. There was only 1 minor bleeding event (hematuria) in the crushed prasugrel arm, which did not require drug discontinuation.

FIGURE 2 Pharmacodynamic Assessment Following Administration of Whole Tablet Versus Crushed Tablet Prasugrel Loading Dose



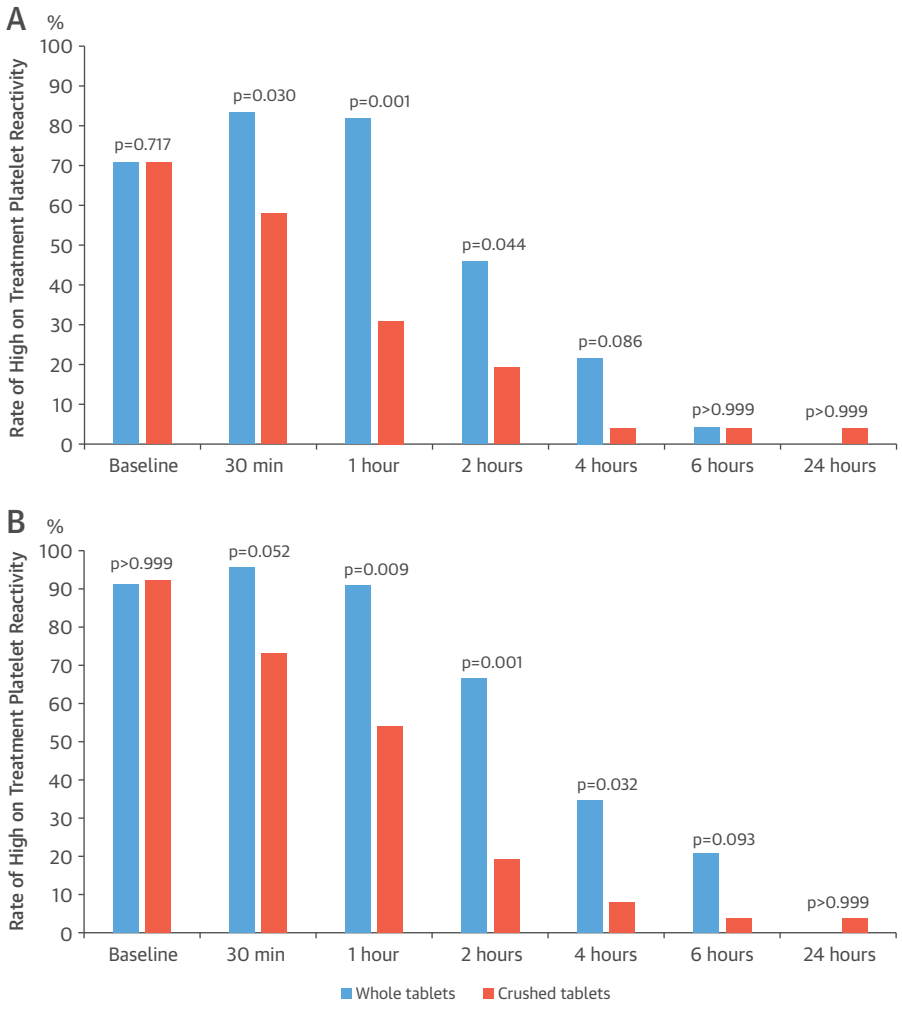
(A) $P2Y_{12}$ reaction units (PRU) measured by the VerifyNow P2Y12 assay. **(B)** Platelet reactivity index (PRI) measured by the vasodilator stimulated phosphoprotein assay. *p > 0.1. Values are expressed as least-square means. **Error bars** indicate 95% confidence intervals. ANOVA = analysis of variance.

DISCUSSION

This is the first investigation to assess the PK and PD profiles associated with crushing prasugrel tablets. Our study showed that, in STEMI patients undergoing PPCI, the use of a standard 60-mg LD of prasugrel administered as crushed tablets was associated with enhanced platelet inhibitory effects compared with prasugrel administered as whole tablets, particularly in the early hours after drug administration (**Central Illustration**). Notably, reduced platelet reactivity with crushed prasugrel was observed as early as 30 min after drug administration and persisted for up to 4 h; the differences between groups started to narrow after 6 h. Importantly, the use of crushed tablets led to a significant reduction in HPR rates, which is a well-recognized marker of thrombotic risk, including stent thrombosis, in patients treated with PCI (20). In particular, at 2 h post-LD, approximately one-half of patients treated with whole prasugrel tablets still had HPR, the rate of which was more than 2-fold higher than that observed with crushed tablets. Importantly, consistent results were observed using 2 different PD assays, supporting the validity of our findings. In line with the PD data, our PK assessments showed that crushed prasugrel was associated with an over 3-fold faster drug absorption and nearly 2-fold higher maximal plasma concentration of its active metabolite compared with whole tablet administration. Although patients had similar exposure to P-AM during the overall study time course, this was approximately 3.5-fold higher with crushed prasugrel during the first 2 h post-LD.

Antiplatelet therapy with a $P2Y_{12}$ receptor inhibitor, in addition to aspirin, is the cornerstone of treatment for the reduction of thrombotic events in

FIGURE 3 Rates of High On-Treatment Platelet Reactivity Following Administration of Whole Tablet Versus Crushed Tablet Prasugrel Loading Dose



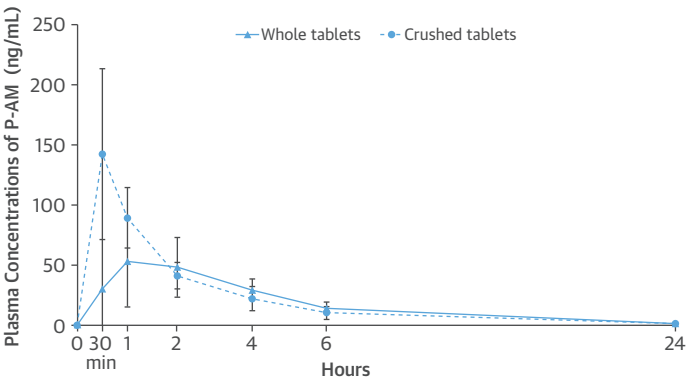
(A) High on-treatment platelet reactivity (HPR) rates as assessed by the VerifyNow P2Y12 assay. **(B)** HPR rates as assessed by the vasodilator-stimulated phosphoprotein assay. Histograms represent rates.

ACS patients, including STEMI (1). The new-generation $P2Y_{12}$ receptor inhibitors prasugrel and ticagrelor are associated with more prompt, potent, and predictable antiplatelet effects compared with clopidogrel. These pharmacological properties translate into better clinical outcomes in ACS patients undergoing PCI, including those presenting with STEMI (1). However, in PPCI, there is a delayed onset of action of oral $P2Y_{12}$ receptor inhibitors, which require >2 h to exert full antiplatelet effects, and thus exposing these high-risk patients to an increased risk of thrombotic complications in the immediate post-PCI period (7–10). In STEMI patients, these observations may be attributed to multiple factors. These include hemodynamic instability, adrenergic activation, systemic vasoconstriction, drug-drug interactions, abnormal muscular activity of the gastrointestinal tract, nausea, and vomiting, which can lead to impaired drug absorption (9,10,12). In a prior investigation with ticagrelor, we demonstrated that this delay in antiplatelet effect was mainly attributed to an altered PK profile ("drug exposure"), with impaired absorption in the early hours after drug administration, which in turn led to high levels of platelet reactivity and elevated HPR rates (10). The prognostic implications of such findings are

noteworthy given the risk of thrombotic complications in the early hours following PPCI, even with the use of prasugrel and ticagrelor (11). These observations underscore the need for strategies that provide enhanced platelet inhibition in the early hours after PPCI. Because the PK/PD profiles of $P2Y_{12}$ receptor inhibitors are dose-dependent, the use of high LD regimens has been tested (10,13-15). However, this was associated with marginal or no additional effects on platelet reactivity (10,13-15). Moreover, the only randomized trial using new-generation $P2Y_{12}$ receptor inhibitors testing upstream versus in-laboratory drug administration as an attempt to achieve greater antithrombotic efficacy at the time of PPCI was not associated with significant differences in platelet reactivity and did not improve pre-PCI markers of coronary reperfusion (24). Overall, these observations suggest that impaired drug absorption has a key role in the delayed antiplatelet effects observed with oral $P2Y_{12}$ receptor inhibitors in STEMI patients. These findings, on the one hand, support a role for intravenous therapies (i.e., glycoprotein IIb/IIIa inhibitors or cangrelor) to achieve immediate effects (7,25), but on the other hand, also underscore the need for strategies associated with improved absorption of orally administered drugs.

Investigations conducted in healthy volunteers treated with clopidogrel and ticagrelor have shown that tablets can be safely crushed and administered, either orally or via nasogastric tube, achieving faster and greater bioavailability than an equal dose taken orally as whole tablets (26,27). Recently, the MOJITO (Mashed Or Just Integral pill of TicagrelOr) study conducted in STEMI patients showed that crushed ticagrelor reduced platelet reactivity and HPR rates to a greater extent than whole tablets only at 1 h after LD administration (16). However, this study was limited to a single PD assay, with fewer time point measures, and without PK assessments (16). A subsequent small sample pilot study suggested that crushed ticagrelor was associated with faster drug absorption than whole tablets in the early phase after LD (17). Our study expands upon these findings by exploring for the first time both the PK and PD effects of crushed prasugrel and showing, in patients undergoing PPCI, a remarkable reduction in platelet reactivity and HPR rates by 30 min with significant differences that persist up to 4 h post-LD. Moreover, we demonstrate that these PD findings are attributed to a more favorable PK profile associated with crushing prasugrel tablets, which leads to faster drug absorption, higher maximum P-AM concentrations, and greater exposure during the first 2 h after drug administration compared with whole tablet ingestion.

FIGURE 4 Pharmacokinetic Profile of Prasugrel's Active Metabolite Following Administration of Whole Tablet Versus Crushed Tablet Prasugrel Loading Dose



Values are expressed as means. **Error bars** indicate standard error. P-AM = prasugrel's active metabolite.

Post hoc analysis of PD studies conducted in patients undergoing PPCI have shown morphine use to be associated with a delayed onset of action of prasugrel and ticagrelor (9,22). In a prospective, randomized trial conducted in patients with ACS, including STEMI and non-STEMI, coadministration of morphine led to delayed absorption and reduced exposure to ticagrelor and its active metabolite, resulting in lower and delayed antiplatelet effects (28). However, in this study, STEMI presentation itself was found to be an independent predictor of reduced ticagrelor exposure. In our study, we found only a marginal effect of morphine administration on exposure to P-AM, which did not translate into any PD differences, irrespective of drug preparation. These findings are in line with a study conducted in healthy volunteers, in which morphine decreased

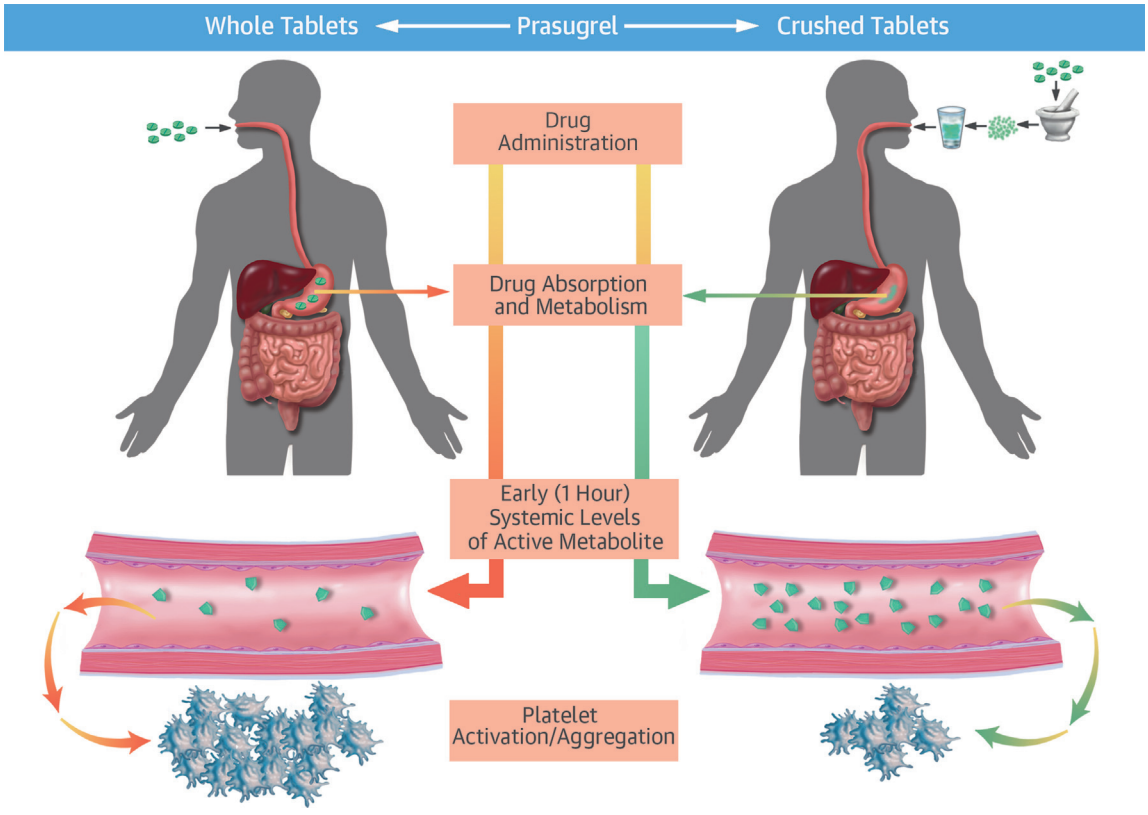
TABLE 2 Pharmacokinetic Profiles of Prasugrel's Active Metabolite After Administration of LD of Whole Versus Crushed Prasugrel

P-AM	Crushed Tablets (n = 26)	Whole Tablets (n = 24)	p Value
T_{max}, h	0.8 (0.5-4.0)	3.0 (0.5-24.0)	<0.001
AUC_{0-t}, ng•h/ml	253 (15.7-738.0)	253 (94.5-519.0)	0.655
C_{max}, ng/ml	114 (4.5-837.0)	63.8 (8.8-426.0)	0.021
AUC_{0-2}, ng•h/ml	113 (7.5-593.0)	32.1 (1.5-375.0)	0.009

T_{max} is median (range); all other values are geometric mean (range).

AUC_{0-t} = area under the plasma concentration vs. time curve from time 0 to the last measurable concentration; AUC_{0-2} = area under the plasma concentration vs. time curve from time 0 to 2 h; C_{max} = maximum observed plasma concentration; LD = loading dose; P-AM = prasugrel's active metabolite; T_{max} = time for the maximum plasma concentration.

CENTRAL ILLUSTRATION **Crushed Prasugrel in STEMI**



Rollini, F. et al. J Am Coll Cardiol. 2016;67(17):1994–2004.

The effect of crushing prasugrel on pharmacokinetic and pharmacodynamic profiles. STEMI = ST-segment elevation myocardial infarction.

only maximal plasma concentrations of P-AM, but not PD profiles (29). Taken together, these data support the hypothesis that, although a drug interaction with morphine is involved, other mechanisms may play a major role in the pathophysiology of delayed absorption of $P2Y_{12}$ receptor inhibitors in patients undergoing PPCI. However, our results need to be interpreted with caution given the post hoc nature of our assessments.

STUDY LIMITATIONS. First, our study was not designed to assess clinical outcomes. Nonetheless, the PD data provided in this study have been consistently associated with thrombotic events in other large investigations (20). Furthermore, the clinical benefits of peri-PCI reduction of platelet reactivity are supported by larger investigations with the potent intravenous $P2Y_{12}$ receptor antagonist cangrelor, showing a significant reduction in early thrombotic events (30). Of note, in these trials, cangrelor was tested against clopidogrel therapy. Indeed, how our strategy of crushing prasugrel tablets compares with cangrelor in patients undergoing PPCI is currently unknown and warrants further investigation. Moreover, the lack of bleeding complications should be interpreted with caution. Indeed, larger investigations are warranted to define the safety and efficacy of crushed prasugrel in PPCI. Second, although the use of morphine, which may impair drug absorption, was not significantly different between the 2 groups, they were not well-balanced. However, morphine use was actually higher in the patients randomized to crushed prasugrel, and did not affect our overall study findings. Moreover, the lack of an interaction between morphine and PK/PD profiles needs to be interpreted with caution as the study was not designed for this analysis and because most

patients were treated with morphine, as per standard of care, limiting the possibility to unravel a potential treatment effect. Ultimately, our data cannot be extrapolated to patients in cardiogenic shock and/or requiring a nasogastric tube. These patients, although in fact attractive for the use of crushed prasugrel as it already frequently occurs in clinical practice, were excluded from our study as they would have introduced heterogeneity to our study population, potentially interfering with our PK/PD assessment.

CONCLUSIONS

Our study showed that in STEMI patients undergoing PPCI, crushed prasugrel administration is associated with faster drug absorption and more prompt and potent antiplatelet effects compared with whole tablet ingestion. Although the clinical effect of our study results warrants a larger-scale efficacy trial, our findings may have potential prognostic implications given the known association among peri-PCI platelet reactivity, thrombotic events, and long-term outcomes.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Crushed prasugrel tablets are associated with more rapid drug availability and platelet inhibition than whole tablets in patients with STEMI undergoing primary PCI.

TRANSLATIONAL OUTLOOK: Prospective clinical studies are needed to define the effect of administering crushed prasugrel tablets on thrombotic and bleeding outcomes in patients with STEMI undergoing primary PCI.

REFERENCES

1. Franchi F, Angiolillo DJ. Novel antiplatelet agents in acute coronary syndrome. Nat Rev Cardiol 2015;12:30–47.

2. 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.

3. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.

4. Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet 2009;373:723–31.

5. Udell JA, Braunwald E, Antman EM, Murphy SA, Montalescot G, Wiviott SD. Prasugrel versus clopidogrel in patients with ST-segment elevation myocardial infarction according to timing of percutaneous coronary intervention: a TRITON-TIMI 38 subgroup analysis (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38). J Am Coll Cardiol Intv 2014;7:604–12.

6. Sherwood MW, Wiviott SD, Peng SA, et al. Early clopidogrel versus prasugrel use among contemporary STEMI and NSTEMI patients in the US: insights from the National Cardiovascular Data Registry. J Am Heart Assoc 2014;3:e000849.

7. Valgimigli M, Tebaldi M, Campo G, et al. Prasugrel versus tirofiban bolus with or without short post-bolus infusion with or without concomitant prasugrel administration in patients with myocardial infarction undergoing coronary stenting: the FABOLUS PRO (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with STsegment elevation myocardial infarction compared to or on top of PRasugrel given at loading dOse) trial. J Am Coll Cardiol Intv 2012;5:268–77.

8. 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.

9. 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.

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. Steg PG, van 't Hof A, Hamm CW, et al. Bivalirudin started during emergency transport for primary PCI. N Engl J Med 2013;369:2207–17.

12. 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.

13. 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.

14. Parodi G, Bellandi B, Valenti R, et al. Comparison of double (360 mg) ticagrelor loading dose with standard (60 mg) prasugrel loading dose in ST-elevation myocardial infarction patients: the Rapid Activity of Platelet Inhibitor Drugs (RAPID) primary PCI 2 study. Am Heart J 2014;167:909–14.

15. 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.

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. Farid NA, McIntosh M, Garofolo F, et al. Determination of the active and inactive metabolites of prasugrel in human plasma by liquid chromatography/tandem mass spectrometry. Rapid Commun Mass Spectrom 2007;21:169–79.

19. 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.

20. Tantry US, Bonello L, Aradi D, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. J Am Coll Cardiol 2013;62:2261–73.

21. Bonello L, Laine M, Camoin-Jau L, et al. Onset of optimal P2Y12-ADP receptor blockade after ticagrelor and prasugrel intake in non-ST elevation acute coronary syndrome. Thromb Haemost 2015; 114:702–7.

22. Parodi G, Bellandi B, Xanthopoulou I, et al. Morphine is associated with a delayed activity of oral antiplatelet agents in patients with ST-elevation acute myocardial infarction undergoing primary percutaneous coronary intervention. Circ Cardiovasc Interv 2014;8: e001593.

23. Diodati JG, Saucedo JF, French JK, et al. Effect on platelet reactivity from a prasugrel loading dose after a clopidogrel loading dose compared with a prasugrel loading dose alone: Transferring From Clopidogrel Loading Dose to Prasugrel Loading Dose in Acute Coronary Syndrome Patients (TRIPLET): a randomized controlled trial. Circ Cardiovasc Interv 2013;6: 567–74.

24. 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.

25. 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.

26. Zafar MU, Farkouh ME, Fuster V, Chesebro JH. Crushed clopidogrel administered via nasogastric tube has faster and greater absorption than oral whole tablets. J Interv Cardiol 2009;22:385–9.

27. Teng R, Carlson G, Hsia J. An open-label, randomized bioavailability study with alternative methods of administration of crushed ticagrelor tablets in healthy volunteers. Int J Clin Pharmacol Ther 2015;53:182–9.

28. Kubica J, Adamski P, Ostrowska M, et al. Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial. Eur Heart J 2016;37: 245–52.

29. Hobl EL, Reiter B, Schoergenhofer C, et al. Morphine interaction with prasugrel: a double-blind, cross-over trial in healthy volunteers. Clin Res Cardiol 2016;105:349–55.

30. Steg PG, Bhatt DL, Hamm CW, et al. Effect of cangrelor on periprocedural outcomes in percutaneous coronary interventions: a pooled analysis of patient-level data. Lancet 2013;382:1981–92.

KEY WORDS crushed tablet, pharmacodynamic, pharmacokinetic, platelets

APPENDIX For a supplemental Methods section and a supplemental figure and table, please see the online version of this article.