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EDITORIAL COMMENT

Different Prasugrel Administration in STEMI Patients

Go Faster and No Fear to Crush!*

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The first goal in ST-segment elevation myocardial infarction (STEMI) patients is "speed": to diagnose, to transfer to the catheterization laboratory, to pre-treat orally, to perform coronary angiography, and to open the culprit vessel. A delay of 1 of these steps could have a negative effect on the clinical outcome. Sometimes, the delay is caused by something that we cannot control, as in the late antiplatelet effects of oral $P2Y_{12}$ receptor inhibitors in STEMI patients undergoing primary percutaneous coronary intervention, as shown by elevated rates of high on-treatment platelet reactivity (HPR) for several hours after drug administration (1). Prasugrel and ticagrelor showed clinical superiority over clopidogrel, with a faster onset of action and greater antiplatelet power in patients with acute coronary syndrome (2,3), and both the American and European societies of cardiology guidelines strongly recommend ticagrelor or prasugrel loading dose in STEMI patients (4,5).

Nevertheless, a major Achilles' heel of this treatment is that it provides an effective platelet inhibition 2 h after the loading dose (LD) in one-half of patients, and at least 4 h are required to achieve an effective platelet inhibition in the majority of patients (6). Therefore, several strategies have attempted to increase the drug absorption and speed up the onset of action, ranging from a double dose (1,7,8) to a different type of administration (9,10). The MOJITO (Mashed Or Just Integral pill of TicagrelOr) study (9) for the first time demonstrated the superiority of ticagrelor crushed pills compared with whole tablets in terms of earlier platelet inhibition. $P2Y_{12}$ reaction units (PRU) were lower in the crushed group at 1 h after the LD, with no differences observed at 2, 4, and 8 h. The clinical implication of this study is evident considering the great amount of STEMI patients that are unable to swallow, such as the elderly, patients with prior stroke or dysphagia, or those who have been sedated or intubated. In this issue of the

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Journal, the CRUSH (Pharmacodynamic and Pharmacokinetic Profiles of Standard versus Crushed Prasugrel in Patients with ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention) study by Rollini et al. (11) elegantly examined the pharmacokinetic (PK) and pharmacodynamic (PD) consequences of crushing prasugrel tablets (11). The STEMI patients were randomized to whole or crushed tablets of prasugrel (60 mg LD) to collect blood samples for PK and PD analysis at baseline, 30 min, and 1, 2, 4, 6, and 24 h after administration of the randomized treatment. Importantly, the LD of prasugrel was administered immediately after removal of the guiding catheter, and a post hoc analysis of morphine use was conducted according with the finding of an association between use of morphine and HPR (12). A significant reduction in PRU with crushed compared with whole tablets was found at 2 h (primary endpoint), and this significant difference was already evident at 30 min and 1 h, even among patients receiving morphine; moreover, at these 2 time points, the mean PRU in the whole group was >208, reflecting an HPR maintained

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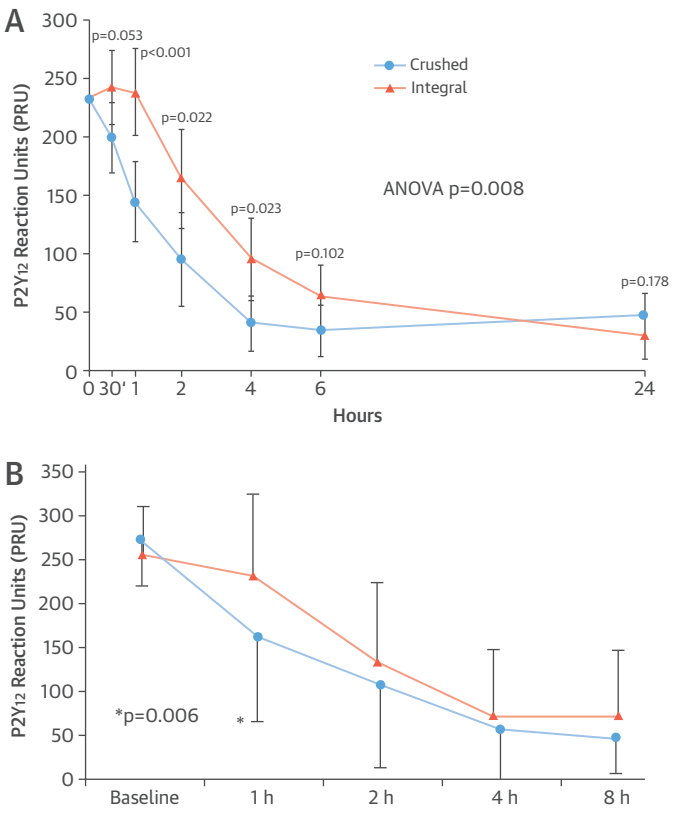
FIGURE 1 PRU Were Assessed By the VerifyNow P2Y12 Assay in Patients Treated With Crushed or Integral Tablets



Results are from the CRUSH (Pharmacodynamic and Pharmacokinetic Profiles of Standard versus Crushed Prasugrel in Patients with ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention) trial **(A)** (reprinted with permission from Rollini et al. [11]) and the MOJITO (Mashed Or Just Integral pill of TicagrelOr) trial **(B)** (reprinted with permission from Parodi et al. [9]). **Blue line** indicates patients treated with crushed tablets; **orange line** indicates patients treated with integral tablets. Data are expressed as mean ± SD. ANOVA = analysis of variance; PRU = platelet reactivity units.

up to 2 h in approximately one-half of the patients. Whole blood vasodilator-stimulated phosphoprotein-platelet reactivity index and rates of HPR were reduced, and prasugrel's active metabolite was already higher at 30 min. Major methodological differences between the MOJITO and CRUSH studies are the study drug, timing of drug administration, timing of platelet function testing, primary endpoint, and PD/PK clinical assays. Whereas in the MOJITO study the crushed tablets showed an earlier and enhanced platelet inhibition at 1 h with no differences observed at 2, 4, and 8 h, in the CRUSH study this reduction was found already at 30 min and was maintained for up to 4 h (**Figure 1**). Moreover, the decision of the investigators to administer prasugrel after procedure, which may seem a limitation of the study, showed that this timing is as safe and effective as the pre-procedural administration.

Unfortunately, a methodological problem was that both studies excluded patients in cardiogenic shock requiring a nasogastric tube, in which the delayed onset of action of oral $P2Y_{12}$ receptor inhibitors may be attributed to a drug absorption impaired (13) for hemodynamic instability, adrenergic activation, systemic vasoconstriction, drug-drug interactions, nausea, and vomiting. In daily practice, this subset of patients could have a greater benefit from the crushed drug, but as the same authors stated (11), we do not yet know what may interfere with a correct PK/PD assessment. A fast antiplatelet action can be obtained with the potent intravenous $P2Y_{12}$ receptor antagonist cangrelor that in a pooled analysis from 3 CHAMPION (Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) trials (14) showed a reduction of percutaneous coronary intervention periprocedural thrombotic complications. Cangrelor is indeed an effective antiplatelet drug, but in this study: it was tested just against clopidogrel therapy; the rate of STEMI was 11.6%; the risk of bleeding increased; and last but not least, its availability and costs compared with a loading dose of an oral antiplatelet drug raise some concerns. The rate of stent thrombosis ≤24 h is 2.1% even with ticagrelor and prasugrel utilization (15); hence, every adjunctive strategy or technique must be used to move faster and safer in STEMI patients with no fear to crush.

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