Loading with Oral P2Y\textsubscript{12} Receptor Inhibitors: To Crush or Not to Crush?

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Abstract

Oral P2Y\textsubscript{12} receptor inhibitors represent a mainstay treatment in patients with acute coronary syndrome and those undergoing percutaneous coronary intervention. In the setting of ST-elevation myocardial infarction, when early platelet inhibition is highly desirable, the onset of action of oral P2Y\textsubscript{12} receptor inhibitors is, however, delayed, likely due to delayed drug absorption. Crushing the tablets, which are to be used for patient loading with an oral P2Y\textsubscript{12} receptor inhibitor, has been shown to provide earlier platelet inhibition than standard, integral tablets administration. Chewed ticagrelor tablets may also result in a similar effect. Such findings should be interpreted with caution, mainly due to the small number of patients enrolled and the nature (pharmacodynamic/pharmacokinetic) of the respective studies. Furthermore, in patients with out-of-hospital cardiac arrest, who remain comatose, crushing tablets is commonly applied in clinical practice for platelet P2Y\textsubscript{12} receptor inhibition. In this review, we focus on current evidence regarding the role of crushed P2Y\textsubscript{12} receptor inhibitor pills, analyzing clinical scenarios where most of the promise exists along with future expectations from this type of formulation. Large randomized studies are needed to draw firm conclusions regarding the clinical benefit of ‘crushing’ over the usual ‘not-crushing’ practice.

Keywords

► anti-platelet agents
► clinical trials: anti-platelet drugs
► platelet pharmacology

Introduction

Platelets play a key role in the pathogenesis of acute coronary syndromes (ACSs) and become highly activated particularly in ST-segment elevation myocardial infarction (STEMI) patients, as well as during percutaneous coronary intervention (PCI).\textsuperscript{1,2} During the last two decades, dual anti-platelet therapy consisting of a combination of aspirin and a P2Y\textsubscript{12} receptor inhibitor has been established as an essential therapy component for the treatment of ACS and/or PCI patients. Clopidogrel is the most broadly used oral P2Y\textsubscript{12} receptor inhibitor worldwide; however, both prasugrel and ticagrelor exhibit a faster and more consistent platelet inhibition than clopidogrel, especially in STEMI patients.\textsuperscript{3–9} Accordingly, ticagrelor administered as a 180-mg loading dose (LD) and 90-mg twice daily thereafter or prasugrel administered as a 60-mg LD orally and 10 mg once daily, are the preferred P2Y\textsubscript{12} receptor inhibitors, provided there are no contraindications.\textsuperscript{10,11} In patients undergoing primary PCI several studies have pointed out the delayed onset of action of oral P2Y\textsubscript{12} receptor inhibitors, most likely attributed to an impaired absorption.\textsuperscript{5,12–14} Opiates, commonly used for pain relief, appear to exacerbate this problem.\textsuperscript{15–19} Given the urgent need for strong and early platelet inhibition especially in this patient population, researchers have tried several ways to bridge this gap with the early LD
administration even in the pre-hospital setting appearing as a promising strategy.\textsuperscript{20,21} However, expectations have clearly not been fulfilled with this approach.\textsuperscript{22–26} Crushing the tablets, which are to be used for patient loading with an oral P2Y$_{12}$ receptor inhibitor, appears as a promising mode of administration able to expedite the onset of platelet inhibition. In this review, we will focus on current evidence regarding the role of crushed P2Y$_{12}$ Receptor inhibitor pills, analysing clinical scenarios where most of the promise exists along with future expectations from this type of formulation.

**How Tablets’ Crushing is Performed?**

Intensive care units’ personnel have traditionally used crushing to administer oral drugs in intubated patients through a nasogastric tube, provided that bioequivalence is maintained. Crushing involves a series of certain steps that ensures the dispersion of all the particles of each crushed tablet into purified water, to form a suspension, which is then administered to the patient. Crushing is performed in a mortar using a pestle for approximately 60 seconds. Thereafter, 20 mL of purified water is added and stirred for 60 seconds. The liquid is transferred to a dosing cup with the addition of another 15 mL of purified water. The mixture is then stirred to form a suspension. The same procedure is repeated with an additional 15 mL of purified water added to the mortar to rinse out any remaining drug. The total contents (50 mL) are stirred for another 30 seconds to ensure the dispersion of all the particles of each crushed tablet into purified water, to form a suspension, which is then administered orally.

**Oral P2Y$_{12}$ Receptor Inhibitors: Onset of Action in Various Clinical Settings**

Clopidogrel—a thienopyridine—is an inactive pro-drug, which requires in vivo oxidation by the hepatic or intestinal cytochrome CYP3A4 and 2C19 isoenzymes. It binds irreversibly to the P2Y$_{12}$ receptor and inhibits platelet aggregation. In PCI candidates and non-ST-segment elevation ACS patients, clopidogrel’s full anti-platelet effect appears within 2 hours after loading.\textsuperscript{27,29} However, its bioavailability is impaired in the setting of STEMI.\textsuperscript{5} Prasugrel is a newer generation thienopyridine that irreversibly inhibits the P2Y$_{12}$ receptor, at the same site as clopidogrel. It is also a pro-drug, meaning that it requires to be converted in vivo to its active metabolite, primarily by CYP3A4 and CYP2B6. Prasugrel is approximately 5 to 9 times more potent than clopidogrel, with an onset of action within 1 hour.\textsuperscript{3,31} Ticagrelor, a cyclopentyl-triazolopyrimidine, is a reversible P2Y$_{12}$ receptor inhibitor, with a plasma half-life of 12 hours.

It requires no hepatic activation as it is not a pro-drug and also exhibits a more rapid and consistent onset of action than clopidogrel, both in stable, as well as unstable coronary artery disease patients.\textsuperscript{5,32} Nevertheless, even the relatively fast-acting prasugrel and ticagrelor used in standard or even increased LD, exhibit a delay in their onset of action when administered in STEMI patients.\textsuperscript{12–14,33,34} As a consequence, a significant proportion of patients undergo primary PCI without adequate platelet inhibition, if standard oral P2Y$_{12}$ administration is used.\textsuperscript{35} These observations fuelled the need to find alternative methods of administration, to facilitate drug absorption and expedite platelet inhibition.

**Early Studies with Crushing Clopidogrel or Ticagrelor Tablets**

Clopidogrel 300 mg administered via a nasogastric tube in crushed form with 30 mL water was compared with oral tablet ingestion in nine healthy volunteers.\textsuperscript{36} Plasma concentration of its primary inactive metabolite peaked earlier and the median peak plasma concentration was 80% higher with crushed clopidogrel than with the whole tablets. Despite the study’s small number of participants, it was clear that the crushed form of clopidogrel administered through a nasogastric tube exhibited significantly faster rates of absorption and increased bioavailability, compared with standard whole tablet administration, when an equal LD was given. One or two crushed 90 mg ticagrelor tablets prepared for either oral or via a nasogastric tube administration, seem to deliver a mean dose of ≥97% of the intact tablet.\textsuperscript{37} In another study conducted in 36 healthy volunteers, crushing a single 90 mg ticagrelor tablet and administered either orally or via a nasogastric tube resulted in increased plasma concentrations of both ticagrelor and its active metabolite ARC124910XX, at 0.5- and 1-hour post-dose, when compared with whole-tablet ingestion.\textsuperscript{38} Plasma concentration-time profiles for both ticagrelor and ARC124910XX at 2 and 3 hours post-dose were comparable between the crushed and intact tablet administration treatment arms. Overall, bioequivalence was proved for crushed over whole-tablet prepreparations of ticagrelor regardless of oral or nasogastric tube administration.

**Crushing P2Y$_{12}$ Receptor Inhibitors Tablets in STEMI Patients**

Considering the aforementioned data, the idea was born that expedition of the onset of action of P2Y$_{12}$ receptor inhibitors in STEMI may be achieved by crushing the integral tablets. The Mashed Or Just Integral pill of Ticagrelor or MojitO study was a prospective, randomized, four-centre study, which evaluated the role of equal doses (180 mg) of crushed versus integral ticagrelor tablets in STEMI patients undergoing primary PCI.\textsuperscript{27} Platelet reactivity was assessed by VerifyNow (Accumetrics, San Diego, California, United States) and expressed in P2Y$_{12}$ reaction units (PRU). At 1-hour postloading, platelet reactivity was significantly lower in the crushed versus integral groups, 168 (interquartile range
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[1Q]: 61–251) versus 252 (IQR: 167–301), respectively, $p = 0.006$. High on-treatment platelet reactivity was found in 35 and 63% of patients in the crushed and integral tablets groups, respectively, $p = 0.011$. No differences in integral tablets reactivity were observed in later time points. Morphine administration was an independent predictor of high-platelet reactivity in the whole population. Crushing ticagrelor tablets did not increase adverse events. Main limitations of this study were the small sample size and the lack of a pharmacokinetic analysis. The Oral crushed and dispersed ticagrelor 180 mg compared with whole tablets of eQual dose in STEMI Patients unDeringoing Primary PCI (LiquiD) study examined the pharmacokinetic and pharmacodynamic interactions of crushed ticagrelor administered in the semi-upright sitting position, in 20 patients with STEMI undergoing primary PCI.\(^{35}\) Ticagrelor plasma exposure at 1 hour and area under the plasma concentration–time curve from time zero to 1 hour were higher in the crushed versus integral tablets group, while time to maximum plasma concentration was 2 versus 4 hours in the crushed versus integral tablets groups, respectively. Parallel findings were observed with AR-C124910XX, ticagrelor’s active metabolite. A more potent anti-platelet activity was apparent during the first hour post-loading in the crushed ticagrelor group, which was attributed to the more rapid absorption and plasma exposure than with standard administration. LIQUID’s major limitation was the small sample size and the fact that the study was not powered for pharmacodynamic superiority of the crushed tablet strategy versus the integral tablet strategy.

The pharmacokinetic and pharmacodynamic profiles of crushed versus whole prasugrel tablets in 50 STEMI patients undergoing primary PCI were described in the CRUSH study.\(^{28}\) The 60-mg LD of crushed prasugrel provided reduced platelet reactivity as early as 30 minutes after drug administration. At 2 hours after loading, platelet reactivity in PRU (primary endpoint of the study), was reduced by crushed versus integral tablets: 95 versus 164, least-square difference interval: 10–126, $p = 0.022$. Parallel findings were observed with vasodilator-stimulated phosphoprotein (VASP) assay. Pharmacodynamic evaluation confirmed that crushed prasugrel was associated with an over threefold faster drug absorption and nearly twofold higher maximal plasma concentration of prasugrel’s active metabolite in the first 2 hours post-loading, compared with whole tablet administration. There were no adverse events related to crushed prasugrel. Based on the aforementioned studies, crushed ticagrelor or prasugrel instead of whole tablet administration, may be a preferable treatment option in patients presenting with STEMI and undergoing primary PCI, to achieve faster gastrointestinal absorption and platelet inhibition (\textit{\textcircled{1}}).\(^{40}\)

\textbf{Alternative to Crushing Modes of Administration}

Although ticagrelor absorption does not seem to occur through the oral mucosa, chewing ticagrelor tablets has been tested as an alternative to crushing mode of administration.\(^{41}\) In a randomized study involving 99 stable angina patients, the 180-mg LD of crushed or chewed ticagrelor tablets achieved a more rapid platelet inhibition, when compared with the standard LD of integral tablets.\(^{42}\) Chewed ticagrelor seemed to exert faster and stronger platelet inhibition compared with crushed or integral tablets, at 20 and 60 minutes after the loading. Initiation of enzymatic metabolic degradation of ticagrelor in the mouth, due to its prolonged exposure to the saliva might contribute to this ‘enhanced’ platelet inhibition after the administration of the chewed ticagrelor formulation. However, given the small number of patient sample and the study’s design (3:1:1 patient assignment to integral:crushed:chewed arms, respectively), the difference between crushed and chewed tablets should be regarded as hypothesis generating only. In another study, in 50 non-STEMI patients chewing a 180-mg LD of ticagrelor provided faster and improved inhibition of platelets aggregation at 1-hour post-loading, compared with standard administration.\(^{43}\) Same investigators further described in 50 patients with STEMI and primary PCI an enhanced platelet inhibitory effect with chewed ticagrelor 180 mg, when compared with the swallowed LD of integral tablets.\(^{44}\) Reduced platelet reactivity with chewed ticagrelor was notable as early as 30 minutes and especially 1 hour after drug administration, while platelet inhibition curves between the two arms of the study converged about 3 to 4 hours after drug administration. Therefore, chewing ticagrelor tablets seems to be an effective way to expedite platelet inhibition, compared with integral tablets administration. Importantly, however, studies supporting chewing ticagrelor tablets lacked pharmacokinetic confirmation. On the other hand, sub-lingual administration of crushed ticagrelor tablets failed to prove superiority over crushed tablets given orally in a randomized study involving 49 unstable angina patients.\(^{45}\) Stronger platelet inhibition at 30 and 45 minutes was seen with crushed ticagrelor given orally instead of sub-lingually. Results within the first hour after the LD were also confirmed by pharmacokinetic analysis of ticagrelor and AR-C124900XX (active metabolite).

Studies with crushed or chewed tablets of P2Y\textsubscript{12} receptor inhibitors in patients with coronary artery disease are summarized in \textit{\textbf{Table 1}}. In-hospital or at most 30 days’ follow-up has been provided in these small-sized (20–99 patients each) studies, with no signs of excess bleeding or other adverse events with crushed or chewed tablets compared with standard, integral tablets administration. However, no clues regarding the clinical value of crushed or chewed modes of administration can be obtained from these purely pharmacodynamic/pharmacokinetic studies.

\textbf{Crushed P2Y\textsubscript{12} Receptor Inhibitors Tablets in Out-of-Hospital Cardiac Arrest Survivors}

Patients with out-of-hospital cardiac arrest (OHCA), who survive cardiac resuscitation, represent a particularly high-risk population of increasing interest. Most of these patients undergo emergency PCI while they remain comatose,
intubated and unable to swallow oral P2Y₁₂ receptor inhibitors. On the other hand, these patients are in utmost need of adequate platelet inhibition. In a randomized study of 37 comatose OHCA survivors undergoing PCI and hypothermia, crushed ticagrelor provided significantly faster and stronger platelet inhibition, 2 hours post-LD and for the 48-hour period, when compared with clopidogrel. In another study, in 40 patients with mild therapeutic hypothermia after cardiac arrest due to MI, platelet inhibition assessed by VASP was proved to be significantly worse during the first 24 hours in clopidogrel- than in ticagrelor- or prasugrel-treated patients. Administration of crushed ticagrelor via a nasogastric tube appeared to reliably and effectively inhibit platelet function in vivo and in vitro, regardless of the presence of hypothermia. The early pharmacokinetic and pharmacodynamic effects of ticagrelor, when administered as crushed tablets through a nasogastric tube, were evaluated in the TICOMA study in 44 comatose OHCA patients who underwent primary PCI. Sufficient platelet inhibition was achieved after 12 hours and in many cases earlier (at a median time of 3 hours). Of note, drug concentrations following the LD administration via the nasogastric tube were much lower than those reported for conscious patients from other studies.

Regarding clinical outcome in this patient population, lower rates of stent thrombosis during hospitalization have been reported with crushed ticagrelor when compared with clopidogrel, without differences in hemorrhagic events. In contrast, in another series, a higher rate of stent thrombosis was observed with novel P2Y₁₂ receptor inhibitors compared with clopidogrel during a median of 2 days after PCI. Both studies were retrospective. –Table 2 summarizes the existing data.
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<td>Parodi et al&lt;sup&gt;27&lt;/sup&gt; (MOJITO study)</td>
<td>Prospective, randomised, 82 STEMI patients undergoing primary PCI</td>
<td>Ticagrelor 180 mg LD crushed vs. integral tablets Platelet function (VerifyNow) at baseline and at 1, 2, 4 and 8 hours. Primary endpoint: PRU 1 hour after LD</td>
<td>PRU 1 hour: 168 (IQR 61–251), 252 (IQR 167–301) in crushed and integral groups, respectively, $p = 0.006$ No differences in PRU at 2, 4 and 8 hours. HPR at 1 hour: in 35% vs. 63%, in crushed and integral groups, respectively, $p = 0.011$</td>
<td>In-hospital adverse events: No increase with crushed tablets</td>
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<td>Alexopoulos et al&lt;sup&gt;39&lt;/sup&gt; (LIQUID study)</td>
<td>Prospective, randomised, 20 STEMI patients undergoing primary PCI</td>
<td>Ticagrelor 180 mg LD crushed administered in the semi-upright sitting position vs. integral tablets administered in the supine position Co-primary endpoints: ticagrelor plasma exposure at 1 hour and AUC&lt;sub&gt;1&lt;/sub&gt; Platelet function (VerifyNow) at baseline and at 0.5, 1, 2, 4 and 6 hour</td>
<td>Ticagrelor plasma exposure at 1 hour: 586 vs. 70.1 ng/mL (median) in crushed vs. integral groups AUC&lt;sub&gt;1&lt;/sub&gt; 234 vs. 24.4 ng·h/mL, in crushed vs. integral groups, respectively Time to maximum plasma concentration 2 vs. 4 hour (median) in crushed vs. integral groups Parallel findings for the AR-C124910XX Platelet reactivity at 1 hour: LSE mean difference (95% CI) 92 (–158.4 to 26.6) PRU, $p = 0.009$</td>
<td>In-hospital 1 case of excessive intracoronary thrombus in crushed group requiring IIb/IIIa inhibitor</td>
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<td>Rollini et al&lt;sup&gt;28&lt;/sup&gt; (The CRUSH study)</td>
<td>Prospective, randomised, 50 STEMI patients undergoing primary PCI</td>
<td>Prasugrel 60 mg LD crushed vs. integral tablets Platelet function (VerifyNow, VASP) at baseline and at 0.5, 1, 2, 4, 6 and 24 hours Plasma levels of P-AM Primary endpoint: PRU 2 hours after LD</td>
<td>At 30 minute post-LD, reduced PRU by crushed vs. integral tablets, persisted at 4 hours post-LD At 2 hour: 164 vs. 95 PRU, LSM (95% CI) 68 (10–126), in integral vs. crushed groups, respectively, $p = 0.022$ Parallel findings with VASP Higher P-AM at 30 minute and 1 hour $T_{\text{max}}$ for P-AM 0.8 and 3 hour, in crushed and whole tablets groups, respectively</td>
<td>In-hospital No major bleeding or other adverse event 1 minor bleeding (haematuria) in crushed group</td>
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<td>Venetsanos et al&lt;sup&gt;42&lt;/sup&gt; (The IPAAD-Tica study)</td>
<td>Prospective, randomised, 99 stable angina patients</td>
<td>Ticagrelor 180 mg LD Integral, crushed or chewed tablets Platelet function (VerifyNow) prior, 20 min, 60 min after LD HPR:PRU &gt; 208 Primary endpoint: HPR rate at 20 minute</td>
<td>PRU at 20 minute: 237 (182–295), 112 (53–238) and 84 (29–129) in integral, crushed and chewed ticagrelor, respectively, $p &lt; 0.01$ Lower PRU with chewed compared with crushed or integral tablets at 20 and 60 minutes At 20 minute, no patient had HPR with chewed compared with 68% with integral and 30% with crushed ticagrelor, $p &lt; 0.01$</td>
<td>1 TIMI minor bleeding in the crushed group 1 TIMI minor bleeding in the integral group 1 TIMI minimal bleeding in the chewed group</td>
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<td>Asher et al(^{43}) (The CHEERS study)</td>
<td>Prospective, randomised, controlled 50 NSTEMI patients</td>
<td>Ticagrelor 180 mg LD&lt;br&gt;Chewing vs. integral tablets&lt;br&gt;Platelet function (VerifyNow) at baseline, 1 and 4 hours&lt;br&gt;Primary endpoint: PRU 1 hour after LD</td>
<td>PRU at 1 hour:&lt;br&gt;45 vs. 130 in the chewing vs. standard group, (p = 0.001)&lt;br&gt;PRU at 4 hours: 39 vs. 60 in the chewing vs. standard group, (p = 0.12), respectively</td>
<td>Major adverse cardiac and cardiovascular events at 30 days: one patient in the standard group</td>
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<td>Asher et al(^{44})</td>
<td>Prospective, randomised, controlled 50 STEMI undergoing primary PCI</td>
<td>Ticagrelor 180 mg LD&lt;br&gt;Chewed vs. integral tablets&lt;br&gt;Platelet function (VerifyNow) at baseline and at 0.5, 1 and 4 hours&lt;br&gt;Primary endpoint: PRU 1 hour after LD</td>
<td>PRU mean (SD)&lt;br&gt;At 30 minutes: 168 (78) vs. 230 (69), (p = 0.003)&lt;br&gt;At 1 hour: 106 (90) vs. 181 (89), (p = 0.005), with chewed vs integral tablets, respectively&lt;br&gt;No difference at 4 hour</td>
<td>At 30 days: 1 cardiogenic shock in the chewing group&lt;br&gt;1 recurrent ACS in the integral group&lt;br&gt;Similar adverse effects rates, 24% vs. 12%, NS</td>
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<td>Niezgoda et al(^{45})</td>
<td>Prospective, randomised controlled 49 unstable angina patients</td>
<td>Ticagrelor 180 mg LD&lt;br&gt;crushed tablets sublingually&lt;br&gt;crushed tablets given orally&lt;br&gt;integral tablets given orally&lt;br&gt;Blood sampling: Baseline, 15, 30, 45 minute, 1, 2, 3, 4 and 6 hours&lt;br&gt;Ticagrelor, AR-C124900XX plasma concentration&lt;br&gt;Platelet function: MEA&lt;br&gt;Primary endpoint: ticagrelor (t_{\text{max}})</td>
<td>AUC(_{C-1}) for ticagrelor within the first hour&lt;br&gt;(936.9 \pm 898.0) vs. (368.0 \pm 422.4), (p = 0.042), in crushed tablets given orally vs. crushed tablets given sub-lingually&lt;br&gt;Similar results for AR-C124900XX&lt;br&gt;Platelet inhibition: higher in patients receiving crushed ticagrelor orally vs. sub-lingually at 30 and 45 minutes, (p = 0.024) and (p = 0.016), respectively</td>
<td>In-hospital no serious adverse events reported</td>
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Abbreviations: ACS, acute coronary syndrome; AUC\(_1\), area under the plasma concentration–time curve from time zero to 1 hour; AUCCT, area under the plasma concentration time curve; CHEERS, Chewing versus Swallowing Ticagrelor to Accelerate Platelet Inhibition in Acute Coronary Syndrome; CRUSH, Pharmacodynamic and Pharmacokinetic Profiles of Prasugrel in Patients With ST Elevation Myocardial Infarction: A Randomized Comparison of Standard Versus Crushed Formulation; HPR, high platelet reactivity; IPAAD-Tica, The inhibition of platelet aggregation after administration of three different ticagrelor formulations; IQR, interquartile range; LD, loading dose; LIQUID, Oral crushed and dispersed ticagrelor 180 mg compared with whole tablets of eQUal dose in STEMI Patients unDergoing Primary PCI; LSM, least squares estimates mean; MEA, multiple electrode aggregometry; MOJITO, Mashed Or Just Integral pill of TicagrelOr; NS, non-significant; NSTEMI, non-ST elevation myocardial infarction; P-AM, prasugrel’s active metabolite; PCI, percutaneous coronary intervention; PD, pharmacodynamics; PK, pharmacokinetic; PRU, P2Y\(_{12}\) reaction units; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction; VASP, vasodilator-stimulated phosphoprotein.
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<td>Steblovnik et al&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Randomised 37 patients undergoing PCI and hypothermia</td>
<td>Ticagrelor 180 mg LD/90 mg twice daily vs. clopidogrel 600 mg LD/75 mg Platelet function by VerifyNow and Multiplate before PCI and 2, 4, 12, 22 and 48 hours after LD</td>
<td>PRU and % inhibition significantly decreased with ticagrelor vs. clopidogrel starting 2 hour after the loading and persisting during the 48-hour period Similar results by Multiplate HPR by VerifyNow at 12 hours was 11% vs. 53% (p = 0.001)</td>
<td>No difference in in-hospital stent thrombosis (5% vs. 6%), BARC 3a and 5 bleeding (15% vs. 13%) and survival with good neurological recovery</td>
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<td>Bednar et al&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Prospective, observational 40 patients treated with hypothermia</td>
<td>Platelet inhibition measured by VASP on days 1, 2, and 3 after drug administration in clopidogrel, prasugrel and ticagrelor treated patients</td>
<td>HPR (PRI &gt; 50%) On day 1: clopidogrel 77%, prasugrel 19% and ticagrelor 1% On day 2: clopidogrel 77%, prasugrel 17% and ticagrelor 0% On day 3: clopidogrel 85%, prasugrel 6% and ticagrelor 0%, p = 0.001</td>
<td>Bleeding requiring blood transfusion in two patients in the ticagrelor group No cases of stent thrombosis or stroke</td>
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<td>Tilemann et al&lt;sup&gt;48&lt;/sup&gt;</td>
<td>Prospective, observational 38 MI patients (27 hypothermia)</td>
<td>Impedance aggregometry 24 hour after admission when all patients had received at least two doses of ticagrelor</td>
<td>37 out of 38 (97.4%) patients had a sufficient platelet inhibition (increase in impedance of &lt; 6 Ω) No difference between the hypothermia and normothermia groups</td>
<td>1 patient: BARC 3a bleeding, 3 patients: BARC2 bleeding No stent thrombosis or recurrent atherothrombotic events</td>
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<td>Ratcovitch et al&lt;sup&gt;49&lt;/sup&gt; (TICOMA study)</td>
<td>Prospective, observational 44 patients undergoing primary PCI (41 with targeted temperature management)</td>
<td>Ticagrelor 180 mg LD/ 90 mg twice daily Blood sampling: baseline, 2, 4, 6, 8, 12 and 24 hours and then daily for up to 5 days. VerifyNow and Multiplate Primary endpoint: HPR 12 hour after the LD</td>
<td>12 hours after the LD VerifyNow: 96 (15.25 – 140.5) PRU, HPR in 12% Multiplate: 19 (12–29) U, HPR in 7% Ticagrelor concentration 85.2 (37.2–178.5) ng/mL AR-C124910XX concentration 18.3 (6.4–52.4) ng/mL Median times to sufficient platelet inhibition 3 and 4 hours</td>
<td>No cases of acute or early stent thrombosis</td>
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<td>Jiménez-Brítez et al&lt;sup&gt;50&lt;/sup&gt;</td>
<td>Retrospective observational 144 patients with hypothermia 98 PCI 61 clopidogrel-treated 32 ticagrelor-treated patients</td>
<td>Baseline and procedural data collected in a dedicated database The primary endpoint: 1. definite and probable stent thrombosis and 2 bleeding during hospitalisation</td>
<td>N/A</td>
<td>Probable or definite ST: 11.4% and 0% in clopidogrel- and ticagrelor-treated patients, p = 0.04 No differences in any (28.6% vs. 25%) or major bleeding (BARC 3 or 5) (11.4% vs. 12.5%) Similar in-hospital mortality between groups (26.2% vs. 25%)</td>
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(Continued)
Given evidence suggests that the crushed formulation of P2Y12 receptor inhibitors tablets appears as an appealing way to overcome, at least partially, the delayed onset of action observed in STEMI patients. Although many centers apply this technique, this superiority of crushing versus standard administration is based on small-sized, pharmacodynamic/pharmacokinetic studies, which have not been designed for clinical outcome differences assessment. However, a recent meta-analysis of clinical studies has clearly shown that an early effective P2Y12 inhibition is desirable, as it significantly reduces ischemic events, without an increase in major bleedings.52 A similar concept is supported by a clinical outcome study of the intravenously administered P2Y12 receptor inhibitors cangrelor, as tested over clopidogrel.53 In the very recently published CANTIC (Platelet Inhibition With CANgrelor and Crushed Ticagrelor in STEMI Patients Undergoing Primary Percutaneous Coronary Intervention) study, cangrelor was compared with placebo in 50 patients all of whom had been loaded with crushed ticagrelor 180 mg LD. Platelet reactivity (assessed by VerifyNow and VASP assays) was reduced by cangrelor versus placebo as early as 5 minutes post-bolus, at 30 minutes (primary endpoint of the study) and during the whole duration of cangrelor infusion. No signs of drug–drug interactions between cangrelor and crushed ticagrelor were observed with concomitant administration of these agents.54 The authors characterized ‘crushed’ as the fastest-acting formulation of P2Y12 receptor inhibitors available. Nevertheless, it has to be recognized that up to one-third of STEMI patients loaded with crushed formulation may still have a high platelet reactivity levels at 2 hours post-LD,54 which is a well-established predictor of thrombotic complications. Furthermore, it is arguable that in the context of almost immediate platelet inhibition, which is obtained by cangrelor, the use of crushed tablets of P2Y12 receptor inhibitors may be futile. However, cangrelor involves a more complex mode of administration (bolus plus infusion), it is expensive and without proven clinical superiority over the novel P2Y12 receptor inhibitors. Moreover, transition from the intravenous agent to oral tablets is inevitable and crushing them is likely to represent the ideal mode of administration. Of note, the potential of drug–drug interaction during transition from cangrelor to prasugrel has been raised, although there are no data regarding crushed prasugrel and cangrelor co-administration.55

Crushing could potentially ameliorate the adverse effect of morphine on platelet inhibition.15–19 This ability has been disputed by some investigators42 and relevant data are scarce. Morphine-treated patients presented higher platelet reactivity than non-morphine ones in the crushed group of the MOJITO study.27 However, in the CRUSH study, morphine (used in 76% of the whole population and 85% in the crushed prasugrel group), was not associated with any significant difference on the primary endpoint (PRU at 2 hours), as well as during the overall 24-hour study time course.28 In both studies, results were based on secondary analyses, with very

<table>
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<tr>
<th>Study</th>
<th>Type of study/Patients</th>
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<tr>
<td>Gouffran et al.51</td>
<td>Retrospective observational</td>
<td>Data at baseline, and anti-thrombotic treatment during hospitalization; systematically collected, probable-stent thrombosis during hospitalization</td>
<td>N/A</td>
<td>11 cases of ST: clopidogrel n = 4, ticagrelor n = 5, prasugrel n = 2, respectively. More ST with new P2Y12 inhibitors compared with clopidogrel: 13% vs. 4.2%, p = 0.05. BARC 5 in 5, BARC 3 in 10, BARC 3a in 3a in 11 patients</td>
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<td>Abbreviations: BARC, Bleeding Academic Research Consortium; HPR, high platelet reactivity; LD, loading dose; MI, myocardial infarction; NA, not applicable; PCI, percutaneous coronary intervention; PRI, platelet reactivity index; PRU, P2Y12 reaction units; ST, stent thrombosis; TICOMA, The effect of Ticagrelor administered through a nasogastric tube to Comatose patients undergoing acute percutaneous coronary intervention; VASP, vasodilator-stimulated phosphoprotein.</td>
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small patients numbers, and do not clearly support or exclude a potential interaction between morphine and crushing.

On-going studies are expected to provide further evidence on the role of crushing in the early STEMI phase. In the COMPARison of Pre-hospital CRUSHed versus Uncrushed Prasugrel Tablets in Patients With STEMI Undergoing primary PCI (CompareCrush) study, pre-hospital administration of crushed versus uncrushed prasugrel is evaluated. Co-primary endpoints are the percentage of patients with Thrombolysis In Myocardial Infarction flow grade 3 at initial angiography or a ≥70% ST-segment resolution directly post-PCI (ClinicalTrials.gov Identifier: NCT03296540). An orodispersible tablet of ticagrelor has also been developed. This is designed to dissolve or disintegrate on the tongue rather than being swallowed whole and could be suitable for patients with swallowing difficulties and who are unable to swallow whole tablets. Promising results have been described in healthy volunteers with reports of a bioequivalence between the orodispersible and the immediate release tablet.56 Nevertheless, comparison between the orodispersible and the crushed, film-coated tablets of ticagrelor has not been performed so far.

Intubated or comatose patients likely represent the ‘ideal’ population for administration of P2Y12 receptor inhibitors in a crushed form through a nasogastric tube. Crushing is in widely spread use in unconscious patients following OHCA. Of note, ticagrelor prescribing information supports crushing for patients who are unable to swallow whole tablets and the administration of the mixture via a nasogastric tube.57 Patients with prior stroke or dysphagia, or those who have been sedated, are other potential candidates for crushed P2Y12 receptor inhibitors tablets administration.

**Conclusion**

In patients with OHCA, who remain comatose, crushing tablets is applied in clinical practice for platelet P2Y12 receptor inhibition. In patients suffering from STEMI, current data likely support the superiority of crushed ticagrelor or prasugrel versus the administration of standard integral tablets orally. Crushed formulations of ticagrelor and prasugrel undoubtedly exhibit early signs of successful platelet inhibition, starting as soon as 30 minutes after their administration, without any bleeding concern. Larger randomized studies would be useful to draw firm conclusions and establish solid evidence on the net clinical benefit of ‘crushing’ over the usual ‘not-crushing’ practice. In their absence, as the use of crushing is not associated with any downside, it may be considered also in routine practice and not only in specific scenarios, if this is not associated with any delays.

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None.

**Conflict of Interest**

D.A. has received lecturing honoraria/advisory board fees from Astrazeneca, Bayer, Boehringer Ingelheim, AMGEN, Chiesi Hellas, Medtronic, Biotronik. Other authors have no disclosure.

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