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BRIEF REPORT

Efficacy and safety of alternative oral administrations of P2Y12-receptor inhibitors: Systematic review and meta-analysis

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Abstract

Background: Early administration of P2Y12-receptor inhibitors is recommended in all patients with acute coronary syndrome undergoing invasive management, with the aim to achieve the fastest and most effective platelet inhibition. Several trials investigated alternative methods of P2Y12-receptor inhibitor administration (mainly chewed or crushed) aimed at ensuring faster and higher platelet inhibition. Thus, we decided to perform a systematic review and meta-analysis analyzing efficacy and safety of alternative P2Y12-receptor inhibitor administration strategies.

Methods: Systematic research was performed on Pubmed, Cochrane Library, Biomed Central, and Web of Science databases. We included randomized or observational trials testing at least one P2Y12-receptor inhibitor alternative administration. The primary outcome of the study was the value of the platelet reactivity unit (PRU) at 1 h after drug administration, assessed by VerifyNow P2Y12 test (Accumetrics, Inc., San Diego, CA). Secondary outcomes were adverse bleeding events (safety outcome).

Results and discussion: Fourteen studies were selected for qualitative analysis. Five studies, all focused on ticagrelor, were selected for quantitative efficacy analyses. These five studies compared the administration of crushed/chewed ticagrelor 180 mg loading dose (LD) with the standard whole tablets LD. The pooled mean difference between the two administrations was −59.24 PRU (95% CI from −30.61 to −87.87 PRU) in favor of the crushed/chewed administration, corresponding to a 25% mean relative PRU reduction between alternative and standard P2Y12-receptor inhibitor administrations at 1 h after drug intake. A similar relationship was found in other studies on alternative administration of clopidogrel and prasugrel, not included in the quantitative analysis.

KEYWORDS
chewed, clopidogrel, crushed, P2Y12, ticagrelor

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1 | INTRODUCTION

As soon as the diagnosis of acute coronary syndrome is established, current European Guidelines recommend an early administration of P2Y12-receptor inhibitors in all patients undergoing invasive management, with the aim to achieve the fastest and most effective platelet inhibition. Clopidogrel was the first P2Y12 inhibitor in which the use of a higher LD was tested (300 mg vs 600 mg) showing that 600 mg clopidogrel reduces the rate of major adverse cardiac events because of the more intense and rapid inhibition of platelet reactivity compared to the 300-mg dose.[1,2] Next, both ticagrelor and prasugrel showed a better pharmacodynamic profile than clopidogrel, reaching quicker and more powerful platelet inhibition.[3,4] Nevertheless, newer P2Y12 receptor inhibitors take at least 30 to 60 min to achieve maximal platelet inhibition in patients with stable ischemic heart disease, and an even longer time in patients with myocardial infarction.[5] Hence, because the delay in platelet inhibition seems to be mostly related to intestinal absorption, in the last few years, several trials tried to investigate different kinds of P2Y12-receptor inhibitor administrations (mainly chewed or crushed) aimed at ensuring faster and higher platelet inhibition. The aim of the present report is to perform a systematic review and meta-analysis analyzing efficacy and safety of alternative P2Y12-receptor inhibitor administration strategies.

Essentials

- Administration of P2Y12-receptor inhibitor is recommended during acute coronary syndrome.
- Several trials investigated administration of chewed or crushed P2Y12-receptor inhibitors.
- Ticagrelor and prasugrel showed a better pharmacodynamic profile than clopidogrel.
- A 25% mean relative PRU reduction with alternative (crushed/chewed) ticagrelor intake at 1 h was found.
- The available data on safety, despite an unstandardized endpoint, seem reassuring.

2 | METHODS

The systematic research was performed on Pubmed, Cochrane Library, Biomed Central, and Web of Science databases using the following words: ((ticagrelor) OR (clopidogrel) OR (prasugrel) OR (p2y12)) AND ((chuw*) OR (chew*) OR (crush*) OR (swallow*)). Inclusion criteria for qualitative analysis were (a) randomized or observational trial, (b) administration of at least one P2Y12-receptor inhibitor (clopidogrel and/or ticagrelor and/or prasugrel) in an alternative way (crushed and/or chewed), (c) reporting at least one measurement of platelet reactivity or drug/active metabolite plasma concentration at definite times from administration. Further inclusion criteria for quantitative analysis were (a) providing at least one control arm with standard P2Y12-receptor inhibitor administration and (b) providing efficacy measurements of interest at 1 h after administration. Exclusion criteria were (a) duplicate reports, (b) duplicate of the sample population, (c) case reports/series, (d) review or meta-analysis, (e) lack of outcome of interest. All the authors agreed on the final number of studies included. The reviewers completed a database with data regarding study title, study authors, type of study, drug investigated, kind of drug administration, clinical presentation, main outcomes analyzed, pharmacokinetic measurements, techniques, and time assessment. The primary outcome of the study (efficacy outcome) was the value of PRU at 1 h after drug administration, assessed by VerifyNow P2Y12 test (Accumetrics, Inc., San Diego, CA). Secondary outcomes were adverse bleeding events (safety outcome). The quality of selected studies included in quantitative analysis was tested with the Cochrane method for randomized clinical studies.[6] The pooled mean difference with 95% CI using the inverse variance method was calculated. Considering the high likelihood of between-study variance, a random effect model was used. Statistical heterogeneity was assessed using Cochran's Q test and I^2 statistic.[7] Publication bias was appraised through the Kendall rank correlation. Prometa software 3 (Internovi, Cesena, Italy) and RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) were the software used for the meta-analysis.

3 | RESULTS AND DISCUSSION

A total of 64 records were screened, of which 14 studies were selected for qualitative analysis.[8–21] Among the 14 studies (Table 1), 10 tested ticagrelor (crushed or chewed) alternative administration,[11–20] 2 tested the effect of crushed clopidogrel,[10,21] 1 of crushed prasugrel[8] and 1 of both crushed clopidogrel and ticagrelor.[9] Only 5 were selected for quantitative efficacy analysis,[11,12,15–17] because only these studies reported PRU value at 1 h and had a control arm with standard P2Y12-receptor inhibitor administration. All these studies were focused on ticagrelor crushed/chewed administration. Of the remaining 9 studies excluded from quantitative analysis, but included in the systematic review, 3 lacked a control group,[9,13,20] whereas 6 lacked of efficacy measurement[8,10,14,18,19,21] (Figure 1).

The studies focused on clopidogrel did not report standardized measurements as required for the present analysis (PRU values 1 h after the intake). Zafar et al reported a plasmatic SR26334 peak concentration earlier after crushed delivery than after standard oral intake (44 minutes vs. 70 minutes, $P = 0.023$).[21] Instead, Khochtali et al[10] reported the absence of a significant difference in PRU with crushed clopidogrel compared with whole tablets at 24 h (199.7 ± 79 vs. 216.9 ± 70, $P = 0.53$). Steblovnik et al compared ticagrelor 180 mg LD with clopidogrel 300 mg LD administered by nasogastric tube in a comatose survivor of out-of-hospital cardiac arrest.[9] The authors found faster platelet inhibition after ticagrelor administration.[9] Only one trial tested alternative administration of

TABLE 1 Clinical trials evaluating the effects of alternative P2Y12 administration

Study	P2Y12 tested	Setting	Administration strategies	No. of patients	Efficacy assessment methods	Safety assessment
Rollini et al 2016[8]	Prasugrel (60 mg LD)	STEMI	Whole tablets Crushed tablets	52	PRU (VerifyNoW®) Plasma concentration of Prasugrel active metabolite (P-AM)	No major bleeding or other serious in-hospital AEs; one minor bleeding event (hematuria) in the crushed Prasugrel arm (which did not require drug discontinuation).
Khochtali et al 2013[10]	Clopidogrel (600 mg LD)	ACS	Whole tablets Crushed tablets	30	PRU (VerifyNoW®)	No data on safety outcomes reported.
Zafar et al 2009[21]	Clopidogrel (300 mg LD)	Healthy volunteers	Crushed tablets (via NG tube) Whole tablets	9	Plasma concentrations of SR26334	None of the participants experienced any AEs during or after the study.
Steblovnik et al 2016[9]	Clopidogrel (600 mg LD) Ticagrelor (180 mg LD)	Cardiac arrest (underwent therapeutic hypothermia)	Crushed tablets (via NG tube)	37	PRU (VerifyNoW®) PRU (Multiplate)	In-hospital incidence of stent thrombosis (5% vs. 6%), BARC 3a and 5 bleeding (15% vs. 13%), and survival with good neurological recovery (both 50%) comparable between the ticagrelor and clopidogrel groups.
Venetsanos et al 2016[15]	Ticagrelor (180 mg LD)	Stable angina	Whole tablets Crushed tablets Chewed tablets	99	PRU (VerifyNoW®)	One patient in integral ticagrelor and one in crushed ticagrelor group had a TIMI minor bleeding. One patient in the chewed ticagrelor group had a TIMI minimal bleeding.
Asher et al 2017[11]	Ticagrelor (180 mg LD)	STEMI	Whole tablets Chewed tablets	50	PRU (VerifyNoW®)	Chewing group and standard group had similar AEs rates (6 [24%] vs. 3 [12%]; 95% CI, 0.09-1.96; $P = 0.46$).
Asher et al 2017[11]	Ticagrelor (180 mg LD)	NSTEMI	Whole tablets Chewed tablets	50	PRU (VerifyNoW®)	Ticagrelor side effects reported at a similar rate for two groups: nine patients (36%) (five dyspnea and four arrhythmias) in chewing group, compared with eight (32%) (four dyspnea and four arrhythmias) in standard group, $P = 1.0$; five patients had ventricular pauses during admission; three patients reported palpitations in the first 2 weeks after discharge.
Ratcovich et al 2017[13]	Ticagrelor (180 mg LD)	Cardiac arrest (underwent targeted temperature management)	Crushed tablets (via NG tube)	44	PRU (VerifyNoW®) Plasma concentration of Ticagrelor and his metabolite AR-C124910XX	Eleven patients (25%) died in intensive care unit, nine due to irreversible neurological injury and two in cardiogenic shock complicated by multiorgan failure; no cases of acute or early stent thrombosis reported.
Niezgoda et al 2017[14]	Ticagrelor (180 mg LD)	Unstable angina	Whole tablets Crushed tablets Crushed tablets (sublingual)	49	PRU (Multiplate® ADPtest) Plasma concentration of Ticagrelor and his metabolite AR-C124910XX	No in-hospital serious AEs (including death, myocardial infarction, stroke, or early stent thrombosis). One patient reported headache and nausea during 6-h blood collection period.
Tileman et al 2016[20]	Ticagrelor (180 mg LD)	Cardiac arrest (NSTEMI, STEMI; undergone therapeutic hypothermia)	Crushed tablets (via NG tube)	38	Impedance aggregometry (CA 560-CA lumi-aggregometer)	Total of four patients (17.4%) experienced bleeding complications after admission. One BARC type 2 and one BARC type 3a bleeding occurred in hypothermia group; two BARC type 2 bleedings occurred in non-hypothermia group

(Continues)

TABLE 1 (Continued)

Study	P2Y12 tested	Setting	Administration strategies	No. of patients	Efficacy assessment methods	Safety assessment
Alexopoulos et al 2016[16]	Ticagrelor (180 mg LD)	STEMI	Whole tablets Chewed tablets	20	PRU (VerifyNoW®) Plasma concentrations of ticagrelor and his metabolite AR-C124910XX	No adverse events in any patient during in-hospital course apart from one patient with excessive intracoronary thrombus during PCI, requiring IIb/IIIa administration in crushed group
Parodi et al 2015[17]	Ticagrelor (180 mg LD)	STEMI	Whole tablets Crushed tablets	82	PRU (VerifyNoW®)	No patients experienced AEs during the study.
Teng et al 2015[18]	Ticagrelor (90 mg LD)	Healthy volunteers	Whole tablets Crushed tablets Crushed tablets (via NG tube)	36	Plasma concentrations of ticagrelor and his metabolite AR-C124910XX	All ticagrelor treatments generally well tolerated. No deaths or serious AEs in study; no volunteers discontinued due to AE; overall, 16/36 (44.4%) volunteers experienced at least one AE; Most common AEs: nervous system disorders (dizziness, headache, migraine, presyncope, and syncope) and infections (oral herpes, tooth infection, upper respiratory tract infections), in 13.9% and 11.1% of volunteers, respectively.
Teng et al 2017[19]	Ticagrelor (90 mg LD)	Healthy volunteers	Crushed tablets (with water) Crushed tablets (without water) Ticagrelor IR formulation (with water)	78	Plasma concentrations of ticagrelor and his metabolite AR-C124910XX	No deaths, serious AEs, or AEs leading to study discontinuation occurred. Seven mild, treatment-related AEs, identified by investigator, were reported in five Western subjects. The numbers (%) of subjects with at least one treatment-related AE were one (3.2%), three (9.4%), one (2.9%), and two (6.1%) with the ticagrelor OD tablet with water, without water, via a nasogastric tube, or the IR tablet, respectively. Six treatment-related AEs, identified by investigator, were reported in four Japanese subjects Numbers (%) of subjects with at least one treatment-related AE were: two (4.9%), three (7.1%), and one (2.4%) with the ticagrelor OD tablet with water, without water, or the IR tablet, respectively.

Abbreviations: ACS, acute coronary syndrome; AEs, adverse events; BARC, Bleeding Academic Research Consortium classification; IR tablets, immediate release tablets, LD, loading dose; NG tube, nasogastric tube; NSTEMI, Non-ST-segment elevation myocardial infarction; OD, once daily; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction classification.

prasugrel in ST-segment elevation MI patients.[8] A crushed prasugrel 60 mg LD led to a significant reduction in 30-min PRU values, which persisted at 1, 2 (164 vs. 95 PRU; least square mean difference = 68; 95% CI 10-126) and 4 h, compared to the whole-tablet prasugrel LD intake.

Conversely, the 10 studies focused on the administration of ticagrelor reported in a consistent fashion the presence of higher plasma concentration and pharmacological activity in patients treated with alternative oral administration of ticagrelor.[8,11,12,14–19] Considering the 5 studies included in the meta-analysis, overall 361 patients were included. The 5 studies were focused on the comparison between the administration of crushed/chewed ticagrelor 180 mg LD with the standard whole-tablet LD (Table 1, Figure 2). A total of 96 patients received crushed ticagrelor, while 44 patients received chewed ticagrelor (Figure 2). The pooled mean difference between the two administrations was −59.24 PRU (95% CI from −30.61 to −87.87 PRU) (Figure 2) in favor of the crushed/chewed administration, corresponding to a 25% mean relative PRU reduction between alternative and standard ticagrelor administrations at 1 h after drug intake. Most of the studies showed lower values of PRU at 1 h, comparable with the value of PRU of the standard administration at 2 h. A similar relationship was found also in the study from Rollini et al regarding crushed administration of prasugrel.[8] The analysis disclosed the absence of publication bias (*Z* value for Kendall's tau 0.56, *P* = 0.573). The presence of risk of selection, analytical, adjudication, attrition, and detection bias has also been evaluated (Figure 3). In

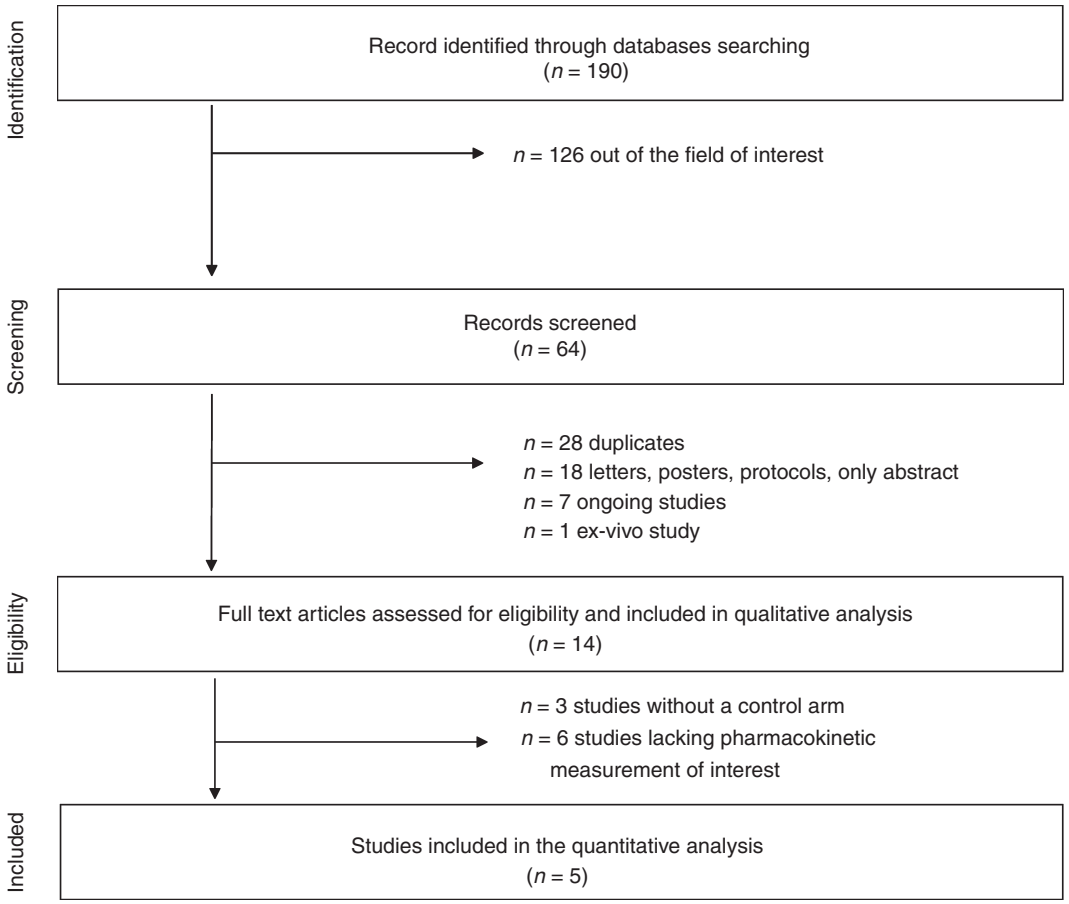

FIGURE 1 Outline of the search strategy

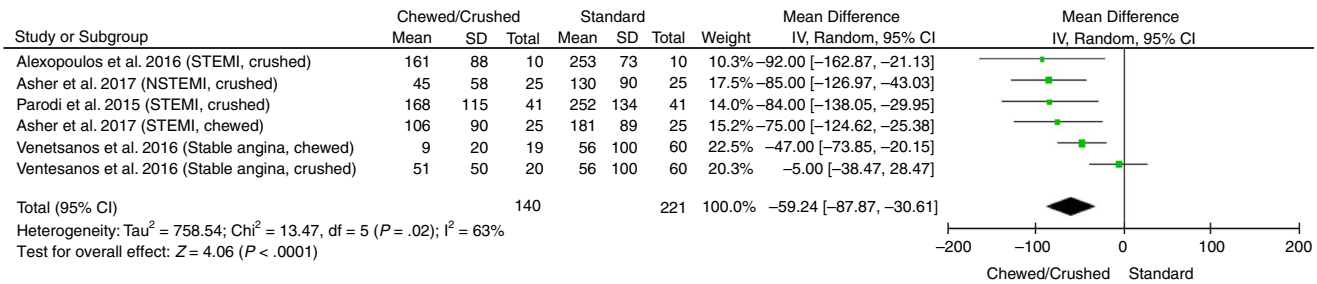

FIGURE 2 Forest plot of mean difference in platelet reactivity unit after ticagrelor alternative versus standard administration

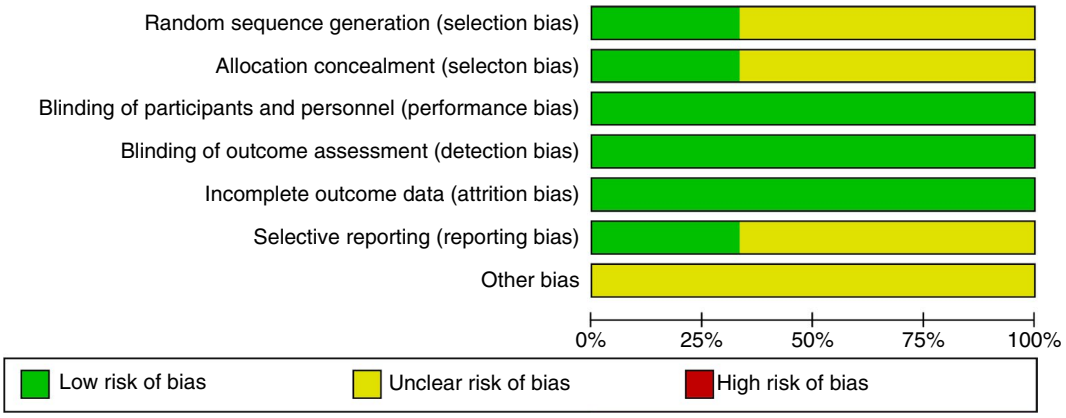

FIGURE 3 Risk of bias assessment by the Cochrane method for randomized clinical studies

all the trials included in the systematic review (n = 14), safety outcomes were also reported, but they were not standardized (Table 1). All data agreed, showing the absence of concerning differences in drug-related adverse event rate, including major and minor bleeding events, after alternative P2Y12-receptor inhibitor administration (Table 1).

Results of this systematic review and meta-analysis show that the administration of crushed/chewed ticagrelor is related to faster platelet inhibition at 1 h after drug intake compared to the whole-tablet administration. These trends are confirmed also for clopidogrel and prasugrel, even if fewer data are available. The delay in platelet inhibition in response to a LD of a P2Y12-receptor is related to several factors including drug-drug interactions, impaired intestinal absorption, increased platelet turnover, active vomiting, the clinical presentation (stable vs. acute), and patient-related factors such as age and diabetes.[22–27] Finally, we did not observe a warning for the increase in bleeding complications in any study (Table 1). The Comparison of prasugrel at the time of percutaneous Coronary intervention Or as pre-treatment At the time of diagnosis in patients with non-ST-segment elevation myocardial infarction (ACCOAST) trial showed that pretreatment with prasugrel was not associated with a decrease in total mortality and in the ischemic outcomes, but with a three-fold to six-fold increase in adverse bleeding events.[28] The ATLANTIC trial [23] failed to show improvement in coronary reperfusion before percutaneous coronary intervention by prehospital administration of ticagrelor in ST-segment myocardial infarction patients, even if a significant reduction in stent thrombosis in the prehospital group at 24 h (P = 0.008) and 30 days (P = 0.02) was found. This finding indirectly supports the hypothesis that faster platelet inhibition during ST-segment myocardial infarction could significantly influence clinical outcomes. Our analysis suggests that higher PRU inhibition could be achieved by the administration of chewed or crushed P2Y12-receptor inhibitors, because of the better bioavailability and more rapid and effective platelet inhibition than whole-tablets administration. This simple change in the administration strategy of the P2Y12 inhibitor might be beneficial in the setting of myocardial infarction. Because of the small sample size of studies considered, data of this meta-analysis have to be considered only hypothesis-generating and thus larger randomized trials are needed to confirm the real impact of administration of different P2Y12 inhibitors on clinical outcomes.

DISCLOSURE OF CONFLICT OF INTEREST

Matteo Serenelli, Rita Pavasini, Francesco Vitali, Elisabetta Tonet, Ferruccio Bilotta, and Gianluca Campo do not report any potential conflict of interest. Guido Parodi reports receiving lecture fees and/or research grants from AstraZeneca, Bayer, Chiesi, Daichii, and Merck.

AUTHOR CONTRIBUTIONS

The authors guarantee that the article is original, is not under consideration by another journal, and has not been previously published. All authors have read and approved the manuscript. The authors contributed to the manuscript as follows: Matteo Serenelli, Francesco Vitali, and Rita Pavasini: concept and design. Ferruccio Bilotta, Matteo Serenelli, Francesco Vitali, and Elisabetta Tonet: analysis and interpretation of data. Gianluca Campo and Guido Parodi: critical writing and revising the intellectual content. Matteo Serenelli and Gianluca Campo: final approval of the version to be published.

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