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ORIGINAL RESEARCH ARTICLE

Randomized, Double-Blind, Active Comparator Pharmacodynamic Study of Platelet Inhibition with Crushed and Integral Formulations of Clopidogrel and Ticagrelor in Acute Coronary Syndrome

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Abstract

Background Crushed formulations of specific antiplatelet agents produce earlier and stronger platelet inhibition. We studied the platelet inhibitory effect of crushed clopidogrel in patients with acute coronary syndrome (ACS) and its relative efficacy compared with integral clopidogrel, crushed and integral ticagrelor.

Objectives We aimed to compare the platelet inhibitory effect of crushed and integral formulations of clopidogrel and ticagrelor in patients with acute coronary syndrome (ACS).

Methods Overall, 142 patients with suspected ACS were randomly assigned to receive crushed or integral formulations of clopidogrel or ticagrelor. Platelet inhibition at baseline and 1 and 8 h was assessed using the VerifyNow assay. High on-treatment platelet reactivity (HTPR) $\geq$ 235 $P2Y_{12}$ reaction units (PRUs) 1 h after the medication loading dose was also determined.

Results The PRU and percentage inhibition median (interquartile range) at 1 h for the different formulations were as follows: crushed clopidogrel: 196.50 (155.50, 246.50), 9.36 (− 1.79, 25.10); integral clopidogrel: 189.50 (159.00, 214.00), 2.32 (− 2.67, 19.89); crushed ticagrelor: 59.00 (10.00, 96.00), 75.53 (49.12, 95.18); and integral ticagrelor: 126.50 (50.00, 168.00), 40.56 (25.59, 78.69). There was no significant difference in PRU or percentage platelet inhibition between the crushed and integral formulations of clopidogrel ($p = 0.990$, $p = 0.479$); both formulations of ticagrelor were superior to the clopidogrel formulations ($p < 0.05$). On paired comparison, crushed ticagrelor showed robust early inhibition of platelets compared with the integral formulation ($p = 0.03$). Crushed clopidogrel exhibited the maximal HTPR of 34.3%, but was < 3% for both formulations of ticagrelor.

Conclusions The platelet inhibitory effect of crushed clopidogrel is not superior to integral preparation in patients with ACS. Crushed ticagrelor produced maximal platelet inhibition acutely. HTPR rates in ACS are similar and very low with both formulations of ticagrelor, and maximal with crushed clopidogrel.

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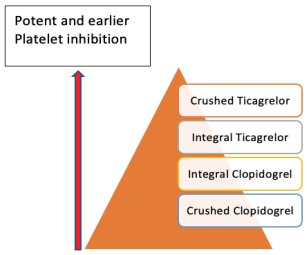
Graphical Abstract

American Journal of Cardiovascular Drugs

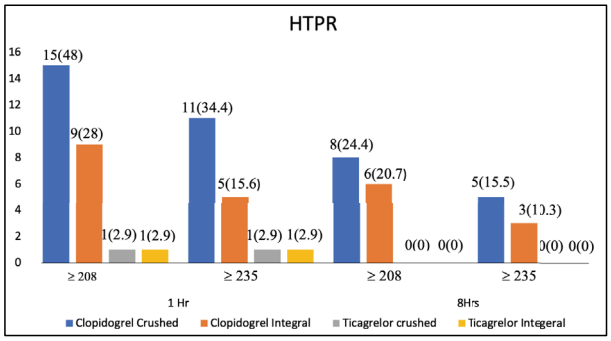
PEER-REVIEWED FEATURE

Randomized double-blind, active comparator pharmacodynamic study of platelet inhibition with crushed and integral formulations of Clopidogrel and Ticagrelor in Acute Coronary Syndrome

[Perla HG, Thomson VS, Attumalil TV, Geevar T, Alex AG, Dave RG, Nair SC, Gowri MS, Mony PK, George P, Joseph G.]



Platelet inhibition with Crushed and Integral preparations of Clopidogrel and Ticagrelor



High-on-treatment platelet reactivity in Indian patients using different PRU cut-off levels

- Crushed Clopidogrel is not superior to integral clopidogrel for acute platelet inhibition
- Crushed Ticagrelor is the most potent among the two formulations of clopidogrel and Integral ticagrelor
- High-on-treatment platelet reactivity (HTPR) to clopipdogrel is low in Indian patients compared to other ethnicities
- High-on-treatment platelet reactivity (HTPR) to ticagrelor is extremely low in Indian patients

[PRU- P2Y12 reactivity units]

Key Points

The crushed clopidogrel formulation does not provide stronger or early platelet inhibition in patients with heart attacks.

Resistance to clopidogrel is not very high in Indian patients compared with other ethnicities.

Crushed ticagrelor produces robust early platelet inhibition compared with integral ticagrelor and clopidogrel formulations in patients with heart attacks, and is more effective in women.

1 Introduction

Optimal platelet inhibition is paramount in percutaneous coronary intervention (PCI), and even more so when these procedures are necessary in the setting of acute coronary syndrome (ACS). Early and predictable platelet inhibition is mandatory to prevent stent thrombosis and ischemic events, but this should be weighed against the bleeding risk that this agent portends. Platelet reactivity is increased in ACS, and high on-treatment platelet reactivity (HTPR) to certain antiplatelet agents is also commonly encountered in this setting. HTPR has been attributed to the (1) extent of myocardial damage; (2) delayed response due to impaired intestinal absorption of medications in myocardial infarction; (3) thrombotic milieu; and (4) drug interactions [1].

Clopidogrel is still the most widely used P2Y12 inhibitor in developing countries. It is a prodrug and the platelet inhibitory effect in ACS is moderate and variable. Although variable, HTPR to integral clopidogrel occurs in up to 40% of patients depending on the platelet assay [2, 3]. Hence, many societal recommendations based on current evidence suggest ticagrelor or prasugrel for acute and improved platelet inhibition in the ACS setting [4, 5]. In a small pharmacokinetic study, crushed clopidogrel administered through a nasogastric tube in healthy volunteers showed earlier and greater bioavailability acutely compared with the integral tablets [6]. Crushed formulations of ticagrelor and prasugrel have shown earlier and more potent platelet inhibition than the integral formulations [7–9]. If the crushed formulation of clopidogrel offers superior platelet inhibition compared with the integral tablet, this could be utilized and adopted widely into practice without incremental cost in countries where treatment cost is borne by the patients (out-of-pocket expenditure) or where ticagrelor or prasugrel are not freely available. In this study, we assessed the platelet inhibitory effect of the crushed and integral formulations of clopidogrel and ticagrelor 1 h after the loading dose, and compared the HTPR with these drug formulations and adverse events in Indian patients. To our knowledge, this is the first study that has compared the crushed formulation of clopidogrel with integral and crushed formulations of ticagrelor.

2 Methods

2.1 Study Setting and Participants

This randomized, double-blind, active comparator, pharmacodynamic study was carried out in a 2800-bed tertiary care teaching hospital in South India from April 2020 through May 2021. The study was approved by the Institutional Review Board and Ethics Committee and was registered with the Clinical Trial Registry of India (CTRI/2020/06/025647).

The study was initially designed for patients with ST-elevation myocardial infarction (STEMI) undergoing primary PCI; however, because of the coronavirus disease 2019 (COVID-19) pandemic and operational issues, the institutional practice was changed to a pharmaco-invasive approach for most cases presenting with STEMI. Subsequently, we enrolled all patients with suspected ACS who satisfied the inclusion criteria. Two formulations of each drug, i.e. crushed and integral, were used, resulting in four groups: crushed clopidogrel (CC), integral clopidogrel (IC), crushed ticagrelor (CT), and integral ticagrelor (IT).

A total of 142 patients were randomized and six patients were excluded—three refused sample collection, one had drug intolerance due to recurrent vomiting, and two withdrew from the study after consenting (Fig. 1).

Consecutive patients over 18 years of age with a presumptive diagnosis of ACS, willing to give informed consent and comply with the study requirements, were eligible for recruitment. Patients already taking clopidogrel, ticagrelor, prasugrel, or glycoprotein inhibitors before randomization, or with swallowing difficulty, ongoing bleeding diathesis, platelet count < 80,000 per cu.mm, or allergy to aspirin, clopidogrel or ticagrelor were excluded.

2.2 Randomization and Treatment Allocation

Using the 'RALLOC' ado function in STATA IC/16.0 software, four permuted block randomization groups were computer-generated. Patients were blinded to the study drug but not the formulations, and the technician who performed the platelet assay was blinded to the treatment allocation of the drug and the formulation. Patients received a loading dose of clopidogrel (600 mg) or ticagrelor (180 mg) in integral or crushed form, followed by a maintenance dose of 75 mg daily or 90 mg twice daily for the initial 24 h based on the

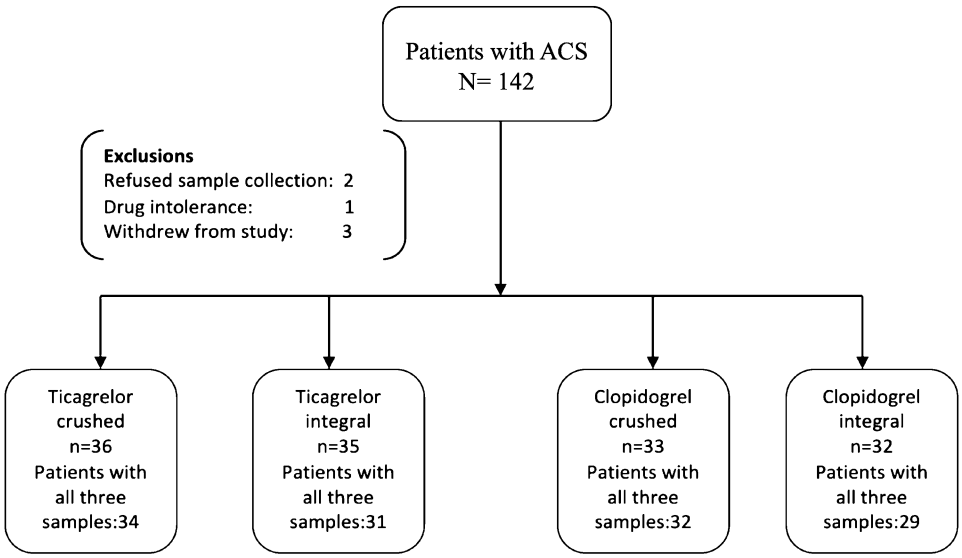


Fig. 1 Study flow chart showing the number of patients excluded from the analysis, subjects in each treatment arm, and patients for whom all three samples were available. *ACS* acute coronary syndrome

randomization protocol. A loading dose of aspirin 300 mg was also administered. Antiplatelet therapy after the completion of 24 h was left to the treating physician's discretion. At 1 month of follow-up, 71% of patients were taking clopidogrel, 6% were taking ticagrelor, and 11% were taking prasugrel.

Patients with ACS received low-molecular-weight heparin and guideline-directed anti-ischemic medications. Most of the patients with STEMI were thrombolysed and taken up for rescue or pharmaco-invasive PCI, depending on the clinical indication with appropriate COVID precautions. Patients with ACS other than STEMI underwent early invasive PCI or conservative medical management. All patients undergoing PCI received 70 units/kg of unfractionated heparin. US FDA-approved drug-eluting stents were used in all cases. Intraprocedural or post-procedural use of GPIIbIIIa inhibitors was not prohibited, and the interventionalist decided its use.

2.2.1 Preparation of the Crushed Tablet Suspension

Two ticagrelor (90 mg) or eight clopidogrel tablets (75 mg) were crushed in a mortar for 30 s using a pestle to form a powder; 20 mL of commercially available water for injection was added and stirred gently for 60 s to create a suspension. The content was transferred to a dosing cup and another 15 mL of sterile water was added and mixed using borosilicate stirring rods. A wooden spatula removed the residual powder attached to the pestle. An additional 15 mL of sterile water was added to the mortar to rinse any remaining drug. This was transferred to the dosing cup and the total contents (50 mL) were stirred for another 60 s to ensure that all remaining particles were dispersed uniformly to form an homogenous suspension.

2.3 Blood Sampling for Platelet Function Testing

Samples for platelet function testing were taken at baseline, 0 h (before drug administration), and then at 1 and 8 h following administration of the loading dose. Blood was collected from the antecubital vein into 2 ml vacutainer tubes that contained 3.2% sodium citrate (Greiner Bio-One Vacuette North America, Inc, Monroe, NC, USA) with an anticoagulant to blood ratio of 1:9. The platelet-function test was performed using the VerifyNow cartridge system (Accumetrics Inc., San Diego, CA, USA). The VerifyNow system is a turbidometric-based optical detection system that measures platelet-induced aggregation of fibrinogen-coated microparticles. Results are reported as $P2Y_{12}$ reaction units (PRU) based on the rate and extent of aggregation, which reflects the amount of $P2Y_{12}$ receptor-mediated aggregation specific to platelets.

2.3.1 Cut-Off Levels for High On-Treatment Platelet Reactivity and Calculation of Percentage Platelet Inhibition

A cut-off of ≥ 235 was used to define HTPR in our study [10–12]. The percentage of platelet inhibition at 1 and 8 h was calculated as ([PRU at 0 h—post treatment PRU]/PRU at 0 h) $\times$ 100.

2.4 Study Endpoints

The primary endpoint was platelet inhibition at 1 h following administration of crushed or integral formulations of

clopidogrel and ticagrelor, while the secondary endpoints were as follows:

1. In-hospital composite of death (all-cause), myocardial infarction, stroke or transient ischemic attack (TIA), urgent coronary revascularization, or stent thrombosis.
2. Composite of death, myocardial infarction, stroke or TIA, urgent revascularization, or stent thrombosis at 30 days.
3. Prevalence of HTPR with the different formulations of clopidogrel and ticagrelor using the VerifyNow assay within 24 h of the loading dose.
4. Association between HTPR and thrombolysis in myocardial infarction (TIMI) flow in the angiogram.
5. Association between HTPR and baseline risk factors.

The safety endpoint was major and minor bleeding as defined by the Plato criteria [13].

2.5 Sample Size Calculation

A minimum of 30 samples in each group would give us an adequate power of 90% to detect a minimum difference of 10 PRUs in delta change between the groups, considering an alpha of 0.01667 (0.05/3 multiple comparisons). We assumed a standard deviation (SD) of 10 and 15% for the delta change at 1 h and 8 h, respectively, for the calculation. This sample size would also be adequate to detect a minimum of 100 PRUs difference (at 1 h) and 90 PRUs difference (at 8 h) between the groups, with 80% power.

2.6 Statistical Analysis

Data were summarized using mean (SD) or median (interquartile range [IQR]) depending on the normality. The clinical and demographical variables among the four groups were compared using analysis of variance (ANOVA) for continuous variables and Chi-square test for categorical variables. A p-value < 0.05 was considered significant for pairwise comparisons; for multiple comparisons, Bonferroni correction was applied to the p-values. A per-protocol analysis was conducted to compare different drug formulations for efficacy in platelet inhibition and adverse events. The PRU at 1 and 8 h had a skewed distribution; thus, PRUs at all time points were log-transformed and a repeated-measures ANOVA was performed to provide the effect of drug over time. The results were visualized with a median (95% confidence interval [CI]) as a connected chart. The association of HTPR with baseline characteristics at both time points (1 and 8 h) was analyzed using the Chi-square test. The Fisher's exact test was used to compare in-hospital and 30-day major cardiovascular event (MACE) outcomes, and logistic regression was performed to assess the effect of opioids on HTPR. A p-value < 0.05 was considered significant for all comparisons. All the analyses were performed using STATA IC/16.0.

3 Results

Baseline samples were available for all 136 patients. One-hour PRU values were unavailable for four patients (two for ticagrelor crushed, one for clopidogrel crushed, and one for ticagrelor integral), and 8-h PRU samples were unavailable for six patients (two for ticagrelor crushed, three for clopidogrel integral, and one for ticagrelor whole) due to technical or processing errors.

The time required for preparing the crushed formulation of the medications was 4.68 ± 1.90 min. Overall, there was an additional 3.47-min delay in administering the crushed (13.91 ±3.90) formulation compared with the integral tablets (9.73 ± 3.25) [$p < 0.001$].

3.1 Baseline Demographics, Risk Factors, Clinical Presentation, Investigations, and Concomitant Medications

All the demographic and baseline characteristics are listed in Table 1; males constituted 72% of the study population. Dyslipidemia was diagnosed less frequently in the crushed clopidogrel group, and tirofiban was used most often in the integral clopidogrel arm. All other parameters were similar in the four groups.

Sixty-five (48%) patients had STEMI, and the remaining were diagnosed with non-STEMI (NSTEMI) or unstable angina. Forty-five patients (69%) with STEMI were thrombolysed, and streptokinase was the lytic agent used in 80% of these cases. Seventy patients (51%) underwent PCI and the remaining patients were either referred for coronary artery bypass surgery or managed conservatively.

3.2 Platelet Inhibition with Different Drugs and Formulations

There was no significant difference in platelet inhibition between the crushed and integral formulations of clopidogrel ($p > 0.990$ for PRU at 1 and 8 h) and for the percentage change in platelet inhibition ($p = 0.479$ at 1 h and $p > 0.990$ at 8 h) (Table 2 and Figs. 2 and 3).

The integral and crushed formulations of ticagrelor showed significantly more potent platelet inhibition (lower PRU and higher percentage of inhibition) compared with the integral and crushed preparations of clopidogrel at both time points ($p < 0.001$ for all comparisons).

On paired comparison of different formulations of ticagrelor, crushed ticagrelor showed robust early platelet

Table 1 Baseline demographics, risk factors, clinical presentation, investigations, and concomitant medications

	Ticagrelor integral $n = 35$	Ticagrelor crushed $n = 36$	Clopidogrel integral $n = 32$	Clopidogrel crushed $n = 33$	p-value
Demographics and risk profile					
Age in years, median (IQR)	56.03 (12.21)	56.39 (12.49)	58.31 (10.85)	59.45 (10.97)	0.583
Sex (male)	30 (85.70)	23 (63.90)	22 (68.80)	23 (69.70)	0.195
Diabetes	17 (48.60)	21 (58.30)	21 (65.60)	22 (66.70)	0.398
Hypertension	14 (40.00)	20 (55.60)	15 (46.90)	13 (40.60)	0.529
Dyslipidaemia	14 (40.00)	19 (52.80)	15 (46.90)	7 (21.20)	0.048
Prior coronary artery Disease	5 (14.30)	1 (2.80)	1 (3.10)	5 (15.20)	0.133
Chronic kidney disease	1 (2.90)	1 (2.80)	1 (3.10)	2 (6.10)	0.872
Smoking	10 (28.60)	6 (16.70)	4 (12.50)	6 (18.20)	0.378
Alcoholism	6 (17.10)	6 (16.70)	3 (9.40)	8 (24.20)	0.465
Patient characteristics and lab parameters					
Pulse	92.80 (20.90)	85.00 (12.52)	86.84 (18.13)	82.39 (15.55)	0.078
Systolic blood pressure	130.26 (23.55)	132.72 (30.36)	126.63 (23.65)	133.61 (27.61)	0.714
Diastolic blood pressure	80.29 (11.54)	79.00 (13.89)	76.81 (14.80)	77.85 (13.91)	0.747
Killip class at admission					
Killip 1/2	29 (93.55)	29 (93.55)	29 (87.88)	28 (84.85)	0.578
Killip 3/4	2 (6.45)	2 (6.45)	4 (12.12)	5 (15.15)	
Heart failure	5 (14.30)	2 (5.60)	2 (6.30)	5 (15.20)	0.454
Type of ACS					
Unstable angina	2 (5.70)	1 (2.80)	1 (3.10)	1 (3.00)	NA
NSTEMI	19 (54.30)	16 (44.40)	10 (31.30)	21 (63.60)	
STEMI	14 (40.00)	19 (52.80)	21 (65.60)	11 (33.30)	
Thrombolysis					
Streptokinase	5 (55.50)	11 (84.61)	13 (86.66)	7 (87.50)	0.233
Reteplase	4 (45.50	2 (15.38)	2 (13.33)	1 (12.50)	
Type of endovascular revascularisation					
Primary	2 (5.70)	3 (8.30)	6 (18.80)	2 (6.10)	NA
Early Invasive	11 (31.40)	10 (27.80)	4 (12.50)	9 (27.30)	
Pharmacoinvasive	3 (8.60)	7 (19.40)	6 (18.80)	2 (6.10)	
Elective	0 (0.00)	1 (2.80)	0 (0.00)	0 (0.00)	
Rescue	0 (0.00)	1 (2.80)	2 (6.30)	1 (3.00)	
No PCI performed	19 (54.30)	14 (38.90)	14 (43.80)	19 (57.60)	
Investigations					
White cell count x 1000 mm^3	9.5 (7.7, 11.7)	10.7 (8.75, 12.2)	10.5 (9.2, 13.1)	9.8 (8.3, 11.3)	0.756
Platelets x 1000 mm^3	272 (231,296)	288 (229, 336)	287 (227, 337)	252 (201, 306)	0.564
Hemoglobin (gm/L)	14.03 (1.83)	13.61 (1.95)	13.98 (1.90)	12.94 (1.89)	0.076
Creatinine (mg/dl)	0.90 (0.80, 1.10)	0.80 (0.70, 0.99)	0.88 (0.72, 1.01)	0.93 (0.72, 1.10)	0.133
Total cholesterol (mg/dl)	185.64 (57.21)	190.26 (50.09)	191.72 (55.93)	166.71 (55.11)	0.242
Triglycerides (mg/dl)	131.00 (92.00, 191.00)	160.00 (128.00, 253.00)	155.00 (106.50, 243.50)	137.00 (107.00, 214.00)	0.194
Low density lipoproteins (mg/dl)	114.50 (88.00, 154.00)	131.50 (113.50, 150.50)	132.50 (96.00, 177.00)	110.00 (80.00, 140.00)	0.137
HBA1C	7.05 (5.80, 8.80)	6.65 (6.00, 7.90)	8.00 (5.50, 9.65)	7.45 (6.25, 9.95)	0.338
Left ventricular ejection fraction (EF)	53.40 (44.80, 57.20)	46.90 (42.25, 54.55)	46.90 (42.45, 54.95)	47.00 (39.00, 56.00)	0.67
Concomitant medications					
Aspirin	35 (100.00)	36 (100.00)	32 (100.00)	33 (100.00)	NA
Unfractionated heparin	10 (28.60)	10 (29.40)	14 (50.00)	12 (37.50)	0.251
Low molecular weight Heparin	25 (71.40)	21 (61.80)	13 (46.40)	17 (53.10)	
Tirofiban	3 (8.57)	6 (16.67)	11 (34.48)	2 (6.06)	0.008

Table 1 (continued)

	Ticagrelor integral $n = 35$	Ticagrelor crushed $n = 36$	Clopidogrel integral $n = 32$	Clopidogrel crushed $n = 33$	p-value
Fentanyl	5 (14.30)	7 (19.40)	3 (9.40)	7 (21.20)	0.555
Morphine	3 (8.60)	0 (0.00)	1 (3.10)	2 (6.10)	0.322
ACE inhibitors	31 (88.60)	32 (88.90)	30 (93.80)	29 (87.90)	0.862
Beta-blockers	32 (91.40)	35 (97.20)	30 (93.80)	33 (100.00)	0.366
Statins	35 (100.00)	36 (100.00)	32 (100.00)	33 (100.00)	NA

Data are expressed as *n* (%) or mean ± SD

ACE angiotensin-converting enzyme, *ACS* acute coronary syndrome, *IQR* interquartile range, *NA* not applicable, *NSTEMI* non-ST elevation myocardial infarction, *PCI* percutaneous coronary intervention, *STEMI* ST elevation myocardial infarction

Table 2 Platelet reactivity units and percentage inhibition at different time points according to treatment allocation

	Ticagrelor integral $n = 35$	Ticagrelor crushed $n = 36$	Clopidogrel integral $n = 32$	Clopidogrel crushed $n = 33$	Overall p-value
PRU zero-hour	201.00 (177.00, 243.00)	211.00 (189.00, 261.00)	204.00 (179.00, 255.50)	243.00 (185.00, 270.00)	0.158
PRU One-hour post-loading dose	126.50 (50.00, 168.00)[*,†,‡]	59.00 (10.00, 96.00)[*,†,§]	189.50 (159.00, 214.00)[‡,§]	196.50 (155.50, 246.50)[‡,§]	< 0.001
PRU Eight hours post-loading dose	39.50 (11.00, 71.00)[*,†]	37.00 (10.00, 54.00)[*,†]	153.00 (96.00, 195.00)[‡,§]	145.00 (88.00, 204.00)[‡,§]	< 0.001
Percentage of platelet inhibition at one hour	40.56 (25.59, 78.69)[*,†,‡]	75.53 (49.12, 95.18)[*,†,§]	2.32 (− 2.67, 19.89)[‡,§]	9.36 (− 1.79, 25.10)[‡,§]	< 0.001
Percentage of platelet inhibition at eight hours	81.61 (67.74, 94.06)[*,†]	82.09 (73.02, 95.80)[*,†]	29.56 (9.45, 55.26)[‡,§]	31.58 (− 1.69, 65.89)[‡,§]	< 0.001

Data are expressed as median (interquartile ranges). *PRU* platelet reactivity units

[*]Significantly different from clopidogrel crushed

[†]Significantly different from clopidogrel integral

[‡]Significantly different from ticagrelor crushed

[§]Significantly different from ticagrelor integral

inhibition (median difference of 152 PRU units and 76% platelet inhibition from baseline) than integral formulations (median difference of 75 PRUs and 41% platelet inhibition from baseline ($p < 0.033$ for PRUs and $p < 0.027$ for percentage inhibition). This difference leveled off at 8 h post-drug administration (Table 2, Figs. 2 and 3).

All four groups had similar in-hospital and 30-day composite outcomes (Table 3). There were numerically more adverse events in the integral ticagrelor group, and bleeding events occurred more frequently in the integral ticagrelor and crushed clopidogrel groups (Table 4)

3.3 High On-Treatment Platelet Reactivity

The crushed clopidogrel treatment group demonstrated the maximum HTPR at 1 and 8 h. On paired comparison of crushed and integral clopidogrel, the difference in HTPR was statistically significant at 1 h (Chi-square statistic 12, $p < 0.001$).

HTPR values were the lowest and identical for both formulations of ticagrelor at 1 and 8 h. There were no patients with HTPR in either of the ticagrelor groups at 8 h (Table 5). HTPR rates were similar to the entire cohort even when patients who received tirofiban were excluded from the analysis (Online Resource Table 1).

Women exhibited higher HTPR 1 h post loading dose of medications. Integral ticagrelor was not superior to crushed or integral clopidogrel tablets in platelet inhibition at 1 h in women compared with men (Online Resource Table 2). None of the coronary risk factors, the severity of disease at presentation (Killip's Class), or TIMI flow in the angiogram was associated with HTPR (Table 6 and Online Resource Table 3). Opioid use was not associated with increased HTPR (Online Resource Table 4).

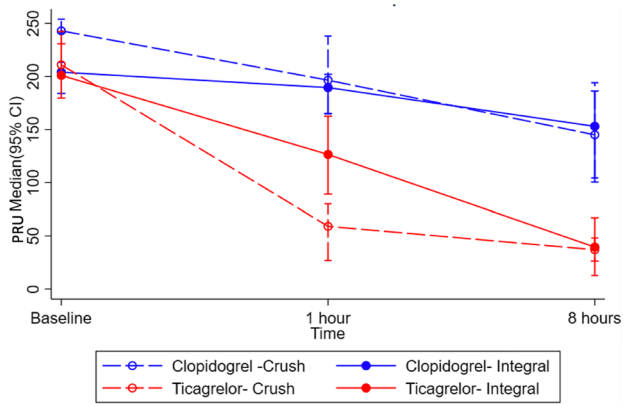


Fig. 2 PRUs at different time points in the four treatment groups. Median (95% CI) PRU values are presented. Platelet reactivity is markedly reduced in the ticagrelor groups, with maximum inhibition in the crushed group at 1 h. Both formulations of ticagrelor produced more potent and earlier platelet inhibition than clopidogrel. There was no difference in the PRU between the two clopidogrel formulations at either time point. *PRU* $P2Y_{12}$ reactivity units, *CI* confidence interval

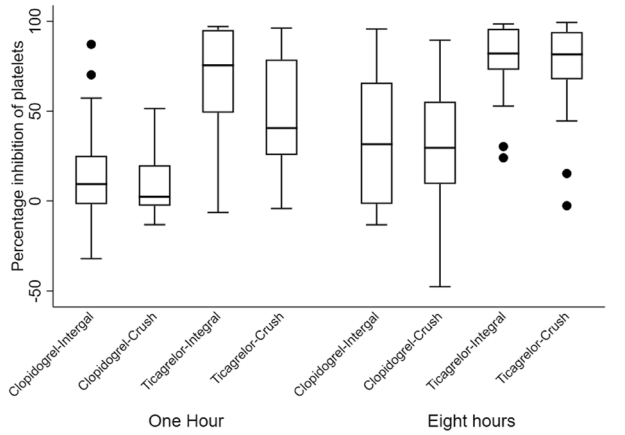


Fig. 3 Percentage inhibition of platelets over time according to treatment allocation. Early platelet inhibition (percentage inhibition from baseline) was much higher in the ticagrelor groups compared with clopidogrel at both time points, and there was no significant difference between the two ticagrelor formulations at either time point. The box-whisker plot represents the percentage of platelet inhibition from baseline; the middle line in the box represents the median; the top and bottom lines of the box represent interquartile ranges; the whiskers represent the 5th and 95th percentiles; and the solid black circles represent outliers

4 Discussion

4.1 Platelet Inhibition with Different Drug Formulations

Contrary to expectation, crushed clopidogrel did not produce earlier or more pronounced platelet inhibition than the integral formulation. There was no difference in platelet inhibition between the two formulations at 1 or 8 h, and thus there is no additional benefit in crushing clopidogrel tablets for earlier platelet inhibition. Only one small study of nine healthy subjects has been described in the literature, where crushed clopidogrel tablets were shown to have better bioavailability, but here, the drug was administered through a nasogastric tube and the platelet reactivity was not measured [6]. The lower efficacy of crushed clopidogrel tablets is probably due to their dissolution characteristics. Clopidogrel dissolves faster in an acidic medium than in a non-acidic medium [14]. The ph of 6.7 in saliva compared with 2.0 in the stomach could explain the poor absorption and blunted platelet inhibitory response compared with the integral formulation. This is the largest pharmacodynamic study that compared crushed and integral clopidogrel in the setting of ACS.

Ticagrelor therapy resulted in earlier and more pronounced platelet inhibition than clopidogrel. This has been previously documented in the Onset/Offset study, which compared ticagrelor and clopidogrel in patients with stable coronary artery disease where platelet inhibition was determined by light transmittance aggregometry (LTA) [15]. The crushed formulation of ticagrelor produced even more potent and early platelet inhibition, similar to another small study that randomized STEMI patients to receive crushed or integral ticagrelor [16]. A systematic review and meta-analysis of five studies comparing crushed and integral ticagrelor (180 mg) demonstrated a pooled mean difference of − 59.2 PRUs in favor of the crushed preparation at 1 h post loading dose [8]. The median difference observed in our study was − 67.5 PRUs. As expected, the superior platelet inhibitory effect of the crushed ticagrelor formulation, as compared with the integral formulation, disappeared in 8 h.

4.2 Difference in Platelet Inhibition in the Indian Population and Other Ethnicities

The mean PRU 8 h following a loading dose of integral ticagrelor (180 mg) was 71 ± 55 and 251 ± 71 for clopidogrel (600 mg), in an East Asian study [17]. The corresponding median (IQR) value in our study for integral ticagrelor was 39.5 (11, 71), and 153 (96, 195) for integral clopidogrel. In predominantly White subjects, a study was undertaken to see the effect of high platelet reactivity on subsequent adverse outcomes in patients undergoing PCI; the PRU, 12 h after a loading dose of clopidogrel 600 mg, was 183 ± 94 [10]. In STEMI patients of European ethnicity whose baseline PRU was similar to our study, the PRU at 1 h after a 180 mg loading dose of integral ticagrelor was 253 (208, 298) Least square estimation (LSE) (95% CI), and 161 (106, 161) LSE (95% CI) with crushed formulations. This was much higher than observed in our study [median (IQR) 126.5 (50, 168) for the integral

Table 3 In-hospital and 30-day adverse events and safety outcomes

Variables	Ticagrelor		Clopidogrel		p-value
	Integral ($n = 35$)	Crushed ($n = 36$)	Integral ($n = 32$)	Crushed ($n = 33$)	
[1]In-hospital composite outcome	5 (14.30)	1 (2.80)	1 (3.10)	0 (0.00)	0.053
[2]30-day composite outcome	5 (14.30)	1 (2.80)	2 (6.30)	0 (0.00)	0.057
Minor Bleeding	2 (5.70)	0 (0.00)	0 (0.00)	2 (6.10)	0.297
Major Bleeding	1 (2.90)	0 (0.00)	0 (0.00)	1 (3.00)	

Values are *n* (%)

[1]Composite of in-hospital death, myocardial infarction, stroke, urgent revascularization, or stent thrombosis

[2]Death, myocardial infarction, stroke, stent thrombosis or urgent revascularization at 30 days. One additional death occurred within 30 days

Table 4 Individual components of major adverse cardiac events and bleeding

Adverse events	Ticagrelor integral $n = 35$	Ticagrelor crushed $n = 36$	Clopidogrel integral $n = 32$	Clopidogrel crushed $n = 33$
[1]Death	2	1	1	0
Myocardial infarction	1	0	0	0
Urgent revascularisation	1	0	0	0
Stroke	1	0	0	0
Stent thrombosis				
Definite	1	0	0	0
Bleeding[2]				
Major	1	0	0	1
Minor	2	0	0	2
Access site hematoma	2	0	0	2
Pulmonary embolism	0	0	1	0

[1]There was an additional death in the integral Clopidogrel group within 30 days presumably due to recurrent pulmonary embolism. All other adverse events and bleeding parameters were the same as in-hospital outcomes

[2]Becker RC, Bassand JP, Budaj A et al. Bleeding complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J 2011;32:2933–44

formulation, and 59 (10, 96) for the crushed formulation]. In the same study, the percentage inhibition of platelets at 1 h was 0.0 (0.0, 20.0) for integral ticagrelor and 48 (18.8, 68.5) for the crushed formulation. In our study, the corresponding values were median (IQR) 40.56 (25.59, 78.69) for integral ticagrelor and 75.53 (49.12, 95.18) for the crushed formulation [16]. Thus, the Indian subjects generally hyper-respond to $P2Y_{12}$ inhibitors compared with East Asian, Western, or European ethnicities. This could be likely due to genetic factors such as gene polymorphisms in CYP2C19*2 loss-of-function allele, which was present in 33% of the participants in an Indian study but translated to clopidogrel resistance in only 1.4% of the patients [18]. In another Indian study that looked at genetic polymorphisms in patients with ischemic stroke taking clopidogrel, none of the genetic variants CYP2C19*2, *3,*4, CYP2C9*3, CYP2B6, and P2Y12 were found to have a significant association with clopidogrel resistance [19].

4.3 High On-Treatment Platelet Reactivity in the Indian Population Compared with Other Ethnicities

In keeping with the above finding, we found a relatively low prevalence of HTPR to integral clopidogrel after a loading dose of 600 mg, using an HTPR cut-off of ≥ 235 PRUs at 1 h. Crushed clopidogrel demonstrated a significantly higher HTPR of 34% compared with integral clopidogrel and both formulations of ticagrelor. The HTPR rate with integral clopidogrel was 15.63% and 10.34% at 1 and 8 h post-drug administration, respectively, which is much lower than observed in the Western population, where the HTPR rate was 40.8% at 12–24 h after clopidogrel administration [2]. The only other study in Indian patients using the VerifyNow assay reported a non-responder rate of 32% in patients receiving clopidogrel 75 mg twice daily approximately 5 days after PCI [20]. However, this study used a PRU cut-off of ≥ 213 to define clopidogrel resistance. In our study, the HTPR rate was 28%, with a PRU cut-off of ≥ 208 at 1 h following a loading dose of clopidogrel 600 mg. We had previously reported a non-responder rate of 29.2% at 24 h following a 300 mg loading dose of clopidogrel by LTA [21]. Patel et al. reported clopidogrel resistance in 15.4%, by LTA, of patients with ischemic stroke receiving clopidogrel 75 mg for at least 15 days [22]. Both these Indian studies

Table 5 High on-treatment platelet reactivity based on different cut-off levels

HTPR	*n*	≥ 208[1] One hour	Eight hour	≥ 235[2] One hour	Eight hour
Clopidogrel Crushed	33	15 (45.45)	8 (24.24)	11 (34.38)	5 (15.15)
Clopidogrel Integral	32	9 (28.13)	6 (20.69)	5 (15.63)	3 (10.34)
Ticagrelor Crushed	35	1 (2.94)	0 (0.00)	1 (2.94)	0 (0.00)
Ticagrelor Integral	36	1 (2.94)	0 (0.00)	1 (2.94)	0 (0.00)
p-value		< 0.001	< 0.001	< 0.001	0.019

Values are *n* (%). HTPR—high on treatment platelet reactivity.

[1]Park et al 7. Park D-W, Lee PH, Jang S et al. Effect of low-dose versus standard-dose ticagrelor and clopidogrel on platelet inhibition in acute coronary syndromes. Journal of the American College of Cardiology 2018;71:1594–1595

[2]Collet et al 6. Collet J-P, Cuisset T, Rangé G et al. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. New England Journal of Medicine 2012;367:2100–2109

Table 6 Association between HTPR and baseline characteristics at one hour post loading dose of drugs

HTPR	≤ 208	≥ 208	p value	≤ 235	≥ 235	p-value
Male	80 (75.50)	16 (61.50)	0.153	88 (77.20)	8 (44.40)	0.004
Female	26 (24.50)	10 (38.50)		26 (22.80)	10 (55.60)	
Diabetes	61 (57.50)	17 (65.40)	0.466	68 (59.60)	10 (55.60)	0.743
Hypertension	47 (44.80)	13 (50.00)	0.631	51 (45.10)	9 (50.00)	0.700
Dyslipidemia	48 (45.30)	6 (23.10)	0.039	49 (43.00)	5 (27.80)	0.223
Prior CAD	9 (8.50)	3 (11.50)	0.628	9 (7.90)	3 (16.70)	0.229
CKD	3 (2.80)	1 (3.80)	0.787	4 (3.50)	0 (0.00)	0.420
Smoking	25 (23.60)	1 (3.80)	0.023	26 (22.80)	0 (0.00)	0.024
Alcohol	21 (19.80)	2 (7.70)	0.144	21 (18.40)	2 (11.10)	0.447
Killip class						
Killip 1-2	90 (90.00)	22 (88.00)	0.770	96 (88.90)	16 (94.10)	0.512
Killip 3-4	10 (10.00)	3 (12.00)		12 (11.10)	1 (5.90)	
TIMI flow in angiogram						
TIMI 0/1	23 (29.49)	3 (18.75)	0.382	24 (28.24)	2 (22.22)	0.701
TIMI 2/3	55 (70.51)	13 (81.25)		61 (71.76)	7 (77.78)	

Values are *n* (%)

HTPR high on treatment platelet reactivity, *CAD* coronary artery disease, *CKD* chronic kidney disease, *TIMI* thrombolysis in myocardial infarction. High on treatment platelet reactivity was associated with female gender

used 10 micromoles of adenosine diphosphate (ADP) as the agonist. Thus, there seems to be a wide range in the clopidogrel responder rate with different platelet assays.

HTPR rates of 12.5% and 70% for crushed and integral formulations of ticagrelor in patients with STEMI were reported in a small European study [16]. In another study comparing ticagrelor with prasugrel in patients with STEMI, the HTPR (defined as ≥ 208 PRUs) was 42.6% for ticagrelor at 2 h post loading of medications [23]. Korean and European studies have previously documented the absence of HTPR with ticagrelor at least 2 h after the loading dose [16, 17]. Ticagrelor exhibited an extremely low HTPR rate of 2.94% 1 h after drug administration, and there were no patients with HTPR at 8 h in our study. Thus, similar to clopidogrel, HTPR rates in ticagrelor were lower in Indian patients than in other ethnicities.

Women exhibited higher HTPR than men 1 h after the loading dose (Table 6, Online Resource Table 2), however this difference disappeared with time. Unlike in men, platelet inhibition with integral ticagrelor was not superior to either formulation of clopidogrel at the earlier time in women. However, crushed ticagrelor formulation retained its potency even in this subgroup of patients. Tavenier et al. also observed and documented the lack of difference in PRU between sexes with the crushed ticagrelor preparation in STEMI patients where the platelet assay was done immediately following primary PCI [24]. Higher on-treatment platelet reactivity in women [25, 26] has been

attributed to the greater leucocyte-platelet aggregation formation and protease-activated receptor (PAR)-1-mediated platelet reactivity. The lack of enhanced benefit with ticagrelor or prasugrel in women with high residual on-treatment platelet reactivity was described in another study [27]. Thus, crushed ticagrelor may be advocated in women with ACS to overcome HTPR, especially in urgent PCI. However, the efficacy of this approach must be proven in adequately powered studies with clinical outcomes as endpoints. We did not observe a significant effect in HTPR with opioid use, and HTPR had no bearing on TIMI flow on the coronary angiogram.

5 Adverse Events

There was a trend toward increased adverse effects in the integral ticagrelor arm. These findings were not replicated in the crushed ticagrelor group, demonstrating more aggressive platelet inhibition. Hence, this is likely due to chance and unlikely to be because of the drug, and larger adequately powered studies may be necessary to confirm or refute these findings. One patient developed stent thrombosis; this patient had a baseline PRU of 78, which decreased to 7 following the loading dose of the drug, but reached pretreatment levels at 8 h. Intravascular ultrasound imaging revealed an undersized and underexpanded stent that was optimized by post-dilatation using a larger balloon catheter. This patient made an uneventful recovery and was continued on ticagrelor therapy. Major bleeding was not different between the different drugs and formulations.

6 Limitations

A pharmacokinetic study was not conducted, therefore the bioavailability of the different drugs and formulations could not be ascertained. Patients were only taking the study drug for 24 h, and only a small proportion of the patients remained on the allocated medications. This was a single-center study and we used only a single modality (VerifyNow) to assess platelet function; therefore, our determination of HTPR cannot be extrapolated to platelet function assessed by other tests. Genotyping was not carried out in patients with HTPR, and therefore prevalent polymorphisms could not be identified. Despite these deficiencies, our study is the first to compare the platelet inhibitory effect of different ticagrelor and clopidogrel drug formulations and document the HTPR rates with these medications in Indian patients with ACS.

7 Conclusion

The crushed clopidogrel formulation is not superior to integral clopidogrel for early platelet inhibition and should not be used in ACS. Ticagrelor is more potent than clopidogrel, and crushed ticagrelor produced earlier platelet inhibition than integral ticagrelor. Bleeding events were not higher with ticagrelor. HTPR rates are low for both clopidogrel and ticagrelor in Indian patients compared with other ethnicities. Multicenter studies with clinical endpoints incorporating pharmacokinetic, pharmacodynamic, and genetic polymorphisms must be undertaken in Indian patients to find the optimal dose of ticagrelor, balancing adverse events and clinical efficacy.

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Declarations

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Consent to participate Informed consent was obtained from all trial participants.

Consent for publication Not applicable.

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Code availability Not applicable.

Authors' contributions HTP: study conception, data interpretation, and manuscript writing. VST: design and conception of the study, data interpretation, intellectual content, and manuscript writing. TVA: design, data interpretation, and manuscript writing. TG: study conception, data interpretation, and writing of the manuscript. AGA: data interpretation and writing of the manuscript. RGD: data verification, analysis, and manuscript editing. SCN: intellectual content, revision, and manuscript writing. MG: data verification, analysis, and manuscript preparation. PKM: design of the study, analysis, and manuscript

revision. PG: intellectual content, revision, and manuscript editing. GJ: intellectual content, revision, and manuscript writing.

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