ORIGINAL RESEARCH

Effects of Crushed Ticagrelor Versus Eptifibatide Bolus Plus Clopidogrel in Troponin-Negative Acute Coronary Syndrome Patients Undergoing Percutaneous Coronary Intervention: A Randomized Clinical Trial

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***Background*—**After a loading dose of ticagrelor, the rate of high on-treatment platelet reactivity remains elevated, which increases periprocedural myocardial infarction and injury. This indicates that faster platelet inhibition with crushed ticagrelor (CTIC) or eptifibatide is needed to reduce high on-treatment platelet reactivity. The efficacy of CTIC versus eptifibatide bolus plus clopidogrel is unknown.

***Methods and Results*—**A total of 100 $P2Y_{12}$ naïve, troponin-negative patients with acute coronary syndrome were randomized to CTIC (180 mg) versus eptifibatide bolus (180 μg/kg×2 intravenous boluses) plus clopidogrel (600 mg) at the time of percutaneous coronary intervention. High on-treatment platelet reactivity was markedly higher with CTIC versus eptifibatide bolus plus clopidogrel (42% versus 0%; $P<0.001$) at 30 minutes and persisted up to 2 hours (12% versus 0%; $P=0.01$, respectively). Platelet aggregation by adenosine diphosphate dropped faster from baseline with eptifibatide bolus plus clopidogrel versus CTIC (0.5 versus 2 hours, respectively) and was higher with CTIC versus eptifibatide bolus plus clopidogrel at 0.5, 2, and 4 hours after loading dose (53±12% versus 1.3±2%; 35±11% versus 0.34±1.0%; and 23±9% versus 3.5±2%, respectively; $P<0.001$). Eptifibatide bolus plus clopidogrel, but not CTIC, significantly inhibited platelet aggregation induced by thrombin-receptor activating peptide. Periprocedural myocardial infarction and injury was higher with CTIC versus eptifibatide bolus plus clopidogrel (48% versus 28%, respectively; $P=0.035$). Post–percutaneous coronary intervention hemoglobin levels were not different between groups.

***Conclusions*—**Eptifibatide bolus plus clopidogrel led to faster and more potent platelet inhibition than CTIC and reduced periprocedural myocardial infarction and injury in troponin-negative acute coronary syndrome patients undergoing percutaneous coronary intervention, with no significant hemoglobin drop after percutaneous coronary intervention.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT02925923. **(*J Am Heart Assoc*. 2019;8: e012844. DOI: 10.1161/JAHA.119.012844.)**

Key Words: crushed ticagrelor • eptifibatide bolus + clopidogrel • high on-treatment platelet reactivity • Unstable angina/ACS

Although early initiation of $P2Y_{12}$ inhibitors before cardiac catheterization in patients with acute coronary syndrome (ACS) may protect them from thrombotic events after percutaneous coronary intervention (PCI), these events are less likely to occur in low-risk ACS patients with negative troponin.[1] Furthermore, upstream administration of $P2Y_{12}$ inhibitors before cardiac catheterization may increase the risk of bleeding complications or prolong hospitalization in patients requiring coronary bypass surgery.[1] In this context, the most recent guidelines provided less emphasis on

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Clinical Perspective

What Is New?

- Administration of eptifibatide bolus plus clopidogrel at the time of percutaneous coronary intervention (PCI) provides faster and more potent platelet inhibition than crushed ticagrelor in troponin-negative acute coronary syndrome patients and reduces periprocedural myocardial infarction and injury with no significant hemoglobin drop after PCI.
- Given that the absorption of ticagrelor is inhibited by narcotics administrated at the time of PCI, this study casts doubt on the benefit of crushed ticagrelor, which is commonly used with narcotics in catheterization laboratories for prompt platelet inhibition.

What Are the Clinical Implications?

- Upstream administration of potent $P2Y_{12}$ inhibitors before cardiac catheterization in patients with acute coronary syndrome may increase bleeding and prolong hospitalization in patients requiring coronary artery bypass grafting.
- Narcotics, administered at the time of PCI, reduce the absorption and platelet inhibition of crushed ticagrelor, but the combination of eptifibatide bolus plus clopidogrel provides immediate and sustained inhibition of platelet reactivity.
- These findings emphasize the importance of the intravenous route to deliver immediate platelet inhibition in patients with acute coronary syndrome undergoing PCI who are not pretreated with $P2Y_{12}$ inhibitors; given more prompt and potent inhibition of platelet reactivity with eptifibatide bolus plus clopidogrel compared with crushed ticagrelor, future randomized trials are warranted to investigate the safety and efficacy of eptifibatide bolus versus cangrelor in patients undergoing ad hoc PCI.

preloading $P2Y_{12}$ inhibitors before catheterization in patients with unstable angina or non–ST-segment–elevation myocardial infarction (NSTEMI).[2]

A recent study[3] showed that after a loading dose of a potent $P2Y_{12}$ inhibitor (ticagrelor) at the time of PCI in low-risk ACS patients, the rate of high on-treatment platelet reactivity (HPR) was still elevated at the end of PCI. This suggests that the onset of platelet inhibition with ticagrelor is delayed, and faster platelet inhibition with crushed ticagrelor (CTIC),[4,5] glycoprotein IIb/IIIa receptor inhibitors (GPI; eptifibatide or tirofiban),[6,7] or cangrelor[8] is needed to promptly inhibit HPR. Several studies[9–11] have shown that HPR increases the risk of periprocedural myocardial infarction and injury (PMI) and thrombotic events after PCI.

The US Food and Drug Administration approved CTIC in 2015, and CTIC is commonly used in catheterization laboratories for prompt platelet inhibition at the time of PCI. Likewise, a number of studies[6,7] have shown that a combination of tirofiban or eptifibatide bolus plus clopidogrel or ticagrelor promptly inhibits HPR and provides sustained platelet inhibition. However, the efficacy of CTIC versus eptifibatide bolus plus clopidogrel has not been studied. Consequently, we compared the effects of CTIC versus eptifibatide bolus plus clopidogrel on platelet inhibition, PMI, and hemoglobin levels in troponin-negative ACS patients undergoing PCI.

Methods

Patient Population

The data that support the findings of this study are available from the corresponding author on reasonable request. This was a prospective, randomized, single-blind study in troponin-negative ACS patients. The inclusion criteria were as follows: troponin-negative patients with ACS-unstable angina undergoing PCI; and cardiac ischemic symptoms with or without ECG changes. Unstable angina was defined as the presence of rest angina, new onset of angina, increasing angina, or angina equivalent.[12,13] Patients with the following criteria were excluded from the study: positive troponin, the use of $P2Y_{12}$ receptor inhibitors or GPI within 7 days, cardiogenic shock, thrombocytopenia (platelet count <100 000) or prothrombin time with international normalized ratio higher than the upper limit of normal (>1.1), anemia with hemoglobin level <10 g/dL, surgery <4 weeks, recent history of bleeding or noncompliance, ejection fraction <30%, renal failure with creatinine levels >2.0 mg/dL, and concomitant therapy with cytochrome P-450 3A inhibitors. The institutional review board of the University of Alabama approved the study, and written informed consent was obtained from all patients.

Study Design and Randomization

The study design is shown in Figure 1. Patients were screened for eligibility, and informed consent was obtained. All patients received aspirin. Baseline blood samples for hemoglobin and hematocrit levels and cardiac troponin I levels were obtained before randomization. Randomization was based on a simple computer-generated list that was placed in sealed envelopes. After performing coronary angiography, eligible patients with a significant coronary stenosis, defined as a stenosis ≥70% or an intermediate stenosis with fractional flow reserve ≤0.80, were randomized to receive CTIC versus eptifibatide bolus plus clopidogrel after drawing baseline blood samples for platelet function testing. The use of CTIC was based on previous studies[4,5] that showed CTIC resulted in faster drug absorption and stronger platelet inhibition than whole tablets. The use of eptifibatide bolus plus clopidogrel was based on a recent study[7] that showed

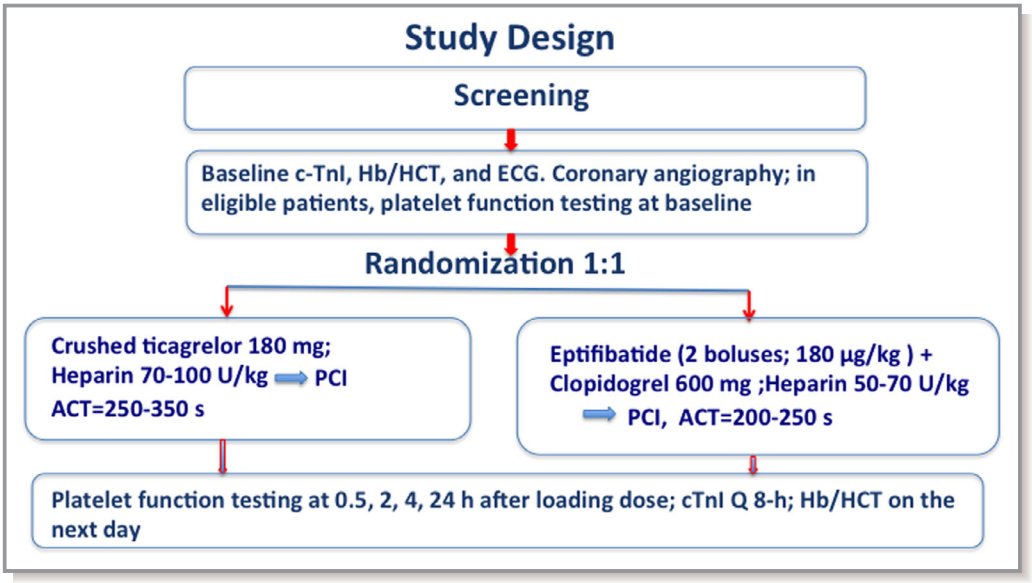

Figure 1. Study design. ACT indicates activated dotting time; cTnI, cardiac troponin I; Hb/HCT, hemoglobin/hematocrit; PCI, percutaneous coronary intervention.

tirofiban bolus promptly inhibited platelet aggregation (PA) and a combination of tirofiban bolus plus clopidogrel provided prompt and sustained platelet inhibition. Patients were blinded to the study drugs. They were not informed about crushing ticagrelor; eptifibatide or heparin was administered in the catheterization laboratory while they were sedated or sleeping.

In the CTIC group, 2 ticagrelor 90-mg tablets were placed in a mortar and crushed for 60 seconds using a pestle, and then 20 mL of purified water was added to the mortar and stirred for 60 seconds. The liquid was transferred to a dosing cup, and another 15 mL of purified water was added to the mortar and stirred, ensuring that all powders were dispersed and none remained on the mortar or pestle, as previously reported.[14] The liquid CTIC was administered orally just before PCI. In the eptifibatide bolus plus clopidogrel group, clopidogrel (600 mg) and eptifibatide bolus (2 intravenous boluses were administered 10 minutes apart at a dose of 180 µg/kg); the first bolus was administered just before PCI. The maintenance dose of clopidogrel (75 mg once a day) or ticagrelor (90 mg twice a day) was started after drawing the last blood sample for pharmacodynamic study at 24 hours. In the CTIC group, standard-dose heparin (70–100 U/kg) was administered; in the eptifibatide bolus plus clopidogrel group, low-dose heparin (50–70 U/kg) was administered. The use of low-dose heparin with GPI was based on previous studies[15,16] and recent guidelines.[2] We aimed to maintain activated clotting time (ACT) between 250 and 350 seconds in the CTIC group versus 200 and 250 seconds in the eptifibatide bolus plus clopidogrel group to reduce bleeding associated with GPI use in the clopidogrel plus eptifibatide group.[2,15,16] Additional unfractionated heparin was administered to maintain ACT at recommended levels. ACT levels were measured by the Hemochron device (International Techidyne Corp). All patients were sedated with a combination of midazolam and fentanyl. Serial ECGs were obtained at baseline, after PCI, and the next day. Blood samples for cardiac troponin I levels were repeated at 8 and 24 hours after PCI. Hemoglobin and hematocrit levels were repeated on the next day after PCI.

Pharmacodynamic Study

Light transmission aggregometry was performed, as previously reported.[6]

Briefly, blood samples were collected in 3.8% sodium citrate tubes. PA was tested using the turbidimetric method in a 2-channel aggregometer (Chrono-log Optical Aggregometer model 490-4D). The following agonists were used for platelet stimulation: ADP (5 and 20 µmol/L) and thrombin receptor-activating peptide (TRAP 10 and 20 µmol/L). Briefly, platelet-rich plasma was stimulated by adding an agonist to the cuvette in the aggregometer, and PA was recorded as aggregation curves after the addition of each agonist for 6 minutes. The maximal extent of aggregation was expressed as the percentage change in light transmittance from baseline. Each measurement was performed in duplicate, and the average of the 2 measurements was recorded. Ticagrelor and clopidogrel inhibit $P2Y_{12}$ receptors, and their efficacy was tested by the inhibition of PA induced with ADP. Eptifibatide strongly inhibits glycoprotein IIb/IIIa receptors, and its efficacy was assessed by TRAP.

Study End Points and Definitions

The primary efficacy measure was HPR, defined as PA >59% at 2 hours measured by the Chrono-log aggregometer after stimulation with ADP 20 μmol/L, as previously reported.[6,17,18] It is noteworthy that HPR cut points differ among the make of aggregometers because some aggregometers use whole blood (multiplate analyzer) and others use plasma (Chrono-log Optical Aggregometer). The secondary efficacy measures were as follows: PA levels, measured by aggregometry at 0.5, 2, 4, and 24 hours after loading dose, and PMI after PCI. PMI was based on the third universal definition of myocardial infarction (MI),[19] which includes type 4a MI related to PCI as an increase in cardiac troponin I levels >5×99th percentile upper reference limit in the presence of ischemia or ECG changes after PCI, and myocardial injury, as a same increase in cardiac troponin I levels in the absence of ischemia. Other secondary efficacy measures include the total dose of heparin and the highest ACT levels during PCI; hemoglobin and hematocrit levels on the next day after PCI versus baseline levels; bleeding complications based on the Bleeding Academic Research Consortium[20] (defined as type 1, minor bleeding, which requires no treatment; type 2, bleeding that requires treatment or intervention; type 3a, bleeding resulting in hemoglobin drop of 3 to <5 g/dL.; type 3b, bleeding plus hemoglobin drop ≥5 g/dL; and type C, intracranial hemorrhage); and the composite of major adverse cardiovascular events (death, myocardial infarction, stent thrombosis, and revascularization).

Clinical Follow-Up

After discharge, patients were scheduled for follow-up at 1 month and every 4 to 6 months thereafter. The major adverse cardiovascular events, including myocardial infarction, death, stent thrombosis, and target vessel revascularization, were recorded during follow-up and by telephone calls.

Statistical Analysis

We estimated that HPR, the primary end point, would be 20% with CTIC[14] versus 0% with clopidogrel plus eptifibatide[17,21] at 2 hours. Including a 5% dropout rate, we estimated that 100 patients, at α=0.05, would have 90% power to detect the difference between groups. In this study, the primary end point at 2 hours is in line with a recent study[22] that showed HPR was significantly lower with crushed prasugrel than with whole tablets at 2 hours, the time frame in which most patients undergo PCI. Likewise, a recent study[23] showed that in NSTEMI patients undergoing PCI, a loading dose of ticagrelor or prasugrel administrated at the time of PCI provided optimal inhibition of platelet reactivity at 2 hours.

Continuous variables are shown as mean±SD and were compared by the unpaired Student *t* test. The χ^2 or Fisher exact test was performed to compare categorical variables between groups. PA levels between the 2 groups were compared using a 2-sample *t* test. A general linear model with repeated measures was used to compare PA levels between the groups and within the group from baseline to 0.5, 2, 4, and 24 hours. Pairwise comparisons were performed using the Bonferroni correction. Statistical analysis was performed using SPSS v25.0 software (IBM Corp).

Results

Patient Population

Between November 2016 and January 2018, 315 consecutive patients were screened; of these, 100 patients met the inclusion and exclusion criteria and were randomized to CTIC (n=50) versus eptifibatide bolus plus clopidogrel (n=50; Figure 2). In the CTIC group, the lesion could not be crossed in 1 patient, and PCI was performed in 49 patients. In the eptifibatide bolus plus clopidogrel group, PCI was successfully performed in all patients; blood samples were hemolyzed in 2 patients, and pharmacodynamic study was performed in 48 patients (Figure 2). The baseline characteristics of the patients were not significantly different between groups (Table 1). The majority of PCIs were performed by the transfemoral approach.

Procedural Characteristics of Patients

The procedural characteristics of patients are displayed in Table 2. The number of the left circumflex coronary arteries was significantly higher with CTIC versus eptifibatide bolus plus clopidogrel. The total dose of heparin and the highest ACT levels were significantly higher with CTIC versus eptifibatide bolus plus clopidogrel. There were no significant differences in the stent diameter and length, number of stents, and postdilation balloon pressure between the groups.

High On-Treatment Platelet Reactivity

As shown in Figure 3, the baseline HPR levels induced by ADP 20 μmol/L were not significantly different with CTIC versus clopidogrel plus eptifibatide bolus (74% versus 68%, respectively; *P*=0.87). HPR levels at 30 minutes and 2 hours after loading dose were significantly higher with CTIC versus clopidogrel plus eptifibatide bolus (42% versus 0% [*P*<0.001] and 12% versus 0% [*P*=0.012], respectively). HPR levels were not significantly different between the groups at 4 and 24 hours after loading dose.

Assessment of PA by Light Transmission Aggregometry

Table 3 demonstrates PA levels induced by ADP 5 μmol/L, ADP 20 μmol/L, TRAP 10 μmol/L, and TRAP 20 μmol/L at

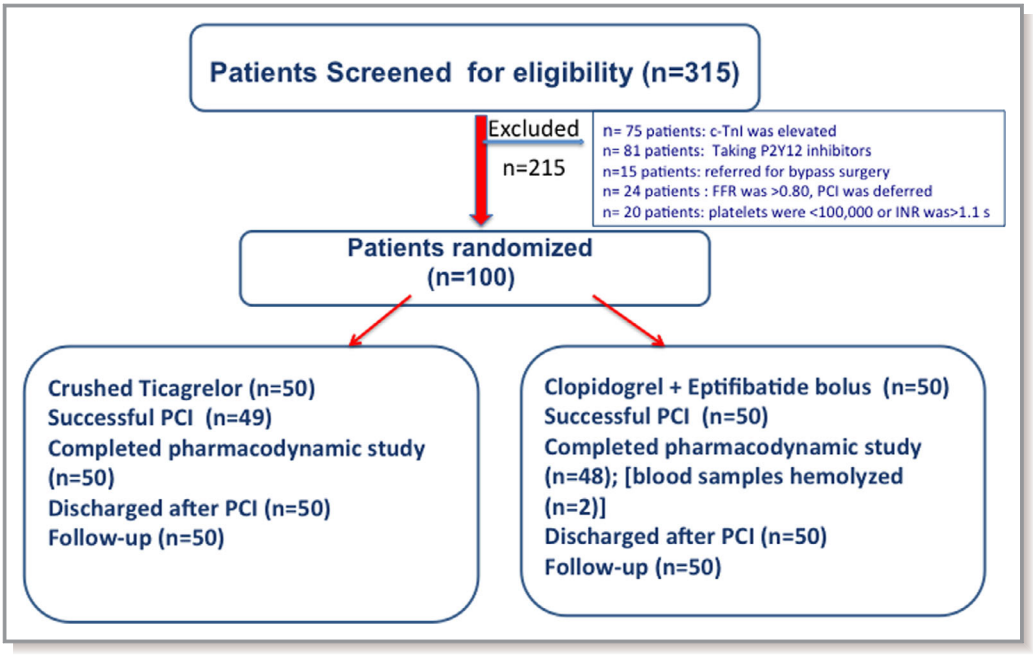

Figure 2. Patient disposition. cTnI indicates cardiac troponin I; FFR, fractional flow reserve; INR, international normalized ratio; PCI, percutaneous coronary intervention.

baseline and at 0.5, 1 2, 4, and 24 hours after loading dose among patients randomized to CTIC versus eptifibatide bolus plus clopidogrel.

As shown in Figure 4, PA levels induced by ADP 20 µmol/L were not significantly different between CTIC and eptifibatide bolus plus clopidogrel at baseline. CTIC significantly dropped PA at 2, 4, and 24 hours but not at 30 minutes. Eptifibatide bolus plus clopidogrel significantly dropped PA at 0.5, 2, and 4 hours. PA dropped faster from baseline with eptifibatide bolus plus clopidogrel versus CTIC (0.5 versus 2 hours, respectively) and was significantly higher with CTIC versus eptifibatide bolus plus clopidogrel at 0.5, 2, and

Table 1. Baseline Demographic and Clinical Characteristics of Patients

	CTIC (n=50)	Eptifibatide Bolus+Clopidogrel (n=50)	*P* Value
Age, y, mean±SD	66±11	64±10	0.40
Sex, male/female, n	31/19	38/12	0.50
Diabetes mellitus	18 (36)	23 (46)	0.30
Hypertension	42 (84)	46 (92)	0.70
Current smoker	12 (24)	6 (12)	0.17
Hyperlipidemia	42 (84)	44 (88)	0.56
TIMI risk score, mean±SD	3.26±0.82	3.52±0.73	0.10
Peripheral vascular disease	7 (14)	6 (12)	0.80
Chronic renal failure	7 (8)	6 (12)	0.80
Prior myocardial infarction or CABG	17 (34)	8 (23)	0.06
Moderate to large ischemia by stress test	13 (26)	10 (20)	0.40

Data are shown as n (%) except as noted. CABG indicates coronary artery bypass grafting; CTIC, crushed ticagrelor; TIMI, Thrombolysis in Myocardial Infarction.

Table 2. Procedural Characteristics of Patients

	CTIC (n=50)	Eptifibatide Bolus+Clopidogrel (n=50)	*P* Value
Coronary lesion			
LAD, n	24	29	0.76
LCx, n	15	8	0.021
RCA, n	11	13	0.70
Heparin dose, U	8854±2287	6021±1328	0.001
ACT, s	332±48	278±47	0.001
Stent diameter, mm	3.30±0.51	3.05±0.38	0.80
Total stent length, mm	26±13.6	27±10.20	0.64
No. of stents	66	58	0.33
PD balloon diameter, mm	3.30±0.58	3.40±0.49	0.35
PD inflation pressure, atm	16.5±1.96	16.03±1.97	0.34
Transfemoral, n (%)	42 (84)	44 (88)	0.82
Transradial, n (%)	8 (16)	6 (12)	0.56

Data are shown as mean±SD except as noted. ACT indicates activated clotting time; CTIC, crushed ticagrelor; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; PD, postdilation.

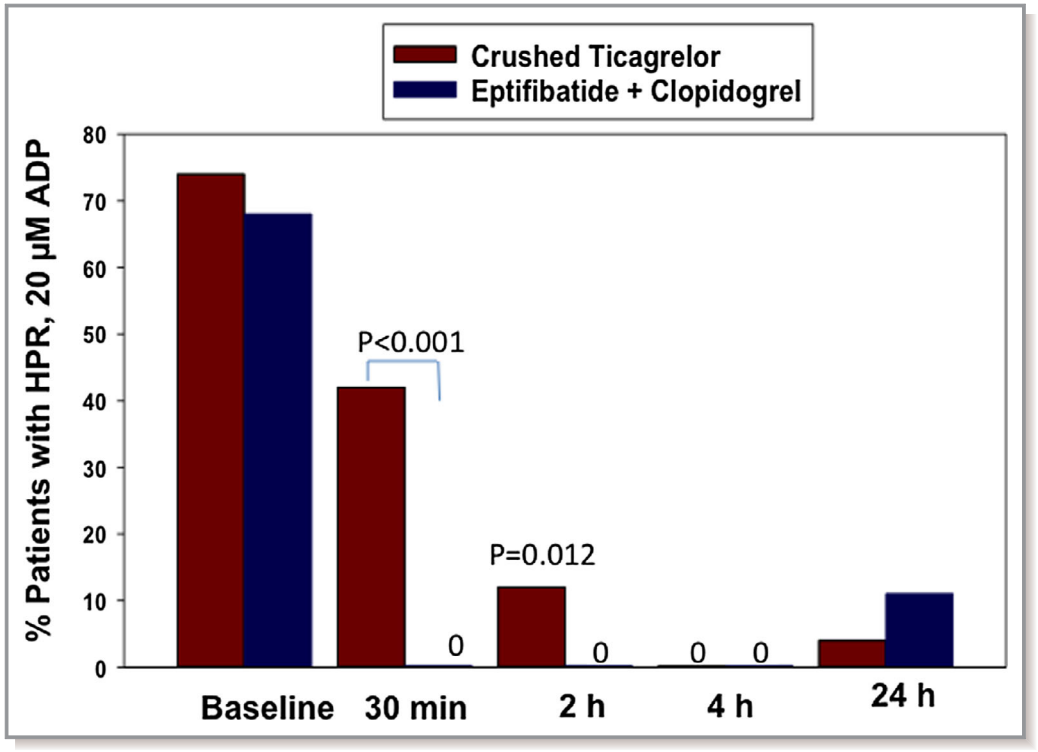

Figure 3. High on-treatment platelet reactivity (HPR). HPR levels were significantly higher with crushed ticagrelor vs clopidogrel plus eptifibatide bolus at 0.5 and 2 hours after loading dose.

4 hours after loading dose. PA was significantly higher with clopidogrel plus eptifibatide bolus versus CTIC at 24 hours.

As shown in Figure 5, PA levels induced by TRAP 20 µmol/L were not significantly different with CTIC versus eptifibatide bolus plus clopidogrel at baseline. CTIC did not significantly affect PA at 0.5, 2, 4, and 24 hours. In contrast, eptifibatide bolus plus clopidogrel significantly reduced PA at 0.5, 2, and 4 hours. Furthermore, PA was significantly higher with CTIC versus clopidogrel plus eptifibatide bolus at 0.5, 2, and 4 hours after loading dose.

Periprocedural Myocardial Infarction and Injury

As shown in Figure 6, PMI was significantly higher with CTIC versus eptifibatide bolus plus clopidogrel (24 patients [48%] versus 14 patients [28%], respectively; *P*=0.039).

Outcomes

The details of in-hospital and follow-up outcomes are shown in Table 4. There were no significant differences between the baseline and post-PCI hemoglobin and hematocrit levels in each group. There was no significant bleeding in either group. In the CTIC group, 1 patient developed small femoral hematoma after removal of the femoral sheath, and it resolved after applying Femstop (Abbott Vascular, Abbott park, Illinois, United States) with no hemoglobin drop. There were no instances of major bleeding. During follow-up, 2 patients died in the CTIC group: one as a result of heart failure and the other died of pneumonia and MI. Furthermore, in the CTIC group, 2 patients were admitted with chest pain during follow-up; cardiac catheterization showed in-stent restenosis in the left circumflex artery in one patient and no significant restenosis in the other. During follow-up, there was no instance of MI or stent thrombosis.

Discussion

To the best of our knowledge, this study is the first to compare the effects of CTIC versus eptifibatide bolus plus clopidogrel in troponin-negative ACS patients undergoing PCI. The results of our study are summarized as follows: HPR was markedly higher with CTIC versus eptifibatide bolus plus clopidogrel within the 30 minutes after loading dose, and this effect persisted up to 2 hours. HPR levels were not significantly different between the groups at 24 hours. PA induced by ADP dropped faster from baseline with eptifibatide bolus plus clopidogrel versus CTIC (30 minutes versus 2 hours, respectively) and was markedly higher with CTIC versus eptifibatide bolus plus clopidogrel. The incidence of PMI was significantly higher with CTIC versus eptifibatide bolus plus clopidogrel. Heparin dose and ACT levels were significantly higher with CTIC versus eptifibatide bolus plus clopidogrel. Finally, post-PCI hemoglobin levels were not significantly different between the groups.

Table 3. Platelet Aggregation

Aggregation, h	CTIC (n=50) Mean±SD, %	Eptifibatide Bolus+Clopidogrel (n=48) Mean±SD, %	*P* Value
ADP 20 μmol/L			
0	65±14	62±10	0.19
0.5	53±12	1.3±2.0	0.001
2	35±11	0.34±1.0	0.001
4	23±9.0	3.5±2.0	0.001
24	25±10	38±9.0	0.002
ADP 5 μmol/L			
0	56±12	54±13	0.66
0.5	44±17	1.18±4	0.001
2	24±13	0.30±0.93	0.001
4	15±9.0	1.60±1.50	0.001
24	18±14	27±17	0.008
TRAP 20 μmol/L			
0	68±14	67±16	0.70
0.5	60±13	3.9±3.6	0.001
2	51±8.0	6±5.0	0.001
4	48±12	14±10	0.001
24	54±11	51±11	0.41
TRAP 10 μmol/L			
0	56±18	54±19	0.74
0.5	48±19	1.18±1.0	0.001
2	37±17	1.57±2.0	0.001

CTIC indicates crushed ticagrelor; TRAP, thrombin-receptor activating peptide.

The clinical utility of this study in troponin-negative ACS patients might be argued. Notably, optimal antiplatelet therapy in $P2Y_{12}$-naïve patients with unstable angina undergoing PCI has not yet been established. Although the ad hoc PCI study[3] showed that PA in $P2Y_{12}$-naïve patients was significantly lower with ticagrelor versus clopidogrel, HPR was still high with ticagrelor at the end of PCI and persisted up to 2 hours. These findings have relevant clinical and pathophysiological implications and emphasize the importance of faster platelet inhibition with intravenous agents in patients who are not pretreated with $P2Y_{12}$ inhibitors and undergoing PCI. It is worth noting that HPR increases the risk of PMI and thrombotic events after PCI.[9–11] Furthermore, PMI increases the rates of ischemic events and mortality even in low-risk patients at 1 year.[24]

Given the slow onset of platelet inhibition with ticagrelor and high HPR at the end of PCI in the ad hoc PCI study, we investigated the effect of faster platelet inhibition with CTIC versus eptifibatide to reduce HPR. In this respect, a number of studies[25,26] showed that GPI plus clopidogrel versus clopidogrel reduced the incidence of PMI in low-risk patients. In the present study, we showed that HPR was 0% versus 42% with eptifibatide bolus plus clopidogrel and CTIC, respectively at 30 minutes, which translated into the reduced incidence of PMI.

A major concern with GPIs is that they increase the risk of bleeding.[27] Notably, 2 large registry studies[28,29] reported that patients receiving GPI bolus versus infusion had significantly lower rates of bleeding events and blood transfusion with no difference in outcomes. Furthermore, Valgimigli et al[7] showed that the inhibition of PA was not significantly different with tirofiban bolus plus clopidogrel versus tirofiban bolus or 2 hours infusion plus clopidogrel. Alternatively, cangrelor provides prompt platelet inhibition and bridges the gap during the first 2 hours until the inhibition of PA with $P2Y_{12}$ inhibitors takes place (within 2 hours). In this context, the CANTIC (Platelet Inhibition With Cangrelor and Crushed Ticagrelor in STEMI Patients Undergoing Primary Percutaneous Coronary Intervention) study[8] showed that HPR was 0% versus 57% with cangrelor versus CTIC, respectively, at 30 minutes. Future randomized trials are needed to investigate the safety and efficacy of GPI bolus versus cangrelor in patients with ACS undergoing PCI.

In this study, PA was higher with eptifibatide plus clopidogrel versus CTIC at 24 hours, but HPR was not significantly different (11% versus 4%, respectively; P=0.16; Figure 3). Given the low-risk nature of patients with unstable angina, we did not use ticagrelor. In this context, the European Society of Cardiology guidelines[2] recommended ticagrelor in moderate- to high-risk ACS patients (eg, with elevated troponin). This was based on a post hoc analysis of the PLATO (Platelet Inhibition and Patient Outcomes) study,[30] which demonstrated no benefit of maintenance therapy with ticagrelor in troponin-negative ACS patients.

Although the gastrointestinal absorption of CTIC is faster than the whole tablets, HPR remains high during the first 2 hours after loading dose, the time frame in which the majority of patients undergo PCI. In this respect, McEvoy et al[31] showed that the use of fentanyl significantly delayed the absorption of ticagrelor, and that increased HPR to 33% at 2 hours among patients undergoing elective PCI. Likewise, Kubica et al[32] demonstrated that morphine delayed the absorption of ticagrelor and increased HPR to 57% at 2 hours among patients with STEMI. To mitigate the effect of narcotics on the absorption of CTIC, Niezgoda et al[4] administered CTIC and conducted the experiment including blood samples before PCI and showed that HPR with CTIC was 0% at 1 and 2 hours after loading dose, which is similar to that of eptifibatide bolus.[6] Thus, in the absence of narcotics, the efficacy of CTIC seems to be equivalent to

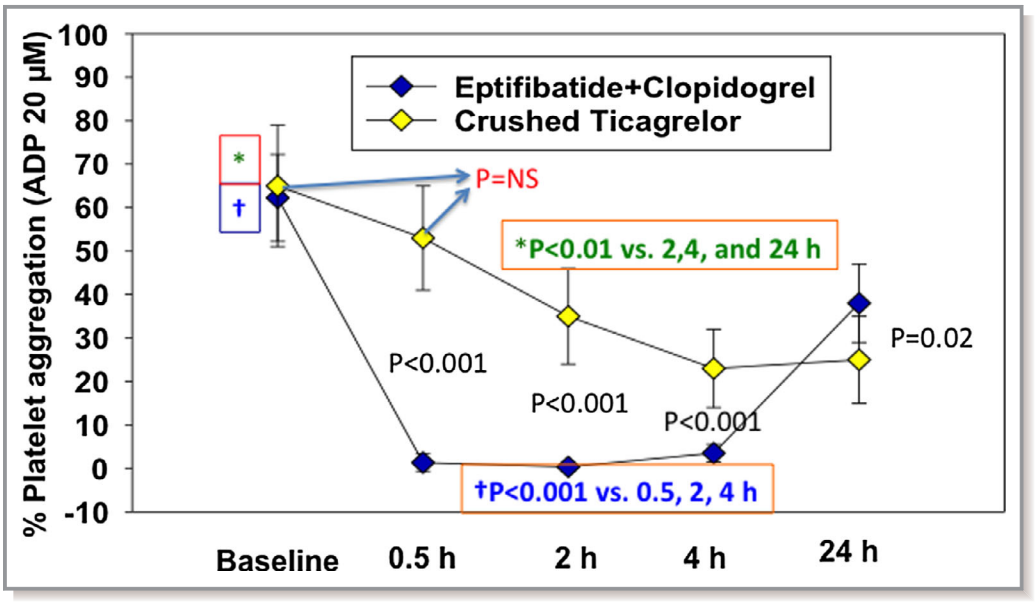

Figure 4. Platelet aggregation (PA) levels induced by ADP. Crushed ticagrelor (CTIC) significantly dropped PA induced by ADP 20 µmol/L at 2, 4, and 24 hours but not at 30 minutes. Eptifibatide bolus plus clopidogrel significantly dropped PA at 0.5, 2, and 4 hours. PA dropped faster from baseline with eptifibatide bolus plus clopidogrel vs CTIC (0.5 vs 2 hours, respectively) and was significantly higher with CTIC vs eptifibatide bolus plus clopidogrel at 0.5, 2, and 4 hours after loading dose. PA level was significantly higher with clopidogrel plus eptifibatide bolus vs CTIC at 24 hours. NS indicates not significant.

that of clopidogrel plus eptifibatide. In this respect, McEvoy et al[31] suggested that, if possible, the routine use of fentanyl with ticagrelor should be discouraged during PCI. Otherwise, there is a need for intravenous agents such as GPI bolus or cangrelor to provide immediate and potent platelet inhibition in these patients.

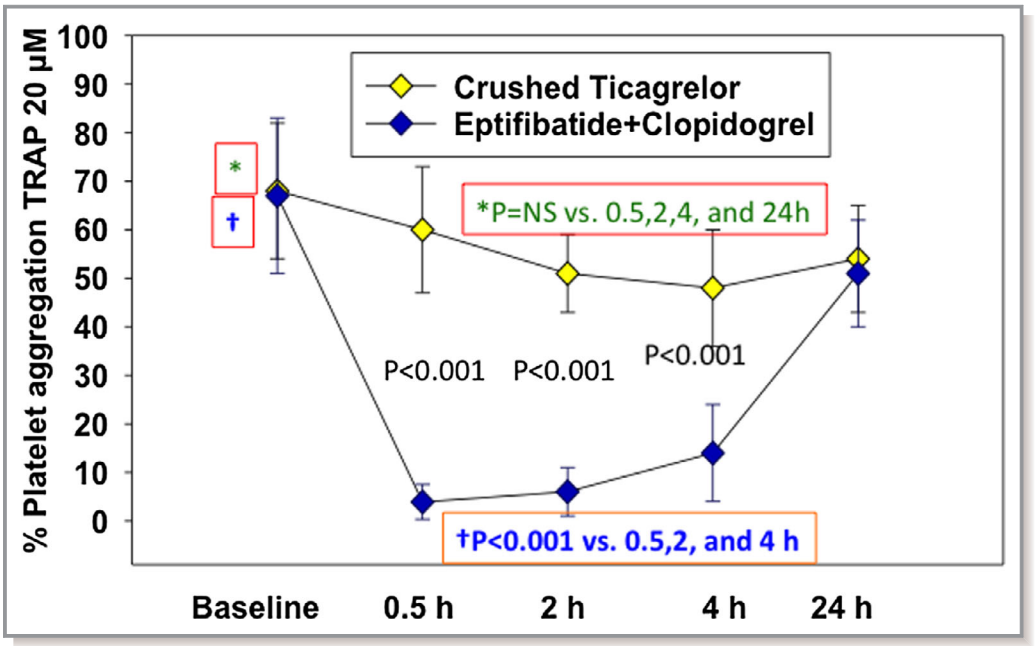

Figure 5. Platelet aggregation levels induced by thrombin receptor-activating peptide (TRAP). Crushed ticagrelor (CTIC) did not significantly affect platelet aggregation (PA) induced by TRAP 20 µmol/L at 0.5, 2, 4, and 24 hours. In contrast, eptifibatide bolus plus clopidogrel significantly reduced PA induced by TRAP at 0.5, 2, and 4 hours. Furthermore, PA was significantly higher with CTIC vs clopidogrel plus eptifibatide bolus at 0.5, 2, and 4 hours after loading dose. NS indicates not significant.

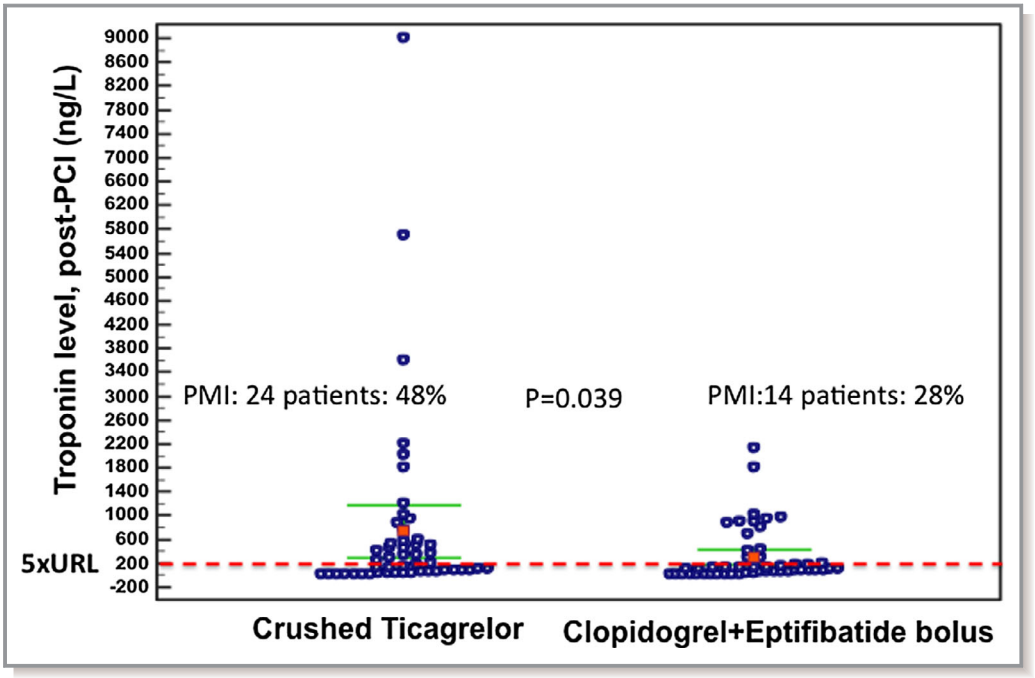

Figure 6. Distribution of troponin I levels after percutaneous coronary intervention (PCI). The rate of periprocedural myocardial infarction and injury (PMI) was significantly higher with crushed ticagrelor vs eptifibatide bolus plus clopidogrel. Bars indicate the mean levels of PMI with 95% CIs for each group. The dotted line indicates the limit of 195 ng/L (5×99th percentile of upper reference limit [URL] of troponin levels=39 ng/L).

We showed that the incidence of PMI, based on troponin elevation using the third universal definition of PMI,[19] was significantly higher with CTIC versus eptifibatide bolus plus clopidogrel (48% versus 28%, respectively). The stent diameter and length, and postdilation balloon pressure were not significantly different between groups. Zeitouni et al[24] demonstrated that PMI, based on troponin elevation using the third universal definition of MI,[19] occurred in 28.7% of patients undergoing elective PCI and was associated with increased ischemic events at 30 days and 1 year. Ndrepepa et al[33] showed that in patients with NSTEMI, the incidence of PMI, based on troponin elevation using the third universal definition of MI, was 44.2%. However, they reported that only high-sensitivity cardiac troponin T elevations >70 times upper limit of normal (occurring in 8.3% of the patients) were associated with mortality. Bonello et al[34] compared ticagrelor preloading versus prasugrel loading at the time of PCI and showed that the rate of PMI, based on troponin elevation, was significantly higher with prasugrel versus ticagrelor (38.3% versus 19.8%, respectively).

Study Limitations

This study has a number of limitations. First, this study was not powered to compare major adverse events between groups. We instead used HPR as a surrogate end point; HPR is strongly associated with an increased risk of PMI and mortality.[5–7] We showed that a combination of clopidogrel plus eptifibatide, compared with CTIC, significantly reduced HPR and PMI. The improved sensitivity of the modern troponin assays has resulted in ever-increasing incidence of PMI. However, prospective studies are needed to determine the relationship among HPR, PMI, and mortality. Second, we used low-dose heparin with eptifibatide bolus plus clopidogrel and showed that post-PCI hemoglobin levels were not significantly different with eptifibatide bolus plus clopidogrel versus CTIC. Likewise, previous studies[28,29] showed that the risk of bleeding was significantly lower with eptifibatide bolus plus clopidogrel versus infusion. However, the incidence of bleeding and the net clinical benefit of CTIC versus eptifibatide bolus plus clopidogrel with low-dose heparin warrant a large study. Third, in this study, we used light transmission aggregometry to assess HPR because we measured PA with both ADP and TRAP using different concentrations at several time points and there was not enough blood sample to perform the vasodilator-stimulated phosphoprotein test, which is the standard test for HPR assay. Notably, a recent study[35] showed an excellent correlation between light transmission aggregometry and vasodilator-stimulated phosphoprotein for HPR assessment. Finally, we did not measure plasma concentrations of ticagrelor and its metabolites to determine the impact of fentanyl on the absorption of

Table 4. Outcomes

	CTIC (n=50)	Eptifibatide Bolus+Clopidogrel (n=50)	*P* Value
In-hospital events			
Baseline hemoglobin, g/dL	13.52±2.0	13.34±1.62	0.97
Post-PCI hemoglobin, g/dL	12.73±1.81	12.71±1.60	0.98
Baseline hematocrit	40.11±5.36	40.02±4.49	0.92
Post-PCI hematocrit	37.68±4.85	37.50±4.20	0.93
BARC type 2 bleeding, n	1	0	
Follow-up events			
Duration of follow-up, mo	8.4±3.8	8.9±4.9	
Death, n	2	0	
Stroke, n	0	0	
TLR, n	1	0	
Myocardial infarction, n	0	0	
Stent thrombosis, n	0	0	
Major adverse cardiovascular events, n	3	0	

Data are shown as mean±SD except as noted. ARC indicates Academic Research Consortium; BARC, Bleeding Academic Research Consortium; CTIC, crushed ticagrelor; PCI, percutaneous coronary intervention; TLR, target lesion revascularization.

ticagrelor. In this respect, 2 recent studies[31,32] showed that fentanyl or morphine significantly delayed the absorption of ticagrelor in patients with stable angina or ACS.

Conclusions

We have shown that in $P2Y_{12}$-naive patients presenting with troponin-negative ACS and undergoing PCI, eptifibatide bolus plus clopidogrel provided faster and more potent platelet inhibition than CTIC and reduced PMI with no significant hemoglobin drop after PCI. Future studies are warranted to investigate the safety and efficacy of CTIC versus GPI bolus or cangrelor in troponin-negative ACS patients undergoing PCI.

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Disclosures

None.

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