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Double-Blind, Randomized, Prospective Comparison of Loading Doses of 600 mg Clopidogrel Versus 60 mg Prasugrel in Patients With Acute ST-Segment Elevation Myocardial Infarction Scheduled for Primary Percutaneous Intervention

The ETAMI Trial (Early Thienopyridine treatment to improve primary PCI in Patients with Acute Myocardial Infarction)

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ABSTRACT

OBJECTIVES This study compared the timing of onset of antiplatelet action after treatment with clopidogrel and prasugrel at first medical contact in patients with ST-segment elevation myocardial infarction (STEMI) scheduled for primary percutaneous coronary intervention (PPCI).

BACKGROUND Little is known about the timing of onset of antiplatelet action after a pre-percutaneous coronary intervention (PCI) loading dose of clopidogrel or prasugrel in patients with STEMI.

METHODS This double-blind, prospective study randomized 62 patients with STEMI scheduled for PPCI in the ambulance or the emergency department to 60 mg prasugrel ($n = 31$) or 600 mg clopidogrel ($n = 31$). The primary endpoint was the platelet reactivity index (PRI) measured with the vasodilator-stimulated phosphoprotein assay 2 h after intake of the study medication. Secondary endpoints were PRI after 4 h, TIMI (Thrombolysis In Myocardial Infarction) patency of the infarct-related artery before and after PCI, and clinical events until day 30.

RESULTS The PRI after 2 h (50.4 ± 32.7% vs. 66.3 ± 22.2%; $p = 0.035$) and after 4 h (39.1 ± 27.5% vs. 54.5 ± 49.3%; $p = 0.038$) were significantly lower with prasugrel compared with clopidogrel. In addition, the rate of patients with a PRI <50% tended to be higher with prasugrel compared with clopidogrel after 2 h (46.7% vs. 28.6%; $p = 0.15$) and after 4 h (63.0% vs. 38.9%; $p = 0.06$). There were no significant differences in TIMI 2/3 patency before PCI (39.2% vs. 31.0%; $p = 0.43$) and TIMI 3 patency after PCI (88.5% vs. 89.3%; $p = 0.92$).

CONCLUSIONS The pre-PCI administration of prasugrel in patients with STEMI undergoing PPCI was associated with a significant faster platelet inhibition compared with clopidogrel. Therefore, prasugrel should be preferred to clopidogrel in this setting. (ETAMI-Study: Early Thienopyridine Treatment to Improve Primary PCI in Patients With Acute Myocardial Infarction; NCT01327534) (J Am Coll Cardiol Intv 2015;8:147–54) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ADP = adenosine diphosphate

GP = glycoprotein

PCI = percutaneous coronary intervention

PPCI = primary percutaneous coronary intervention

PRI = platelet reactivity index

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

Effective platelet inhibition is a cornerstone of therapy in patients with ST-segment elevation myocardial infarction (STEMI) (1,2). In several randomized trials, acetylsalicylic acid has been shown to improve short- and long-term clinical outcome after STEMI; therefore, it is recommended as standard therapy in recent guidelines (1,2). The thienopyridine clopidogrel acts synergistically with acetylsalicylic acid and improved outcome in patients with STEMI without primary percutaneous coronary intervention (PPCI) in the COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) (3). However, in patients with STEMI scheduled for PPCI, a fast, effective inhibition of adenosine diphosphate (ADP)-induced platelet aggregation, preferably within 60 to 90 min after administration of the drug, is desirable, which in most cases cannot be achieved with clopidogrel (4). The new thienopyridine prasugrel has been shown to achieve a more complete and even more rapid platelet inhibition compared with clopidogrel in healthy volunteers (5). This has been shown to be especially beneficial in patients with STEMI scheduled for PPCI (6). In these patients, activation of platelets is more pronounced compared with healthy volunteers or with patients undergoing percutaneous coronary intervention (PCI) for stable coronary artery disease (7). In a small substudy of the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction-38), inhibition of platelet aggregation measured with the vasodilator-stimulated phosphoprotein (VASP) assay was more effective with prasugrel than with clopidogrel (8). However, this substudy was done predominantly in patients with non-ST-segment elevation ACS. In addition, none of these patients were treated in the pre-hospital phase. Nowadays, antithrombotic therapies in patients with STEMI are often given in the ambulance or at first medical contact. Therefore, it is necessary to determine if, in patients with acute STEMI, an early administration of a high loading dose of prasugrel in comparison with clopidogrel before planned PPCI improves the speed and intensity of inhibition of platelet aggregation, which might have contributed to the improvement in clinical outcome observed in the TRITON-TIMI 38 trial (9). However, recent studies suggest that platelet inhibition in patients with STEMI, even with prasugrel, is deferred compared with healthy volunteers and is not optimal about 2 h after intake of the loading dose (10–12).

METHODS

STUDY DESIGN. ETAMI (Early Thienopyridine Treatment to Improve Primary PCI in Patients With Acute Myocardial Infarction) was an international, double-blind, randomized, prospective, 2-arm study. The study was approved by the local ethics committees of the participating centers. All patients gave written informed consent. The study has been registered at ClinicalTrials.gov as NCT01327534.

OBJECTIVES AND PATIENT POPULATION. The objective of the ETAMI trial was to compare the efficacy of a 60 mg loading dose of prasugrel followed by a 10 mg maintenance dose with a 600 mg loading dose of clopidogrel followed by a 75 mg maintenance dose in patients with acute STEMI scheduled for PPCI with respect to inhibition of platelet aggregation. The loading dose was given at first medical contact either in the pre-hospital setting or in a PCI hospital if the expected time until the start of the scheduled PPCI was at least 20 min. The inclusion criteria were: age ≥18 years and <75 years; acute STEMI ≤12 h defined as: 1) angina or equivalent symptoms >30 min; or 2) ST-segment elevation ≥2 electrocardiogram leads (≥2 mm precordial leads, ≥1 mm limb leads, or ST depression ≥1 mm pre-cordial leads in posterior myocardial infarction); planned PPCI; legal capacity (including ability to understand the nature, scope, and possible consequences of the study participation); and informed consent. Exclusion criteria included: age ≥75 years; body weight <60 kg; thrombolytic therapy within 24 h before randomization; oral anticoagulation; known hemorrhagic diathesis; history of stroke or transient ischemic attack; cardiogenic shock; evidence of an active

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gastrointestinal or urogenital bleeding; major surgery within 6 weeks; contraindication to prasugrel or clopidogrel; severe renal or hepatic insufficiency; contraindication to coronary angiography; planned administration of a glycoprotein (GP) IIb/IIIa inhibitor before angiography; pregnant or nursing (lactating) women; treatment within the last 10 days with clopidogrel, prasugrel, ticlopidine, or ticagrelor; uncontrollable hypertension (blood pressure ≥200/110 mm Hg in repeated measurements); treatment with NSAIDs; and participation in another clinical or device trial within the previous 30 days.

STUDY PROCEDURES. In the ambulance or in the emergency department of a PCI hospital after diagnostic confirmation of STEMI, all patients received a baseline treatment of aspirin (500 mg intravenously or 300 mg orally). Patients in the prasugrel group received a loading dose of 60 mg prasugrel and 8 tablets of clopidogrel placebo, and patients in the clopidogrel group received a loading dose of 600 mg clopidogrel and 6 tablets of prasugrel placebo as early as possible. Randomized patients were transferred to the catheterization laboratory, where diagnostic coronary angiography and PPCI with stent implantation was done according to the local guidelines but within 3 h after randomization. The administration of GP IIb/IIIa inhibitors after the diagnostic angiography and prior to or during PPCI was left to the discretion of the treating physician. Blood for the determination of the platelet reactivity index (PRI) was drawn 120 and 240 min after administration of the double-blind study medication, and all samples were processed within 24 h after collection. PRI was measured with CY-QUANT VASP/P2Y12 assay (Stago, Parsippany-Troy Hills, New Jersey).

DEFINTION OF ENDPOINTS. Platelet reactivity index. VASP phosphorylation data were expressed as PRI in percent, defined as:

$$(\text{MFI}\,[\text{PGE1}] - \text{MFI}\,[\text{PGE1} + \text{ADP}])/\text{MFI}\,[\text{PGE1}] \times 100$$

where MFI indicates mean fluoroscopy intensity, and PGE1 indicates prostaglandin E1. A lower PRI indicates a greater antiplatelet effect. Sufficient PRI was defined as <50% (13).

Patency of the infarcted vessel before and after PCI. Based on the TIMI (Thrombolysis In Myocardial Infarction) classification, patency of infarct-related coronary arteries was evaluated, centralized, and blinded in a core laboratory (14).

Reinfarction. Within the first 48 h after primary event: recurrent angina and recurrent increase of creatine kinase-MB over 50% of the last level or over the norm (if creatine kinase-MB has already normalized) or angiographic documentation of reocclusion.

Bleeding complications. Safety endpoints were bleeding complications according to the GUSTO (Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries) (15) and TIMI (14) criteria.

STATISTICS. The primary aim of the study was a statistical comparison of the PRI measured by VASP phosphorylation 2 h after the initiation of the therapy in the study groups A and B. So, the statistical approach was formulated as follows:

Hypothesis: the expected mean PRI in both groups is the same.

Alternative: the expected mean PRI in both groups is different.

In a homogeneous target population, we assumed that PRI could be modeled as a continuous random variable whose distribution was characterized by the expected value μ. With the indexes A and B we signed the defined groups.

$$\text{Hypothesis}: \mu_A = \mu_B$$

$$\text{Alternative}: \mu_A \neq \mu_B$$

The test level alpha was 5%. The statistical test for the primary target parameter was the Satterthwaite's t-test for comparing means with unequal SDs. The mean difference was estimated, and a corresponding confidence interval was calculated.

The secondary target parameters underwent descriptive analyses, and explorative statistical evaluation was performed for comparing the 2 groups. All statistical analyses were performed with the "intention-to-treat" dataset.

Assuming a PRI of 75 ± 15% in the clopidogrel group (group B), a PRI of 60 ± 25% in the prasugrel group (group A), a power of 80%, and an alpha error of 5%, 31 patients per group were needed.

RESULTS

Between December 2011 and March 2013, a total of 63 patients were enrolled in 4 centers: 31 were randomized to clopidogrel and 32 to prasugrel. One patient in the prasugrel group withdrew informed consent and was excluded from the analysis. The patient flow chart is given in **Figure 1**. The baseline characteristics of the 2 groups are given in **Table 1** and did not show any significant differences between the 2 groups. All patients received the double-blind study medication. In these 62 patients fulfilling the inclusion criteria, STEMI was confirmed in 57 cases (28 prasugrel, 29 clopidogrel), whereas in 5 cases, the initial diagnosis was not confirmed

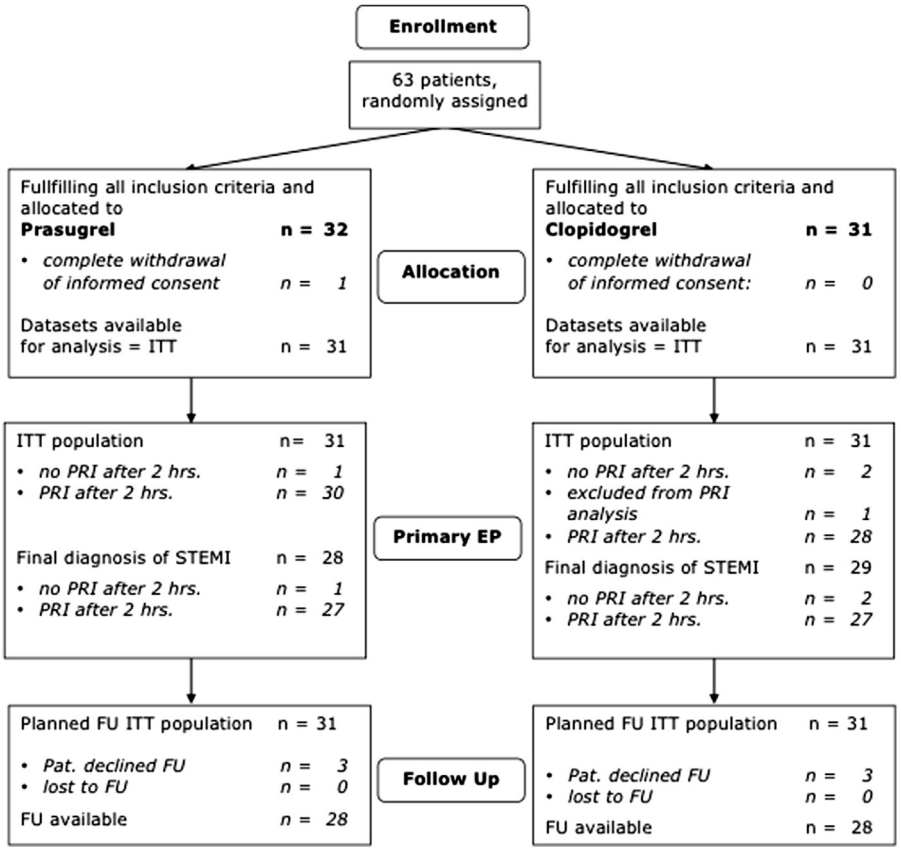

FIGURE 1 Study Flow Chart of the Design and Patients of the Study

Depicted are the patients randomized, the intention-to-treat (ITT) population, and patients with the final diagnosis of ST-segment elevation myocardial infarction (STEMI). FU = follow-up; Pat = patients; PRI = platelet reactivity index.

TABLE 1 Baseline Characteristics of Patients Randomized to Prasugrel or Clopidogrel

	Prasugrel (n = 31)	Clopidogrel (n = 31)	p Value
Mean age, yrs	59.0 (55–70)	64.0 (49–70)	0.45
Women	10 (32.3)	7 (22.6)	0.39
Medical history			
Prior myocardial infarction	2 (6.5)	3 (9.7)	0.64
Prior PCI	3 (9.7)	4 (12.9)	0.68
Prior coronary artery bypass grafting	0	0	
Coronary risk factors			
Hypertension	17 (54.8)	17 (54.8)	1.0
Hyperlipidemia	15 (48.4)	12 (38.7)	0.44
Diabetes mellitus	6 (19.4)	6 (19.4)	1.0
Smoker within last 12 months	24 (78.4)	22 (71)	0.56

Values are median (interquartile range) or n (%).
PCI = percutaneous coronary intervention.

(3 and 2 patients, respectively). A PRI value 2 h after the loading dose was not available in 3 patients; in addition, for 1 patient, the actual diagnosis turned out to be pulmonary embolism, and for this patient, study guidance decided that his data should not be included in the intention-to-treat analysis of PRI values. The time intervals between symptom onset and first medical contact (median 60 min, 35 to 128 min vs. median 85 min, 44 to 194 min; p = 0.08), first medical contact to study drug (40 min, 9 to 56 min vs. 52 min, 10 to 64 min; p = 0.55), study drug to coronary angiography (15 min, 7 to 42 min vs. 23 min, 5 to 43 min; p = 0.87) and study drug to blood sampling for PRI (120 min, 110 to 130 min vs. 120 min, 109 to 131 min) did not significantly differ between the 2 groups.

The TIMI patency rates of the infarct-related artery as evaluated in a central core laboratory are shown in Table 2. PPCI was performed in 26 and 28 patients,

TABLE 2 Angiographic Findings and Interventional Features

	Prasugrel (n = 31)	Clopidogrel (n = 31)	p Value
Angiography performed	31 (100)	31 (100)	0.99
No STEMI	3	2	
STEMI	28	29	
Patency of the infarct-related artery before PPCI			
TIMI flow grade 0/1	17 (60.7)	20 (69.0)	0.76
TIMI flow grade 2	4 (14.2)	2 (6.9)	
TIMI flow grade 3	7 (25.0)	7 (24.1)	
TIMI flow grade 2/3	11 (39.2)	9 (31.0)	0.43
PPCI performed	26	28	
Stent	25 (96.2)	25 (89.3)	
Patency of the infarct related artery after PPCI			
TIMI flow grade 0/1	0	0	0.92
TIMI flow grade 2	3 (11.5)	3 (10.7)	
TIMI flow grade 3	23 (88.5)	25 (89.3)	

Values are n (%) or n.

PPCI = primary percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

respectively, and TIMI flow grade 3 patency after PCI was not different between the 2 groups. The concomitant medication administered in the acute phase is given in Table 3 and did not show any significant differences between the 2 groups.

The PRI at baseline was 76% in the 2 groups (Table 4). The primary endpoint PRI after 2 h as well as the secondary endpoint PRI after 4 h were significantly lower with prasugrel compared with clopidogrel in the intention-to-treat analysis (Table 4). The time-course of PRI is given in Figure 2. The distribution of PRI is given in Figure 3 and showed a wide variability both with clopidogrel and prasugrel. In the patients with confirmed STEMI, PRI was lower in the prasugrel-treated compared with the clopidogrel-treated patients both after 2 h (48.7 ± 31.6% vs. 65.3 ± 22.1%; p = 0.04) and 4 h (38.9 ± 28.1% vs. 54.7 ± 24.5%; p = 0.03). The rate of patients with a sufficient PRI of <50% tended to be higher with prasugrel compared with clopidogrel after 2 and 4 h (Table 4).

Clinical events until day 30 were rare and are listed in Table 5. Bleeding complications were observed only in 1 and 0 patients, respectively.

TABLE 3 Periprocedural Antithrombotic and Adjunctive Therapy During the First 48 h

	Prasugrel (n = 31)	Clopidogrel (n = 31)	p Value
ASA	31 (100)	31 (100)	0.9
GP IIb/IIIa inhibitors	4 (12.9)	2 (6.4)	0.31
Unfractionated heparin	28 (90.3)	30 (96.8)	0.3
Enoxaparin	2 (6.5)	0	0.15
Bivalirudin	17 (54.8)	15 (48.4)	0.6
Beta-blockers	24 (77.4)	28 (90.3)	0.16
ACE inhibitors/ARBs	28 (90.3)	29 (93.5)	0.64
Statins	27 (87.1)	28 (90.3)	0.68
Morphine	19 (61.3)	13 (41.9)	0.12

Values are n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; ASA = acetylsalicylic acid; GP = glycoprotein.

TABLE 4 Results of the PRI Measurements in the 2 Groups

	Prasugrel (n = 31)	Clopidogrel (n = 31)	p Value
PRI			
Baseline	76.2 ± 16.0	76.7 ± 22.3	0.94
2 h	50.4 ± 32.7	66.3 ± 22.2	0.035
4 h	39.2 ± 29.3	54.5 ± 24.1	0.038
Rate of patients with PRI <50%			
2 h	14/30 (46.7)	8/28 (28.6)	0.15
4 h	17/27 (63.0)	11/29 (37.9)	0.06

Values are mean ± SD or n/N (%).

PRI = platelet reactivity index.

DISCUSSION

ETAMI is the first randomized, double-blind study to compare the pre-PCI administration of loading doses of 600 mg clopidogrel and 60 mg prasugrel in patients with STEMI scheduled for PPCI. The principal result

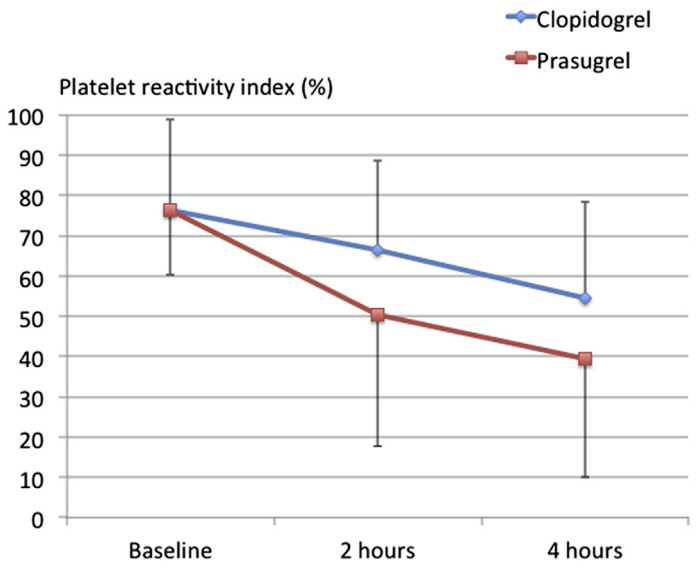

FIGURE 2 Time Course of the PRI Measured With the VASP Assay

Time course of the median values of the platelet reactivity index (PRI) measured with the vasodilator-stimulated phosphoprotein (VASP) assay in the 2 groups randomized to prasugrel or clopidogrel at baseline and 2 and 4 h after intake of the study medication.

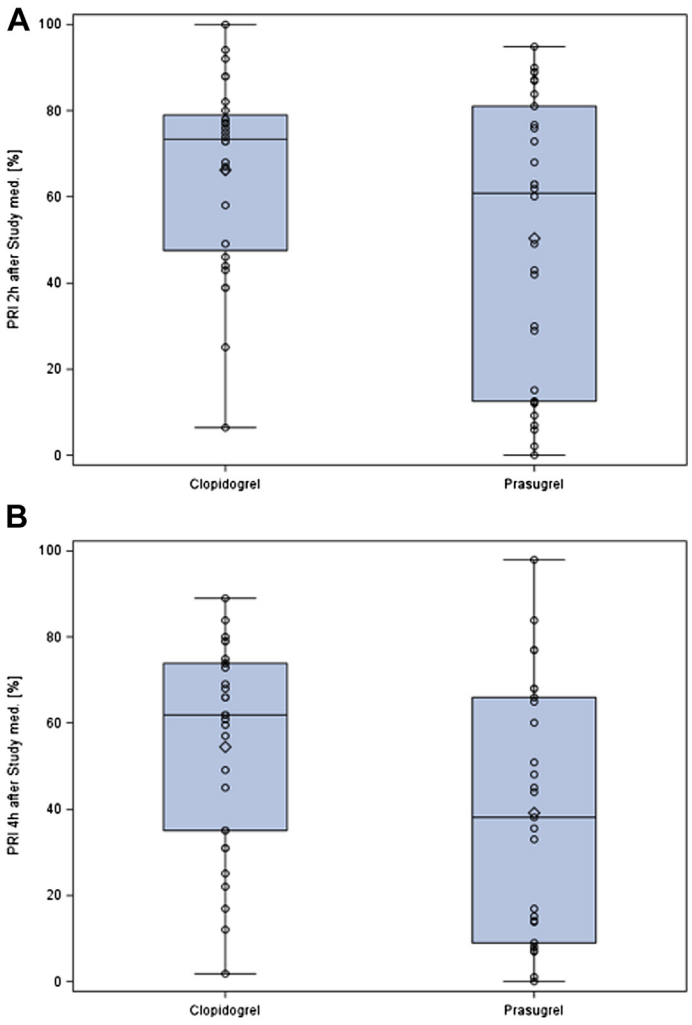

FIGURE 3 Distribution of Individual PRIs After 2 and 4 Hours

Distribution of individual platelet reactivity indexes (PRI) after **(A)** 2 h and **(B)** 4 h in the 2 patient groups randomized to prasugrel or clopidogrel.

of the study is that prasugrel achieves a faster and more intense inhibition of platelet inhibition than clopidogrel. After prasugrel, about 50% and 65% of the patients will have a VASP index of <50% within 2 and 4 h, respectively, whereas with clopidogrel, these rates are around 30% and 40%, respectively. That means that 60% of patients with STEMI will have insufficient inhibition of platelet aggregation within 4 h after intake of clopidogrel compared with only one-third after prasugrel.

The strength of our study was the randomized, double-blind design, which excludes any bias associated with nonrandomized comparisons or open randomized trials. The 600-mg loading dose of clopidogrel was selected because it has been shown that it achieves a faster and more effective platelet inhibition than the approved 300-mg loading dose in randomized trials (4,16). This effect was associated with an improved clinical outcome of 600 to 300 mg clopidogrel in patients with primary PCI (16,17) and in PCI, in patients with ACS with and without ST-segment elevation (18). However, in a randomized trial, the pre-hospital administration of 600 mg clopidogrel did not significantly improve patency of the infarct-related artery before PCI compared with the control group (19). Because in this trial the clopidogrel was given at a mean of 47 min before angiography, only a few patients have had a sufficient level of inhibition of platelet aggregation according to the results of the present study.

Randomized data on the results of platelet function tests in patients undergoing primary PCI for STEMI treated by clopidogrel or prasugrel are scarce. We have chosen the VASP-PRI as primary outcome because the result is not affected by the concomitant use of GP IIb/IIIa inhibitors and the results correlate well with those of platelet aggregometry and tests of activation by flow cytometry (20). In addition, it can be stored for up to 48 h without affecting the results, which makes the tests highly suitable for an acute study with STEMI patients. However, faster processing of blood samples might be associated with more reliable and reproducible results (21); therefore, all samples in our study were handled within 24 h after collection.

The pharmacodynamic substudy of the TRITON-TIMI 38 trial (8) included only 4 patients with STEMI. In the overall population, in 99 evaluable patients 60 mg prasugrel compared with 300 mg clopidogrel showed a more potent platelet inhibition assessed with the VASP-PRI 1 to 2 h after loading dose and PCI (51.8% vs. 78.8%, $p = 0.001$). In healthy volunteers, prasugrel was associated with an even faster onset of action. Effective ADP receptor inhibition was observed within 30 min in most volunteers, whereas 300 mg clopidogrel needed several hours to become effective (22). In a nonrandomized comparison, a 60 mg prasugrel loading dose about 50 min before PPCI was associated with a better inhibition of ADP-induced platelet aggregation compared with a 600 mg loading dose of clopidogrel (23). However, only 47% of patients after prasugrel and 29% after clopidogrel achieved an adequate platelet inhibition, defined as ADP-induced platelet aggregation of <70%, during a clinically-relevant door-to-balloon time of about 50 min. Another observational study observed again more effective platelet inhibition and a trend toward a better angiographic outcome before and after PPCI with prasugrel compared with clopidogrel (24). These

TABLE 5 Clinical Events Until Day 30 or Hospital Discharge

	Prasugrel (n = 31)	Clopidogrel (n = 31)	p Value
Death	1	1	1.00
Cardiogenic shock	1	2	0.27
Reinfarction	0	0	1.0
Stent thrombosis	0	0	1.0
Stroke	0	0	1.0
TIMI major or minor bleeding	1	0	0.31
GUSTO major or moderate bleeding	1	0	0.31

TIMI = Thrombolysis In Myocardial Infarction.

results support our findings of a significantly faster onset of platelet inhibition with prasugrel compared with clopidogrel in patients with primary PCI.

In the randomized TRITON-TIMI 38 trial and in observational nonrandomized studies, prasugrel was associated with an improved clinical outcome in patients with PPCI for STEMI (8,25,26). These findings might be explained at least in part by the faster and more potent platelet inhibition, as shown in our trial.

In 2 studies comparing the antiplatelet effects of prasugrel and ticagrelor in patients with PPCI, no significant differences were reported between these drugs (10,11). However, in both trials, around 50% of patients did not achieve adequate platelet inhibition as assessed by different methods 2 h after the loading dose.

We observed a wide patient variability of the response to the 2 drugs, which was more pronounced with clopidogrel, suggesting that the gastrointestinal absorption of orally-administered drugs may be limited or delayed in STEMI patients for multiple reasons, including reduced or delayed drug adsorption in patients with hemodynamic disarrangement, systemic vasoconstriction, adrenergic activation, and a high risk of vomit (27).

Therefore, it might be necessary to use faster-acting antiplatelet drugs to achieve an adequate level of platelet inhibition at the time of PPCI. One option is GP IIb/IIIa inhibitors, such as tirofiban, which was associated with a more potent platelet inhibition than prasugrel in the randomized FABOLUS-PRO (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with ST-segment elevation myocardial infarction compared to on top of PRasugrel given at loading dOse) trial (12). Another candidate is cangrelor, an intravenous ADP-receptor inhibitor with a rapid onset of action and a short half-life (28).

CONCLUSIONS

The pre-PCI administration of prasugrel in patients with STEMI undergoing primary PCI was associated with significantly faster ADP receptor inhibition compared with clopidogrel. Therefore, prasugrel should be preferred to clopidogrel in this patient population. However, even with prasugrel, inhibition of ADP-induced platelet aggregation is not as fast as in healthy volunteers and is still not optimal within 2 h after a loading dose of 60 mg.

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