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$P2Y_{12}$ receptor inhibition with prasugrel and ticagrelor in STEMI patients after fibrinolytic therapy: Analysis from the SAMPA randomized trial☆

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ABSTRACT

Background: A pharmacodynamic comparison between ticagrelor and prasugrel after fibrinolytic therapy has not yet been performed.
Methods: In the single-center SAMPA trial, 50 consecutive STEMI patients previously treated with clopidogrel and undergoing a pharmacoinvasive strategy were randomized to either a ticagrelor (n = 25) 180 mg loading dose followed by 90 mg bid, or a prasugrel (n = 25) 60 mg loading dose followed by 10 mg/day, initiated after fibrinolytic therapy but before angiography. Platelet reactivity was assessed with the VerifyNow $P2Y_{12}$ assay at 0, 2, 6, and 24 h after randomization.
Results: Mean times from fibrinolysis to prasugrel or ticagrelor administration were 11.1 ± 6.9 and 13.3 ± 6.3 h, respectively ($p = 0.24$). The values of PRU decreased significantly from baseline to 2 h (all $p < 0.001$) and from 2 h to 6 h (all $p < 0.001$) in both groups. There was no difference in PRU values between 6 h and 24 h. The mean PRU values at 0, 2, 6, and 24 h were 234.9, 127.8, 45.4, and 48.0 in the prasugrel group and 233.1, 135.1, 67.7, and 56.9 in the ticagrelor group, respectively. PRU values did not significantly differ between groups at any time period of the study.
Conclusions: In patients with STEMI treated with fibrinolytic therapy, platelet inhibition after clopidogrel is suboptimal and can be further increased with more potent agents. Ticagrelor and prasugrel demonstrated a similar extent of $P2Y_{12}$ receptor inhibition within 24 h, although maximal platelet inhibition after these potent agents was not achieved for 6 h.

1. Introduction

Current guidelines on the management of patients with acute coronary syndromes (ACS) recommend the combination of aspirin with a $P2Y_{12}$ receptor inhibitor [1–3]. For many years clopidogrel was the major option for inhibiting the $P2Y_{12}$ receptor [4–6]; however, clopidogrel has several limitations, including a prolonged time to peak platelet inhibition, substantial individual variability in response, and relatively high residual platelet reactivity. Previous studies have demonstrated that up to one-third of patients are hyporesponders to clopidogrel and maintain high on-treatment platelet reactivity levels [7–9]. Compared with clopidogrel, the new $P2Y_{12}$ receptor inhibitors prasugrel and ticagrelor have more uniform pharmacodynamic activity, stronger platelet inhibition, more rapid onset of action, and have proven to be superior in reducing ischemic events in ACS and after percutaneous coronary intervention (PCI) in large clinical trials [10–13].

In patients with ST-segment elevation myocardial infarction (STEMI), fibrinolytic agents may stimulate platelet hyperactivity due to thrombin-mediated platelet stimulation [14] and affect $P2Y_{12}$ inhibition up to 3 days after drug administration [15]. Therefore, patients with STEMI undergoing treatment with fibrinolytic agents and $P2Y_{12}$ receptor inhibitors may have suboptimal platelet inhibition, contributing to a heightened susceptibility to recurrent ischemic events. Furthermore,

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a pharmacodynamic comparison between ticagrelor and prasugrel in STEMI patients after fibrinolytic therapy is unknown. Thus, this study aimed to compare the pharmacodynamics of prasugrel and ticagrelor in patients with STEMI previously treated with clopidogrel and undergoing a pharmacoinvasive strategy.

2. Methods

This was a prospective, randomized, single-center study that compared the platelet aggregation activity of prasugrel and ticagrelor in patients with STEMI undergoing a pharmacoinvasive strategy. We enrolled 50 patients presenting with STEMI at a non-interventional hospital who were treated with a full dose of tenecteplase (30–50 mg IV according to patient weight) between July 2013 and December 2015. Patients also received loading doses of clopidogrel (300 mg or 600 mg) at the discretion of treating physician, aspirin (200–300 mg), and enoxaparin 30 mg intravenous bolus followed by 1 mg/kg subcutaneous and were later transferred for an invasive procedure (coronary angiography and planned PCI) in a tertiary center. Angiography was performed between 3 and 24 h after fibrinolysis in patients with clinical and electrocardiographic criteria of successful coronary reperfusion (pharmacoinvasive therapy) or on an emergency basis in patients without reperfusion criteria (rescue angioplasty).

Patients were randomized using computer-generated random numbers in a 1:1 ratio to receive a loading dose of prasugrel (60 mg) or a loading dose of ticagrelor (180 mg). Immediately before the angiography, patients received either ticagrelor 90 mg bid (beginning 12 h after the 180-mg loading dose) or prasugrel 10 mg/d (beginning 24 h after the 60-mg loading dose). Clinical follow-up was conducted in the hospital and by phone at 30 days, and bleeding complications were recorded using the Bleeding Academic Research Consortium (BARC) criteria [16].

The inclusion criteria included patients with a clinical and electrocardiographic diagnosis of STEMI who received tenecteplase in the past 24 h and signed informed consent. The exclusion criteria were the following: history of stroke or transient ischemic attack, age >75 years, weight <60 kg, use of oral anticoagulants, history of bleeding diathesis, severe hepatic dysfunction, contraindication to antiplatelet agents, history of angioplasty or bypass surgery within 3 months, periprocedural use of glycoprotein IIb/IIIa inhibitors, use of strong inducers or CYP3A4 inhibitors, and hemodynamic instability.

The study protocol was approved by the ethics committee, and all patients signed written informed consent. The study was registered at ClinicalTrials.gov (Identifier: NCT02215993).

Platelet aggregation was evaluated at the time of randomization (time 0) immediately after the loading dose of prasugrel or ticagrelor, and at 2, 6, and 24 h after the initial dose. Peripheral venous blood samples were obtained using a tourniquet after the insertion of a venous catheter into a peripheral vein. The first 2–4 mL of blood was discarded to avoid spontaneous platelet activation, and the collected blood was transferred to a tube containing 3.2% citrate. The VerifyNow (Accumetrics Inc., San Diego, California) platelet function test was performed. High platelet reactivity was defined as a $P2Y_{12}$ reaction unit (PRU) value >208, as this level has been associated with an increased risk of stent thrombosis and ischemic events after PCI as demonstrated in the ADAPT-DES study and the updated consensus report of the Working Group on On-Treatment Platelet Reactivity [17,18].

Quantitative characteristics were evaluated in each group using summary measures (mean, standard deviation, median, 25th percentile, and 75th percentile) and compared between the groups using the Student *t*-test or Mann-Whitney test. Qualitative characteristics were evaluated in each group using absolute and relative frequencies, and comparisons between the groups were performed using the χ^2 test, Fisher exact test, or likelihood ratio.

The PRU values were described for each group at each evaluation time using summary measures and were compared between the groups and between the evaluation times using generalized estimation equations with an autoregressive correlation matrix of order 1 between the evaluation times with normal marginal distribution and identity link function followed by the Bonferroni adjustment for multiple comparisons to evaluate when differences in the PRU values occurred.

On the basis of previously published studies, the variability in the PRU values 2 h after the loading dose of prasugrel or ticagrelor was assumed to be 53.7 units (SD = 53.7) [19]. It was expected that in the present study ticagrelor would result in lower PRU values by at least 50 units compared with prasugrel. With a power of 90% and testing at a 2-sided alpha = 0.05, the sample size required for the study was 25 patients in each group. Statistical analysis was performed using SPSS version 22 (IBM, Armonk, New York).

3. Results

Of the 50 randomized patients, 25 were treated with prasugrel and 25 were treated with ticagrelor. There were no significant differences in clinical or demographic characteristics between the groups (Table 1). The average age was 53.8 years, 80% were men, 26% had diabetes, and 58% were smokers. The average time after tenecteplase until administration of the loading dose of prasugrel or ticagrelor was 11.1 ± 6.9 h vs. 13.3 ± 6.2 h, respectively ($p = 0.24$). Angiographic and procedural data are summarized in Table 2. Clopidogrel was administered at the time of tenecteplase infusion, and the average period between loading dose of clopidogrel plus tenecteplase and angiography was 12.2 ± 6.6 h. The average SYNTAX score was 12.4 ± 8.8 in the prasugrel group vs. 10.2 ± 7.1 in the ticagrelor group ($p = 0.50$).

The mean PRU values at 0, 2, 6, and 24 h were 234.9, 127.8, 45.4, and 48.0 in the prasugrel group, and 233.1, 135.1, 67.7, and 56.9 in the ticagrelor group, respectively. There was no statistical difference in the primary endpoint between the groups (PRU values at 2, 6, and 24 h after administration of ticagrelor or prasugrel). Table 3 and Fig. 1 show the differences in platelet reactivity between the groups. There was a significant decrease in PRU values with both agents between time 0 and 2 h ($p < 0.001$) and between 2 and 6 h after antiplatelet administration ($p < 0.001$); however, the PRU values did not decrease further between 6 and 24 h (Table 4).

Baseline PRU, measured immediately before coronary angiography, was <208 in only 19 of the patients (38%). Of note, only one patient had received a 600-mg loading dose of clopidogrel; the other 49 patients received a 300-mg dose. Two hours after administration of the

Table 1
Clinical and demographic characteristics.

	Prasugrel (n = 25)	Ticagrelor (n = 25)	Total (N = 50)	*p* Value
Age, years	55.5 ± 8.3	52.2 ± 8.1	53.8 ± 8.3	0.15
Men	22 (88)	18 (72)	40 (80)	0.16
Hypertension	16 (64)	18 (72)	34 (68)	0.54
Diabetes	8 (32)	5 (20)	13 (26)	0.33
Current smoker	13 (52)	16 (64)	29 (58)	0.67
Hyperlipidemia	10 (40)	10 (40)	20 (40)	>0.99
eGFR < 60 mL/min/1.73 m^2	4 (16)	2 (8)	6 (12)	0.67
Previous myocardial infarction	0 (0)	1 (4)	1 (2)	>0.99
Previous PCI	3 (12)	0 (0)	3 (6)	0.24
GRACE score	133 ± 24.5	127 ± 21.4	130 ± 22.9	0.40
Troponin peak (ng/dL)	6395 ± 5423	8002 ± 8011	7199 ± 6819	0.74
Aspirin	25 (100)	25 (100)	50 (100)	>0.99
Statin	25 (100)	25 (100)	50 (100)	>0.99
BMI	27 ± 4.3	27.2 ± 4.6	27.1 ± 4.4	0.86
Hemoglobin (g/dL)	15.0 ± 1.9	14.6 ± 1.8	14.8 ± 1.8	0.41
Platelets (×1000 mm^3)	232 ± 73	225 ± 45	228 ± 60	0.94
Cholesterol total (mg/dL)	205 ± 50.7	213 ± 56.8	209 ± 53.4	0.63
LDL (mg/dL)	133 ± 37.6	134 ± 44.6	133 ± 40.8	0.97
HDL (mg/dL)	37 ± 10.3	41 ± 12.9	39 ± 11.7	0.31
Triglycerides (mg/dL)	173 ± 160	204 ± 250	189 ± 208	0.83

Values are mean ± SD (N), (n) %. eGFR = estimated glomerular filtration rate. PCI: percutaneous coronary intervention. BMI = body mass index. HDL = high density lipoprotein. LDL = low density lipoprotein.