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Distribution of clinical events across platelet aggregation values in all-comers treated with prasugrel and ticagrelor

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ABSTRACT

The aim of this study was to investigate the distribution of clinical events across the platelet aggregation values in patients treated with prasugrel and ticagrelor. This prospective observational study enrolled 226 patients treated with prasugrel (n = 121) or ticagrelor (n = 105). Adenosine diphosphate (ADP)-induced platelet aggregation was determined by Multiplate Analyzer in the maintenance phase of treatment with prasugrel or ticagrelor. Clinical outcome was evaluated over 12 months. Platelet aggregation values were divided into quartiles. The first quartile comprised values <8 U, the second quartile values between 8 U and <15 U, the third one values between 15 U and 23 U, and the forth one values >23 U. Myocardial infarction events were observed in patients within the third quartile of aggregation values (15–23 U), and were not associated with high on-treatment platelet reactivity (HTPR > 46 U). All bleeding events occurred in patients with aggregation values ≤23 U, which corresponded to the 75 percentile (p = 0.031). There was no difference in the distribution of bleeding events between the 1st–3rd quartiles (p = 0.873). In conclusion, patients with ADP-induced aggregation values over 23 U (fourth quartile) were at the lowest risk to develop bleeding during the follow-up.

1. Introduction

High on-treatment platelet reactivity (HTPR) to clopidogrel has led to the development of third generation $P2Y_{12}$ inhibitors prasugrel and ticagrelor, which reduce the rate of ischemic adverse events in patients suffering from acute coronary syndrome (ACS) [1,2]. This improvement in clinical outcome is due to more consistent, more potent and more rapid platelet inhibition by prasugrel and ticagrelor [3,4]. Nevertheless, recent studies suggested that HTPR also occurs in up to 20% of patients treated with novel platelet inhibitors [5,6]. Moreover, when platelet function assessment was performed 2 h after loading in patients presenting with ST-elevation myocardial infarction (STEMI), 46% of HTPR was reported with ticagrelor, and 35% with prasugrel [7]. As expected, use of prasugrel and ticagrelor was associated with a higher risk of bleeding events compared with clopidogrel in clinical trials, which might be explained by a high level of platelet inhibition achieved by those drugs [8–13]. We aimed in this study to determine the proportion of patients who develop bleeding or ischemic events during the follow-up and to determine the distribution of events across the platelet aggregation values.

2. Methods

2.1. Study design

The study was a prospective observational cohort study in consecutive patients performed at the Medical University of Vienna. The Ethics Committee of the Medical University of Vienna approved the study protocol in accordance with the Declaration of Helsinki. Participants were included into the study between July 2012 and February 2014 and followed-up for 12 months. Clinical follow-up information was obtained by contacting all patients by phone and/or mail every three months, and by queries from the national death registry. Inclusion criteria were a written informed consent obtained before the study entry, treatment with prasugrel or ticagrelor for ACS and age > 18 years. The only exclusion criterion was participation in another trial. Two hundred twenty six patients with ACS were enrolled. All patients received a loading dose of prasugrel (60 mg) or ticagrelor (180 mg) followed by a once daily dose of 10 mg prasugrel or twice daily dose of ticagrelor (90 mg), respectively. The type of the P2Y12 blocker use was at the discretion of the treating interventional cardiologist according to the current guidelines and the intern standard operating procedures (SOP) for the antiplatelet treatment of ACS patients. These SOP recommend a following treatment algorithm: prasugrel is a drug of choice in STEMI patients or NSTE-ACS with diabetes, unless contraindicated, ticagrelor is a drug of choice in the NSTE-ACS setting, unless contraindicated). All interventions were

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performed according to current guidelines, and the type of stent implanted was at the discretion of the interventional cardiologist. Blood samples from patients were obtained during the treatment with maintenance doses of prasugrel and ticagrelor at 8 a.m. (at least one day after loading).

The study is reported according to the STROBE (strengthening the reporting of observational studies in epidemiology) standards.

2.2. Impedance aggregometry

Whole blood aggregation was determined using Multiple Electrode Aggregometry (MEA) on a new generation impedance aggregometer (Multiplate Analyzer, Roche Munich, Germany). The system detects the electrical impedance change due to the adhesion and aggregation of platelets on two independent electrode-set surfaces in the test cuvette as described [14]. We used hirudin as anticoagulant and adenosine diphosphate (ADP) as agonist. A 1:2 dilution of whole blood anticoagulated with hirudin and 0.9% NaCl was stirred at 37 °C for 3 min in the test cuvettes, ADP: 6.4 μM was added and the increase in electrical impedance was recorded continuously for 6 min. The mean values of the 2 independent determinations are expressed as U (units). MEA was performed at the Department of Cardiology at the Medical University of Vienna. According to the position document, values >46 U have been classified as HTPR [1,15].

2.3. Study endpoints

The primary endpoint was ADP-induced platelet aggregation. The secondary efficacy end points were the incidence of ischemic events such as myocardial infarction, cardiac death, stroke and stent thrombosis. Definite stent thrombosis was defined according to the Academic Research Consortium criteria as the occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis within the stent [16]. Myocardial infarction was defined according to the universal definition [17]. The secondary safety end point was the incidence of TIMI major, minor and minimal bleeding events [18].

2.4. Statistical analysis

We estimated an exploratory sample size of 226 patients to characterize patients treated with prasugrel and ticagrelor with regard to platelet aggregation and clinical events under real life clinical conditions. Normal distribution was tested with the Kolmogorov Smirnov test. Data are expressed as mean, standard deviation (SD) or 95% confidence intervals (CI) as appropriate. Statistical comparisons were performed with the t-test and the X^2-test when applicable. A comparison between prasugrel and ticagrelor is only of descriptive nature. All statistical calculations were performed using commercially available statistical software (SPSS Version 21.0; Chicago).

3. Results

3.1. Patient demographics

Patient demographics and co-medications are shown in Table 1. The majority of patients had cardiovascular risk factors as high blood pressure (67%), hyperlipidemia (60%), smoking history (71%) or family history of coronary artery disease (48%). Diabetes mellitus was diagnosed in 21% of patients. Use of beta-blockers (93%), statins (95%) and proton

Table 1
Patient demographics.

Patient demographics	Overall N = 226	Prasugrel N = 121	Ticagrelor N = 105
Age (years)	59 ± 11	57.74 ± 10.37	60.70 ± 13.07
Gender (male) n (%)	174 (77)	100 (83)	74 (70)*
Risk factors/past medical history n (%)			
Body mass index (BMI; mean ± SD)	27.97 ± 4.92	28.00 ± 5.02	27.94 ± 4.82
Hypertension	149 (67)	72 (60)	77 (74)*
Hyperlipidemia	134 (60)	68 (57)	66 (63)
Smoking	161 (71)	95 (79)	66 (63)*
Family history of CAD	108 (48)	65 (54)	43 (41)*
Diabetes mellitus	48 (21)	18 (15)	30 (29)*
Prior PCI	16 (7)	9 (8)	7 (7)
Prior myocardial infarction	47 (21)	22 (18)	25 (24)
Peripheral arterial occlusive disease	12 (5)	6 (5)	6 (5)
Cerebrovascular disease	8 (4)	2 (2)	6 (6)
Laboratory data (mean ± SD)			
White blood cell count (WBC; $\times 10^9$/L)	10.69 ± 3.81	11.35 ± 3.82	9.92 ± 3.72
Platelets ($\times 10^9$/L)	245 ± 69	241 ± 64	248 ± 76
C reactive protein (mg/dl)	0.98 ± 2.07	0.85 ± 1.96	1.11 ± 2.20
Hemoglobin (g/dl)	14.40 ± 1.85	14.78 ± 1.71	13.98 ± 1.90
Fibrinogen (mg/dl)	396 ± 96	388 ± 89	407 ± 104
Creatinine (mg/dl)	0.98 ± 0.37	0.939 ± 0.23	1.02 ± 0.49
Concomitant medications n (%)			
Aspirin	226 (100)	121 (100)	105 (100)
Proton pump inhibitors (PPI)	169 (77)	89 (75)	80 (80)
ß blockers	200 (93)	109 (96)	91 (90)
Statins	205 (95)	111 (97)	94 (93)
Angiotensin converting enzyme (ACE) inhibitors	187 (87)	100 (88)	87 (86)
Calcium channel blockers	27 (13)	9 (8)	18 (18)*
ACS data			
NSTE-ACS	119 (60)	8 (7)	71 (77)***
STEMI	79 (40)	98 (93)	21 (23)
PCI	203 (89)	105 (86)	98 (93)*
Number of stents per patient	1.44 ± 0.97	1.47 ± 0.81	1.40 ± 1.12
Total stent length	30.99 ± 20.48	30.04 ± 15.43	31.80 ± 25.36

Data are reported as mean ± standard deviation (SD), n (number of patients) or percentages; CAD = coronary artery disease; PCI = percutaneous coronary intervention; MEA = multiple electrode aggregometry; PCI = percutaneous coronary intervention, STEMI = ST-elevation myocardial infarction; NSTE-ACS = none ST-elevation acute coronary syndrome. * = $p < 0.05$; ** = $p < 0.005$.