Original Research Article

A study on platelet reactivity and associated clinical characteristics in acute coronary syndrome patients treated with Ticagrelor and Clopidogrel

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Abstract

Background: The pathophysiology of the acute coronary syndrome (ACS) is characterized by the rupture of an atherosclerotic plaque within the coronary artery, with subsequent platelet aggregation, thrombus formation, and ischemia. Before platelets aggregate, they must first be activated to express activated glycoprotein IIb/IIIa receptors on the cell surface. This activation is the result of stimulation from endogenous platelet agonists, such as thromboxane A2 and adenosine diphosphate (ADP). ADP activates platelets by binding to P2Y12 receptors on the cell surface. Despite clinical efficacy in a broad range of coronary artery disease patients, pharmacodynamic studies conducted in patients undergoing stenting showed that clopidogrel therapy was associated with variable and moderate platelet inhibition (50% inhibition at steady state as demonstrated by ex-vivo ADP-induced platelet aggregation) as well. Ticagrelor, a cyclopentyl-triazolo-pyrimidine acting as an analog of adenosine triphosphate (ATP), constitutes a first non-thienopyridine direct platelet P2Y12 receptor blocker.
Aim of the study: To investigate factors linked to HOTPR on ticagrelor and whether they differ from factors linked to HOTPR on clopidogrel.
Materials and methods: Totally 300 patients were included in the study Patients presenting to the Department of Cardiology, SRM Medical College Hospital and Research Institute, Kattangulathur,

Kanchipuram District, Chennai with an ACS between January 2018 to May 2019 were eligible for inclusion in the study if coronary angiography (±PCI) was planned and they were adequately pretreated with Ticagrelor or clopidogrel and aspirin. An ACS was defined as symptoms suggestive of myocardial ischemia lasting > 15 min with either troponin elevation or new electrocardiogram (ECG) changes consistent with myocardial ischemia. ECG changes consistent with myocardial ischemia included ≥ 1 mm of ST-segment deviation or T wave inversion ≥ 1 mm in at least 2 contiguous leads. Troponin was considered elevated if greater than 14 ng/L, with a rise and/or fall of 50% if 14-50 ng/L or 20% if >50 ng/L in a subsequent measure.

Results: The mean age was 63 ± 12 years with 71.9% being male and 18% having diabetes. Patients predominantly presented with NSTEMI 76% and 24% as STEMI. Patients treated with Ticagrelor were younger, more likely to be male, less likely to present with STEMI, have suffered a previous MI, experience atrial fibrillation and be taking proton pump inhibitors or calcium channel blockers. Patients who were administered Ticagrelor demonstrated significantly lower platelet reactivity when stimulated with ADP compared to patients administered clopidogrel (30.3 AU vs 43.7 AU respectively, $p<0.0001$).

C**onclusion:** This study demonstrates that Ticagrelor provides more potent platelet inhibition than clopidogrel measured by MEA. This is reflected in ticagrelor's ability to reduce the proportion of ACS patients experiencing HOTPR. Different clinical factors contribute to HOTPR in ACS patients treated with Ticagrelor or clopidogrel. Clopidogrel dose, renal insufficiency, clinical presentation, and platelet count are linked to clopidogrel HOTPR. In contrast, only a history of myocardial infarction is associated with Ticagrelor HOTPR.

Key words

Acute Coronary Syndrome, Acute Catheterisation and Urgent Triage Strategy, Assessment of Dual Antiplatelet Therapy with Drug-Eluting Stents, High On-Treatment Platelet Reactivity (HOTPR).

Introduction

Acute coronary syndrome (ACS) refers to a group of clinical conditions such as coronary atherosclerosis rupture, platelet aggregation, and thrombosis. Platelet aggregation has a close relationship with the occurrence and development of ACS; thus, antiplatelet therapy is the most common treatment for ACS. Second-generation thienopyridines (clopidogrel and prasugrel) are widely used in antiplatelet therapy [1]. Clopidogrel is converted to its active metabolites in vivo by a 2-step process, and these active metabolites irreversibly inhibit the platelet P2Y12 adenosine diphosphate receptor, Therefore, clopidogrel is a prodrug, and its onset of action is relatively slow Moreover, 30% of patients show drug resistance to clopidogrel, which can induce a high risk of myocardial infarction recurrence and stent thrombosis. Prasugrel is another antiplatelet drug with the same mechanism as clopidogrel. Its active metabolites are produced in a 1-step metabolic process; thus, its onset of action is shorter Furthermore, compared with clopidogrel, it has a series of advantages, such as greater efficacy and lower variability. However, it probably has an increased risk of bleeding, including fatal bleeding [2]. Given the limitations of these two widely used drugs, such as the delayed onset of action and variability of clopidogrel and prasugrel bleeding risk, additional studies were critical in developing efficient new P2Y12 receptor antagonists. Ticagrelor (AZD6140) is the first reversibly binding oral P2Y12 receptor antagonist that blocks ADP-induced platelet aggregation [3]. The discovery of ticagrelor began with adenosine triphosphate (ATP). The subsequent identification of a novel series of P2Y12 receptor antagonists and the exploitation of their SAR has been described. Modifications of the acidic side chain and purine core, in addition to experimentation with hydrophobic

substituents, led to the development of a series of neutral molecules [4]. Ultimately, the leading compound, AZD6140, was developed as a novel platelet aggregation inhibitor there is substantial variance in the level of platelet inhibition achieved with clopidogrel [5]. A threshold of suboptimal platelet reactivity has been established that is associated with an increased risk of ischaemic events, above which patients are defined as having HOTP. HOTPR measured by MEA significantly predicts MI and stent thrombosis, with a trend towards predicting cardiovascular death in patients with CAD, including ACS. Numerous factors have been linked to the presence of HOTPR in patients treated with clopidogrel. These include age, gender, BMI, diabetes, ACS, reduced LVF, renal insufficiency, inflammation, platelet count, underdosing, compliance, drug interactions and genetic polymorphisms [6]. Ticagrelor has been demonstrated as a superior drug compared to clopidogrel by its ability to reduce ischemic events as shown in the PLATO trial. Part of ticagrelor's benefit over clopidogrel has been attributed to more potent and consistent platelet inhibition [7]. Ticagrelor is direct acting and is not affected by genetic polymorphisms that compromise clopidogrel bioavailability. The rate of MEA measured HOTPR in ACS patients treated with Ticagrelor has not been clearly defined in the literature to date. Clinical factors that may contribute to the rate of MEA measured HOTPR in ACS patients treated with Ticagrelor is also unknown. Determining the rate of HOTPR in an ACS population treated with Ticagrelor and what factors may contribute to this is important due to the ischaemic risk associated with HOTPR [8].

Materials and methods

Totally 300 patients were included in the study. Patients presenting to the Department of Cardiology, SRM Medical College Hospital and Research Institute, Kattangulathur, Kanchipuram District, Chennai with an ACS between January 2018 to May 2019 were eligible for inclusion in the study if coronary angiography (±PCI) was planned and they were adequately pretreated with Ticagrelor or clopidogrel and aspirin. An ACS was defined as symptoms suggestive of myocardial ischemia lasting > 15 min with either troponin elevation or new electrocardiogram (ECG) changes consistent with myocardial ischemia. ECG changes consistent with myocardial ischemia included ≥ 1 mm of new ST-segment deviation or T wave inversion ≥ 1 mm in at least 2 contiguous leads. Troponin was considered elevated if greater than 14 ng/L, with a rise and/or fall of 50% if 14-50 ng/L or 20% if >50 ng/L in a subsequent measure. Adequate pretreatment was defined as chronic therapy (> 7 days) with aspirin (≥ 100 mg once daily) and Ticagrelor (90 mg twice daily) or clopidogrel (≥ 75 mg once daily). If patients were not on chronic therapy with these agents then adequate pretreatment was defined as loading with aspirin ≥ 300 mg and Ticagrelor 180 mg at least 2 hours, or clopidogrel ≥ 300 mg at least 6 hours, prior to enrolment followed by maintenance therapy. Exclusion criteria included a known platelet function disorder, platelet count <100 x 10^9/L, hemoglobin <100 g/L, administration of a fibrinolytic agent within 24 hours of enrolment, administration of a glycoprotein IIb/IIIa receptor antagonist within a week prior to enrolment and inability to provide informed consent. Patient demographics, prior medical history, clinical characteristics, admission medications, clinical management, procedural variables, and in-hospital outcomes were obtained prospectively from a review of medical records and cardiac catheterization database. Ethnicity was self-identified by the patient. Clinical management, including the prescription of an antiplatelet agent, was at the discretion of the attending physicians.

Blood collection and platelet function testing [9, 12, 13]

Whole blood samples for platelet function testing were collected from either a peripheral vein using a 21-gauge needle before angiography or in the cardiac catheterization laboratory from the arterial sheath immediately after insertion and prior to heparin administration. All samples were

collected into tubes anticoagulated with hirudin and platelet function testing was performed 30 ± 15 min following collection as described below. Platelet aggregation was measured in whole blood by MEA using the Multiplate analyzer in accordance with the manufacturer's instructions. Briefly, whole blood was diluted 1:1 with 300 μL 0.9% NaCl solution in the test cell, which contained a Teflon coated magnetic stirring bar. Following incubation at 37°C for 3 min, 20 μL of ADP was added to the test cuvette to a final concentration of 6.5 μM. ADP stimulates platelets to aggregate and adheres to the test cell electrodes, impeding the current between them. The increase in impedance due to the attachment of platelets to electrodes is detected for each sensor unit separately and recorded continuously for 6 min with the mean being transformed to arbitrary aggregation units (AU) that are plotted against time. This can be expressed as arbitrary aggregation units (AU x min) or as arbitrary units (AU), with 10 AU x min being equivalent to 1 AU.

Statistical analysis

All continuous variables were normally distributed and are expressed as means and standard deviations (mean ± SD). Chi-square tests were used to compare the proportion of Ticagrelor patients with HOTPR by prior MI and the proportion of clopidogrel patients with HOTPR by renal insufficiency and clinical presentation. Student's *t*-test was used to compare absolute values of platelet reactivity by prior MI in Ticagrelor patients and renal insufficiency, clinical presentation, platelet count and dosing regimen in clopidogrel-treated patients. ANOVA was used to compare the proportion of clopidogrel patients with HOTPR by their dosing regimen classification. All statistical tests were performed using SPSS 22.0.

Results

Table - 1 shows during the study period 300 patients with ACS met the inclusion criteria and were enrolled in the study. Their baseline demographics, clinical characteristics, and laboratory data were shown. The mean age was 63 ± 12 years with 71.9% being male and 18% having diabetes. Patients predominantly presented with NSTEMI 76% and 24% as STEMI. Patients treated with Ticagrelor were younger, more likely to be male, less likely to present with STEMI, have suffered a previous MI, experience atrial fibrillation and be taking proton pump inhibitors or calcium channel blockers.

Table – 1: Patient demographics, clinical characteristics and laboratory data by antiplatelet agent.

Demographic data	All n(300)	Ticagrelor n(150)	Clopidogrel n(150)	P value
Age (years)	63 ± 12	61 ± 10	65 ± 12	<0.0001
Male, n (%)	387 (71.9)	177 76.0)	210 68.9)	0.027
BMI	29.2 ± 5.5	29.3 ± 5.2	29.1 ± 5.7	0.695
Hypertension	319 (59.3)	129(55.3)	190 62.3)	0.105
Dyslipidaemia	336 (62.5)	145(62.2)	191(62.6)	0.926
Diabetes	95 (17.8)	38 (16.3)	57 (18.7)	0.473
Current Smoker	118 (21.9)	53 (22.7)	65 (21.3)	0.69
Prior MI	107 (19.9)	37 (15.9)	70 (23.0)	0.042
Atrial fibrillation	30 (5.6)	7 (3.0)	23 (7.5)	0.023
Renal insufficiency	27 (5.0)	8 (3.4)	19 (6.2)	0.141
STEMI	129 (24.0)	30 (12.9)	99 (32)	0.998
NSTEMI	409 (76.0)	203 87.1)	206 (68)	0.678
Creatinine (μmol/L)	90 ± 26	90 ± 18	91 ± 31	0.536
Platelet count (10^9/L)	235 ± 64	237 ± 61	234 ± 66	0.526

Table – 2: Platelet reactivity and proportion of HOTPR by antiplatelet agent.

Platelet reactivity	**All n(300)**	**Ticagrelor n(150)**	**Clopidogrel n(150)**	**P value**
Platelet reactivity (AU)	37.8 ± 22.8	30.3 ± 17.5	43.7 ± 24.8	**<0.0001**
HOTPR	152 (28.3)	37 (15.9)	115 (37.7)	**<0.0001**

Table – 3: Ticagrelor group demographics, clinical characteristics and laboratory data by HOTPR.

Demographics	**Ticagrelor N (150)**	**HTOPR (40)**	**NO-HTOPR (110)**	**P value**
Age (years)	61 ± 10	62 ± 10	61 ± 10	0.511
Male, n (%)	177 (76.0)	31 (83.8)	146 (74.5)	0.225
BMI	29.3 ± 5.2	30.6 ± 5.4	29.0 ± 5.2	0.081
Hypertension	129 (55.3)	20 (54.1)	109 (55.6)	0.861
Dyslipidaemia	145 (62.2)	22 (59.5)	123 (62.8)	0.705
Diabetes	38 (16.3)	9 (24.3)	29 (14.8)	0.15
Current Smoker	53 (22.7)	7 (18.9)	46 (23.5)	0.545
Prior MI	37 (15.9)	11 (29.7)	26 (13.3)	0.012
Atrial fibrillation	7 (3.0)	2 (5.4)	5 (2.6)	0.351
Renal insufficiency	8 (3.4)	1 (2.7)	7 (3.6)	0.79
STEMI	30 (12.9)	5 (13.5)	25 (13)	0.99
NSTEMI	203 (87.1)	32 (86.5)	171 (87)	0.23
Creatinine (µmol/L)	90 ± 18	94 ± 20	89 ± 18	0.144
Platelet count (109/L)	237 ± 61	231 ± 51	238 ± 62	0.543

Table – 4: Clopidogrel group demographics, clinical characteristics and laboratory data by HOTPR.

Demographics	**CLOPIDOGREL n(150)**	**HTOPR (35)**	**NO-HTOPR (115)**	**P value**
Age (years)	65 ± 12	66 ± 13	65 ± 11	0.309
Male, n (%)	210 (68.9)	73 (63)	137 (72)	0.115
BMI	29.1 ± 5.7	29.8 ± 6.0	28.6 ± 5.5	0.075
Hypertension	190 (62.3)	77 (67.0)	113 (59.5)	0.191
Dyslipidemia	191 (62.6)	71 (61.7)	120 (63.2)	0.804
Diabetes	57 (18.7)	27 (23.5)	30 (15.8)	0.095
Current Smoker	65 (21.3)	25 (21.7)	40 (21.1)	0.887
Prior MI	70 (23.0)	22 (19.1)	48 (25.3)	0.217
Atrial fibrillation	23 (7.5)	13 (11.3)	10 (5.3)	0.053
Renal insufficiency	19 (6.2)	12 (10.4)	7 (3.7)	**0.018**
STEMI	99 (32)	48 (41.7)	51 (26.8)	2.080
NSTEMI	206 (68)	67 (58.2)	139 (73.2)	0.345
Creatinine (µmol/L)	91 ± 31	94 ± 40	89 ± 23	0.297
Platelet count (109/L)	234 ± 66	250 ± 68	224 ± 64	**0.001**

Table - 2 shows Patients who were administered Ticagrelor demonstrated significantly lower platelet reactivity when stimulated with ADP compared to patients administered clopidogrel (30.3 AU vs 43.7 AU respectively, p<0.0001), The proportion of patients with HOTPR was also lower in the ticagrelor group (15.9% vs 37.7% respectively, p<0.0001).

Table – 5: Platelet reactivity and proportion HOTPR in the clopidogrel group, in patients, presenting as STEMI or NSTEMI.

Clopidogrel	STEMI (65)	NON STEMI(85)	P VALUE
HOTPR (%)	48 (48.5)	67 (32.5)	**0.007**
Platelet reactivity	50 ± 25	41 ± 24	**0.003**

Table – 6: Platelet reactivity and proportion of HOTPR in the clopidogrel group, by clopidogrel dosing regimen.

CLOPIDOGREL	High (N= 50)	Intermidetate (N= 60)	Low (N= 40)	P VALUE
HOTP (%)	11 (27.5)	42 (32.3)	62 (45.9)	0.026
Platelet reactivity	39 ± 21	43 ± 26	46 ± 25	0.199

A prior MI was the only factor significantly different in the ticagrelor group of patients with and without HOTPR (29.7% vs 13.3%, respectively, p=0.012), shown in **Table – 3**. However, the mean values of platelet reactivity between patients treated with ticagrelor with and without a history of MI were not significantly different (p=0.321).

Patients treated with clopidogrel presenting with a STEMI had greater absolute values of platelet reactivity and an elevated HOTPR prevalence, Increasing platelet count was associated with increased platelet reactivity, shown in **Table - 4**. HOTPR incidence was significantly different by clopidogrel dosing regimen, but not by absolute values of platelet reactivity.

The mean and standard deviation are represented in blue. B) The rate of HOTPR in the clopidogrel group, in patients presenting as STEMI or NSTEMI (p=0.007, Chi-squared test) as per **Table - 5**.

The mean and standard deviation are represented in blue. B) The rate of HOTPR in the clopidogrel group increased significantly with decreasing clopidogrel dosing regimen (p=0.026, Chi-square test) as per **Table - 6**.

Discussion

In contrast, only a history of prior MI was associated with the rate of HOTPR in patients treated with ticagrelor. Ticagrelor exerted more potent residual platelet inhibition compared to clopidogrel (30.3 AU ± 17.5 vs 43.7 AU ± 24.8, p<0.0001). As a consequence of the more potent platelet inhibition, a reduced proportion of patients treated with Ticagrelor experienced HOTPR (15.9% vs 37.7%, p<0.0001). Our absolute values of platelet reactivity and the corresponding proportion of patients with HOTPR on ticagrelor are higher than reported for ACS patients in the literature using ME [9]. Our study differs in the inclusion of both STEMI and NSTEMI patients treated with ticagrelor and substantially larger sample size. A possible reason for our higher values of platelet reactivity on Ticagrelor may be due to the optimization of our protocol in testing platelet function to reduce variability [10]. We perform MEA between 15 and 45 minutes of sample collection as there is a significant reduction in platelet aggregation after 60 minutes. Large interstudy and interassay heterogeneity in the measurement of platelet reactivity has also been documented with clopidogrel, with HOTPR prevalence ranging from 6% to 80 % [11]. Ticagrelor has been repeatedly shown to be a more potent antiplatelet agent than clopidogrel in both stable and acute coronary disease settings, using LTA, VerifyNow and VASP-P assay. Indeed, Ticagrelor's mortality benefit has been in part attributed to more potent and consistent platelet inhibition in ACS patients [13]. A loading dose of ticagrelor achieves greater platelet inhibition, measured by LTA and Verify Now assays than both 300 mg and 600 mg loading dose of clopidogrel. This treatment effect is maintained

throughout chronic therapy in patients with both stable CAD and AC [14]. The proportion of patients with a history of MI was 29.7% in patients with HOTPR, compared to 13.3% in patients within the therapeutic range. However, absolute values of platelet reactivity did not differ significantly between those with and without a prior MI, 33 ± 19 AU and 30 ± 17 AU, respectively [15]. In STEMIs treated with primary PCI, 31.8% of ticagrelor patients had HOTPR (≥46.8 AU) measured with MEA 2 hours post-loading with 180 mg. The incidence of HOTPR reduced with time, occurring in 9.1% at 6 hours, 4.8% at 24 hours, to no patients with HOTPR after 5 days. STEMI was not associated with HOTPR in our cohort, with STEMIs comprising 13.5% of patients experiencing HOTPR, compared to 13.0% of patients within the therapeutic range (p=0.899) [16]. STEMI patients receiving primary angioplasty were excluded from this study due to insufficient time between antiplatelet loading and PCI [17]. The majority of STEMI patients in this study received clopidogrel (76.7%) due to guidelines recommending clopidogrel as adjunctive antiplatelet therapy to fibrinolytic therapy and additionally not to administer ticagrelor within 24 hours of thrombolysis [18]. Furthermore, we excluded patients who were switched from clopidogrel to ticagrelor 24 hours post-thrombolysis due to clopidogrel's irreversible platelet inhibition which may have an unknown impact on ticagrelor platelet function measurements. In the five ticagrelor STEMI patients with HOTPR, the minimum time between ticagrelor loading and platelet function testing was 8 hours. Hence insufficient time between ticagrelor loading and PCI did not appear to be contributing to HOTPR. Furthermore, baseline ADP-induced platelet aggregation is subject to significant interindividual variability. Hence the absolute or relative measure of antiplatelet responsiveness may overestimate the ischaemic risk in nonresponders with low baseline platelet reactivity, whilst conversely underestimating the risk in clopidogrel responders who maintain high platelet reactivity during treatment [19]. On this basis the measure of an on-treatment absolute level of platelet reactivity has been proposed as a superior measure of thrombotic risk. The incidence of HOTPR on clopidogrel in this study (37.7%) was similar to that observed in a previous cohort of ACS patients treated with clopidogrel published by our research group, where 38% of the clopidogrel group experienced HOTPR as measured by MEA. Clinical factors associated with HOTPR in this cohort. included Maori ethnicity, diabetes, previous PCI and a low clopidogrel dosing regimen [20]. Although the relationship did not reach statistical significance, there was a trend towards BMI being associated with HOTPR. Further clinical factors associated with HOTPR in the literature include age, ACS, reduced LVF, renal failure, inflammation, gender, platelet count, fibrinogen levels, underdosing, compliance, gene polymorphisms, and drug interactions [21]. Clopidogrel under-dosing is a pivotal cause of HOTPR, higher clopidogrel dosing regimens have been demonstrated to reduce platelet reactivity and the proportion of patients experiencing HOTPR.STEMI patients in our study treated with clopidogrel had greater platelet reactivity (50 ± 25 AU) and HOTPR incidence (48.5%) than NSTEMI patients (41± 24 AU, p=0.003 and 32.5%, p=0.007 respectively). It is possible that this is due to greater activation of platelets in STEMI than NSTEMI, or alternatively a reduced intestinal absorption of clopidogrel in STEMI patients [22, 23].

Conclusion

This study demonstrates that ticagrelor provides more potent platelet inhibition than clopidogrel measured by MEA. This is reflected in ticagrelor's ability to reduce the proportion of ACS patients experiencing HOTPR. Different clinical factors contribute to HOTPR in ACS patients treated with ticagrelor or clopidogrel. Clopidogrel dose, renal insufficiency, clinical presentation, and platelet count are linked to clopidogrel HOTPR. In contrast, only a history of myocardial infarction is associated with ticagrelor HOTPR.

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