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RESEARCH ARTICLE

An assessment of platelet response to ticagrelor in post-percutaneous coronary intervention patients using light transmission platelet aggregometry (LTA)

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Abstract

Background: Low on-treatment platelet reactivity (LTPR) or High on-treatment platelet reactivity (HTPR) with P2Y12 inhibitors is associated with bleeding (LTPR) or ischemic events (HTPR) in patients on dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI). **Objective:** Mapping of Indonesian patients' platelet response secondary to ticagrelor and thus identifying either LTPR or HTPR. **Method:** During May – June 2019, 20 post-PCI patients on aspirin–ticagrelor combination were included. Light transmission aggregometry (LTA) for monitoring platelet function was used. Ticagrelor's LTA <40% is LTPR while >70% is HTPR. **Result:** Patients were mostly male (18 patients) and aged between 40-73 years old with a history of diabetes and/or hypertension and smoking. About eight patients (40%) were LTPR and one (5%) patient was HTPR. **Conclusion:** A personalised DAPT strategy for preventing bleeding events, a de-escalation, might be valuable for Indonesian patients.

Introduction

The use of dual antiplatelet therapy (DAPT) following percutaneous coronary intervention (PCI) is a cornerstone pharmacotherapeutic management in acute coronary syndrome (ACS) patients. DAPT prevents stent thrombosis (ST). Previously, aspirin and clopidogrel combination is widely used as DAPT. However, clopidogrel (a non-potent P2Y12 receptor inhibitor) resistance occurred due to loss of function (LoF) CYP2C19*2. Clopidogrel is a prodrug, and its active metabolite is responsible for preventing platelet aggregation. LoF CYP2C19*2 prevents clopidogrel to be converted to its active metabolite. Ticagrelor, a more potent P2Y12 receptor inhibitor with greater antithrombotic efficacy, was developed as an alternative to clopidogrel albeit at the expense of increased bleeding (Angiolillo *et al.*, 2022). Interindividual variability to P2Y12 receptor inhibitors due to individual differences in platelet responsiveness resulted in clinical differences in drug efficacy. Thus it may increase the risk of bleeding or ischemic events. Platelet function testing for monitoring antiplatelet therapy can predict ischemic or bleeding events (Lordkipanidzé *et al.*, 2019). Low on-treatment platelet reactivity (LTPR) or High on-treatment platelet reactivity (HTPR) with P2Y12 receptor inhibitors is associated with bleeding (LTPR) or ischemic events (HTPR). It has been postulated that there is a therapeutic window strategy for P2Y12 receptor inhibitor, targeted patient platelet function testing between LTPR and HTPR to minimise both risks (Siller-Matula *et al.*, 2015). The Asian population is unique as this race contributes only a small portion of

several big clinical trials worldwide. Some studies on the East Asian race showed most East Asian is HTPR. Even though East Asians mostly have HTPR, the most adverse event of using P2Y12 inhibitors is bleeding. This phenomenon is called East Asian Paradox. Several studies have been conducted on the East Asian race (Kang & Kim, 2018; Misumida *et al*., 2018; Wang *et al*., 2020; Jeong *et al*., 2021). Likewise, even though Indonesian is an Asian race, Indonesian is different from East Asian countries such as Japan, Korea, and China. Up till now, there has been sparse data on the Indonesian platelet function's status on ticagrelor. A study in Indonesian patients showed about 33% HTPR on clopidogrel (Karunawan & Pinzon, 2021). Ticagrelor is much more a promising alternative to clopidogrel nowadays due to clopidgrel resistance and its antithrombotic efficacy is more than clopidogrel (Angiolillo *et al*., 2022). However, several drawbacks of ticagrelor occurred, including a high prevalence of LTPR and increased bleeding events with ticagrelor use (Park *et al*., 2019; Charpentier *et al*., 2020; Cho *et al*., 2021). According to the authors' personal communication with the cardiologists in Dr. Soetomo Hospital, the use of ticagrelor in Indonesian patients is increasing. Thus, it is interesting to map the ticagrelor platelet function status of either normal response, LTPR, or HTPR in Indonesian patients. Mapping ticagrelor LTA will help further DAPT strategies for personalised antiplatelet therapy, either escalation strategy (switching from non-potent to potent P2Y12 inhibitor, i.e., from clopidogrel to ticagrelor) due to the risk of ischemic events (HTPR) or de-escalation strategy (switching from potent to non-potent P2Y12 inhibitor, i.e., from ticagrelor to clopidogrel) due to risk of bleeding events (LTPR) (Claassens & Sibbing, 2020; Wang *et al*., 2020; Jeong *et al*., 2021; Angiolillo *et al*., 2022).

Methods

This prospective cross-sectional study was conducted from May 2019 to June 2019 among post-percutaneous coronary intervention ACS patients. Non-probability, consecutive sampling was carried out, and the patient's selection was based on inclusion criteria. Inclusion criteria were: acute coronary syndrome patient post-PCI, male or female, age> 18 years old, receive a maintenance dose of aspirin 100 mg daily and ticagrelor 90 mg twice daily, willing to join the study with informed consent. Exclusion criteria were: history of non-steroidal anti-inflammatory or anticoagulants (except for temporary use for medical treatment), thrombolytics, glycoprotein IIb/IIIa inhibitors, steroids, and proton pump inhibitors a week before the study. Drop-out criteria were: early discontinuation of DAPT due to allergic reactions or any side effects, death, or discharge against medical advice. Dr. Soetomo Hospital Ethical Committee approved this study.

Assessment

Light transmission platelet aggregometry (LTA) was used to measure the platelet function of the ticagrelor. LTA percentage of aggregation between 40% - 70% was considered a normal response. LTPR is defined LTA value of <40% while HTPR is >70% (Siller-Matula *et al*., 2015). The aggregation percentage is the platelet's ability to aggregate with adenosine diphosphate (ADP) induction. LTA measurement was carried out after two days of maintenance dose of aspirin–ticagrelor. A 5 ml venous whole blood was drawn and collected in a 3.8% sodium citrate tube. After centrifugation, platelet-rich plasma (PRP) and platelet-poor plasma (PPP) proceeded for LTA analysis using ADP agonist induction. Data on the percentage of platelet aggregation (LTA) from an individual patient and demographic data were analysed using descriptive analysis. The correlation of demographic data with LTA ticagrelor status of a normal response, LTPR, or HTPR were analysed using Mann-Whitney U.

Results

Demographic data are shown in Table I. About 20 patients, mostly male (90%), were included in this study. The average age is 52 years old (40–73 years old). The statistical analysis comparing ticagrelor LTA status with demographic data of age, sex, or ACS risk factors (smoking, diabetes, and or hypertension) resulted in no statistically significant difference (p > 0.05). Age was classified dichotomously as either non-elderly (<60 years old) or elderly (≥60 years old). Smoking was the most common ACS risk factor. Next, Figure 1 shows the LTA mapping of ticagrelor, either normal response, LTPR, or HTPR. LTA normal response measurements for these patients ranged from 41.4% - 59.1%; LTPR ranged from 5.5% - 37.8%; and HTPR was 80.9%. About eight patients (40%) on ticagrelor were LTPR, while one patient (5%) patient was HTPR. Table II shows that six out of eight LTPRs (75%) were male. Also, this study's oldest patient, 73 years old, had the lowest LTA of 5.5%. Furthermore, monitoring of bleeding events was carried out for a short period (several days) shortly after the maintenance dose of aspirin–ticagrelor post-PCI by reviewing the patient's medical record and conducting a random interview. There was no report of bleeding events.

Table I: Demographic data and ticagrelor LTA status

		Number	Percentage	Normal response[‡]	LTPR	HTPR	*p-value*
Sex	Male	18	90%	10	7	1	$p > 0.05$
	Female	2	10%	1	1	-	
Age (years)	< 60	14	70%	8	4	1	$p > 0.05$
	≥ 60	6	30%	3	4	-	
ACS risk factors[†]	Smoking	17	85%	1	2	-	
	Diabetes	9	45%	7	2	-	$p > 0.05$
	Hypertension	8	40%	5	3	-	

[†]Patient can have more than 1 ACS risk factors; [‡]Met Ticagrelor LTA therapeutic window; LTPR = low on-treatment platelet reactivity; HTPR = high on treament platelet reactivity

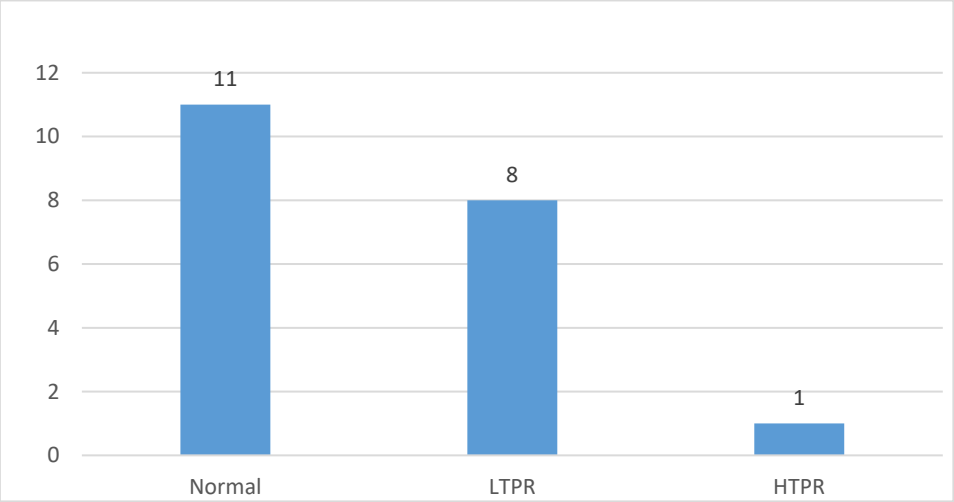

Figure 1: Ticagrelor's platelet function status based on LTA

Table II: Characteristics of individuals with LTPR or HTPR patient

	Age (years)	Sex	ACS risk factors[‡]	
LTPR	<60	Male	Non-DM, smoking	24.2% - 37.8%
		Male	Non-DM, smoking	
		Male	Non-DM, smoking	
		Male	DM, hypertension, smoking	
	≥ 60	Female	DM, hypertension, non-smoking	5.5% - 27.6%
		Male	Non-DM, smoking	
		Male	Non-DM, smoking	
		Male[†]	Non-DM, hypertension, non-smoking[†]	
HTPR	<60	Male	Non-DM, smoking	80.9%

[†]Oldest patient was 73 years old and had the lowest LTA of 5.5%; [‡]DM = Diabetes Mellitus

Discussion

This study consists of mostly male patients with an average age of 56 years old, this result was almost similar to other South East Asian Countries such as Thailand. About 70% of PCI patients in Thailand were male, with an average age of 63 years old (Krittayaphong *et al.*, 2017). PCI is a gold standard medical treatment for ACS nowadays, and DAPT has a pivotal role in optimizing

outcomes in PCI patients to prevent acute and long-term ischemic events. Platelet function testing guides the optimisation or individualisation of antiplatelet use to therapeutic window targets (Siller-Matula *et al.,* 2015; Angiolillo *et al.,* 2022).

ACS risk factors such as smoking, diabetes, and hypertension correlate well with platelet function. Platelet function abnormalities in hypertension, diabetes, and smoking were well established. Even though this study showed no correlation between those three factors to platelet function, diabetes impacts HTPR (Tatarunas *et al*., 2020; Li *et al*., 2021;). Moreover, smoking may cause LTPR, but the combination of current smoking and HTPR is associated with the highest rates of stent thrombosis (Table II) (Gupta *et al*., 2019). About 40% of patients in this study were LTPR. LTPR is more frequent with ticagrelor use (Deharo *et al*., 2017; Wen *et al*., 2020). In addition, six out of eight LTPR patients were non-diabetic. Other studies showed that LTPR patients were less likely to have diabetes (non-diabetes), low body mass index, anemia, and reduced glomerular filtration rate (GFR) (Deharo *et al*., 2017; Cho *et al*., 2021)

Ticagrelor is associated with increased bleeding risk. In East Asian patients (Japan, South Korea, and China), ticagrelor bleeding was the major problem (Misumida *et al*., 2018; Park *et al*., 2019). Furthermore, the elderly patient showed increased bleeding risk with ticagrelor (>75 years) (Alaamri & Dalbhi, 2021). The oldest patient in this study was 73 years old, with the lowest LTA of 5.5%. Moreover, due to more LTPR patients in this study, patient education explains that BARC-1 bleeding, such as easy bruising, bleeding from small cuts, petechia, ecchymosis, and or bleeding after shaving, after teeth brushing, or any other superficial bleeding, may have positive impacts on patient's safety (Mehran *et al*., 2011). Ultimately, the benefit of switching back from potent (ticagrelor) to non-potent P2Y12 receptor inhibitor (clopidogrel) in the LTPR group (de-escalation) seems a valuable strategy to reduce the risk of bleeding in these patients (Deharo *et al*., 2017; Claassens & Sibbing, 2020).

Conclusion

Even though this was a pilot study, the prevalence of LTPR on ticagrelor was significant enough to raise awareness of potential bleeding among Indonesian patients. Thus, a de-escalation strategy might be of benefit to minimise the bleeding risk and personalise antiplatelet therapy to the therapeutic window.

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