

Platelet reactivity in patients with coronary artery disease undergoing dual antiplatelet therapy with aspirin and clopidogrel

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ABSTRACT

Introduction: Dual antiplatelet therapy (DAPT), incorporating aspirin and a P2Y12 receptor inhibitor, is advised for patients experiencing acute coronary syndrome and for those with coronary artery stents, aiming to mitigate the risk of cardiac events attributable to thromboses. Nevertheless, the therapeutic challenge lies within the narrow therapeutic window where either excessive or deficient platelet reactivity (PR) during DAPT can predispose to thrombotic events or hemorrhage, respectively. This underscores the criticality of attaining an optimal PR level throughout the course of therapy. Accordingly, this study was conducted to evaluate PR among Vietnamese patients administered with DAPT, examining the implications for coronary artery disease management. This study aimed to evaluate PR in the context of aspirin therapy, utilizing the VerifyNow system, and to evaluate PR in the context of clopidogrel therapy, also utilizing the VerifyNow system. **Methods:** A prospective, cross-sectional, descriptive analysis was executed over the period April 2020 to August 2020. In total, 55 patients diagnosed with coronary artery disease and receiving DAPT comprising aspirin and clopidogrel were enrolled from the Interventional Cardiology Department at Cho Ray Hospital. PR was assessed via blood samples using PRU and ARU measurement kits for clopidogrel and aspirin, respectively. Data were compiled and subjected to analysis employing SPSS version 20. The delineation of high PR was set at >550 ARU for aspirin and >208 PRU for clopidogrel. **Results:** The cohort's mean age stood at 65.7 years, with a male predominance (male-to-female ratio of 1.6). Mean PR values for clopidogrel and aspirin were 158.9 ± 66.8 and 462.5 ± 78 , respectively. A significant 25.5% of the population demonstrated high PR to clopidogrel, whereas aspirin-related high PR was observed in 7.1% of the patients. **Conclusion:** In the subset of Vietnamese patients undergoing coronary stent implantation, a notable proportion exhibited high PR in response to clopidogrel, aligning with observations in international cohorts. Elevated age emerged as a contributing factor for increased PR, while diabetes was implicated in diminished platelet responsiveness. This investigation enriches the comprehension of PR dynamics in patients subjected to DAPT, suggesting a pressing need for additional studies to corroborate these findings and explore therapeutic adjustments.

Key words: platelet reactivity with clopidogrel (PRU - P2Y12 reaction unit), platelet reactivity with aspirin (ARU - aspirin reaction unit), dual antiplatelet therapy (DAPT)

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INTRODUCTION

Dual antiplatelet therapy, which consists of aspirin and a P2Y12 receptor inhibitor, is recommended for patients with acute coronary syndrome and for those undergoing coronary artery stent implantation to prevent cardiac events related to blood clot formation. Clopidogrel is the most frequently used P2Y12 inhibitor. However, unlike ticagrelor, which is immediately active upon administration, both prasugrel and clopidogrel require metabolic activation to inhibit platelet aggregation effectively. This metabolic process is dependent on several hepatic enzymes, including CYP2C19, CYP3A4/5, CYP2B6, CYP2C9, and CYP1A2. Notably, mutations in the CYP2C19 gene can lead to a loss of enzymatic function, thereby reducing the metabolism of clopidogrel. This reduc-

tion in metabolism can result in decreased effectiveness of clopidogrel in inhibiting platelet aggregation, which may be associated with adverse cardiovascular outcomes, including stent thrombosis. CYP2C19 is identified as the critical enzyme in the metabolism of clopidogrel¹. Furthermore, a high prevalence of mutations in this enzyme has been reported in the Asian population, affecting up to 60% of individuals². This diminished platelet inhibition manifests as high platelet reactivity (HPR) in platelet function tests. On the contrary, low platelet reactivity (LPR) or an excessive response to antiplatelet therapy increases the risk of bleeding complications. Therefore, optimizing platelet reactivity is crucial within the therapeutic window. To address this, we conducted research to assess platelet reactivity in Vietnamese patients with

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coronary artery disease who were receiving dual antiplatelet therapy with aspirin and clopidogrel.

METHODS

Study Design

This research was conducted as a cross-sectional descriptive analysis.

Study Participants

The inclusion criteria targeted patients receiving treatment within the Interventional Cardiology Department at Cho Ray Hospital for coronary artery disease that required dual antiplatelet therapy. This therapy consisted of Aspirin at a minimum dosage of 162 mg at least 3 hours prior to testing or 81 mg for at least 5 days before testing, coupled with Clopidogrel administered at a minimum dosage of 300 mg at least 3 hours prior to testing or 75 mg for at least 5 days before testing. The exclusion criteria eliminated patients with a history of myocardial infarction (MI) or prior coronary artery interventions, patients who experienced bleeding events or mortality, and those not consenting to participate in the study.

Procedure

Prior to undergoing cardiac catheterization and percutaneous coronary intervention, 4ml of the patient's blood was collected into anticoagulant tubes. These tubes were then incubated at room temperature for 10 minutes before undergoing platelet reactivity testing utilizing an aspirin-specific (ARU test) and a clopidogrel-specific (PRU test) kit. Results from the platelet reactivity tests were documented for each participant.

Diagnostic Criteria

Coronary artery disease

The diagnosis follows the 2019 criteria established by the American College of Cardiology and the European Society of Cardiology for stable angina and acute coronary syndromes, which include unstable angina, non-ST elevation myocardial infarction, and ST elevation myocardial infarction.

Diabetes mellitus (DM)

The condition is diagnosed based on a pre-existing patient history or as newly diagnosed DM, adhering to the criteria defined by the American Diabetes Association in 2013.

Hypertension (HTN)

Diagnosis is founded on pre-existing patient history or as newly identified HTN, in line with the Vietnam Heart Association's 2014 guidelines for prevention, detection, evaluation, and treatment of high blood pressure.

Dyslipidemia (DL)

DL definitions and classifications adhere to the criteria from the NCEP (ATP III) study.

Smoking (SM)

Smoking status is diagnosed using the COMMIT study criteria, differentiating between current smokers (those with a history of smoking 100 or more cigarettes or those who have ceased smoking within the last 5 years) and non-smokers (those who have never smoked or have quit smoking for more than 5 years prior to the onset of disease).

Heart failure with preserved ejection fraction (HFpEF)

Diagnosis aligns with the diagnostic criteria from the American College of Cardiology in 2016.

Platelet reactivity was determined using the VerifyNow test, a point-of-care platelet function test known for its convenience and proven accuracy, showing high congruence with the gold-standard LTA test among available market options. High platelet reactivity (HPR) is identified when results exceed 208 for clopidogrel (PRU > 208) and 550 for aspirin (ARU > 550), whereas low platelet reactivity (LPR) for clopidogrel is marked by results below 95 (PRU < 95). Therapeutic range platelet reactivity for clopidogrel is delineated between 95 and 208, and for aspirin as less than 550 (ARU < 550).

Variables

Considered variables include Age, Gender, BMI, Hypertension (HTN), Smoking status (SM), Diabetes Mellitus (DM), Dyslipidemia (DL), Heart failure, and platelet reactivity to Aspirin (ARU) and Clopidogrel (PRU), with cutoff points established at 550 for high aspirin platelet reactivity and 208 for high clopidogrel platelet reactivity. The cutoff for low clopidogrel platelet reactivity is set at 95.

Data Processing and Analysis

Data analysis was executed using SPSS 20 software, with results presented as mean values (\pm standard deviation) or median (interquartile range), and as percentages (%).

Table 1: Characteristics of the Study Population

Characteristics	Frequency (Percentage)
Age (Mean ± SD)	65.7 (±9.9)
Gender Male	34 (62%)
Weight (Mean ± SD)	60.6 (±1.3)
Hypertension	49 (89%)
Diabetes Mellitus	10 (18%)
Smoking	36 (65%)
Dyslipidemia	53 (96%)
Heart Failure	12 (22%)
Clinical Presentation	
Unstable Angina	17 (31%)
Non-ST Elevation MI	3 (5%)
ST Elevation MI	16 (29%)
Non-Fatal MI	19 (35%)

Table 2: Mean Age of the Sample by Gender

	Sample	Male	Female	P
	(mean ± SD)			
Age	65.7 ± 9.91	63.5 ± 8.7	69.1 ± 11	0.039

Table 3: BMI of the Sample by Gender

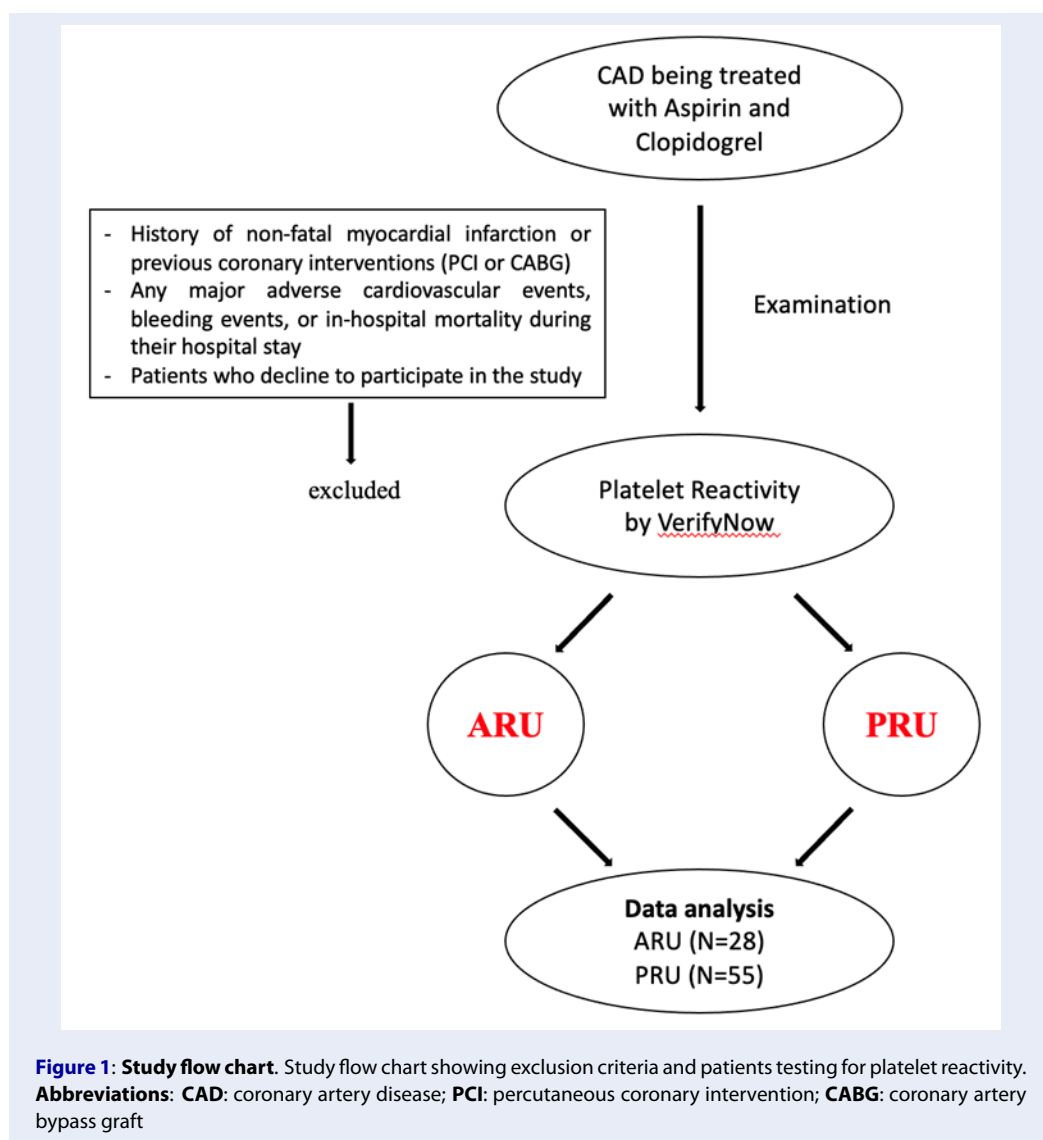
	Sample	Male	Female	P
	(mean ± SD)			
BMI (kg/m ²)	23.2 ± 2.9	23.6 ± 3.2	22.4 ± 2.2	0.13

Table 4: Characteristics of Platelet Reactivity with Clopidogrel and Aspirin

Index	Mean (± SD)	Min	Max	Median	Interquartile Range
PRU	159 (±69)	7	282	167	101
ARU	463 (±78)	350	650	465	145

Table 5: Distribution of Platelet Reactivity with Clopidogrel and Aspirin

Cut-off	PRU		Cut-off	ARU	
	N	%		N	%
≥ 208	14	25.5	≥ 550	2	7.1
95 - 208	32	58.2	< 550	26	92.9
< 95	9	16.4			



RESULTS

Study Population Characteristics

This study comprised 55 patients diagnosed with coronary artery disease undergoing percutaneous coronary intervention. The mean age of the participants was 65.7 years, with a predominant male representation of 62% (Table 1). The average age of male participants was significantly lower than that of their female counterparts, a disparity that was statistically significant ($p=0.039$, student's t-test) (Table 2). The mean body mass index (BMI) across the cohort was 23, with no significant difference observed between genders (student's t-test) (Table 3).

Clinical characteristics of the study population revealed a high prevalence of hypertension and dyslipi-

demia, followed by smoking, which affected approximately two-thirds of the participants. Diabetes and heart failure were present in about one-fifth of the cohort. Furthermore, patients were categorized based on specific medical conditions, with the largest subgroup having NMCTSTCL, followed by ĐTNÔĐ and NMCTKSTCL, while the smallest subgroup was identified as ĐTNKÔĐ.

Platelet Reactivity to Clopidogrel and Aspirin

In terms of platelet reactivity, measured by platelet reactivity unit (PRU) and aspirin reaction unit (ARU), the PRU levels varied between 7 and 282, with a median of 167, whereas ARU levels ranged from 350 to 650, with a median of 465 (Table 4). Clopido-

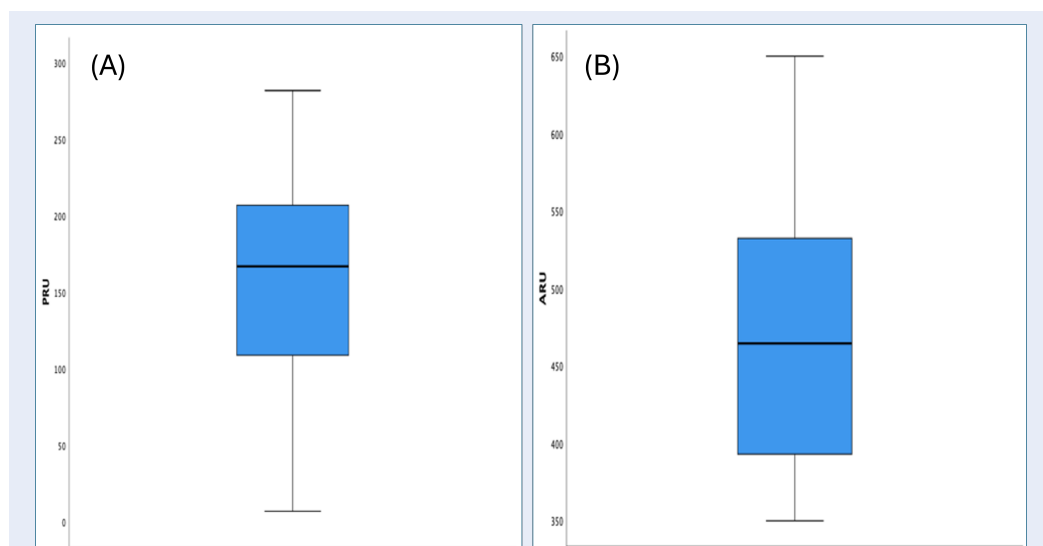


Figure 2: Box plot chart. Box plot chart showing the distribution of PRU to clopidogrel (A) and aspirin (B). **Abbreviation:** PRU: platelet reactivity unit

Table 6: Characteristics of Patients with High Platelet Reactivity to Clopidogrel

Characteristics	Normal/Low Platelet Reactivity (N=41)	High Platelet Reactivity (N=14)	p
Characteristics	66.5	63.2	<0.001
Age (Mean ± SD)	28	6	0.117
Gender Male	61.7	57.4	0.12
Weight (Mean ± SD)	29	7	0.159
Hypertension	35	14	0.129
Diabetes Mellitus	39	14	0.399
Smoking	5	5	0.048
Dyslipidemia	7	5	0.144
Clinical Presentation			
Unstable Angina	12	5	0.742
Non-ST Elevation MI	3	0	1
ST Elevation MI	12	4	1
Non-Fatal MI	12	5	0.099

grel response categorization using predefined cutoffs showed that 25.5% of the patients exhibited high PRU levels (≥ 208), 58.2% were within the therapeutic range (95-208), and 16.4% had low PRU levels (< 95) (Table 5). For aspirin, based on the cutoffs for classifying PRU levels, high (>550) and within therapeutic range (< 550), the distributions were 7.2% and 92.9%, respectively.

An analysis of the clinical characteristics among patients exhibiting high PRU levels on clopidogrel, indicative of suboptimal drug response, revealed a significantly lower mean age ($p < 0.001$) and an increased prevalence of type 2 diabetes mellitus ($p = 0.048$) in comparison with patients achieving therapeutic PRU levels (Table 6).

DISCUSSION

Clopidogrel Platelet Reactivity

In our investigation, the mean platelet reactivity in response to clopidogrel administration was documented at 159 ± 69 P2Y₁₂ Reaction Units (PRU), exhibiting a broad range from 7 to 282 PRU. This contrasts with the findings from the study by Fakilahiel *et al.*^{3,4}, conducted on a similar cohort of patients with coronary artery disease, which reported an average of 178 ± 88 PRU and a range from 4 to 385 PRU. Our results indicate a relative decrease in platelet reactivity and a narrower distribution in comparison. Several international studies have highlighted that the prevalence of resistance to clopidogrel is notably higher among Asian populations than those in European and American groups, challenging the prevalent assumptions. This discrepancy may stem from differences in racial composition and clinical profiles of the studied populations. A more definitive metric of interest has been the incidence of elevated clopidogrel platelet reactivity, frequently linked to adverse outcomes such as all-cause mortality, non-fatal myocardial infarctions, stent thrombosis, and ischemic strokes^{5,6}. In our research, a cutoff of 208 PRU was employed to delineate between high and normal clopidogrel platelet reactivity, given its established utility in predicting cardiovascular events across multiple large-scale international studies. The prevalence of patients manifesting high platelet reactivity was 25.5%, aligning with global observations on suboptimal platelet inhibition⁷⁻⁹. This rate is comparable to that found in the 3T/2R study¹⁰ and lower than those reported in TRIGGER-PCI¹¹, ARCTIC¹², and GRAVITAS¹³.

Pertaining to the correlation of clinical factors such as age, weight, and diabetes mellitus with high PRU levels, our analysis and other studies, including the

GRAVITAS trial, show statistically significant outcomes that suggest heavier patients tend to have higher PRU levels ($p < 0.001$). Despite varying BMI associations across different studies, our findings did not replicate this trend, possibly due to the specific characteristics of our study population and the need for more extensive data sets. A detailed examination of individuals with elevated PRU levels demonstrated a significantly younger average age in this subgroup ($p < 0.001$), consistent with characterized trends from other research and a higher prevalence of diabetes mellitus ($p = 0.048$), underlining the potential contribution of hyperglycemia, insulin resistance, or deficiency to heightened inflammatory responses and endothelial dysfunction¹⁴.

Aspirin Platelet Reactivity

The VerifyNow assay employing arachidonic acid, for assessing the antiplatelet effects of aspirin, proved equivalent to the light transmission aggregometry (LTA), the accepted standard for platelet function assessment¹⁵. Our data indicated an average aspirin reactivity unit (ARU) of 463 ± 78 , spanning from 350 to 650 ARU, with a high platelet reactivity occurrence of 7.1%. This rate is in line with findings from the ADAPT-DES study¹⁶, modestly surpasses the 2.1% observed in Lee's Korean cohort¹⁷, and is significantly lower than the 13.5% reported in the 3R/2T study¹⁰. The term "aspirin resistance" frequently misused to describe patients with elevated platelet reactivity under aspirin therapy scarcely reflects the true resistance mechanism, which involves the failure of aspirin to acetylate COX-1, a phenomenon established as exceedingly rare by laboratory analyses. In effect, high platelet reactivity during aspirin therapy may largely attribute to suboptimal drug absorption or might improve with increased aspirin dosages¹⁸⁻²⁰, without necessitating prior assessment of platelet responses to aspirin.

Limitations and Conclusion

The study's limitations include a potentially non-generalizable finding due to the sample size or selection criteria, the cross-sectional design precluding causal relationships, and the lack of longitudinal data to evaluate the temporal evolution of platelet reactivity. Future research should focus on elucidating mechanisms underpinning high platelet reactivity in specific patient groups, evaluating alternative antiplatelet strategies, and exploring long-term outcomes associated with heightened platelet reactivity. Approximately a quarter of patients with coronary

artery disease undergoing angiography or intervention in this study presented with elevated clopidogrel platelet reactivity, corresponding with global reports. Notably, advanced age and diabetes mellitus emerged as risk factors for increased platelet reactivity. Platelet reactivity testing in patients experiencing cardiac events or suspected of clopidogrel resistance could inform tailored therapeutic approaches.

ABBREVIATIONS

ARU: Aspirin Reaction Unit, **COMMIT:** Clopidogrel and Metoprolol in Myocardial Infarction Trial, **CYP1A2:** Designations for specific cytochrome P450 enzyme involved in drug metabolism, **CYP2B6:** Designations for specific cytochrome P450 enzyme involved in drug metabolism, **CYP2C19:** Designations for specific cytochrome P450 enzyme involved in drug metabolism, **CYP2C9:** Designations for specific cytochrome P450 enzyme involved in drug metabolism, **CYP3A4/5:** Designations for specific cytochrome P450 enzymes involved in drug metabolism, **DAPT:** Dual Antiplatelet Therapy, **DL:** Dyslipidemia, **DM:** Diabetes Mellitus, **HFpEF:** Heart Failure with Preserved Ejection Fraction, **HTN:** Hypertension, **LTA:** Light Transmission Aggregometry, **MI:** Myocardial Infarction, **NCEP (ATP III):** National Cholesterol Education Program (Adult Treatment Panel III), **PR:** Platelet Reactivity, **PRU:** P2Y12 Reaction Unit, **SM:** Smoking, **SPSS:** Statistical Package for the Social Sciences

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Phan Thi Bach Tuyet, RN (Cho Ray hospital) was involved in performing the tests.

AUTHOR'S CONTRIBUTIONS

Nghia T N, MD: Conceptualization; Writing - original draft; Critical Review. My H T N, MD: Formal analysis; Writing - original draft; Manuscript editing; Critical Review. All authors read and approved the final manuscript.

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None.

AVAILABILITY OF DATA AND MATERIALS

Data and materials used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted in accordance with the amended Declaration of Helsinki. The institutional

review board approved the study, and all participants provided written informed consent.

CONSENT FOR PUBLICATION

Following information must be provided in order for this form to be processed accurately. Patients have the right to refuse to sign this consent form; refusal to sign this form will not affect the care in any way. "I hereby give my consent for images or other clinical information relating to my case to be reported in a medical publication. I understand that my name and initials will not be published and that efforts will be made to conceal my identity, but that anonymity cannot be guaranteed. I understand that the material may be published in a journal, website or other form of publication. As a result, I understand that the material may be seen by the general public. I understand that the material may be included in medical books."

COMPETING INTERESTS

The authors declare that they have no competing interests.

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