ORIGINAL ARTICLE

Platelet to red cell distribution width ratio for predicting clopidogrel efficacy in patients undergoing percutaneous coronary interventions: insights from the ONSIDE-TEST study

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KEY WORDS

clopidogrel, percutaneous coronary intervention, platelet, prediction, red cell distribution width

ABSTRACT

INTRODUCTION Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel remains a cornerstone of pharmacotherapy after percutaneous coronary intervention (PCI). It has been demonstrated that even up to 30% of patients receiving DAPT have inadequate response to clopidogrel, namely, high on-treatment platelet reactivity (HPR). The platelet to red cell distribution width (P-RDW) ratio represents an indicator of cardiovascular risk and may be related to HPR.

OBJECTIVES The aim of the present study was to establish whether the P-RDW ratio predicts HPR in clopidogrel-treated patients undergoing elective PCI.

PATIENTS AND METHODS This was a subanalysis of the prospective randomized-controlled ONSIDE TEST study. A total of 70 patients were included in the analysis, of whom 12 were identified with HPR. The HPR was defined as the values above the threshold of 208 platelet reactivity units (PRU >208) by the VerifyNowP2Y$_{12}$ assay.

RESULTS The P-RDW ratio was lower in patients with HPR than in those without HPR (mean [SD], 14.37 [4.13] vs 17.734 [4.96]; $P = 0.03$). A logistic regression analysis showed that the P-RDW ratio was associated with HPR ($P = 0.03$). Using a cut-off level of 15.23, the P-RDW ratio predicted HPR with a sensitivity of 69% and specificity of 75% (odds ratio, 6.67; 95% CI, 0.561–0.890; $P = 0.02$; are under the receiver operating characteristic curve, 0.723).

CONCLUSIONS The P-RDW ratio may serve as a supplementary tool for identification of patients at risk of HPR. Further studies are warranted to assess its role in planning DAPT among patients undergoing PCI.

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INTRODUCTION Dual antiplatelet therapy (DAPT) combining aspirin and P2Y$_{12}$ antagonists represents a gold standard of adjunctive pharmacotherapy among patients undergoing percutaneous coronary interventions (PCIs). It is currently recommended for at least 6 months after implantation of drug-eluting stents in patients with stable coronary artery disease (CAD).[1] While prasugrel and ticagrelor are characterized by a more rapid onset of action and greater efficiency in patients with acute coronary syndromes (ACSs) in large clinical trials, as compared with clopidogrel,[2,3] the data on their safety and efficacy among patients with stable CAD are still limited.[4] This evidence gap is underlined by the fact that up to 40% of the population receiving DAPT is characterized by an insufficient response to clopidogrel, namely, high

on-treatment platelet reactivity (HPR).[5] Some studies showed that patients with stable CAD and HPR receiving clopidogrel have an increased risk of adverse major cardiovascular events after PCI, including stent thrombosis and more extensive periprocedural myocardial injury.[6-9] Hence, the diagnosis of HPR is relevant for appropriate treatment planning, ensuring the maximal prevention of thrombotic events at the lowest risk of bleeding complications.

Recently, the links between red blood cells and platelet function have received increasing attention, and the association between erythrocyte deformability and adenosine 5'-diphosphate–dependent platelet reactivity has been documented.[10-12]

The platelet to red blood cell distribution width (P-RDW) ratio is one of the most recent markers of inflammatory response that reportedly allows to predict the prognosis of patients in numerous clinical situations. The ease of assessing such an index makes it attractive for evaluation as a potential predictor of various clinical instances. Given that red blood cell distribution width (RDW) is indicative of decreased erythrocyte deformability, we hypothesized that the P-RDW ratio may be associated with HPR and, subsequently, adverse cardiovascular events, among patients with stable CAD undergoing elective PCI. Although the effect of RDW on the risk of ischemic events has been described in the literature,[13,14] to our knowledge, so far no study has specifically elaborated on the relationship between P-RDW and HPR.

PATIENTS AND METHODS The ONSIDE TEST study is a prospective open-label randomized clinical trial (phase IV) conducted in cooperation between academic centers from Poland, Hungary, and Lithuania (ClinicalTrials.gov; NCT01930773). Consecutive patients with stable CAD scheduled for an elective PCI with stent implantation were screened. The inclusion and exclusion criteria were described in detail previously.[15]

All the included patients were on DAPT, comprising aspirin (75 mg/d) and clopidogrel (which was either continued at a dose of 75 mg/d or administered at a loading dose of 600 mg at least 6 hours before PCI). All participants had their platelet reactivity tested, using the point-of-care VerifyNow $P2Y_{12}$ assay (Accumetrics, Inc., San Diego, California, United States) and the rapid, point-of-care Spartan RX CYP2C19 System (Spartan Bioscience Inc., Ottawa, Canada). The values above the threshold of 208 platelet reactivity units (PRU) and identification of at least 1 copy of the loss-of-function *2 allele in the cytochrome P450 2C19 (*CYP2C19*) gene were considered as inadequate response to antiplatelet therapy.

Here we report the outcomes of the first 70 patients enrolled in the 1st Department of Cardiology at the Medical University of Warsaw, in whom the P-RDW ratio was determined.

Statistical analysis The PQStat software (version 1.6.6, PQStat, Poznań, Poland) and Statistica software (version 13, StatSoft, Kraków, Poland) were used for statistical analysis. The normality of distribution for continuous variables was confirmed with the Shapiro–Wilk test. The variables were presented as mean (SD) or median and interquartile range, depending on the distribution. The study groups were compared with the *t* test or the Mann–Whitney test. *P* values lower than 0.05 were considered significant. A logistic regression analysis was performed to identify the predictors of HPR. The following variables were included in the model: white blood cells (WBC), C-reactive protein (CRP), red blood cells, hemoglobin, and P-RDW ratio. The values of odds ratio (OR) and 95% CI were reported. A receiver operating characteristic (ROC) curve analysis was performed to determine the optimum cutoff level of the P-RDW ratio to predict HPR. A logistic regression analysis was performed to identify the predictors of HPR and to determine whether the P-RDW ratio is significantly associated with HPR.

RESULTS A total of 70 patients undergoing PCI and treated with clopidogrel were included in the present study. HPR was observed in 12 patients, while the loss of function *2 allele in the *CYP2C19* gene occurred in 11 patients. The baseline characteristics of the study population are presented in **TABLE 1**.

There were no significant differences in the baseline hemoglobin, WBC, and CRP levels between patients with HPR and those without HPR. The P-RDW ratio was lower in patients with HPR (n = 12), as compared with those with adequate response to clopidogrel (mean [SD], 14.37 [4.13] vs 17.73 [4.96]; *P* = 0.03). The logistic regression analysis showed that the P-RDW ratio was associated with HPR (*P* = 0.03) (**TABLE 2**). The column scatter graphs for P-RDW in patients with and without HPR are presented in **FIGURE 1**.

The cutoff value of the P-RDW ratio was calculated with a receiver operating characteristic (ROC) curve analysis. Using the cutoff level of 15.23, the P-RDW ratio predicted HPR with a sensitivity of 69% and specificity of 75% (OR, 6.67; 95% CI, 0.561–0.890; *P* = 0.02; area under the ROC curve, 0.723).

DISCUSSION Routine platelet function testing is not recommended in the current European Society of Cardiology guidelines, given the lack of evidence from randomized trials that such a strategy of tailored antiplatelet therapy during PCI may decrease the risk of cardiovascular events. However, it may be considered in some individuals presenting with a particularly increased risk of either ischemic or bleeding complications.[16] Nevertheless, the nonnegligible cost of platelet function testing remains a serious obstacle for its wider application in clinical practice. Hence, the search for simple surrogate

TABLE 1 Baseline characteristics of the patients included in the study (continued on the next page)

Parameter		HPR PRU >208 (n = 12)	Non–HPR PRU <208 (n = 58)
Age, y, mean (SD)		65.6 (6.7)	60.9 (8.9)
Male sex, n (%)		11 (91.7)	46 (79.3)
Cardiac risk factors, n (%)			
Symptomatic stable CAD		12 (100.0)	58 (100.0)
Stable CAD classified according to the CCS grading system	CCS 1	1 (8.3)	21 (36.2)
	CCS 2	8 (66.7)	23 (39.7)
	CCS 3	3 (25.0)	14 (24.1)
Hypertension, n (%)		9 (75.0)	44(75.9)
Diabetes mellitus, n (%)		4 (25.0)	22 (37.9)
Hyperlipidemia, n (%)		6 (50.0)	46 (79.3)
Heart failure (according to NYHA), n (%)		3 (25.0)	8 (13.8)
LVEF, %, mean (SD)		45.3 (15.9)	50.5 (10.2)
Chronic obstructive pulmonary disease, n (%)		1 (8.3)	1 (1.7)
Smoking history, n (%)		7 (63.6)	39 (69.6)
Current smoking, n (%)		3 (27.3)	19 (33.3)
Previous myocardial infarction, n (%)		8 (75.0)	34 (58.6)
Previous myocardial infarction, depending on location, n (%)	Anterior wall	5 (45.5)	15 (41.7)
	Lateral wall	0 (0.0)	5 (15.2)
	Inferior wall	4 (36.4)	13 (38.2)
	Posterior wall	0 (0.0)	3 (9.1)
Previous PCI, n (%)		4 (25.0)	38 (65.5)
Laboratory characteristics			
CK-MB, ng/ml, median (IQR)		1.85 (0.88–3.45)	1.60 (0.90–3.43)
Troponin I, ng/ml, median (IQR)		0.2 (0.06–0.90)	0.23(0.06–0.62)
Creatinine, mg/dl, mean (SD)		0.99 (0.25)	1.05 (0.26)
Red blood cells, 10^6/µl, mean (SD)		4.53 (0.20)	4.70 (0.45)
Hemoglobin, g/dl, mean (SD)		13.88 (1.00)	14.29 (1.66)
Platelet count, 10^3/µl, mean (SD)		191.08 (48.53)	235.03 (67.84)
INR, mean (SD)		1.00 (0.05)	0.99 (0.07)
APTT, s, mean (SD)		37.35 (19.51)	28.59 (2.93)
Lipid profile, mg/dl, mean (SD)			
Total cholesterol		141.60 (38.47)	157.45 (39.33)
HDL cholesterol		44.50 (15.80)	44.43 (9.41)
LDL cholesterol		68.33 (25.09)	81.75 (33.36)
Triglycerides		119.50 (60.26)	147.18 (84.59)
Baseline pharmacotherapy, n (%)			
Aspirin		11 (91.7)	58 (100.0)
Clopidogrel		8 (66.7)	53 (91.4)
Statin		9 (75.0)	57 (98.3)
β-Blocker		10 (83.3)	57 (98.3)
ACEI or ARB		10 (83.3)	56 (96.6)
Calcium channel blocker		3 (25.0)	5 (8.6)
Proton pump inhibitor		7 (58.3)	31 (53.4)
Lesion location, n (%)			
Left main coronary artery		1 (8.3)	0 (0.0)
Left anterior descending artery		5 (41.7)	32 (55.2)
Circumflex artery		4 (25.0)	11 (19.0)
Right coronary artery		4 (25.0)	16 (27.6)

TABLE 1 Baseline characteristics of the patients included in the study (continued from the previous page)

Parameter		HPR PRU >208 (n = 12)	Non–HPR PRU <208 (n = 58)
Stent implantation			
No. of stents, n (%)	POBA	1 (8.3)	2 (3.4)
	1	6 (50.0)	44 (75.9)
	2	5 (41.7)	7 (12.5)
	3	0 (0.0)	5 (8.9)
Drug-eluting stent, n (%)		9 (75.0)	56 (94.5)
Bare metal stent, n (%)		2 (16.7)	0 (0.0)
Direct stenting, n (%)		2 (16.7)	4 (7.5)
Postdilation, n (%)		8 (66.7)	43 (78.2)
Total length of stent, mm, mean (SD)		29.5 (17.3)	28.6 (21.7)
Total vessel occlusion time, s, mean (SD)		82.7 (53.5)	81.8 (46.5)
Periprocedural pain, n (%)		1 (14.3)	3 (8.8)
Contrast volume, ml, median (IQR)		120.0 (100.0–250.0)	150.0 (120.0–200.0)
Fluoroscopy exposure, mGy, median (IQR)		1222.5 (641.0–1870.0)	1395.7 (669.9–2151.9)
Fractional flow reserve, n (%)		0 (0.0)	7 (12.3)
Intravascular ultrasound, n (%)		1 (9.1)	6 (11.8)
Optical coherence tomography, n (%)		0 (0.0)	2 (3.6)
Periprocedural pharmacotherapy			
Unfractionated heparin, 10^3 units, median (IQR)		8.0 (7.0–9.0)	8.0 (5.5–10.0)
Abciximab, n (%)		1 (9.1)	1 (2.1)
Eptifibatide, n (%)		0 (0.0)	2 (4.2)
Angiographic outcomes, n (%)			
TIMI 3 flow		8 (88.9)	39 (97.5)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; APTT, activated partial thromboplastin time; ARB, angiotensin receptors blockers; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CK-MB, creatine kinase–MB; HDL, high-density lipoprotein; HPR, high on-treatment platelet reactivity; INR, international normalized ratio; IQR, interquartile range; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; POBA, plain old balloon angioplasty; PRU, platelet reactivity units; TIMI, thrombolysis in myocardial infarction

predictors of HPR, based on blood count parameters, is warranted. This constituted the main goal of our present study, in which we verified the potential relationship between the P-RDW ratio and HPR defined as PRU exceeding 208. We found that the P-RDW ratio was significantly elevated among patients with HPR. To the best of our knowledge, this is the first study evaluating the use of P-RDW in the context of inadequate response to antiplatelet therapy among patients undergoing PCI. Although the counterbalance between the platelet and red blood cell counts is intrinsic to response to antiplatelet therapy, to date, no studies have elaborated on the relationship between RDW or the P-RDW ratio and altered response to newer thienopyridines (prasugrel, ticagrelor) in patients who underwent PCI.

Some authors previously attempted to evaluate the relationship between an objective measure of the heterogeneity in red blood cell size (RDW) and inadequate response to clopidogrel among patients with ACS who underwent PCI. In a study by Budak et al,[17] 232 patients receiving aspirin (100 mg/d) and clopidogrel (75 mg/d) before and after PCI with stenting were included. Resistance to antiplatelet therapy was defined as $P2Y_{12}$ reactivity exceeding 240 units. The median RDW levels were higher (14.4% vs 13.9%; P = 0.01) and the mean (SD) hemoglobin levels were lower (12.0 [1.6] g/dl vs 13.2 [1.7] g/dl; P<0.001) in patients with HPR than in patients with adequate response to clopidogrel.[17] Of note, the differences in the WBC count, mean platelet volume, as well as neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios were nonsignificant.[17]

In a study by Yao et al,[18] high RDW was shown to be an independent predictor of long-term adverse clinical outcomes (all-cause death: hazard ratio [HR], 1.37; stent thrombosis and outcomes of death / myocardial infarction / stroke: HR, 1.21) in nonanemic patients with stable CAD treated with drug-eluting stents. In addition, RDW was identified as an independent indicator of 1-year mortality after PCI (HR, 1.65).[19]

A study by Uzun et al[20] included 207 patients undergoing elective PCI. Aspirin and clopidogrel resistance was defined as above the fifth quartile with a value of 20% or higher: 601.8 arbitrary units (AU)/min for clopidogrel and 447.6 AU/min for aspirin. Inadequate response to clopidogrel

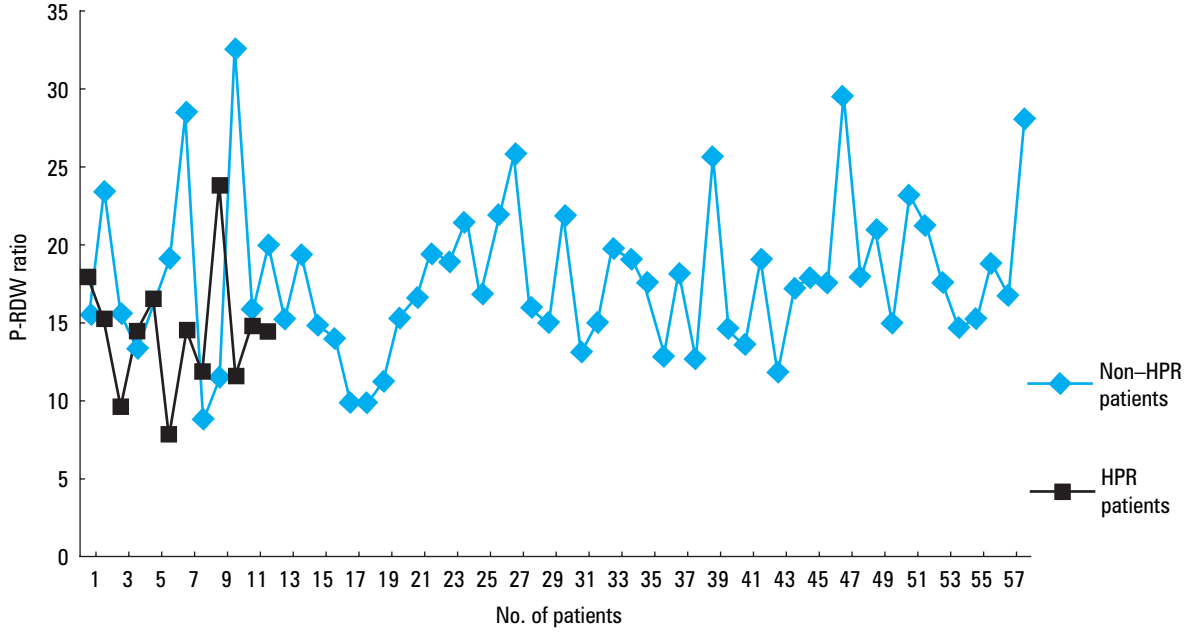

FIGURE 1 Platelet to red cell distribution width (P-RDW) ratio in patients with and without high on-treatment platelet reactivity

was associated with male sex, higher body mass index, aspirin resistance, lower hemoglobin and hematocrit levels, higher platelet count, angiotensin II receptor blocker use, and higher RDW.

It should be noted, however, that RDW itself was shown to be highly influenced by several confounders, including inflammation and oxidative stress. A strong correlation between RDW and inflammatory biomarkers was observed by Salvagno et al.[21]

Of note, in our study, no significant differences were found for hemoglobin, WBC, and CRP concentrations between patients with and without HPR. Hence, it may be assumed that neither anemia nor inflammation affects the differences in the P-RDW ratio between the study groups.

In a further analysis, Uzun et al[20] revealed that the higher platelet count (OR, 1.009; $P = 0.06$) was one of the significant independent variables associated with clopidogrel resistance in a multivariate analysis.[20]

The links between P-RDW and response to antiplatelet therapy that were confirmed in the present study warrant further research in a larger cohort. Nevertheless, the potential mechanisms underlying the association between the P-RDW ratio and poor response to clopidogrel[10] corresponded with the previous research demonstrating that RDW is associated with reduced erythrocyte deformability, which apart from hematocrit has been demonstrated to exert effects on adenosine 5'-diphosphate–dependent platelet reactivity.[11] Subsequently, poor response to antiplatelet drugs can be modulated not only by the properties of platelets but also by other hematologic parameters of the RBC and WBC system[12] and a simple hematologic parameter, P-RDW, may constitute a reliable surrogate or estimate of platelet response to antiplatelet treatment.

Given the potential roles of platelet count and RDW as a surrogate predictor of HPR after clopidogrel administration, our attempt to evaluate the role of a ratio combining the complex interactions between one another, in the context of response to clopidogrel therapy, seems rational. Such an indicator may even be more sensitive than single platelet function or RDW in predicting HPR; however, larger studies, powered for the assessment of clinical endpoints and accompanied by an assessment of both well-established and novel platelet activation biomarkers,[22] are necessary to verify this hypothesis.

Despite recent progress in antiplatelet therapy, including newer $P2Y_{12}$ antagonists that are currently being developed, clopidogrel still remains an oral antiplatelet prodrug prescribed to more than 40 million patients worldwide. Moreover, in some clinical scenarios, such as patients with cancer, it is considered a $P2Y_{12}$ antagonist of choice, both in patients with stable CAD and ACS,[23] thereby posing a higher risk for thrombotic events in patients with HPR undergoing PCI.[24] The search for an easily available measure to identify patients at a particularly increased risk of events appears to be a relevant direction for current research.

The main limitation of the present study is a small sample size. In addition, the specificity and sensitivity of the P-RDW are moderate. Nevertheless, at the P-RDW threshold of 17.90, HPR may be excluded with a specificity of 91.7%, potentially indicating the subgroup eligible for additional platelet function testing. Such an assessment may therefore serve as a screening tool for patients that may require additional evaluation for HPR.

In conclusion, the P-RDW ratio, an easy-to-assess parameter derived from complete blood

TABLE 2 Comparison of platelet to red cell distribution width ratio in patients with high-on treatment platelet reactivity (HPR) versus patients without high-on treatment platelet reactivity. A logistic regression analysis of predictors of HPR

Parameter	PRU >208	PRU <208	95% CI	OR	*P* value
No. (%) of patients	12 (17.1)	58 (82.9)	–	–	–
WBC, 10^3/µl, mean (SD)	8.57 (5.11)	8.45 (2.97)	0.702–2.784	0.74	0.91
CRP, mg/l, mean (SD)	9.01 (18.37)	3.86 (5.13)	1.322–10.391	0.49	0.18
RBC, 10^6/µl, mean (SD)	4.53 (0.20)	4.70 (0.45)	0.102–0.105	0.63	0.64
Hemoglobin, g/dl, mean (SD)	13.88 (1.0)	14.29 (1.66)	0.378–0.524	0.81	0.98
P-RDW ratio, mean (SD)	14.37 (4.13)	17.73 (4.96)	0.561–0.890	6.67	0.03

Abbreviations: CRP, C-reactive protein; P-RDW, platelet to red blood cell distribution width; RBC, red blood cells; WBC, white blood cells; OR, odds ratio; others, see **TABLE 1**

count, may be associated with the occurrence of HPR among patients with stable CAD undergoing PCI. Further larger clinical trials are warranted to confirm these observations.

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CONTRIBUTION STATEMENT MT conceived the concept of the study. MT, LK and SJ contributed to the design of the research. All authors were involved in data collection. MT, LK and SJ analyzed the data. All authors edited and approved the final version of the manuscript.

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