Platelet Volume Indices are Associated with High Residual Platelet Reactivity after Antiplatelet Therapy in Patients Undergoing Percutaneous Coronary Intervention

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Aim: It is well known that platelet volume indices are associated with adverse outcomes following percutaneous coronary intervention (PCI). In this study, we investigated the hypothesis whether the association between platelet size and clinical outcomes is the result of high residual platelet reactivity after antiplatelet therapy in patients with large platelets.

Methods: Between February 2010 and December 2011, a total of 462 consecutive patients with coronary artery disease who were scheduled to undergo planned PCI were enrolled in this study. The degree of platelet aggregation induced by arachidonic acid (AA) and adenosine diphosphate (ADP) was assessed using the Multiple Electrode Platelet Aggregometry (Multiplate®, Dynabyte, Munich, Germany) (MEA) test. We simultaneously measured the mean platelet volume (MPV) in the same period (Sysmex XE-2100, Mundelein, IL).

Results: The study population consisted of 462 consecutive patients, including 371 stable angina patients and 91 acute coronary syndrome patients. The patients with large platelets (upper quintile of MPV ≥ 10.6 fL) had significantly high residual platelet reactivity after both aspirin (MEA ASP 9 [5-14] Units vs. 13 [8-18.5] Units, p < 0.001) and clopidogrel (MEA ADP 21 [15-30] Units vs. 24 [18.5-40] Units, p = 0.003) treatment. According to a multivariate analysis, having large platelets was independently associated with high residual platelet reactivity after both aspirin (OR 2.52, 95% CI 1.50-4.24, p < 0.001) and clopidogrel (OR 2.86, 95% CI 1.59-5.15, p < 0.001) treatment. Platelet volume indices were not associated with any differences in the incidence of major adverse cardiac events during follow-up.

Conclusions: Platelets with a higher volume are associated with high residual platelet reactivity after conventional dual antiplatelet therapy.


Key words: Platelet volume, Platelet function test, Antiplatelet therapy

Introduction

The use of drug-eluting stent (DES) implantation has substantially reduced the rate of restenosis and expanded the clinical applications of percutaneous coronary intervention (PCI)\(^1\). Dual antiplatelet therapy, primarily consisting of aspirin and adenosine diphosphate (ADP) receptor inhibitor, is currently the standard of patient care after DES implantation.

Platelets are heterogeneous in both size and density, and it has been shown that platelet size, as measured according to the mean platelet volume (MPV), is correlated with reactivity\(^2\).\(^3\). A positive association between MPV and indicators of platelet activity, such as the expression of glycoprotein Ib and glycoprotein IIb/IIIa receptors, has been demonstrated\(^4\). MPV is
also associated with adverse clinical outcomes. Greisenschegger S. et al. proved that there is a positive relationship between MPV and the severity of acute ischemic cerebrovascular events. Recently, it has been demonstrated that MPV is a strong predictor of impaired reperfusion and mortality in ST segment elevation myocardial infarction (STEMI) patients treated with primary PCI. The exact process underlying the association between an increased MPV and adverse clinical outcomes in coronary artery disease patients is still not fully understood. There is some evidence that platelets obtained from patients with coronary artery disease and elevated platelet turnover, based on the proportion of circulating reticulated platelets, exhibit significantly increased aggregation and activation responses, even after dual antiplatelet therapy. However, a direct association between platelet size and responsiveness to antiplatelet therapy has not yet been proven.

**Aim**

In current clinical practice, measurements of the MPV are easily available in both inpatient and outpatient settings at a relatively low cost. As an increased MPV is associated with increased platelet reactivity and adverse clinical outcomes, we conducted this study in order to test the hypothesis whether this association is due to decreased responsiveness to dual antiplatelet therapy in patients with large platelets.

**Methods**

**Patients**

Between February 2010 and December 2011, consecutive patients with coronary artery disease who were scheduled to undergo planned PCI at Seoul National University Bundang Hospital were enrolled in this study. Both stable coronary artery disease patients and acute coronary syndrome patients, including non-ST segment elevation myocardial infarction (NSTEMI) and STEMI patients, were included in this study. There were no specific exclusion criteria, except for contraindications to aspirin and/or clopidogrel treatment. Before PCI, the patients were given both aspirin and clopidogrel. Loading doses of aspirin (300 mg) and clopidogrel (300 mg) were administered in patients who had not previously taken aspirin or clopidogrel. After the initial procedure, aspirin (100 mg daily) and clopidogrel (75 mg daily) were administered for at least six months. Coronary angiography and PCI were performed in accordance with the current standard guidelines. During the procedure, aspirin and Clopidogrel were used to prevent platelet aggregation.

**Table 1. Baseline clinical characteristics of the study patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=462)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67.00 [58.00-72.00]</td>
</tr>
<tr>
<td>Male sex</td>
<td>325 (70.3%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.29 [23.41-27.42]</td>
</tr>
<tr>
<td>Hypertension</td>
<td>280 (60.6%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>142 (30.7%)</td>
</tr>
<tr>
<td>On insulin therapy</td>
<td>28 (6.1%)</td>
</tr>
<tr>
<td>Smoking history</td>
<td>217 (47%)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>83 (18.0%)</td>
</tr>
<tr>
<td>Previous CVA</td>
<td>6 (1.3%)</td>
</tr>
<tr>
<td>SA</td>
<td>340 (73.6%)</td>
</tr>
<tr>
<td>UA</td>
<td>55 (11.9%)</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>19 (4.1%)</td>
</tr>
<tr>
<td>STEMI</td>
<td>17 (3.7%)</td>
</tr>
<tr>
<td>CTO</td>
<td>31 (6.7%)</td>
</tr>
<tr>
<td>1 vessel disease</td>
<td>151 (32.7%)</td>
</tr>
<tr>
<td>2 vessel disease</td>
<td>158 (34.2%)</td>
</tr>
<tr>
<td>3 vessel disease</td>
<td>132 (28.6%)</td>
</tr>
<tr>
<td>Target vessel</td>
<td></td>
</tr>
<tr>
<td>LM</td>
<td>39 (4.9%)</td>
</tr>
<tr>
<td>LAD</td>
<td>401 (50.3%)</td>
</tr>
<tr>
<td>RI</td>
<td>10 (1.3%)</td>
</tr>
<tr>
<td>LCx</td>
<td>151 (18.9%)</td>
</tr>
<tr>
<td>RCA</td>
<td>196 (24.6%)</td>
</tr>
<tr>
<td>Medication before PCI</td>
<td></td>
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<tr>
<td>Aspirin</td>
<td>462 (100%)</td>
</tr>
<tr>
<td>Adenosine receptor antagonist</td>
<td>462 (100.0%)</td>
</tr>
<tr>
<td>Cilostazole</td>
<td>97 (21.0%)</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>253 (54.8%)</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>316 (68.4%)</td>
</tr>
<tr>
<td>Statin</td>
<td>393 (85.1%)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>137.00 [125.00-149.00]</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79.00 [71.00-86.00]</td>
</tr>
<tr>
<td>Platelet count (10²/mm³)</td>
<td>205.00 [174.00-240.00]</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>13.70 [12.70-14.70]</td>
</tr>
<tr>
<td>Cr (mg/dL)</td>
<td>0.83 [0.72-0.99]</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.10 [5.70-6.90]</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>158.00 [135.75-183.00]</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>122.00 [88.75-170.50]</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>41.00 [35.75-48.00]</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>89.00 [69.00-112.00]</td>
</tr>
</tbody>
</table>

BMI: body mass index; PCI: percutaneous coronary intervention; CVA: cerebrovascular accident; SA: stable angina; UA: unstable angina; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction; CTO: chronic total occlusion; LM: left main; LAD: left anterior descending; RI: ramus intermedius; LCx: left circumflex; RCA: right coronary artery; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; SBP: systolic blood pressure; DBP: diastolic blood pressure; Hb: hemoglobin; Cr: creatinine; TC: total cholesterol; TG: triglyceride; HDL: high-density lipoprotein; LDL: low-density lipoprotein.
Impact of Platelet Size

Statistical Analysis
The statistical analysis was conducted using the SPSS V18.0 software program (SPSS Inc., Chicago, IL, USA). The values are expressed as the mean ± standard deviation or median with interquartile range [IQR]. For the statistical analysis, categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. The Kolmogorov-Smirnov test was used to test for a normal distribution among the continuous data, and normally distributed variables were compared using the unpaired t-test. The Mann-Whitney U test was used to evaluate non-normally distributed variables. Platelet function data obtained with MEA and the platelet volume indices are presented as the median [IQR] due to their non-normal distribution. A correlation analysis was also performed using the Spearman correlation coefficient (r). A multivariate analysis using a logistic regression model was performed to evaluate the effects of MPV and PDW on antiplatelet responsiveness. The Kaplan-Meier method was used to calculate the rate of adverse events. All tests of significance were two-tailed, and p values of less than 0.05 were considered to indicate statistical significance.

Results

Patients
A total of 462 consecutive patients were enrolled in this study. The baseline clinical and procedural characteristics of the 462 patients are presented in Table 1. The median age was 67 [58-72] years and the proportion of men was 70.3% (325 patients). The median platelet count was 205 [174-240] (10^2/mm^3). A total of 91 patients (19.7%) had acute coronary syndrome. Procedural success was achieved in all patients. Aspirin and clopidogrel were administered in all patients. The median value of AA-induced platelet aggregation was 10 [6-15] (Units) measured using the MEA ASP test. The median value of ADP-induced platelet aggregation was 21 [15-31] (Units) measured using the MEA ADP test.

Blood Sampling
Whole blood was drained from the patients before the initial PCI procedure. A complete blood cell count, including the MPV and platelet distribution width (PDW), was obtained (Sysmex XE-2100, Mundelein, IL). The blood samples were obtained prior to the administration of any antiplatelet agents or anticoagulation therapy in every patient.

Platelet Function Tests
For the platelet function tests, blood samples were obtained from the patients one day after the initial PCI procedure. The blood samples were placed in 4.0-mL plastic tubes containing the anticoagulant lepirudin (25 g/mL, Refludan, hirudin blood collection tubes, Dynabyte), as recommended by the manufacturer. The blood samples were maintained at room temperature for at least 30 minutes prior to platelet function testing. The platelet function was measured using Multiple Electrode Platelet Aggregometry (Multiplate®, Dynabyte, Munich, Germany) (MEA), a whole blood impedance aggregometer. The degree of platelet aggregation induced by arachidonic acid (AA) and ADP in whole blood was assessed as previously described in other studies. In our study, aggregation measured with the MEA was quantified as Units [(AU*min)/10]. All materials used in this study, including ADP, were obtained from the manufacturer (Dynabyte).

The aim of this study was to evaluate the relationships between platelet volume indices and antiplatelet responsiveness. We evaluated antiplatelet responsiveness using an MEA assay. The correlations between the platelet volume indices and platelet function test parameters were evaluated. We also investigated whether patients with high residual platelet reactivity after antiplatelet treatment, defined according to the upper quintile on MEA tests, exhibited significant differences in the MPV or PDW values compared to other patients. Finally, we compared the clinical outcomes according to the quintiles of MPV, MEA ASP and MEA ADP. For the clinical outcome analysis, major adverse cardiac event (MACE) was defined as the composite of cardiac death, myocardial infarction, stroke and target vessel revascularization (TVR).

Table 2. Baseline laboratory data for MEA, MPV and PDW

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 462)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEA ASP</td>
<td>10.00 [6.00-15.00]</td>
</tr>
<tr>
<td>MEA ADP</td>
<td>21.00 [15.00-31.00]</td>
</tr>
<tr>
<td>MPV (fL)</td>
<td>9.90 [9.40-10.50]</td>
</tr>
<tr>
<td>PDW (%)</td>
<td>11.20 [10.20-12.30]</td>
</tr>
</tbody>
</table>

MEA ASP: multiple electrode platelet aggregometry aspirin test; MEA ADP: multiple electrode platelet aggregometry ADP test; MPV: mean platelet volume; PDW: platelet distribution width.
Kim et al. vs. 13 [8-18.5] Units, \( p < 0.001 \), Fig. 1A) and clopidogrel (MEA ADP 21 [15-30] Units vs. 24 [18.5-40] Units, \( p = 0.003 \), Fig. 1B) treatment. Patients with a PDW level in the upper quintile (PDW ≥ 12.6%) also exhibited high residual platelet reactivity after both aspirin (MEA ASP 10 [5-14] Units vs. 13 [8-19] Units, \( p < 0.001 \), Fig. 1C) and clopidogrel (MEA ADP 21 [14.75-30.25] Units vs. 24 [19-38.25] Units, \( p = 0.01 \), Fig. 1D) treatment. Fig. 2 demonstrates the receiver operating characteristic curve analysis of the

**Association between Platelet Size and Responsiveness to Antiplatelet Therapy**

Patients with large platelets (upper quintile of MPV ≥ 10.6 fL) had significantly high residual platelet reactivity after both aspirin (MEA ASP 9 [5-14] Units vs. 13 [8-18.5] Units, \( p < 0.001 \), Fig. 1A) and clopidogrel (MEA ADP 21 [15-30] Units vs. 24 [18.5-40] Units, \( p = 0.003 \), Fig. 1B) treatment. Patients with a PDW level in the upper quintile (PDW ≥ 12.6%) also exhibited high residual platelet reactivity after both aspirin (MEA ASP 10 [5-14] Units vs. 13 [8-19] Units, \( p < 0.001 \), Fig. 1C) and clopidogrel (MEA ADP 21 [14.75-30.25] Units vs. 24 [19-38.25] Units, \( p = 0.01 \), Fig. 1D) treatment. Fig. 2 demonstrates the receiver operating characteristic curve analysis of the

Fig. 1. Box plot analyses showing that large platelets are associated with high residual platelet reactivity after antiplatelet therapy.

The boxes indicate the 25th and 75th percentiles, and the whiskers denote the 10th and 90th percentiles.
Impact of Platelet Size

The MPV level had a weak positive correlation with both the MEA ASP ($r = 0.183$, $p < 0.001$, Fig. 3A) and MEA ADP ($r = 0.147$, $p = 0.002$, Fig. 3B) values. The PDW level also had a similar correlation with both the MEA ASP ($r = 0.200$, $p < 0.001$, Fig. 3C) and MEA ADP ($r = 0.150$, $p = 0.001$, Fig. 3D) values. After defining patients with high residual platelet reactivity after aspirin treatment as those with MEA ASP assay results in the upper quintile, these patients had higher MPV levels than their counterparts (9.8 [9.4-10.4] fL vs. 10.3 [9.6-10.8] fL, $p = 0.001$, Fig. 4A). Patients with high platelet reactivity after clopidogrel treatment (upper quintile group of MEA ADP assay) also exhibited higher MPV levels (9.9 [9.4-10.4] fL vs. 10.2 [9.7-10.8] fL, $p = 0.032$, Fig. 4B).

Cardiac Death, Myocardial Infarction, Stroke and TVR

There were a total of 37 MACEs, including two cardiac deaths, five cases of myocardial infarction, six cases of stroke and 24 cases of target vessel revascularization. The patients with high residual platelet reactivity (upper quintile group of MEA ASP assay) after aspirin (MEA ASP $\geq 17$ Units) and clopidogrel (MEA ADP $\geq 34$ Units) treatment did not exhibit any significant differences in the incidence of MACE (including cardiac death, myocardial infarction, stroke and TVR) (cumulative incidence: 8.49\% vs. 5.49\%, $p = 0.362$ for MEA ASP test and 8.45\% vs. 5.38\%, $p = 0.352$ for MEA ADP test). Patients with an MPV level in the upper quintile also did not show any differences in clinical outcomes (cumulative incidence: 7.82\% vs.
alpha-granules\(^{15}\), platelet factor 4\(^{16}\), P-selectin\(^{13}\) and platelet-derived growth factor\(^{17}\), have been implicated as factors of increased aggregability in large platelets.

In the present study, we suggest that adverse clinical outcomes in patients with large platelets are at least partially related to high residual platelet reactivity after dual antiplatelet therapy.

Platelets can be activated by multiple pathways\(^{18}\). The cyclooxygenase-mediated platelet aggregation pathway is inhibited by aspirin, while the P2Y12 receptor-related pathway is inhibited by ADP receptor inhibitors, such as clopidogrel. There is individual variation in the response to clopidogrel treatment, and it is well known that a poor response to clopidogrel is associated with adverse outcomes after PCI\(^{19-21}\). Resistance to aspirin, very much like resistance to clopidogrel, is also associated with adverse outcomes in coronary artery disease patients. George K et al.\(^{22}\) concluded in their meta-analysis that patients classified as aspirin-resistant are at an approximately four-fold increased risk of non-fatal and fatal cardiovascular, cerebrovascular and vascular events while taking aspirin than their aspirin-sensitive counterparts. Therefore, it is clinically important to identify patients with a poor response to antiplatelet therapy. However, although we raised the hypothesis that increased MPV and PDW levels are associated with high residual platelet reactivity after aspirin and clopidogrel treatment.

In two large clinical trials performed decades ago, the MPV level was shown to be an independent risk factor for recurrent ischemia or death following myocardial infarction\(^{11,12}\). In these studies, the MPV was not correlated with known ischemic heart disease risk factors, suggesting that an elevated MPV level may contribute to adverse events through a novel mechanism\(^{2}\). To date, it is not fully understood how an increased MPV level influences the clinical outcomes of patients with ischemic heart disease. One possible mechanism is that larger platelets are metabolically and enzymatically more active than smaller platelets, containing more prothrombotic material, with increased amounts of thromboxane A2 and B2 per unit of volume and a higher glycoprotein IIb-IIIa receptor expression\(^{13,14}\). Various substances, including alpha-granules\(^{15}\), platelet factor 4\(^{16}\), P-selectin\(^{13}\) and platelet-derived growth factor\(^{17}\), have been implicated as factors of increased aggregability in large platelets.

In the current study, we evaluated the hypothesis that platelet size has a positive correlation with both MEA ASP and MEA ADP test parameters. In this study, higher MPV and PDW levels were associated with high residual platelet reactivity after aspirin and clopidogrel treatment.

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**Table 3.** Multivariate analysis using a logistic regression model to predict high residual platelet reactivity after aspirin treatment

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR</th>
<th>95% confidence interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>0.73</td>
<td>0.39-1.38</td>
<td>0.33</td>
</tr>
<tr>
<td>Age</td>
<td>0.98</td>
<td>0.96-1.00</td>
<td>0.09</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.99</td>
<td>0.96-1.01</td>
<td>0.28</td>
</tr>
<tr>
<td>DM</td>
<td>0.73</td>
<td>0.42-1.26</td>
<td>0.26</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.46</td>
<td>0.84-2.53</td>
<td>0.18</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.92</td>
<td>0.67-1.25</td>
<td>0.59</td>
</tr>
<tr>
<td>MPV upper quintile</td>
<td>2.52</td>
<td>1.50-4.24</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Table 4.** Multivariate analysis using a logistic regression model to predict high residual platelet reactivity after clopidogrel treatment

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR</th>
<th>95% confidence interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>2.26</td>
<td>1.07-4.77</td>
<td>0.03</td>
</tr>
<tr>
<td>Age</td>
<td>0.99</td>
<td>0.97-1.02</td>
<td>0.53</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.97</td>
<td>0.95-1.00</td>
<td>0.05</td>
</tr>
<tr>
<td>DM</td>
<td>1.23</td>
<td>0.67-2.27</td>
<td>0.50</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.79</td>
<td>0.89-3.60</td>
<td>0.10</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.48</td>
<td>0.14-1.59</td>
<td>0.23</td>
</tr>
<tr>
<td>MPV upper quintile</td>
<td>2.86</td>
<td>1.59-5.15</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

6.38%, \(p=0.634\)). The median follow-up duration was 18.8 months and the follow-up loss rate was 1.3%.

**Discussion**

In the current study, we evaluated the hypothesis that platelet size has a positive correlation with both MEA ASP and MEA ADP test parameters. In this study, higher MPV and PDW levels were associated with high residual platelet reactivity after aspirin and clopidogrel treatment.

In two large clinical trials performed decades ago, the MPV level was shown to be an independent risk factor for recurrent ischemia or death following myocardial infarction\(^{11,12}\). In these studies, the MPV was not correlated with known ischemic heart disease risk factors, suggesting that an elevated MPV level may contribute to adverse events through a novel mechanism\(^{2}\). To date, it is not fully understood how an increased MPV level influences the clinical outcomes of patients with ischemic heart disease. One possible mechanism is that larger platelets are metabolically and enzymatically more active than smaller platelets, containing more prothrombotic material, with increased amounts of thromboxane A2 and B2 per unit of volume and a higher glycoprotein IIb-IIIa receptor expression\(^{13,14}\). Various substances, including alpha-granules\(^{15}\), platelet factor 4\(^{16}\), P-selectin\(^{13}\) and platelet-derived growth factor\(^{17}\), have been implicated as factors of increased aggregability in large platelets.

In the present study, we suggest that adverse clinical outcomes in patients with large platelets are at least partially related to high residual platelet reactivity after dual antiplatelet therapy.

Platelets can be activated by multiple pathways\(^{18}\). The cyclooxygenase-mediated platelet aggregation pathway is inhibited by aspirin, while the P2Y12 receptor-related pathway is inhibited by ADP receptor inhibitors, such as clopidogrel. There is individual variation in the response to clopidogrel treatment, and it is well known that a poor response to clopidogrel is associated with adverse outcomes after PCI\(^{19-21}\). Resistance to aspirin, very much like resistance to clopidogrel, is also associated with adverse outcomes in coronary artery disease patients. George K et al. concluded in their meta-analysis that patients classified as aspirin-resistant are at an approximately four-fold increased risk of non-fatal and fatal cardiovascular, cerebrovascular and vascular events while taking aspirin than their aspirin-sensitive counterparts\(^{22}\). Therefore, it is clinically important to identify patients with a poor response to antiplatelet therapy. However, although we raised the hypothesis that increased MPV and PDW levels are associated with high residual platelet reactivity after aspirin and clopidogrel treatment.
Impact of Platelet Size

Although it is possible that large platelets exert adverse effects via, in part, decreased responsiveness to antiplatelet medications, we do not know whether the administration of intensified antiplatelet therapy would benefit this patient group. Second, the correlation coefficients between the MEA test parameters and platelet volume indices were very low. The weak correlation between the two tests was likely due to the diversity of factors that contribute to antiplatelet drug responsiveness, as mentioned above. Platelet volume indices can account for some, but not all, of the observed antiplatelet responsiveness. Third, our study failed to prove that patients with high residual platelet reactivity after aspirin and clopidogrel treatment or hyporesponsiveness to antiplatelet therapy cannot be explained by a single factor. Various factors, including sex, race, certain genetic mutations, concurrent medications and diabetes mellitus, participate in individual variation in responsiveness to antiplatelet therapy. Clinicians should consider diverse factors, including platelet size, when prescribing antiplatelet agents.

There are several limitations to this study. First, there are currently no studies showing that individualizing antiplatelet therapy according to platelet function test results improves clinical outcomes. Furthermore, there are no specific guidelines or consensus regarding how to treat patients with large platelets.

Although it is possible that large platelets exert adverse effects via, in part, decreased responsiveness to antiplatelet medications, we do not know whether the administration of intensified antiplatelet therapy would benefit this patient group. Second, the correlation coefficients between the MEA test parameters and platelet volume indices were very low. The weak correlation between the two tests was likely due to the diversity of factors that contribute to antiplatelet drug responsiveness, as mentioned above. Platelet volume indices can account for some, but not all, of the observed antiplatelet responsiveness. Third, our study failed to prove that patients with high residual platelet reactivity after aspirin and clopidogrel treatment or
Conclusion

Large platelets are possibly associated with a decreased response to aspirin and clopidogrel. Clinicians should be aware that the characteristics of platelets themselves can affect the effectiveness of antiplatelet therapy. Whether patients with increased MPV and/or PDW levels need intensified antiplatelet therapy requires further investigation.

Acknowledgement

The original manuscript was written by Yun Gi Kim. All authors contributed to drafting and editing the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Abbreviations

PCI: percutaneous coronary intervention; AA: arachidonic acid; ADP: adenosine diphosphate; MEA: Multiple Electrode Platelet Aggregometry; MPV: mean platelet volume; PDW: platelet distribution

Fig. 4. Box plot analyses comparing the MPV levels between the patients with and without high residual platelet reactivity after aspirin and clopidogrel treatment.

The boxes indicate the 25th and 75th percentiles, and the whiskers denote the 10th and 90th percentiles.

those with large platelets have a higher incidence of adverse clinical outcomes. We believe that this finding is due to the small sample size. In current practice using second- and third-generation DES and standardized dual antiplatelet therapy according to guidelines, major adverse cardiac events, such as cardiac death, MI and stent thrombosis, are exceedingly rare. Thrombotic complications are additionally rare in Asian populations due to ethnic differences. The sample size of 462 patients was too small to demonstrate differences in clinical outcomes according to platelet function test parameters or platelet size. Fourth, we did not perform light transmission aggregometry. However, light transmission aggregometry, the standard test for evaluating the platelet function, is time and labor intensive and, therefore, impractical. It also has several other disadvantages, such as the need for immediate processing, variable reproducibility, large sample volumes and a lengthy processing time. Fifth, no genetic tests, including that for the CYP2C19 polymorphism, were performed in our study patients. The response to clopidogrel treatment is closely related to the CYP2C19 polymorphism. Previous studies have reported that the proportion of patients carrying the CYP2C19 loss of function allele is 60% among Koreans. A high prevalence of the CYP2C19 polymorphism, which is expected in our study population, may have confounded the results of our study.
width; MACE: major adverse cardiac event; TVR: target vessel revascularization; DES: drug-eluting stent; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction.

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