Joint effect of platelet distribution width and stent surface area on major adverse cardiovascular events after percutaneous coronary intervention

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Contributions: (I) Conception and design: C Li; (II) Administrative support: X Zhang, C Li; (III) Provision of study materials or patients: X Zhang, H Ge, X Gong; (IV) Collection and assembly of data: X Zhang, H Ge, X Gong; (V) Data analysis and interpretation: X Zhang, J Wang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: This study was conducted to analyze the influences of stent surface area (SSA), platelet distribution width (PDW), and the joint effect of these 2 risk factors on major adverse cardiovascular events (MACEs) in patients treated with percutaneous coronary intervention (PCI) together with drug-eluting stent (DES) implantation.

Methods: Based on a cross-sectional survey conducted between 2011 and 2012, a prospective cohort study was enrolled consisting of 442 patients who had undergone PCI with DES implantation. We categorized the participants into 4 subgroups according to PDW and SSA. Cox proportional hazards models were applied to explore the correlation of PDW and SSA with MACE incidence.

Results: During the 12 months of follow-up time, 87 patients experienced MACEs, which included 4 deaths (4.6%), 5 nonfatal myocardial infarctions (MIs) (5.75%), 9 ischemic strokes (10.34%), and 73 clinically relevant bleeding episodes (83.91%). The risks of MACEs were decreased by SSA and increased by PDW. However, the association of PDW or SSA with MACE was not statistically significant. Compared with the patients with PDW $\geq$13.5% and SSA $<$358.14 mm², the multivariable adjusted hazard ratios [HRs; 95% confidence interval (CI)] of the total MACEs for the patients with PDW $<$13.5% and SSA $\geq$358.14 mm², and with PDW $\geq$13.5% and SSA $\geq$358.14 mm² were 0.94 (95% CI: 0.55–1.64) and 0.37 (95% CI: 0.18–0.76), respectively. Additionally, the patients in the group of PDW $<13.5%$ and $SSA <358.14 \text{ mm}^2$ had respective HRs of 0.47 (95% CI: 0.24–0.91) and 0.28 (95% CI: 0.13–0.63) for 12-month bleeding events when PDW $\geq$13.5% and SSA $<358.14 \text{ mm}^2$ was used as a group reference.

Conclusions: Our present results suggest that the joint effect of PDW and SSA was significantly correlated to MACE development in the patients treated with PCI (with DES implantation).

Keywords: Stent surface area(SSA); platelet distribution width (PDW); percutaneous coronary intervention (PCI); major adverse cardiovascular events (MACEs)

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**Introduction**

Coronary artery disease (CAD) accounts for more than 610,000 deaths annually worldwide and is a leading cause of global morbidity and mortality (1). With the development of percutaneous coronary intervention (PCI) over the past decades, substantial breakthroughs have been made in the treatment of CAD (2,3). Moreover, the incidence of major adverse cardiovascular events (MACEs), including cardiovascular death, nonfatal myocardial infarction (MI), and ischemic stroke, have been further reduced in the patients since the second-generation drug-eluting stent (DES) was introduced into clinical practice (4-6). However, some patients still show poor prognosis after DES implantation.

Being an index reflecting heterogeneous platelet size, platelet distribution width (PDW), plays an important role in the development of atherothrombosis and atherosclerotic plaque rupture (7-9). In a Polish study, Kern et al. reported that PDW is a low-cost and reliable parameter for the 1-year MACE rate after PCI within coronary bifurcation lesions (10). In addition, several stent characteristics, such as stent length and diameter, have also been reported as important parameters for the subsequent risk of MACEs after PCI procedures (10). For instance, Plitt et al. reported that a stent diameter (SD) value of 3.25–3.5 mm and an SD value >3.5 mm were significantly associated with a 21% and 34% lower risk for MACE rates, respectively, in comparison with an SD level of ≤2.5 mm (11). Stent surface area (SSA) is a comprehensive index value that can reflect the length and diameter of stent. However, the effect of SSA on the risk of adverse outcomes after PCI remains unclear. Therefore, the purpose of our research was to explore SSA, PDW, and the combined effect of SSA and PDW on the occurrence of MACEs in patients who undergo PCI with DES implantation. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/apm-21-1088).

**Methods**

*Research design and patients characteristics*

This study was conducted in the First Affiliated Hospital of Nanjing Medical University, Nanjing, China (12). The study protocol received approval from the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (No. 2011036) and conformed to the ethical principles of the Declaration of Helsinki (as revised in 2013). Briefly, between January 2011 and December 2012, patients with acute coronary syndrome (ACS) or stable CAD with coronary stent implantation were consecutively screened for the present study. Patients were eligible for enrollment (I) if they were ≥18 years of age, and (II) if they had undergone PCI with second-generation DES implantation for CAD. The exclusion criteria were the following: (I) patients had previously undergone coronary artery bypass surgery; and (II) patients suffered from debilitating conditions, including advanced malignancies, severe liver and kidney dysfunctions, severe autoimmune diseases, or cerebrovascular accidents with major sequelae. Finally, 442 patients were recruited in the present analysis. The written informed consents were asked from each patient before their enrollment in the study.

*Data collection, follow-up, and sample measurements*

The demographic characteristics, and medical and social histories were collected from each included patient. The synergy between PCI with taxus and cardiac surgery (SYNTAX) score, a validated scoring system for the complexity of coronary lesions, was prospectively calculated (using the online tool accessed at http://www.syntaxscore.com/calculator/start.htm) by 3 experienced investigators. In the present study, body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. We measured the blood pressure (BP) with an Omron HEM-907 sphygmomanometer in sitting position after 5 minutes rest (Omron Corp., Tokyo, Japan). SSA was calculated using the following formula: SSA = \( \pi \times SD \times SL \) (stent diameter) × SL (stent length). Triglycerides (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), fasting plasma glucose (FPG), and (TC) were detected using commercial reagents on a chemistry analyzer (AU5400 Analyzer, Beckman Coulter, CA, USA).

We defined the success of PCI according to following criteria determined by consensus of the international experts in our field: (I) a residual diameter stenosis >25% and (II) obtaining an enhanced figure without further delay to the distal coronary artery (thrombolysis in MI3 flow) in patients’ selected lesions. After the PCI procedure, all patients received aspirin 81–100 mg qd, and clopidogrel 75 mg qd or ticagroler 90 mg bid. Clinical follow-up was arranged at 30 days, 3 months, 6 months, and 12 months by inviting patients or their relatives to finish a standardized questionnaire. The participants who dropped out of follow-up...
up were excluded from the survival analysis of the study.

**Primary endpoint**

The primary endpoint of MACEs included all-cause death, nonfatal MI, ischemic stroke, and clinically relevant bleeding within 1-year after PCI. We defined all-cause deaths as any death during or after the PCI procedure that was considered to be of cardiac origin unless a diagnosis of anoncardiac cause could be assessed. MI was defined as an ischemic symptom arising within 3 months before enrollment with new electrocardiographic changes and increased concentration of circulating cardiac troponin (≥0.5 μg/L). Ischemic stroke events were determined according to the Bleeding Academic Research Consortium classification (13). In addition, clinically relevant bleeding was defined as bleeding meeting any of the major criteria according to GUSTO (global utilization of streptokinase and TPA for occluded arteries) or ACUITY (acute catheterization and urgent intervention triage strategy) scales, as well as any other types of bleeding that required medical care after hospital discharge.

**Statistical analysis**

According to the PDW and SSA, we divided patients into 4 subgroups: PDW ≥13.5% with SSA <358.14 mm², PDW <13.5% with SSA <358.14 mm², PDW ≥13.5% with SSA ≥358.14 mm², and PDW <13.5% with SSA ≥358.14 mm². For the comparison of baseline characteristics, continuous variables are displayed as mean ± standard deviation if the sample was normally distributed, or as median with 25th and 75th percentiles if it was skewed. Categorical variables are shown as numbers or percentages. The χ² test or Fisher's exact test was used to compare the characteristics of participants. We used log-rank tests to adjust the cumulative risk of outcomes among the 4 subgroups. For the purpose of testing joint effects of PDW and SSA on the clinical outcomes after PCI, we used multivariate Cox proportional hazard models for calculation of the hazard ratios (HRs) with 95% confidence intervals (CIs) of MACE across the 4 subgroups, adjusting for potential confounders of age, sex, current smoking habits, drinking habits, BMI, hypertension, diabetes mellitus (DM), and SYNTAX score. Statistical analysis was performed with R 3.4.0 (Vienna, Austria) and SAS version 9.1 (Cary, NC, USA). All P values <0.05 (2-tailed) were deemed statistically significant.

**Results**

During the follow-up period, 87 patients experienced MACEs, which included 4 deaths (4.6%), 5 nonfatal MIs (5.7%), 9 ischemic strokes (10.34%), and 73 clinically relevant bleeding episodes (83.91%). Patients’ baseline clinical and demographic characteristics are summarized according to PDW and SSA in Table 1. The patients with PDW <13.5% either in the SSA <358.14 mm² group or in the SSA ≥358.14 mm² group tended to have higher amounts of TC, HDL-c, and LDL-c. Moreover, patients with SSA ≥358.14 mm² either in the PDW <13.5% group or in the PDW ≥13.5% group tended to have higher SYNTAX score, longer stent length, and larger SSA.

We tested the effects of PDW and SSA with MACE in the patients after PCI (Table 2). The risks of clinically relevant bleeding were decreased by SSA and increased by PDW. However, HRs of MACEs for PDW ≥13.5% and SSA ≥358.14 mm² were respectively 0.94 (95% CI: 0.62–1.44) and 0.86 (95% CI: 0.55–1.36), after adjustments were made for the possible confounders of age, sex, smoking habits, drinking, BMI, hypertension, DM, and SYNTAX score. Additionally, we found no significant association between PDW or SSA and bleeding events in these patients after PCI procedure.

The cumulative incidence rates of total MACEs among the 4 subgroups were 27.82% for PDW ≥13.5% and SSA ≥358.14 mm², 26.09% for PDW <13.5% and SSA ≥358.14 mm², 17.14% for PDW <13.5% and SSA <358.14 mm², and 10.28% for PDW ≥13.5% and SSA ≥358.14 mm² (log-rank P=0.007). As shown in Table 3, compared with the patients with PDW ≥13.5% and SSA <358.14 mm², the multivariable adjusted HRs of total MACEs for the patients with PDW <13.5% and SSA ≥358.14 mm² were 0.94 (95% CI: 0.55–1.64). The patients with PDW ≥13.5% and SSA ≥358.14 mm² were at the lowest risk of total MACEs during 12-month follow-up (HR = 0.37, 95% CI: 0.18–0.76, P<0.007).

Because more than 80% of the MACEs were clinically relevant bleeding events, we further analyzed the combined effect of PDW and SSA on the risk of bleeding in this follow-up study. The cumulative incidence rates of bleeding among the 4 subgroups were 24.35% for PDW ≥13.5% and SSA <358.14 mm², 20.00% for PDW <13.5% and SSA ≥358.14 mm², 13.33% for PDW <13.5% and SSA <358.14 mm², and 7.48% for PDW ≥13.5% and SSA ≥358.14 mm² (log-rank P=0.004). Compared with those of patients with PDW ≥13.5% and SSA <358.14 mm², the
multivariable adjusted HRs of bleeding for the patients with PDW <13.5% and SSA <358.14 mm², and PDW ≥13.5% and SSA ≥358.14 mm² were 0.47 (95% CI: 0.24–0.91, P=0.026) and 0.80 (95% CI: 0.44–1.45, P=0.457), respectively. The patients with PDW ≥13.5% and SSA ≥358.14 mm² were at the lowest risk of clinically relevant bleeding (HR =0.28, 95% CI: 0.13–0.63, P=0.002; Table 4). However, other than clinically relevant bleeding, no significant combined effects were detected between PDW and SSA on the development of MACEs in the patients who underwent PCI with DES implantation.

### Discussion

Although the data on the association between SSA and MACEs after PCI is very limited, the length and diameter of stent have been reported as independent predictors of MACEs after PCI with DES implantation (11,14–17). For instance, the results from a meta-analysis found that females with smaller SDs treated with PCI had a higher risk of definite stent thrombosis and target lesion revascularization, consistent with early and new generations of DES (18). However, in a prospective study, Adnan et al. (19)
### Table 2

<table>
<thead>
<tr>
<th>Variables</th>
<th>Age and gender adjusted</th>
<th>Multivariable adjusted*</th>
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<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
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<td><strong>MACE</strong></td>
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<tr>
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<tr>
<td>SSA (per 1 mm²)</td>
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<td>SSA ≥358.14 mm²</td>
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* Adjusted for potential confounders: age, sex, smoking habits, drinking habits, BMI, hypertension, diabetes mellitus, and SYNTAX score. PDW, platelet distribution width; SSA, stent surface area; MACEs, major adverse cardiovascular events; PCI, percutaneous coronary intervention; DES, drug-eluting stent; CI, confidence interval; HR, hazard ratio.

### Table 3

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<tr>
<td>PDW &lt;13.5% with SSA ≥358.14 mm²</td>
<td>0.87</td>
<td>0.52–1.45</td>
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</table>

* Adjusted for potential confounders: age, sex, smoking habits, drinking, BMI, hypertension, diabetes mellitus, and SYNTAX score. PDW, platelet distribution width; SSA, stent surface area; MACEs, major adverse cardiovascular events; PCI, percutaneous coronary intervention; DES, drug-eluting stent; CI, confidence interval; HR, hazard ratio.

### Table 4

<table>
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<th>Variables</th>
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<tr>
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<tr>
<td>PDW &lt;13.5% with SSA ≥358.14 mm²</td>
<td>0.78</td>
<td>0.45–1.35</td>
</tr>
</tbody>
</table>

* Adjusted for for potential confounders: parameters including age, sex, smoking habits, drinking habits, BMI, hypertension, diabetes mellitus, and SYNTAX score. PDW, platelet distribution width; SSA, stent surface area; PCI, percutaneous coronary intervention; DES, drug-eluting stent; CI, confidence interval; HR, hazard ratio.
reported that the length and diameter of stent did not have any impact on the short-term clinical outcomes of DES inpatients in stable CAD status. In addition, results from another meta-analysis observed mean stent length was longer in those patients suffering stent thrombosis, indicating that the risk of stent thrombosis after DES implantation is related to stent length (20). Although we observed that MACE incidence was increased with SSA, no statistically significant association between SSA and the risk of MACE development was detected in this study. Considering that the patients receiving the stent with larger SSA had a decreased prevalence of MACEs during a follow-up period of 12 months, more trials should be made to study the influence of SSA on the clinical outcomes in the patients after the PCI procedure.

PDW is generally used to measure fractions of enzymatically and metabolically more active, and larger platelets. PDW refers to the variability in the size of platelet, which is enlarged when platelets become activated (21,22). PDW is regarded as a more specific marker of platelet reactivity, as it is stable and not affected by the distention of a single swollen platelet (23,24). However, the associations between PDW and MACEs in the patients undergoing PCI have not been fully understood. For example, Celik et al. (25) found that PDW is an independent parameter of no reflow and in-hospital MACEs in ST-elevation myocardial infarction (STEMI) patients undergoing PCI. In addition, a Polish study found that PDW with a cutoff value of 15.8% could predict the risk of MACEs with 79% sensitivity and 47% specificity (9). However, Verdoia et al. (26) reported that PDW did not add to the risk of periprocedural MI, and thus suggested it should not be regarded as a risk factor of thrombotic periprocedural complications in patients after PCI. In our analysis, we observed that PDW did not have any influence on the risks of total MACEs or clinically relevant bleeding events. One possible explanation for this finding is the shorter follow-up period of our research compared with the patients with SSA ≥358.14 mm², respectively. The results indicate that stents with a larger SSA might have an additional preventive effect on MACE development in the patients with larger PDW. In addition, among the patients SSA <358.14 mm², we observed that the patients with PDW ≥13.5% were associated with a 1.92-fold and 2.13-fold increased risk for MACEs and bleeding compared with the patients with PDW <13.5%, respectively. It suggested that the smaller PDW could prevent MACE occurrence in patients undergoing PCI with stents of larger SSA. However, the combined effect of smaller PDW (<13.5%) and larger SSA (≥358.14 mm²) did not have any influence on MACE development when compared to parameters of PDW ≥13.5% and SSA <358.14 mm². In order to obtain solid and consistent results, future trials are needed to further confirm our conclusion of the joint effect of PDW and SSA on MACE development in patients undergoing PCI with DES implantation.

There are several limitations in this study that should be considered. First, as they were derived from study with a single-center design, our findings might not be generalizable to other populations. In addition, considering that our sample size was relatively small, subanalyses were not performed according to SSA and PDW for specific MACEs. Therefore, caution should be taken when interpreting the results. Second, although SSA is strongly correlated with reference vessel diameter and SD (11,27). However, no information on reference vessel diameter has been reported thus far. Third, although we used random monitoring during enrollment of patients and adjudicated the events by reviews of electrocardiogramstocollect the information about MACEs, inaccurate outcomes could not be fully avoided. Furthermore, because data were collected up to a 12-month follow-up, the information on MACEs past this time were not acquired. Finally, although multivariable Cox regressions were used to analyze the HRs (95% CIs) of MACEs, due to the observational nature of the study, the possibility of unknown and unmeasured confounding factors remains.

In summary, our results suggest that the joint effect of PDW and SSA was significantly correlated to MACE development in patients undergoing PCIs with DES implantation. Additional longitudinal studies with large study samples are needed to further clarify the precise effect of PDW and SSA on the long-term clinical effects occurring
in patients after PCI.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/apm-21-1088

Data Sharing Statement: Available at http://dx.doi.org/10.21037/apm-21-1088

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-21-1088). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol received approval from the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (No. 2011036) and conformed to the ethical principles of the Declaration of Helsinki (as revised in 2013). The written informed consents were asked from each patient before their enrollment in the study.

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