# Platelet Distribution Width on Admission Predicts In-Stent Restenosis in Patients with Coronary Artery Disease and Type 2 Diabetes Mellitus Treated with Percutaneous Coronary Intervention

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## Abstract

**Background:** It is known that there is a definite association between platelet distribution width (PDW) and poor prognosis in patients with coronary artery disease (CAD) and type 2 diabetes mellitus (T2DM). However, there are no data available regarding the prognostic significance of PDW for in-stent restenosis (ISR) in patients with CAD and T2DM. We aimed to determine the value of PDW on admission that predicted ISR in patients with CAD and T2DM.

**Methods:** Between January 2012 and December 2013, a total of 5232 consecutive patients diagnosed with CAD and T2DM undergoing percutaneous coronary intervention were admitted. Three years of retrospective follow-up was undertaken. A total of 438 patients with second angiography operations were included. ISR was defined as $\geq$50% luminal stenosis of the stent or peri-stent segments. Continuous data were presented as the mean $\pm$ standard deviation or median ($P_{25}$, $P_{75}$) and were compared by one-way analysis of variance or Kruskal-Wallis $H$-test. Categorical variables were presented as percentages and were compared by Chi-square test or Fisher's exact test. The association between PDW and ISR was calculated by logistic regression analysis. A two-sided value of $P < 0.05$ was considered statistically significant. Statistical analyses were performed by SPSS version 22.0 for windows.

**Results:** Fifty-nine patients with ISR, accounting for 13.5% of the total, were included. ISR was significantly more frequent in patients with higher PDW quartiles compared with lower quartiles. We observed that PDW had a strong relationship with mean platelet volume ($r = 0.647$, 95% confidence interval [$CI$]: 0.535–0.750, $P < 0.0001$). The receiver-operating characteristic curves showed that the PDW cutoff value for predicting ISR rate was 13.65 fl with sensitivity of 59.3% and specificity of 72.4% (area under curve [AUC] = 0.701, 95% $CI$: 0.625–0.777, $P < 0.001$). Multivariate analysis showed that the risk of ISR increased approximately 30% when PDW increased one unit (odds ratio [$OR$]: 1.289, 95% $CI$: 1.110–1.498, $P = 0.001$). Patients with higher PDW, defined as more than 13.65 fl, had a 4-fold higher risk of ISR compared with lower PDW ($OR$: 4.241, 95% $CI$: 1.879–9.572, $P = 0.001$). Furthermore, when patients were divided by PDW quartiles values, PDW was able to predict ISR (Q2: $OR = 0.762$, 95% $CI$: 0.189–3.062, $P = 0.762$; Q3: $OR = 2.782$, 95% $CI$: 0.865–8.954, $P = 0.086$; and Q4: $OR = 3.849$, 95% $CI$: 1.225–12.097, $P = 0.021$, respectively; $P$ for trend <0.0001).

**Conclusion:** PDW is an independent predictor of ISR in patients with CAD and T2DM.

**Key words:** Blood Platelet; Coronary Restenosis; Mean Platelet Volume; Percutaneous Coronary Intervention

## INTRODUCTION

In-stent restenosis (ISR) is an important factor for successful percutaneous coronary intervention (PCI). In the bare-metal stent era, the incidence of ISR was 32–55%. This incidence subsequently decreased but remained 5–15% with the increasing use of drug-eluting stents.[1] Platelets play an important role in the course of restenosis and neointimal proliferation.[2] Platelet activation after PCI is persistent

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and is accompanied by morphological changes.[3] Larger platelets tend to be more adhesive and more prone to aggregation.[4] Mean platelet volume (MPV) and platelet distribution width (PDW) are simple platelet parameters that increase during platelet activation. MPV was associated with poor outcome following PCI, including ISR.[5,6] PDW is regarded as a more specific marker of platelet activation, as it does not increase during simple platelet swelling.[7,8] The aim of this study was to evaluate the relationship between PDW and ISR in patients with coronary artery disease (CAD) and type 2 diabetes mellitus (T2DM).

## METHODS

### Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Anzhen Hospital Institutional Ethical Review Board. As a retrospective study and data analysis was performed anonymously, this study was exempt from the informed consent from patients.

### Study population

We screened a total of 5232 patients with CAD and T2DM who underwent PCI for the first time from January 2012 to December 2013. A total of 438 patients who underwent coronary angiography again during 3 years of follow-up were included retrospectively. The inclusion criteria were as follows: age ≥18 years, diagnosis of T2DM, and stents implanted were drug eluting stent (DES). The following patients were excluded: acute ST segment elevation myocardial infarction (STEMI), severe heart dysfunction (left ventricle ejection <30%), end-stage renal dysfunction (evaluated glomerular filtration rate [eGFR] <30%), long-term oral anticoagulation drugs, anemia, and thrombocytopenia below 100,000/μl.

### Diagnostic criteria

Diabetes was diagnosed based on plasma glucose criteria, either fasting plasma glucose, 75-g oral glucose tolerance test, or A1C criteria.[9] ISR was defined as narrowing of a stent >50%, including the original treated site and the adjacent vascular segments 5 mm proximal and 5 mm distal to the stent.[10]

### Main measurements

Blood samples were taken from all patients on admission. The blood samples obtained were kept in standard test tubes containing dipotassium ethylenediaminetetraacetic acid. All samples were analyzed on a Sysmex KX-21N auto-analyzer (Sysmex Corp., Kobe, Japan) within 2 h. All results of coronary angiography were analyzed by two experienced cardiologists and by a third in case of discrepancies.

### Statistical analysis

Continuous data were presented as the mean ± standard deviation (SD), while data not in normal distribution were reported as medians ($P_{25}$, $P_{75}$). Groups of continuous data were compared by Student's *t*-test or one-way analysis of variance (ANOVA). If variables were not in normal distribution, the Kruskal-Wallis *H*-test was performed. Categorical variables were presented as percentages and were compared by Chi-square test or Fisher's exact test if necessary. The association between PDW and MPV was calculated by the Spearman correlation coefficient. Receiver-operating characteristic (ROC) curve analysis was used to evaluate the best cutoff PDW value for predicting ISR. Logistic regression analysis was used to identify risk factors for ISR. Variables with important clinical meaning and unadjusted $P < 0.1$ in univariate analysis were entered in the multivariate model. Stepwise selection multivariate logistic regression analyses were performed. The values of the models for predicting ISR were estimated by concordance index (C-index). All probability values were two-sided, and $P < 0.05$ was considered statistically significant. All analyses were performed with SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

## RESULTS

### Characteristics of patients

Fifty-nine patients with ISR, accounting for 13.5% of all patients, were included. Patients were divided by PDW quartile values (Q1: ≤11.40%, Q2: 11.41–12.80%, Q3: 12.81–14.20%, and Q4: ≥14.21%). The baseline characteristics of patients according to PDW quartiles are displayed in Table 1. Seventy percent of patients were male with a mean age of 59.4 years. All patients took aspirin (300 mg loading lose and 100 mg maintenance dose), clopidogrel (300 mg loading dose and 75 mg maintenance dose), and 70 U/kg intravenous heparin perioperatively unless there was a contraindication. In general, there were no significant differences between subgroups in terms of clinical and measurement data aside from the parameters of renal function and platelets values. As this study showed, patients in the higher quartile of PDW value had higher MPV and lower (but normal) platelet counts (PCs). The group of lower quartile of PDW had lower (but normal) eGFR.

### Procedural characteristics

Procedural characteristics of patients as divided according to PDW values are displayed in Table 2. A transradial approach using 6 or 7 Fr guiding catheters and second-generation DESs was used. The particular type of stent was decided by the operator. No significant differences among quartiles were shown with respect to procedural data. ISR was significantly more frequent in patients with higher PDW quartiles compared with lower quartiles. Incidence of ISR of group Q1–Q4 was 7.1%, 9.3%, 17.4%, and 28.4%, respectively ($\chi^2 = 20.512$, $P < 0.0001$). As shown in Figure 1, we observed that PDW had a strong relationship with MPV ($r = 0.647$, 95% confidence interval [*CI*]: 0.535–0.750, $P < 0.0001$).

### Relationship between platelet distribution width and in-stent restenosis

As shown in Figure 2, ROC curves showed that the PDW cutoff value for predicting ISR rate was 13.65 fl with

## Table 1: Baseline characteristics according to PDW quartiles

| Parameters | Total (*n* = 438) | Q1 (≤11.40) (*n* = 98) | Q2 (11.41–12.80) (*n* = 97) | Q3 (12.81–14.20) (*n* = 92) | Q4 (≥14.21) (*n* = 95) | Statistics | *P*[§] |
|---|---|---|---|---|---|---|---|
| Age (years) | 59.4 ± 9.6 | 60.4 ± 9.6 | 58.7 ± 9.1 | 59 ± 10.2 | 59.2 ± 9.8 | 0.627* | 0.598 |
| Gender (male) | 272 (71.2) | 65 (66.3) | 72 (74.2) | 63 (68.5) | 72 (75.8) | 2.877[†] | 0.411 |
| BMI (kg/m²) | 26.4 ± 3.0 | 26.4 ± 3.0 | 26.3 ± 2.7 | 26.6 ± 3.2 | 26 ± 3.1 | 0.540* | 0.655 |
| Medical history | | | | | | | |
| Hypertension | 264 (69.1) | 63 (64.3) | 71 (73.2) | 71 (77.2) | 59 (62.1) | 6.813[†] | 0.078 |
| Dyslipidemia | 49.5 (189) | 47 (48.0) | 48 (49.5) | 47 (51.1) | 47 (49.5) | 0.186[†] | 0.980 |
| Current smoker | 140 (36.6) | 30 (30.6) | 40 (41.2) | 32 (34.8) | 38 (40.0) | 3.015[†] | 0.389 |
| Family history of CAD | 64 (16.8) | 8 (8.2) | 21 (21.6) | 18 (19.6) | 17 (17.9) | 7.462[†] | 0.059 |
| PAD | 3 (0.8) | 1 (1.0) | 0 | 1 (1.1) | 1 (1.1) | 1.032[†] | 0.794 |
| Prior stroke | 24 (6.3) | 5 (5.1) | 3 (3.1) | 7 (7.6) | 9 (9.5) | 3.826[†] | 0.281 |
| Prior MI | 42 (11.0) | 12 (12.2) | 8 (8.2) | 8 (8.7) | 14 (14.7) | 2.761[†] | 0.430 |
| Prior PCI | 50 (13.1) | 14 (14.3) | 6 (6.2) | 17 (18.5) | 13 (13.7) | 6.566[†] | 0.087 |
| Prior CABG | 5 (1.3) | 2 (2.0) | 1 (1.0) | 0 | 2 (2.1) | 2.140[†] | 0.544 |
| Concomitant medication | | | | | | | |
| Aspirin | 376 (98.4) | 96 (98.0) | 95 (97.9) | 92 (100) | 93 (97.9) | 1.935[†] | 0.586 |
| Clopidogrel | 379 (99.2) | 98 (100.0) | 97 (100.0) | 91 (98.9) | 93 (97.9) | 3.775[†] | 0.287 |
| β-blocker | 288 (75.4) | 73 (74.5) | 71 (73.2) | 69 (75.0) | 75 (78.9) | 0.950[†] | 0.813 |
| ACEI or ARB | 166 (49.0) | 42 (42.8) | 51 (52.6) | 49 (53.2) | 46 (48.4) | 0.102[†] | 0.992 |
| Statin | 360 (94.2) | 93 (94.9) | 94 (96.9) | 88 (95.7) | 85 (89.5) | 3.435[†] | 0.129 |
| CCB | 120 (31.4) | 31 (31.6) | 31 (32.0) | 33 (35.9) | 25 (26.3) | 5.664[†] | 0.570 |
| Hypoglycemic drugs | 237 (60.0) | 52 (53.1) | 61 (62.9) | 60 (65.2) | 64 (67.4) | 4.924[†] | 0.177 |
| Insulin | 82 (21.5) | 23 (23.5) | 20 (20.6) | 16 (17.4) | 23 (24.2) | 1.605[†] | 0.658 |
| Clinical presentation | | | | | | | |
| Stable angina | 70 (18.3) | 22 (22.4) | 19 (19.6) | 14 (15.2) | 15 (15.8) | 2.219[†] | 0.528 |
| Unstable angina | 310 (81.2) | 75 (76.5) | 78 (80.4) | 77 (83.7) | 80 (81.2) | 2.373[†] | 0.499 |
| Examination finding on admission | | | | | | | |
| LVEF (%) | 62 (58, 68) | 60 (58, 66) | 61 (58, 66) | 64 (58, 69) | 64 (59, 69) | 3.517[‡] | 0.319 |
| TG (mmol/L) | 1.7 (1.2, 2.4) | 1.8 (1.2, 2.4) | 1.7 (1.3, 2.4) | 1.6 (1.1, 2.3) | 1.8 (1.3, 2.8) | 2.305[‡] | 0.512 |
| TC (mmol/L) | 4.4 ± 1.1 | 4.4 ± 1.0 | 4.5 ± 1.1 | 4.3 ± 1.1 | 4.5 ± 1.1 | 0.853* | 0.466 |
| LDL-C (mmol/L) | 2.8 ± 0.9 | 2.7 ± 0.9 | 2.8 ± 0.8 | 2.7 ± 0.9 | 2.8 ± 1.0 | 0.521* | 0.668 |
| HDL (mmol/L) | 1.0 (0.8, 1.2) | 1.0 (0.8, 1.2) | 1.0 (0.9, 1.2) | 1.0 (0.9, 1.2) | 0.9 (0.8, 1.1) | 5.546[‡] | 0.136 |
| VLDL (mmol/L) | 0.6 (0.3, 0.8) | 0.5 (0.4, 0.8) | 0.6 (0.4, 0.8) | 0.5 (0.3, 0.7) | 0.6 (0.3, 0.8) | 3.489[‡] | 0.322 |
| HbA1C (mmol/L) | 7.0 (6.4, 7.9) | 7.0 (6.4, 7.8) | 7.1 (6.5, 7.9) | 7.0 (6.2, 7.8) | 7.0 (6.4, 8.0) | 2.846[‡] | 0.416 |
| Creatine (μmol/L) | 76.6 ± 17.5 | 80.1 ± 15.3 | 79.1 ± 20.5 | 75.5 ± 17.4 | 73.8 ± 15.9 | 2.773* | 0.041 |
| eGFR (ml·min⁻¹·1.73 m⁻²) | 97.6 (82.2, 115.5) | 89.8 (76.4, 108.70) | 98.4 (79.5, 114.1) | 98.6 (85.5, 115.6) | 103.0 (88.4, 123.7) | 12.735[‡] | 0.005 |
| Uric acid (μmol/L) | 338.8 (283.5, 115.5) | 346.8 (285.9, 415.5) | 362.8 (298.8, 427.7) | 341.1 (290.0, 406.7) | 335.4 (287.2, 411.3) | 3.797[‡] | 0.284 |
| CRP (mg/L) | 1.7 (0.8, 3.5) | 1.3 (0.8, 3.0) | 1.6 (0.6, 3.7) | 2.0 (0.7, 4.0) | 1.8 (0.9, 3.3) | 2.180[‡] | 0.536 |
| CK-MB (U/L) | 10 (1, 13) | 9.0 (0.5, 12.8) | 9.0 (1.1, 13.0) | 10.5 (1.2, 14.0) | 9.0 (0.9, 13) | 2.601[‡] | 0.457 |
| HGB on admission (g/L) | 140.2 ± 18.8 | 138.1 ± 15.3 | 144.6 ± 15.3 | 141.7 ± 19.5 | 138.6 ± 23.5 | 1.807* | 0.146 |
| Platelet count (×10⁶/L) | 186 (162, 234) | 219 (174, 261) | 205 (177, 250) | 203 (167, 237) | 163 (133, 202) | 44.596[‡] | <0.0001 |
| PCT (%) | 20.0 (16.8, 24.0) | 21.0 (16.0, 25.8) | 21.0 (18.0, 25.0) | 21.0 (18.0, 25.0) | 18.0 (10.5, 21.5) | 29.345* | <0.0001 |
| MPV (fl) | 10.5 (9.8, 11.1) | 9.8 (9.3, 10.0) | 10.5 (10.2, 10.7) | 11.1 (10.9, 11.3) | 11.7 (8.4, 12.1) | 133.662[‡] | <0.0001 |

Data are shown as mean ± SD, median ($P_{25}$, $P_{75}$) or *n* (%). *Analysis of variance, *F* values; [†]Chi-square test, $\chi^2$ values; [‡]Kruskal-Wallis *H*-test, *H* values; [§]*P*: Q1 versus Q2 versus Q3 versus Q4. BMI: Body mass index; CAD: Coronary artery disease; PAD: Peripheral vascular disease; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blocker; CCB: Calcium channel blockers; LVEF: Left ventricular ejection fraction; TG: Triglyceride; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL: High-density lipoprotein; VLDL: Very low-density lipoprotein; eGFR: Evaluated glomerular filtration rate; CRP: C-reactive protein; CK-MB: Creatine kinase-MB; HGB: Hemoglobin; PCT: Plateletcrit; MPV: Mean platelet volume; SD: Standard deviation; HbA1C: Glycated hemoglobin; PDW: Platelet distribution width.

### Table 2: Procedural characteristics according to PDW quartiles

| Parameters | Total (n = 438) | Q1 (≤11.40) (n = 98) | Q2 (11.41–12.80) (n = 97) | Q3 (12.81–14.20) (n = 92) | Q4 (≥14.21) (n = 95) | Statistics | P‡ |
|---|---|---|---|---|---|---|---|
| SYNTAX score | 10 (7, 16) | 10 (7, 15) | 10 (7, 15) | 11 (7, 16) | 11 (7, 17) | 0.783* | 0.853 |
| Number of lesion vessels | 2 (1, 3) | 2 (1, 3) | 2 (1, 3) | 2 (1, 3) | 2 (1, 2) | 2.780* | 0.427 |
| One-vessel disease | 128 (33.5) | 37 (37.8) | 34 (35.1) | 25 (27.2) | 32 (33.7) | 2.555† | 0.465 |
| Two-vessel disease | 142 (37.2) | 34 (34.7) | 30 (30.9) | 37 (40.2) | 41 (43.2) | 3.700† | 0.296 |
| Multivessel disease (≥2) | 112 (66.5) | 27 (62.3) | 33 (64.9) | 30 (72.8) | 22 (66.4) | 3.403† | 0.334 |
| LM | 9 (2.4) | 2 (2.0) | 2 (2.1) | 2 (2.2) | 3 (3.2) | 0.358† | 0.949 |
| LAD | 209 (54.7) | 57 (58.2) | 55 (56.7) | 52 (56.5) | 45 (47.4) | 5.017† | 0.542 |
| LCX | 128 (33.5) | 27 (27.6) | 28 (28.9) | 32 (34.8) | 41 (43.2) | 9.355† | 0.155 |
| RCA | 132 (34.6) | 37 (37.8) | 31 (32.0) | 29 (31.5) | 35 (36.8) | 4.337† | 0.631 |
| CTO | 14 (3.7) | 3 (3.1) | 4 (4.1) | 3 (3.3) | 4 (4.2) | 0.145† | 0.986 |
| Bifurcation | 3 (0.8) | 0 | 0 | 2 (2.2) | 1 (1.1) | 3.907† | 0.272 |
| Number of stents | 2 (1, 3) | 2 (1, 3) | 2 (1, 3) | 2 (1, 2) | 1 (1, 3) | 0.376* | 0.945 |
| Minimum stent diameter, mm | 2.75 (2.5, 3.5) | 2.9 (2.5, 3.5) | 3.0 (2.5, 3.5) | 3.0 (2.5, 3.5) | 3.0 (2.5, 3.5) | 0.733* | 0.865 |
| Mean length of stent, mm | 20.5 (17.5, 26.0) | 20.8 (18.0, 25.7) | 19.2 (16.4, 25.6) | 23.0 (16.5, 28.0) | 20.0 (18, 24.0) | 2.576* | 0.462 |
| ISR | 59 (15.4) | 7 (7.1) | 9 (9.3) | 16 (17.4) | 27 (28.4) | 20.512† | <0.0001 |

Data are shown as $n$ (%) or median ($P_{25}$, $P_{75}$). *Kruskal-Wallis $H$-test, $H$ values; †Chi-square test, $\chi^2$ values; ‡$P$: Q1 versus Q2 versus Q3 versus Q4. SYNTAX score: Synergy between percutaneous coronary intervention with TAXUS and cardiac surgery score; LM: Left main artery; LAD: Left anterior descending coronary artery; LCX: Left anterior descending coronary artery; RCA: Right coronary artery; CTO: Chronic total occlusion; PDW: Platelet distribution width; ISR: In-stent restenosis.
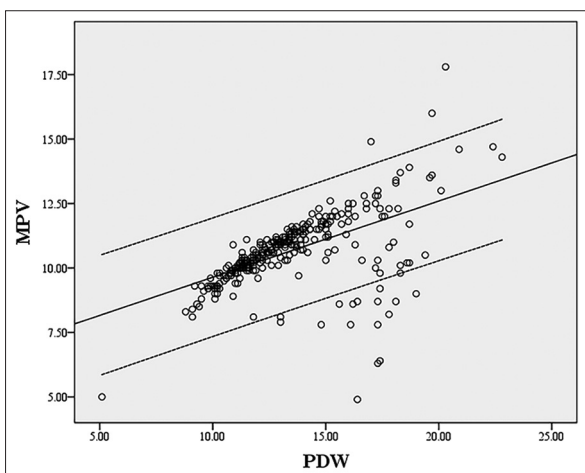


**Figure 1:** Correlation between mean platelet volume and platelet distribution width. $r$ = 0.647, 95% $CI$: 0.535–0.750, $P$ < 0.0001. MPV: Mean platelet volume; PDW: Platelet distribution width; $CI$: Confidence interval.
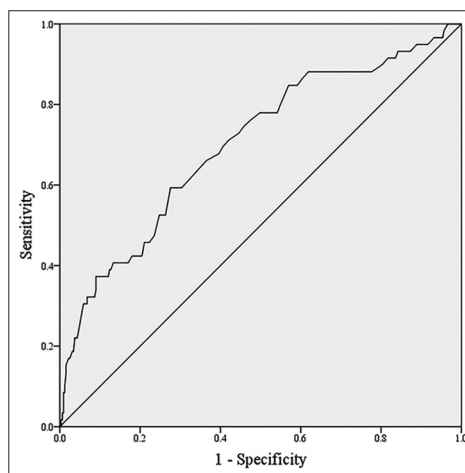


**Figure 2:** Receiver-operating characteristic curve for platelet distribution width for predicting in-stent restenosis. AUC = 0.701, 95% $CI$: 0.625–0.777, $P$ < 0.0001. AUC: Area under curve; $CI$: Confidence interval.

sensitivity of 59.3% and specificity of 72.4% (area under the curve [AUC] = 0.701; 95% $CI$: 0.625–0.777; $P$ < 0.001). We defined high PDW as more than 13.65 fl.

As shown in Table 3, univariate logistic regression analysis demonstrated that variables, such as uric acid, MPV, SYNTAX score, and number of stents, were statistically significant risk factors for ISR in accordance with previous study.[11] To describe the relationship between PDW and ISR, we used three models of PDW, that is, PDW, high PDW, defined as more than 13.65 fl, and PDW quartiles, as variables. As shown in Table 4, the unadjusted odds ratio ($OR$) was 1.335 (95% $CI$: 1.199–1.488, $P$ < 0.0001) for PDW to predict ISR, 3.834 (95% $CI$: 2.160–6.807, $P$ < 0.0001) for high PDW to predict ISR. Compared with Q1, the unadjusted

$OR$ was 1.33 (95% $CI$: 0.475–3.725, $P$ = 0.588 ) for Q2 to predict ISR , 2.737 (95% $CI$: 1.070–6.999, $P$ = 0.036) for Q3 to predict ISR, 5.162 (95% $CI$: 2.122–12.553, $P$ < 0.0001) for Q4 to predict ISR, respectively. On multivariate analysis, variables such as age, sex, body mass index, hypertension, dyslipidemia, prior myocardial infarction, prior PCI, prior stoke, current smoking, aspirin use, clopidogrel use, statin use, eGFR, glycated hemoglobin, C-reactive protein, PC, plateletcrit, MPV on admission, SYNTAX score, mean stent length, and number of stents were entered into stepwise logistic regression models. Multivariate analysis revealed that the risk of ISR increased approximately 30% when PDW increased one unit ($OR$: 1.289, 95% $CI$: 1.110–1.498, $P$ = 0.001). Patients with higher PDW, defined as more than

13.65 fl, had a 4-fold higher risk of ISR compared with lower PDW ($OR$: 4.241, 95% $CI$: 1.879–9.572, $P$ = 0.001). Furthermore, when patients were divided by PDW quartiles, PDW had a great value of predicting ISR (Q2: $OR$ = 0.762, 95% $CI$: 0.189–3.062, $P$ = 0.762; Q3: $OR$ = 2.782, 95% $CI$: 0.865–8.954, $P$ = 0.086; and Q4: $OR$ = 3.849, 95% $CI$: 1.225–12.097, $P$ =0.021, respectively;  $P$ for trend <0.0001). To evaluate the prognostic power of multivariate model as shown in Table 3, the concordance (C) index was calculated (C-index for PDW: 0.731, 95% $CI$: 0.642–0.819, $P$ < 0.0001; C-index for high PDW: 0.692, 95% $CI$: 0.610–0.773, $P$ < 0.0001; and C-index for PDW quartiles: 0.690, 95% $CI$: 0.608–0.773, $P$ < 0.0001, respectively).

## Table 3: Univariate logistic regression analysis of predictors for ISR

| Variable | OR (95% CI) | Wald $\chi^2$ | P |
|---|---|---|---|
| Age | 0.990 (0.962–1.018) | 0.521 | 0.471 |
| Current smoking | 0.628 (0.341–1.157) | 2.229 | 0.135 |
| Hypertension | 0.797 (0.445–1.428) | 0.580 | 0.447 |
| Dyslipidemia | 0.645 (0.375–1.141) | 2.233 | 0.135 |
| Prior MI | 0.933 (0.378–2.305) | 0.022 | 0.881 |
| Prior PCI | 1.477 (0.700–3.117) | 1.049 | 0.306 |
| Aspirin | 0.933 (0.110–7.890) | 0.004 | 0.949 |
| Clopidogrel | 0.151 (0.021–1.095) | 3.498 | 0.061 |
| Statin | 0.930 (0.311–2.781) | 0.017 | 0.896 |
| LDL-C | 0.861 (0.629–1.178) | 0.872 | 0.350 |
| Creatine | 0.998 (0.982–1.014) | 0.077 | 0.782 |
| eGFR | 1.000 (0.998–1.001) | 0.077 | 0.782 |
| HbA1C | 1.057 (0.858–1.303) | 0.270 | 0.604 |
| Uric acid | 0.997 (0.995–1.000) | 4.359 | 0.037 |
| CRP | 0.991 (0.930–1.058) | 0.068 | 0.795 |
| Platelet | 0.998 (0.992–1.003) | 0.767 | 0.381 |
| PCT | 0.903 (0.002–39.254) | 0.001 | 0.974 |
| MPV | 1.267 (1.037–1.548) | 5.373 | 0.020 |
| Syntax score | 1.043 (1.004–1.083) | 4.672 | 0.031 |
| Mean stent length | 1.011 (0.981–1.043) | 0.536 | 0.464 |
| Mean stent diameter | 0.605 (0.300–2.128) | 0.238 | 0.686 |
| Number of stents | 1.411 (1.152–1.729) | 11.047 | 0.001 |

MI: Myocardial infarction; PCI: Percutaneous coronary intervention; LDL-C: Low-density lipoprotein cholesterol; eGFR: Evaluated glomerular filtration rate; CRP: C-reactive protein; PCT: Plateletcrit; MPV: Mean platelet volume; SYNTAX score: Synergy between percutaneous coronary intervention with TAXUS and cardiac surgery score; $CI$: Confidence interval; HbA1C: Glycated hemoglobin; $OR$: Odds ratio; ISR: In-stent restenosis.

## DISCUSSION

We observed that PDW is an independent risk factor for ISR in patients with CAD and T2DM. Another study showed that ISR was an independent risk factor for mortality.[12]

Vascular endothelium suffers mechanical damage post-PCI, which induces such overreactions as plaque rupture, and platelet and leukocyte activation. This effect can induce the release of inflammatory mediators and chemical chemokines and can increase the risk of ISR and cardiovascular events post-PCI.[13] Platelet activation is caused by the release of inflammatory mediators from α particles, which induces smooth muscle cell proliferation and spread, as well as vascular spasm. Fibrin and platelets play important roles in the process of ISR post-PCI.[14] Fuster *et al*.[15] demonstrated mural thrombi in vascular walls postoperatively, promoting the occurrence of ISR.

During activation, platelets reorganize their cytoskeleton and change shape through a process of metamorphosis.[16] *In vitro*, larger platelets are more rapidly aggregated compared with small platelets induced by ADP, collagen, and adrenaline. These platelets produce more prothrombotic and vasoactive factors (e.g., thromboxane A2, serotonin, ATP, and dense granules). Large platelets express higher levels of adhesion molecules (e.g., P-selectin, GpIIb/IIIa).[17] The major factor influencing platelet-dependent hemostatic function in healthy people is platelet mass (PM), which is the product of PC × platelet volume (MPV). The two parameters had an inverse curvilinear relationship, and PM remained stable.[18] However, the relationship could be disrupted in disease states.

MPV and PDW are well-known morphological parameters in platelets. It has been shown that there was a strong relationship between MPV and prognosis post-PCI with a higher 6-month mortality rate in patients with higher MPV (12.1% vs. 5.1%, $P$ = 0.0125).[5]

Recent studies observed that PDW may be considered to be a more specific marker than MPV, enabling early and easy identification of patients with poor prognosis. Studies suggested that PDW had an association with the severity of coronary disease. Vatankulu *et al*.[19] showed that the cutoff PDW value for identifying patients with CTO was 15.7% with a sensitivity of 64.0% and a specificity of

## Table 4: Prognostic significance of PDW of predicting ISR

| Model | OR (95% CI) | Wald $\chi^2$ | P | Adjusted OR (95% CI) | Wald $\chi^2$ | P |
|---|---|---|---|---|---|---|
| Total | 1.335 (1.199–1.488) | 27.615 | <0.0001 | 1.289 (1.110–1.498) | 11.002 | 0.001 |
| High PDW | 3.834 (2.160–6.807) | 21.065 | <0.0001 | 4.241 (1.879–9.572) | 20.516 | 0.001 |
| Q1 (≤11.40)* | 1.00 (reference) | | | 1.00 (reference) | | |
| Q2 (11.41–12.80) | 1.33 (0.475–3.725) | 0.294 | 0.588 | 0.762 (0.189–3.062) | 0.147 | 0.762 |
| Q3 (12.81–14.20) | 2.737 (1.070–6.999) | 4.417 | 0.036 | 2.782 (0.865–8.954) | 2.945 | 0.086 |
| Q4 (≥14.21) | 5.162 (2.122–12.553) | 13.103 | <0.0001 | 3.849 (1.225–12.097) | 19.231 | 0.021 |

High PDW defined as more than 13.65 fl calculated by this study. *$P$ for trend <0.0001; C-index for total: 0.731, 95% $CI$: 0.642–0.819, $P$<0.0001; C-index for high PDW: 0.692, 95% $CI$: 0.610–0.773, $P$<0.0001; C-index for PDW quartiles: 0.690, 95% $CI$: 0.608–0.773, $P$<0.0001. PDW: Platelet distribution width; $CI$: Confidence interval; $OR$: Odds ratio; ISR: In-stent restenosis.

66% (AUC = 0.64, 95%$CI$: 0.54–0.75). Akin et al.[20] showed that PDW was positively associated with SYNTAX score ($r$ = 0.209, $P$ < 0.001) in patients with STEMI who underwent primary PCI, and PDW was an independent risk factor for high SYNTAX score ($OR$ = 1.229, 95% $CI$: 1.072–1409, $P$ = 0.003).

In addition, it was demonstrated that PDW had a strong association with major adverse cardiac event in patients undergoing PCI. Ulucan et al.[21] showed that preprocedural PDW was an independent predictor of both in-hospital and long-term adverse outcomes in patients with ACS ($OR$ = 1.081, 95% $CI$: 1.003–1.165, $P$ = 0.0001). Cetin et al.[22] observed that PDW was significantly higher in the thrombolysis failure group than that in the success group (17.7 ± 1.0 vs. 16.4 ± 2.1 fl, $P$ < 0.001) in patients with STEMI. PDW was an independent predictor of thrombolysis failure.

According to recent studies, monitoring and personalizing antiplatelet therapy failed to improve the prognosis of patients with PCI. This failure could be explained by neither the risk level of the population nor the type of P2Y12 antagonist.[23,24] Given the complexity of the pathophysiology of thrombosis, it might be wise to integrate platelet function tests, platelet morphological examination, and MDR1 or CYP2C19*2 genetic tests to guide antithrombotic therapy to eliminate the risk of ISR. Of course, we need further larger studies to demonstrate the relationship between PDW and ISR and the benefits of PDW-guiding antithrombotic therapy.

There were several limitations in this study. First, this study was a retrospective study with single-center design. Second, the study might underestimate the incidence rate because only patients undergoing second coronary angiography were included. Third, we did not consider other platelet volume indices, such as platelet large cell ratio, which has been shown to be linked with platelet functional and perioperative anticoagulant therapy, possibly affecting the outcome.

In conclusion, PDW is an independent predictor of ISR in patients with CAD and PCI.

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### Conflicts of interest

There are no conflicts of interest.

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# 冠心病合并2型糖尿病患者经皮冠脉支架术后血小板分布宽度与支架内再狭窄的关系

## 摘要

**背景：** 既往研究表明血小板分布宽度（PDW）与冠心病（CAD）患者预后关系密切。但PDW预测支架内再狭窄（ISR）的价值尚未得到充分研究。本研究目的在于探讨PDW与CAD合并2型糖尿病（T2DM）患者经皮冠脉介入支架术（PCI）后支架内再狭窄的关系。

**方法：** 收集2012年1月至2013年12月于中国北京安贞医院住院的冠心病合并2型糖尿病并于我院行经皮冠脉介入支架术的5232名患者。回顾分析入选患者其后3年我院的就诊资料，最终438名再次于我院行经皮冠脉造影的患者纳入本研究。支架内再狭窄定义为造影发现支架内及支架旁5mm内不少于50%管腔丢失。采用SPSS22.0统计软件进行数据处理。符合正态分布的计量资料采用平均值±标准差描述，组间比较采用单因素方差分析；不符合正态分布的计量资料采用中位数（$P_{25}$，$P_{75}$）描述，组间比较采用非参数检验；计数资料组间比较采用$\chi^2$检验。受试者工作特征曲线(ROC)分析预测ISR事件最佳的PDW值，并作为高PDW的定义标准。将对PDW以及ISR具有明显影响和单因素分析中$P$值＜0.1的变量放入Logistic回归模型，以向后逐步选择法作为自变量筛选方法，研究分析PDW与ISR的关系。双侧$P<0.05$为差异有统计学意义。

**结果：** 438名患者中59名（13.5%）发生ISR。患者基线资料通过PDW四分位分组比较发现PDW高四分位组患者ISR发生风险显著高于低四分位组。线性相关分析发现PDW与ISR密切相关( $r$=0.647, 95%置信区间［$CI$］：0.535-0.750, $P<0.0001$)。ROC曲线显示PDW以13.65fl预测ISR的敏感度以及特异度分别为59.3%、72.4%（曲线下面积［AUC］= 0.701, 95% $CI$：0.625-0.777, $P<0.001$）。 多因素分析发现PDW每升高1个单位，ISR发生风险增加约30%(比值比 ［$OR$]:1.289, 95% $CI$: 1.110-1.498, $P$=0.001)，高PDW（定义为PDW≥13.65fl）患者ISR发生风险是低PDW的4倍($OR$:4.241, 95% $CI$: 1.879-9.572, $P$=0.001)。将PDW四分位分组后变量放入Logistic回归，分析发现ISR风险随四分位PDW组升高而逐渐升高（Q2: $OR$=0.762, 95%$CI$ 0.189-3.062, $P$=0.762，Q3:$OR$=2.782, 95%$CI$ 0.865-8.954, $P$=0.086, Q4: $OR$=3.849, 95%$CI$ 1.225-12.097, $P$ =0.021; $P$ for trend＜0.0001）。

**结论：** PDW是冠心病合并2型糖尿病患者PCI术后ISR的独立危险因素。