

# Mean Platelet Volume as a Predictor of One-Year Major Adverse Cardiac Events following Elective Percutaneous Coronary Interventions

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## Abstract

**Background:** Mean platelet volume (MPV) correlates with platelet activity. The relation between MPV and long-term outcome in patients undergoing percutaneous coronary intervention (PCI) has been investigated in several studies. The aim of the present study was to investigate the utility of MPV in prognosticating the long-term outcome after elective PCI.

**Methods:** The study cohort included 2627 patients undergoing elective PCI between September 2008 and June 2010, whose baseline MPV measurements before PCI were available. The patients were divided into three groups of MPV < 9.1 fL, MPV = 9.1 to 10 fL, and MPV > 10 fL, and they were assessed for developing major adverse cardiac events (MACE), comprising death, myocardial infarction (MI), target vessel revascularization (TVR), and target lesion revascularization (TLR) over a one-year follow-up.

**Results:** Of 2539 patients, major adverse cardiac events (MACE) at one year occurred in 77 (3.0%) patients, including mortality in 26 (1.0%). The patients in the highest tertile (MPV > 10 fL) had no increased frequency of MACE compared to those in the mid (9.1 to 10 fL) and lowest (< 9.1 fL) tertiles (3.3%, 2.2%, and 3.8%, respectively; *p* value = 0.14).

No significant differences were found for each of the primary endpoints among the MPV tertiles. In multivariate logistic regression, we investigated the association between high MPV and total MACE (OR = 1.10, 95%CI: 0.69-1.77; *p* value = 0.68), death (OR = 1.14, 95%CI: 0.51-2.54; *p* value = 0.74), and non-fatal MI (OR = 1.85, 95%CI: 0.73-4.67; *p* value = 0.19) at one year's follow-up but MPV did not remain in the model in any of the cases.

In the diabetic patients, the one-way analysis of variance demonstrated that mortality was 1.6% (4 patients) in the highest tertile, 0.8% (2 patients) in the mid tertile, and 0.5% (one patient) in the lowest tertile.

**Conclusion:** There was no direct correlation between pre-procedural MPV and MACE in elective PCI. MPV can only be considered as an appropriate factor for predicting mortality in diabetic patients undergoing elective PCI.

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**Keywords:** Coronary artery disease • Angioplasty • Mean platelet volume • Treatment outcome

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## Introduction

Platelets play a pivotal role in the development of atherosclerotic lesions, plaque destabilization, and atherothrombosis.<sup>1</sup> Antiplatelet therapy reduces both procedural-related complications and subsequent ischemic cardiovascular events after coronary revascularization.<sup>2,3</sup> However, despite targeted therapy,  $\leq 1/4$  of patients after percutaneous coronary intervention (PCI) demonstrate high platelet activity and a greater rate of major adverse cardiovascular events (MACE) compared to patients without high platelet activity.<sup>4,5</sup> The methods of testing platelet activity can be time-consuming, expensive, and technically difficult.<sup>6</sup> Unlike more expensive or time-consuming methods of assessing platelet function,<sup>6</sup> the determination of platelet size by quantification of mean platelet volume (MPV), using automated hemograms, is simple and inexpensive.<sup>7</sup> The biologic rationale linking MPV to clinical outcomes, along with its universal availability, has made it a promising indirect marker of platelet reactivity in the PCI setting.

MPV is a marker of platelet size and activity and a predictor of cardiovascular risk.<sup>8</sup> It is quantified on automated hemograms routinely measured before coronary revascularization. In the setting of PCI, increased mortality due to a rise in MPV during the postoperative period has been reported.<sup>9</sup> Large platelets have enhanced reactivity compared with normal-sized platelets.<sup>10,11</sup> MPV has been associated with clinical and angiographic outcomes. Patients with a high MPV before balloon angioplasty have been more likely to develop restenosis.<sup>12</sup> In patients undergoing primary PCI, a high MPV has been associated with impaired angiographic reperfusion and increased 6-month mortality.<sup>13</sup>

We sought to evaluate the effect of the pre-procedural MPV level on the long-term clinical outcome in patients undergoing elective PCI.

## Methods

The present analysis was a historical cohort within the Tehran Heart Center PCI Registry. The study cohort included consecutive patients undergoing PCI between September 2008 and June 2010. Totally, 2627 patients were identified retrospectively from the registry and then followed up prospectively for a one-year period. The patients were included if a baseline MPV measurement for up to two weeks before PCI was available. The exclusion criteria comprised chronic renal failure, hyperthyroidism, myeloproliferative diseases, and PCI failure (Figure 1).

In the event that the patients required more than one PCI during the study period, the entry date was recorded as the date of the index procedure. The study complied with the Declaration of Helsinki, and the institutional Human Research Ethics Review Board approved the study. All the

patients received 325 mg of ASA and at least 300 mg of Plavix before PCI and received 100 IU/kg of unfractionated Heparin. After PCI, the patients received 75 mg/d of Plavix. Additionally, the patients without allergy or increased risk of bleeding were administered 325 mg of Aspirin daily for at least one month after bare-metal stent implantation, 3 months after Sirolimus-eluting stent implantation, and 6 months after Paclitaxel-eluting stent implantation, after which daily long-term Aspirin (80 mg) was continued.

The end point of the study was MACE, comprising death, myocardial infarction (MI), target vessel revascularization (TVR), and target lesion revascularization (TLR) during the follow-up. MI was defined as a clinical episode of chest pain with an increase in serum cardiac enzyme greater than the upper normal limit with or without electrocardiographic (ECG) change. TVR and TLR were defined as subsequent PCI to the same vessel or lesion as the index PCI.

EDTA blood samples drawn at admission were analyzed in an automated hematology analysis system (SysmexKX21Autoanalyzer, Sysmex Europe GmbH, Norderstedt, Germany), which measures the platelet size using aperture-impedance technology. Daily quality controls showed an intra-assay coefficient of variation of 2.5% and an intra-assay coefficient of variation of 3.0%.

All the samples were processed within 2 hours after vein punctures, as is recommended in the literature,<sup>14</sup> to avoid bias due to excessive platelet swelling. The range of the expected values for MPV in our laboratory is 7 to 13 fL. According to the baseline MPV, the patients were divided into three groups: first tertile (MPV < 9.1 fL); second tertile (MPV = 9.1 to 10 fL); and third tertile (MPV > 10 fL).

The normally and non-normally distributed continuous variables were analyzed using the non-parametric Kolmogorov-Smirnov test. The analyses were done using the chi-squared test for the categorical data and the one-way analysis of variance for the continuous data and the Tukey post-hoc test. A *p* value < 0.05 was considered statistically significant. The association between the variables was assessed via the Pearson correlation coefficient. The multivariate logistic regression was performed to calculate the odds ratio (OR). The statistical analyses were conducted using the Statistical Package for Social Sciences, version 18.0 (SPSS, Chicago, Illinois).

## Results

During the study period, 2627 patients underwent elective PCI. The study population was comprised of 1840 (70%) men and 787 (30%) women, at a mean age of  $58 \pm 10.5$  years. Of the total study population, 508 (19.3%) patients had three-vessel involvement and only one (0.04%) patient had left main coronary artery disease. The procedure was unsuccessful in 84 (3.2%) patients, 3 (0.1%) patients died

during hospitalization, and only one (0.03%) patient referred for emergent coronary artery bypass grafting surgery (CABG).

The patients were grouped according to the baseline MPV tertile: the first tertile, MPV < 9.1 fL (n = 773); second tertile, MPV = 9.1 to 10 fL (n = 882); and third tertile, MPV > 10 fL (n = 884). The baseline demographics of the study population stratified into the MPV tertiles are listed in Table 1. Expected inverse association between platelet count and MPV was seen (Pearson correlation factor = - 0.32; p value < 0.001). Furthermore, diabetes mellitus, previous history of MI, and cigarette smoking were seen more frequently in the patients with the highest tertile of MPV.

At one year's follow-up (follow-up rate = 96.5%), MACE was detected in 77 patients (3.0%), including mortality in 26 (1.0%). The frequencies of MACE stratified into the MPV tertiles are listed in Table 2. No significant differences were found for each of the primary endpoints between the MPV tertiles. Only a trend was seen for the patients with the highest and lowest tertiles to be more prone to develop mortality during the first year after the PCI procedure. In addition, as is shown in Table 3, the mean value of MPV and other platelet indices in the patients with MACE in comparison with the same values in the other patients did not significantly differ.

There were statistically significant differences between the MPV tertiles in the prevalence of diabetes, smoking,

Table 1. Baseline characteristics according to the mean platelet volume (MPV) tertile\*

Characteristics	Total (n=2539)	Tertile			P value
		Lower (n=773)	Mid (n=882)	Upper (n=884)	
Age (y)	58.02±10.55	57.71±10.49	57.88±10.51	58.42±10.65	0.312
Male gender	1773 (69.8)	547 (70.8)	603 (68.4)	623 (70.5)	0.499
Diabetes Mellitus	698 (27.5)	182 (23.5)	266 (30.2)	250 (28.3)	0.009
Current smoker	719 (28.3)	192 (24.8)	258 (29.3)	269 (30.4)	0.031
Hypertension	1272 (50.1)	358 (46.3)	441 (50.0)	473 (53.5)	0.014
Dyslipidemia	1712 (67.4)	525 (67.9)	602 (68.3)	585 (66.2)	0.610
Positive family history	507 (20.0)	157 (20.3)	173 (19.6)	177 (20.0)	0.938
Previous Aspirin usage	2488 (98.0)	758 (98.1)	861 (97.6)	869 (98.3)	0.584
Previous myocardial infarction	1295 (49.6)	354 (45.8)	429 (48.6)	476 (53.8)	0.004
Platelet count (10 <sup>9</sup> /L)	226.30±63.29	249.55±65.61	228.70±57.04	203.58±59.23	< 0.001
Hemoglobin (mg/dL)	13.98±1.74	13.86±1.68	13.95±1.73	14.12±1.79	0.014
Creatinine (mg/dL)	1.06±0.41	1.06±0.33	1.08±0.55	1.06±0.31	0.534

\*Data are presented as mean±SD or n (%)

Table 2. Major adverse cardiac events at one year's follow-up according to mean platelet volume (MPV) tertiles\*

MACE	Total (n=2539)	Tertile			P value
		Lower (n=773)	Mid (n=882)	Upper (n=884)	
Mortality	26 (1.0)	12 (1.6)	4 (0.5)	10 (1.1)	0.080
TVR	42 (1.7)	15 (1.9)	13 (1.5)	14 (1.6)	0.744
TLR	15 (0.6)	5 (0.6)	4 (0.5)	6 (0.7)	0.802
Non-fatal MI	18 (0.7)	7 (0.9)	2 (0.2)	9 (1.0)	0.103
CABG	21 (0.8)	6 (0.8)	9 (1.0)	6 (0.7)	0.718
Total	77 (3.0)	29 (3.8)	19 (2.2)	29 (3.3)	0.145

\*Data are presented as n (%)

MACE, Major adverse cardiac events; TVR, Target vessel revascularization; TLR, Target lesion revascularization; MI, Myocardial infarction; CABG, Coronary artery bypass graft surgery

Table 3. Platelet indices in the MACE group compared with no-MACE group\*

Platelet Indices	Total (n=2539)	MACE (n=77)	No MACE (n=2462)	P value
Platelet count (10 <sup>9</sup> /L)	226.30±63.29	230.42±56.83	226.17±63.49	0.562
MPV (fL)	9.61±0.98	9.56±0.97	9.60±0.99	0.679
PDW (%)	12.57±2.01	12.49±2.00	12.57±2.01	0.727
PLCR (%)	23.33±7.27	23.03±7.17	23.33±7.28	0.719

\*Data are presented as mean±SD or n (%)

MACE, Major adverse cardiac events; MPV, Mean platelet volume; PDW, Platelet distribution width; PLCR, Platelet large cell ratio

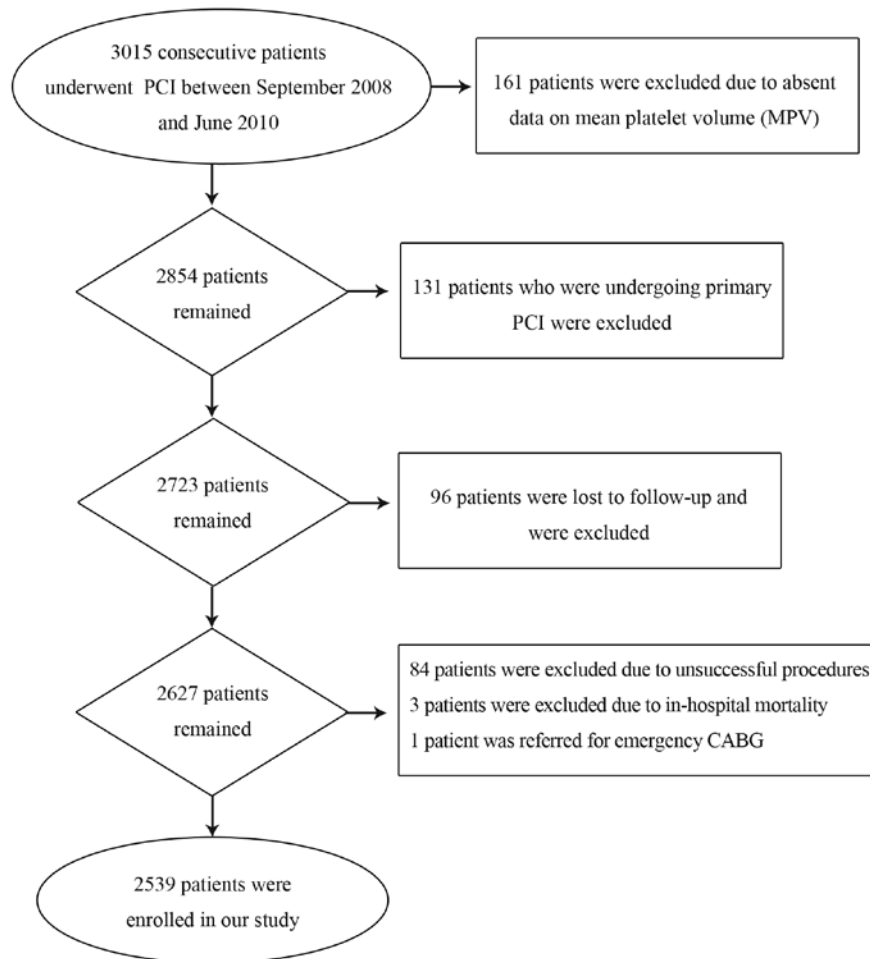


Figure 1. Patient selection and study design  
PCI, Percutaneous coronary intervention; CABG, Coronary artery bypass graft surgery

hypertension, and history of previous MI; accordingly, we tried to adjust the covariates by logistic regression analysis. In the multivariate logistic regression, we investigated the association between high MPV and total MACE (OR = 1.10, 95%CI: 0.69-1.77;  $p$  value = 0.68), death (OR = 1.14, 95%CI: 0.51-2.54;  $p$  value = 0.74), non-fatal MI (OR = 1.85, 95%CI: 0.73-4.67;  $p$  value = 0.19) at one year's follow-up, but MPV did not remain in the model in any of the cases. We also imported platelet counts in the multivariate logistic regression model to investigate its association with mortality (OR = 1.38, 95%CI: 0.62-3.08;  $p$  value = 0.43), non-fatal MI (OR = 1.21, 95%CI: 0.45-3.25;  $p$  value = 0.71), and total MACE (OR = 1.16, 95%CI: 0.71-1.89;  $p$  value = 0.55), but it did not remain in the model even when MPV was not included in the model.

We also performed several subgroup analyses among the study population. In the diabetic patients, the one-way analysis of variance demonstrated that mortality was 1.6% (4 patients) in the highest tertile, 0.8% (2 patients) in the mid tertile, and 0.5% (one patient) in the lowest tertile.

## Discussion

The results of the present study demonstrated no association between elevated MPV and the one-year incidence of death, MI, and the other MACE in a large, unselected cohort of patients undergoing elective PCI. A high MPV has been previously observed in patients with a history of smoking, diabetes mellitus, and acute coronary syndrome.<sup>15-17</sup> Among patients with acute MI, high MPV values 6 months after infarction have been associated with increased subsequent ischemic events at 2 years.<sup>18</sup> In patients undergoing PCI, the pre-procedural MPV has been demonstrated to correlate with restenosis at 6 months.<sup>12</sup> The admission MPV has also been demonstrated to be an independent predictor of impaired angiographic reperfusion and 6-month mortality after MI treated with primary PCI.<sup>13</sup> Previously, the platelet count was linked to mortality after acute coronary syndrome.<sup>19, 20</sup> The platelet count has also been shown to be inversely related to MPV.<sup>7</sup> The association between MPV and clinical outcomes in our study does not chime in with previous

findings supporting an independent role for larger platelets in adverse outcomes after PCI. After adjustment for multiple covariates, we still observed no significant association between an elevated MPV and subsequent death and other primary endpoints at one year's follow-up. The admission platelet count inversely associated with the value of MPV but did not demonstrate an independent predictive value for the clinical outcomes in the multivariate analysis even when MPV was not included in the model.

In concordance with our study, in a recent study conducted by B. Shah et al.,<sup>9</sup> MPV was not associated with long-term mortality in patients undergoing elective PCI. The rationale for this lack of association might reflect the difference in patient populations or low MACE rates. In addition, most of the previous studies include patients with acute coronary syndrome or ST-elevation myocardial infarction (STEMI), in which inflammation and unstable plaques play a major role. In elective PCI, however, theoretically there is no inflammation and, accordingly, MPV does not play a significant role. The variability in the preparation of blood samples and role of EDTA in the fluctuation of the MPV size could potentially be a contributory factor.

Diabetes is a significant risk factor for adverse events after PCI.<sup>21</sup> Patients with diabetes have enhanced platelet activation with a greater MPV than do those without diabetes.<sup>16</sup> It has previously been demonstrated that an increase in MPV is independent of glycemic control or the duration of diabetes.<sup>22</sup> In our study, the diabetics with a high MPV had a trend toward a higher rate of MACE. Nevertheless, the low number of such cases rendered this difference statistically non-significant. Additional studies are required to elucidate whether or not high MPV in diabetic patients could be predictive of MACE.

## Conclusion

MPV measurement is a simple and inexpensive test and is routinely measured by automated cell counters. Many studies have identified MPV as a predictor of long-term outcome and mortality in patients undergoing coronary intervention. In our study, there was no direct correlation between MPV and MACE in elective PCI. However, MPV could be regarded as an appropriate factor for predicting mortality in diabetic patients undergoing elective PCI. Further studies are needed to prove these findings.

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## References

1. Davi G, Patrono C. Platelet activation and atherothrombosis. *N Engl J Med* 2007;357:2482-2494.
2. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA; Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;358:527-533.
3. Steinhubl SR, Berger PB, Mann JT, 3rd, Fry ET, DeLago A, Wilmer C, Topol EJ; CREDO Investigators. Clopidogrel for the reduction of events during observation. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;288:2411-2420.
4. Eikelboom JW, Hirsh J, Weitz JI, Johnston M, Yi Q, Yusuf S. Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. *Circulation* 2002;105:1650-1655.
5. Bonello L, Pansieri M, Mancini J, Bonello R, Maillard L, Barnay P, Rossi P, Ait-Mokhtar O, Jouve B, Collet F, Peyre JP, Wittenberg O, de Labriolle A, Camilleri E, Cheneau E, Cabassome E, Dignat-George F, Camoin-Jau L, Paganelli F. High on-treatment platelet reactivity after prasugrel loading dose and cardiovascular events after percutaneous coronary intervention in acute coronary syndromes. *J Am Coll Cardiol* 2011;58:467-473.
6. Michelson AD. Methods for the measurement of platelet function. *Am J Cardiol* 2009;103:20A-26A.
7. Boos CJ, Lip GY. Assessment of mean platelet volume in coronary artery disease - what does it mean? *Thromb Res* 2007;120:11-13.
8. Chu SG, Becker RC, Berger PB, Bhatt DL, Eikelboom JW, Konkle B, Mohler ER, Reilly MP, Berger JS. Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis. *J Thromb Haemost* 2010;8:148-156.
9. Shah B, Oberweis B, Tummala L, Amoroso NS, Lobach I, Sedlis SP, Grossi E, Berger JS. Mean platelet volume and long-term mortality in patients undergoing percutaneous coronary intervention. *Am J Cardiol* 2013 ;111:185-189.
10. Kamath S, Blann AD, Lip GY. Platelet activation: assessment and quantification. *Eur Heart J* 2001;22:1561-1571.
11. Endler G, Klimesch A, Sunder-Plassmann H, Schillinger M, Exner M, Mannhalter C, Jordanova N, Christ G, Thalhammer R, Huber K, Sunder-Plassmann R. Mean platelet volume is an independent risk factor for myocardial infarction but not for coronary artery disease. *Br J Haematol* 2002;117:399-404.
12. Yang A, Pizzulli L, Lüderitz B. Mean platelet volume as marker of restenosis after percutaneous transluminal coronary angioplasty inpatients with stable and unstable angina pectoris. *Thromb Res* 2006;117:371-377.
13. Huczek Z, Kochman J, Filipiak KJ, Horszczaruk GJ, Grabowski M, Piatkowski R, Wilczynska J, Zielinski A, Meier B, Opolski G. Mean platelet volume on admission predicts impaired reperfusion and long-term mortality in acute myocardial infarction treated with primary percutaneous coronary intervention. *J Am Coll Cardiol* 2005;46:284-290.
14. Smyth DW, Martin JF, Michalis L, Bucknall CA, Jewitt DE. Influence of platelet size before coronary angioplasty on subsequent restenosis. *Eur J Clin Invest* 1993;23:361-367.
15. Kario K, Matsuo T, Nakao K. Cigarette smoking increases the mean platelet volume in elderly patients with risk factors for atherosclerosis. *Clin Lab Haematol* 1992;14:281-287.
16. Papanas N, Symeonidis G, Maltezos E, Mavridis G, Karavageli E, Vosnakidis T, Lakasas G. Mean platelet volume in patients with type 2 diabetes mellitus. *Platelets* 2004;15:475-478.
17. Pizzulli L, Yang A, Martin JF, Lüderitz B. Changes in platelet size and count in unstable angina compared to stable angina or non-



- cardiac chest pain. *Eur Heart J* 1998;19:80-84.
18. Martin JF, Bath PM, Burr ML. Influence of platelet size on outcome after myocardial infarction. *Lancet* 1991;338:1409-1411.
  19. Mueller C, Neumann FJ, Hochholzer W, Trenk D, Zeller T, Perruchoud AP, Buettner HJ. The impact of platelet count on mortality in unstable angina/non-ST-segment elevation myocardial infarction. *Am Heart J* 2006;151:1214.e1-7.
  20. Sjaauw KD, van der Horst IC, Nijsten MW, Nieuwland W, Zijlstra F. Value of routine admission laboratory tests to predict thirty-day mortality in patients with acute myocardial infarction. *Am J Cardiol* 2006;97:1435-1440.
  21. Champney KP, Veledar E, Klein M, Samady H, Anderson D, Parashar S, Wenger N, Vaccarino V. Sex-specific effects of diabetes on adverse outcomes after percutaneous coronary intervention: trends over time. *Am Heart J* 2007;153:970-978.
  22. Hekimsoy Z, Payzin B, Ornek T, Kandoğan G. Mean platelet volume in Type 2 diabetic patients. *J Diabetes Complications* 2004;18:173-176.