Prognostic effect of mean platelet volume in patients with coronary artery disease

A systematic review and meta-analysis

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Summary

Large platelets with high haemostatic activity may lead to increased platelet aggregation.. Mean platelet volume (MPV), an indicator of platelet reactivity, may emerge as a prognostic marker in patients with coronary artery disease (CAD). It was the objective of this study to conduct a systematic review and meta-analysis to assess prognostic effects of MPV on cardiovascular events (CVE) in CAD patients. We searched MEDLINE and SCOPUS from inception to January 2, 2014. All studies that reported MPV and the incidence of cardiovascular events in CAD patients were included. Two reviewers independently extracted the data. A random-effects model was applied for pooling the mean difference of MPV between patients with vs without CVE. Among 30 eligible studies, eight studies reported mean difference of MPV between CVE groups, 11 studies reported MPV dichotomous into high vs low MPV groups, and 11 studies reported both. The pooled mean difference was 0.69 fL (95 %CI = 0.36, 1.01), i. e. patients with CVE had a MPV about 0.69 fL higher than non-CVE. Patients with higher MPV were about 12 % more likely to die than patients with lower MPV (RR 1.12; 95 %CI = 1.02–1.24). However, pooling these effects was based on high heterogeneity and the source of heterogeneity could not be identified. This might be explained by many differences among included studies (e. g. study population, outcomes of interest, analysate, time between blood collection and MPV analysis, etc). These findings suggest that MPV may be a useful prognostic marker in patients with CAD.

Keywords

Mean platelet volume, coronary artery disease, cardiovascular diseases, prognosis, meta-analysis

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Introduction

Patients with coronary artery disease (CAD) have increased risk of death, myocardial infarction (MI) and other cardiovascular events (CVE). Many factors (e.g. age, vital status, underlying disease, etc) have been used to predict CVEs in various subgroups of CAD patients. These factors have been included in some prediction scores (GRACE [1, 2], TIMI [3], PURSUIT [4], etc.) that are widely used in clinical practice for predicting risk of future events in CAD patients. However, these known prognostic factors only partially explain the risk and the current prediction scores still have some limitations (5). Therefore, there is still a need for new markers that are easy to measure and available in routine practice, which can be used to predict progression of CVE and improve the prediction score in order to achieve better stratification of disease progression.

Platelets play a pivotal role in the pathophysiology of cardiovascular events in all types of CAD patients (6). Platelet activation is a fundamental step in triggering acute coronary syndrome (ACS)

which leads to mortality in many CAD patients. Antiplatelet agents have been shown to reduce CVE in CAD patients and are recommended by every guideline as secondary prevention in patients with CAD (7–9). High residual platelet activity in patients taking antiplatelet agents have also been shown to be a predictor of increased risk of CVE (10, 11). However, platelet function tests are time consuming, expensive, technically difficult and not widely available; therefore limiting its use in clinical practice.

Mean platelet volume (MPV) is a measurement of platelet size. Larger platelets contain more dense alpha granules, express more adhesive receptors, and have higher thrombotic activity (12, 13). Although measurement of MPV is inexpensive, simple, easy to interpret, and already widely available from the complete blood count (CBC); it has received little attention until the last five years.

In addition, there have been a number of studies that have assessed the effects of MPV on CAD progression. Many studies reported that MPV is a valuable prognostic factor in CAD patients (14–16); however, some studies were unable to replicate these

findings (17–19). Therefore, the role of MPV as a potential marker for prognosis of CAD patients remains uncertain. The objective of this study is to perform a systematic review and meta-analysis of all studies that reported MPV as a prognostic marker in patients with CAD.

Materials and methods
Search strategy

We searched MEDLINE and SCOPUS databases from the inception of each database up to January 2, 2014 for potential relevant studies. Search terms included: cardiovascular disease, coronary blood flow, coronary flow, ejection fraction, mortality, death, restenos*, Ventricular Function, Left[Mesh], Heart Failure[Mesh], Coronary Restenosis[Mesh], Death[Mesh], myocardial infarction, Myocardial Infarction[Mesh], Cardiovascular Diseases[Mesh], platelet volume. The search strategies for both databases are described in detail in the Suppl. Material A and B (available online at www.thrombosis-online.com). Reference lists of all included studies and previous systematic reviews were additionally explored to identify additional eligible studies.

Selection of studies

The selection of eligible studies was performed by two independent reviewers (N. S. and P. N.). Inconsistencies regarding the decision of the two reviewers, were resolved by consensus. Any remaining disagreement was resolved by the senior consultant (A. T.). Observational studies published in English were included if they met the following criteria: 1) study design was cohort; 2) had MPV as a study factor; 3) the studied patients had any type of CAD including ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), unstable angina (UA), chronic stable angina (CSA), coronary artery stenosis (CS), and cardiac syndrome X; 4) had CVEs as the outcome of interests which included either death/cardiovascular death, MI, stroke, or stent thrombosis; 5) had sufficient data for pooling, i. e. mean MPV and standard deviation (SD) between CVE and non-CVE groups for continuous data; frequencies of subjects in a contingency table of high/low MPV and CVE groups for categorical data; 6) had full text available.

Data extraction

Data such as baseline characteristics of included studies (i. e. mean age, sex, smoking status, types of study population, study outcomes, analyser used for measurement of MPV, timing of measurement of MPV, mean MPV and SD in patients with and without outcomes, and frequency of outcomes in high and low MPV) were extracted by two independent reviewers (N. S. and P. N.) using a standardised data extraction form. Disagreements were resolved by consensus after discussion between both authors and the senior consultant (A. T.). Missing/insufficient information was obtained by contacting the authors of the included studies.

Risk of bias assessment

Two authors (N. S. and P. N.) independently assessed risk of bias of each study using Newcastle and Ottawa risk of bias criteria (20). Three domains were assessed; representativeness of studied participants; comparability between exposed and non-exposed participants for cohort study and ascertainment of exposures and outcome.

Statistical analysis

For continuous outcomes, mean difference of MPV between patients with and without CVE was estimated for each study and then pooled across studies using unstandardised mean difference (USMD). Heterogeneity of the mean difference was assessed using Q statistics and the degree of heterogeneity was quantified using I^2. If heterogeneity was detected (p-value < 0.10 or $I^2 \geq 25\%$), a random-effect model was applied; otherwise, a fixed-effect model was used.

For dichotomous outcomes, MPV was classified as high or low MPV according to original studies. A few studies had categorised MPV into more than two groups; these were then re-categorised into two groups for ease of pooling. The risk ratio (RR) for having CVE by comparing high versus low MPV was then estimated for each study. Heterogeneity was then assessed using the same methods described previously. The RRs were then pooled using the Der-Simonian and Laird method if heterogeneity was present; otherwise they were pooled using a fixed-effect model.

Sources of heterogeneity were explored by fitting each of the co-variables (i. e. mean age, study setting, percentages of male, diabetes, hypertension, and smoking, type of anticoagulant used (either EDTA or citrate), timing of MPV test, type of cases and type of controls) in a meta-regression model. Publication bias was assessed using Egger tests and funnel plots. All analyses were performed using STATA software, version 13. Two-sided tests with P-value < 0.05 were considered statistically significant except for the heterogeneity test, for which a p-value threshold < 0.1 was used.

Results

We identified 526 publications in MEDLINE and 995 publications in SCOPUS databases. Of these 1,521 studies, 414 were duplicate studies and thus were excluded. After applying eligibility criteria to 1,107 studies, 30 studies met the inclusion criteria and were included in the review (15–46). Reasons for exclusion of the studies have been presented in ▶ Figure 1.

Of 30 included cohorts, nine studies reported a mean difference of MPV between outcome groups (19, 21–27), while 11 studies reported odds ratios (ORs) of high MPV (28–38), and 11 studies reported both (14–16, 18, 39–46), see ▶ Table 1. Mean age of study participants ranged from 54.1 to 76 years. Percentages of male, smoking, and diabetes mellitus (DM) patients ranged from 54.1 to 100 %, 10 % to 63.2 %, and 3 % to 100 %, respectively.
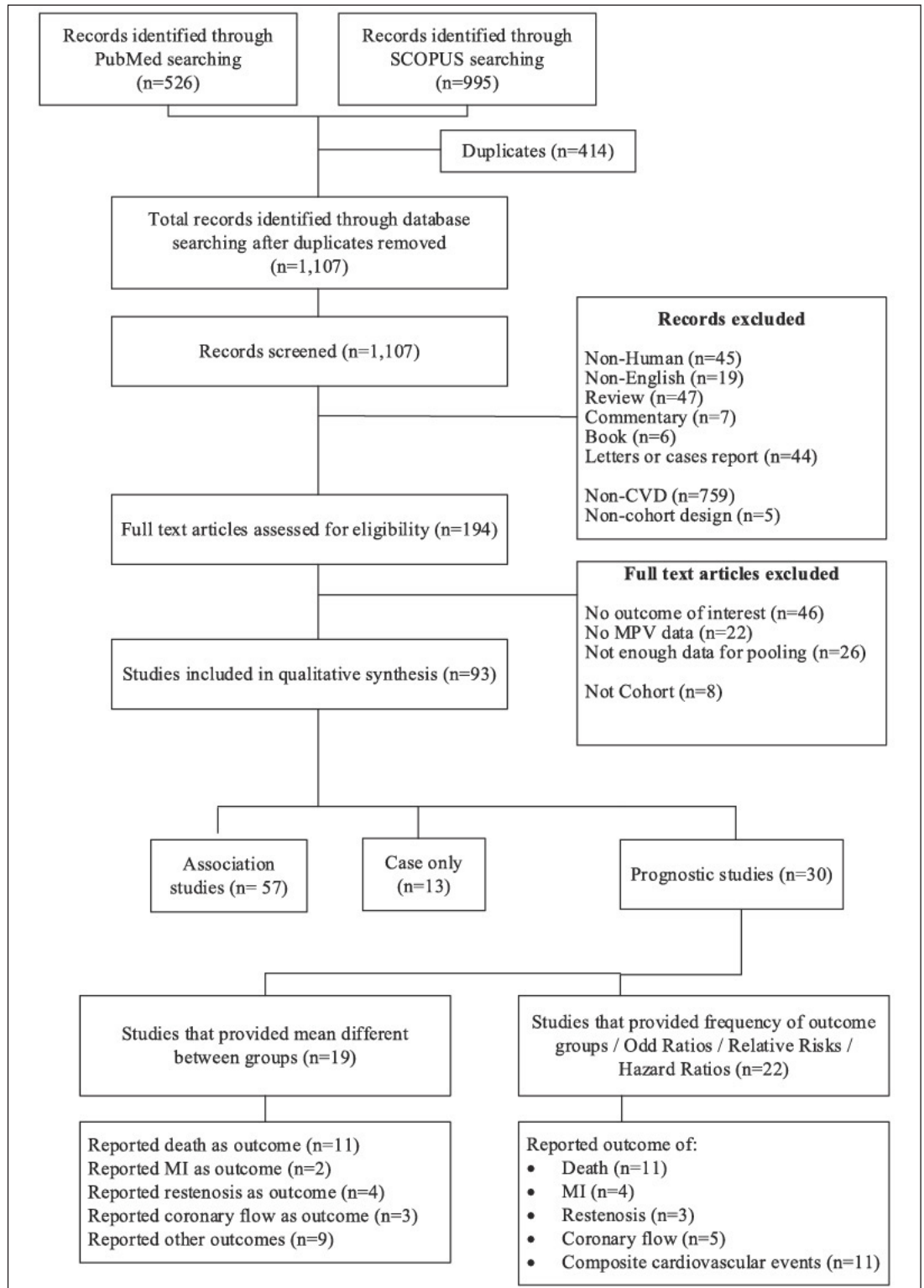
Figure 1: PRISMA flow diagram of study selection.

Pooling cardiovascular events as outcome

Pooling mean differences

We performed overall pooling in 13 studies (14, 15, 18, 19, 21–23, 40–45) comparing MPVs in CAD patients who developed CVEs (including death, MI, stent thrombosis or composite endpoints that contained either death or MI) with patients who had no CVEs.

CAD patients with CVEs (n=2,846) had significantly larger MPV compared with those who did not develop CVE (n=12,854)

Table 1: Baseline characteristic of included studies.

Study ID	Author	Year	Type of analysate	Time until MPV analysis (min)	Country of study	Number of population	Mean age	Percentage of patients with DM	Percentage of patients with HT	Type of case	Mean Time of outcome measurement
Studies which reported mean											
106	Burr ML21	1992	N/A	N/A	England	1755	56.4	N/A	N/A	MI	18 months
2087	Cesari F22	2013	N/A	120	Italy	229	76	24.9	57.2	ACS	12 months
437	Martin JF23	1991	EDTA	1440	England	1716	N/A	N/A	N/A	MI	18 months
491	Norgaz T24	2004	N/A	N/A	Turkey	60	N/A	N/A	N/A	CAD	6 months
592	Smyth D25	1993	EDTA	180	England	47	57	3	11	Post PCI	N/A
605	Susam I26	2011	N/A	30	Turkey	164	58.4	36.6	35.4	STEMI	N/A
622	Terres W27	1995	EDTA	N/A	Germany	47	58.5	8.5	N/A	CAD	8 weeks
2379	Verdoia M19	2013	EDTA	120	Italy	1055	68	29.9	72.8	Post PCI	Immediate post procedure
Studies which reported relative risks											
21	Aksu H28	2009	EDTA	N/A	Turkey	220	60.9	21.9	48.7	ACS	14.9 months
48	Azab B29	2011	EDTA	45	USA	619	64.5	35.2	71.6	NSTEMI	4 years
2082	Celik T30	2013	EDTA	10	Turkey	306	59.4	24.2	42.5	STEMI	In hospital admission
2096	Choi SW31	2013	EDTA	120	Korea	208	65.4	32.7	54.8	Post PCI	7.6 months
221	Elbasan Z32	2012	N/A	N/A	Turkey	840	58.6	28.9	38.8	STEMI	N/A
235	Estevez-Loureiro R33	2009	N/A	N/A	Spain	617	63	17.5	37.5	STEMI	30 days
2195	Ki YJ34	2013	EDTA	120	Korea	372	65.3	33.3	57.3	Post PCI	25.8 months
526	Pereg D35	2010	EDTA	N/A	Israel	122	58.8	25.4	31.1	N/A	N/A
2293	Rechcński T36	2013	EDTA	N/A	Poland	538	58	11.3	32.5	STEMI	26.3 months
607	Taglieri N37	2011	EDTA	N/A	Italy	1041	76	25.4	79.7	NSTEMI	1 year
696	Vrsalovic M38	2012		60	Croatia	543	72	30.5	55	STEMI	30 days
Studies which reported both mean and relative risks											
44	Avci A39	2004	EDTA	180	Turkey	102	56	14.7	42.2	CSA	N/A
206	Dogan A15	2012	EDTA	30	Turkey	344	62.1	34	49.4	NSTEMI	12 months
2128	Eisen A41	2013	EDTA	N/A	Israel	7585	67.7	41.3	73.8	Post PCI	4 years
2141	Fabregat-Andres O18	2013	EDTA	30	Spain	128	59.5	37.9	59.2	STEMI	12 months
258	Goncalves SC42	2011	EDTA	N/A	Canada, Australia	1432	62.8	27.9	60.2	CAD	1 year
289	Huczek Z40	2005	EDTA	30	Poland, Switzerland	388	60	17.3	64.7	STEMI	6 months
2232	Liu Q43	2013	EDTA	60	China	190	66.5	31.1	68.4	NSTEMI	In hospital admission
617	Tekbas E14	2011	EDTA	N/A	Turkey	429	61.9	52.2	43.4	MI	2 years
659	Vakili H44	2009	EDTA	120	Iran	203	57	22.7	31.5	STEMI	In hospital admission
2382	Wan ZF45	2013	EDTA	120	China	286	59.4	21.3	42	ACS	52 months
719	Yang A46	2006	EDTA	N/A	Germany	174	60	N/A	59	CAD	6 months

with USMD of 0.69 fL (95% confidence interval [CI] = 0.36, 1.01), see ►Figure 2. However, there was a high degree of heterogeneity around this estimate (Chi-square = 458.85, df = 12, p-value <0.001, I^2 = 97.4%). We therefore explored the source of heterogeneity using a Galbraith plot. This suggested that the study by Tekbas et al. (14) was different to other studies, see Suppl. Figure 1 (available online at www.thrombosis-online.com). This study was a retrospective cohort where diabetes was as prevalent as 52.2%. A sensitivity analysis was performed by excluding this study did not reduce the heterogeneity (I^2 = 94.7%) with the USMD of MPV of 0.515 fL (95% CI = 0.275, 0.755). Meta-regression was performed by fitting each variable (i.e. age, sex, underlying disease) in the model but none of them could explain the source of heterogeneity (data not shown).

We performed a further subgroup analysis by dividing the studies according to their population: 1) studies with ACS which consisted of STEMI, NSTEMI, UA, MI; 2) stable coronary disease which comprised of chronic stable angina (CSA) and coronary artery stenosis (CS); and 3) studies with post-PCI patients. The MPV difference in ACS patients vs controls was greater than stable angina patients (vs controls) and post PCI patients (vs controls) with an USMD of 0.84 fL (95% CI = 0.41,1.27), 0.6 fL (95% CI= 0.26,0.94), and 0 fL (95% CI = –0.37,0.37), respectively, see ►Figure 2.

Publication bias was assessed using Egger tests and funnel plots (see Suppl. Figure 2, available online at www.thrombosis-online. com). For the overall pooling, a funnel plot suggested asymmetry although the Egger's test yielded borderline non-statistically significant result (Coefficient = 3.14, p-value = 0.136). A contour enhanced-funnel plot was then performed and suggested that the symmetry of the funnel was more likely due to heterogeneity than publication bias (see Suppl. Figure 2, available online at www. thrombosis-online.com).

Pooling relative risks

Six studies provided numbers of patients with high and low MPV with death or MI as the outcomes (i.e. in a two-by-two table format) (15, 28, 31, 35, 37, 42), death only in four studies (14, 29, 36, 40), whereas an additional two (18, 33) and single (38) studies reported MPV effects as an adjusted hazard ratio (HR) and odds ratio (OR), respectively. Use of cut-offs for defining high MPV varied from 8.4fL to 11.7fL. Among those studies with frequency data, the effects of MPV were heterogeneous (Chi-square = 97.16, df = 9, p-value <0.01, I^2 = 90.7%) with a pooled RR of 1.16 (95%CI = 1.07, 1.26), see ►Figure 3. This suggested that patients with high MPV were at 16% higher risk of dying or developing an MI compared to patients with low MPV.
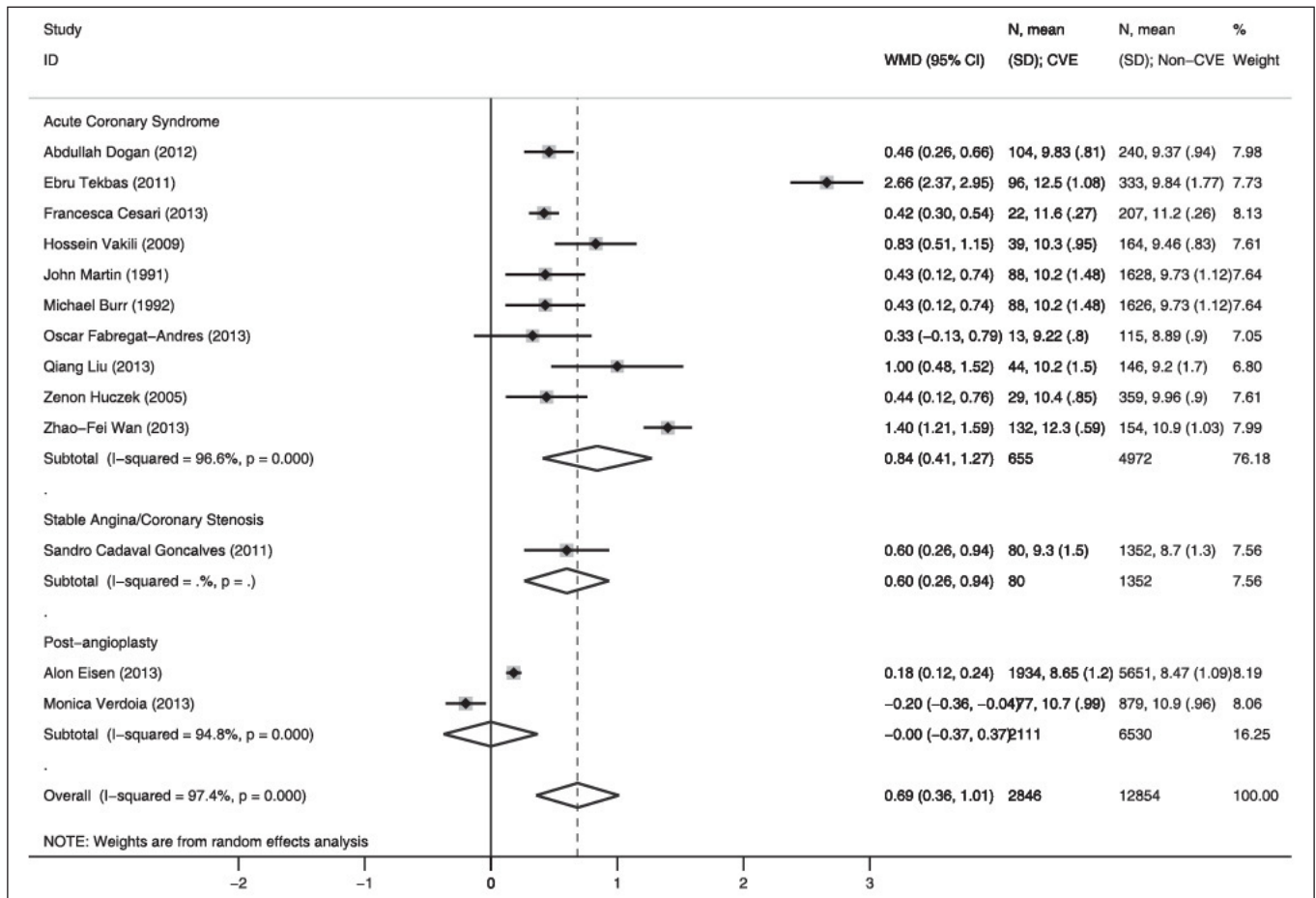

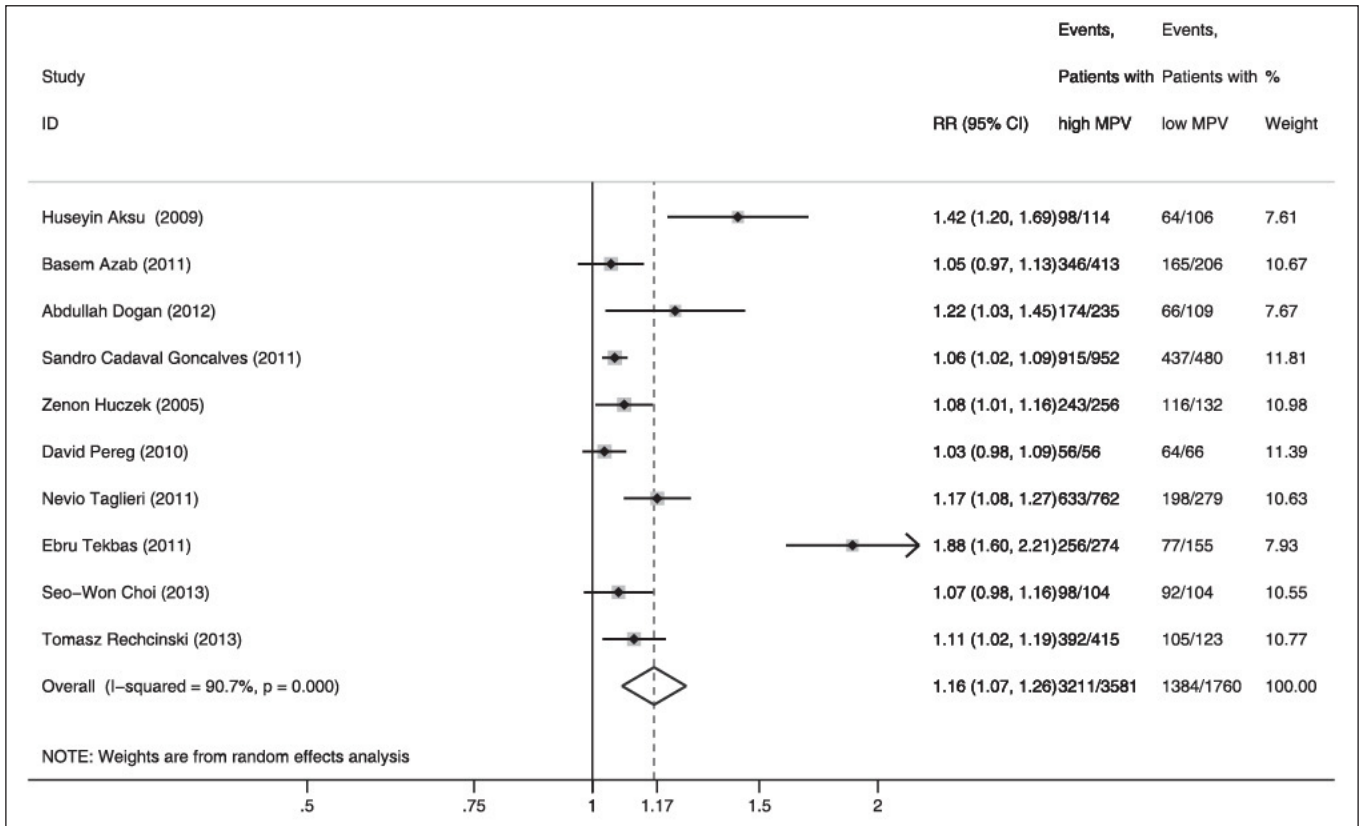Figure 2: Pooling of USMD according to study population.

Figure 3: Pooling relative risks of CVE in patients with high vs low MPV.
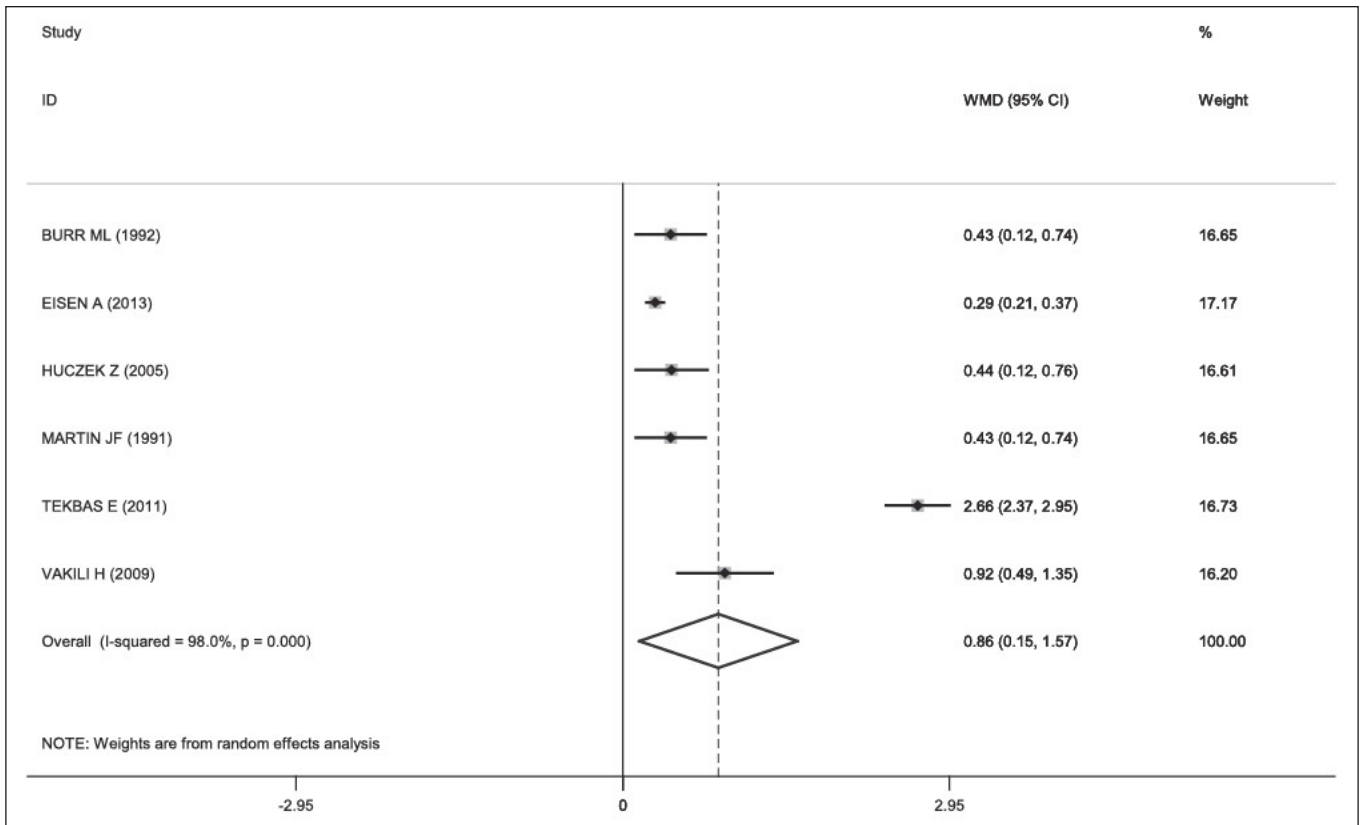

Figure 4: Pooling of mean difference of MPV in patients who died compared with patients who survived.

Including the other three studies that reported a HR or OR in the pooling of frequency data yielded very little change in the MPV effect (pooled RR of 1.18, 95% CI = 1.10, 1.27; I^2 = 85.5%).

The choice of MPV cut-off might be a source of heterogeneity; thus cut-offs were re-categorised as studies with a MPV cut-off of ≤9.1 vs >9.1 fL. Fitting this variable in a meta-regression did not significantly reduce the degree of heterogeneity (I^2 = 79.9% vs 94.7%). An additional subgroup analysis for patients with ACS was performed where data were sufficient (see Suppl. Figure 3, available online at www.thrombosis-online.com), and this indicated that patients with high MPV were at 20% higher risk (RR= = 1.20, 95% CI = 1.07, 1.35) of dying or developing MI compared to low MPV patients.

There was evidence of asymmetry of the funnel for the overall pooling (see Suppl. Figure 4, available online at www.thrombosis-online.com) and Egger test suggested publication bias (Egger Test Coefficient = 4.96, p-value = 0.027). A contour-enhanced funnel plot was done and indicated similar findings (see Suppl. Figure 5, available online at www.thrombosis-online.com).

Pooling death as outcome

Pooling mean differences

Six studies reported MPV as a predictor of death (14, 21, 23, 40, 41, 44). Mean differences of MPV were highly heterogeneous across studies (Chi-squared test = 247.45, p-value <0.001, I^2 = 98%) with the USMD of 0.86 fL (95% CI= 0.147–1.573); indicating that deceased patients had a higher MPV than survived patients, see ►Figure 4. A sensitivity analysis was performed by excluding the study by Tekbas et al. (14) due to the same reasons described above, and this yielded an USMD of 0.442 fL (95% CI = 0.260, 0.624) with moderate heterogeneity (I^2 = 58.1%).

Pooling relative risk

Seven studies (14, 15, 29, 31, 36, 37, 40) were included in the pooling of the RR for high MPV and death (n=3,825) with a range of cut-off levels (8.55fL to 11.7fL). The high MPV effects were heterogeneous (Chi-square = 64.15, df = 6, p-value <0.01, I^2 = 90.6%) with a pooled RR of 1.14 (95% CI = 1.04, 1.25). This indicated that patients with higher MPV were about 14% more likely to die than patients with lower MPV (see Suppl. Figure 6, available online at www.thrombosis-online.com). We explored the source of heterogeneity by performing subgroup analysis by prevalence of diabetes and hypertension. This suggested that a subgroup of studies with low prevalence of diabetes (<32%) was a source of heterogeneity, however this was not found for studies with high prevalence (≥32%); the pooled RRs were 1.10 (95% CI = 1.06, 1.15, I^2 = 0%) and 1.20 (95% CI 0.99–1.46, I^2 = 96.3%), respectively. The pooled RRs in those studies with a high (≥52%) and low (<52%) prevalence of hypertension were 1.08 (95% CI 1.04–1.12, I^2 = 0%) and 1.29 (95% CI 0.93–1.78 I^2 = 97.8%), respectively. These may simply be chance findings given the number of subgroups tested.
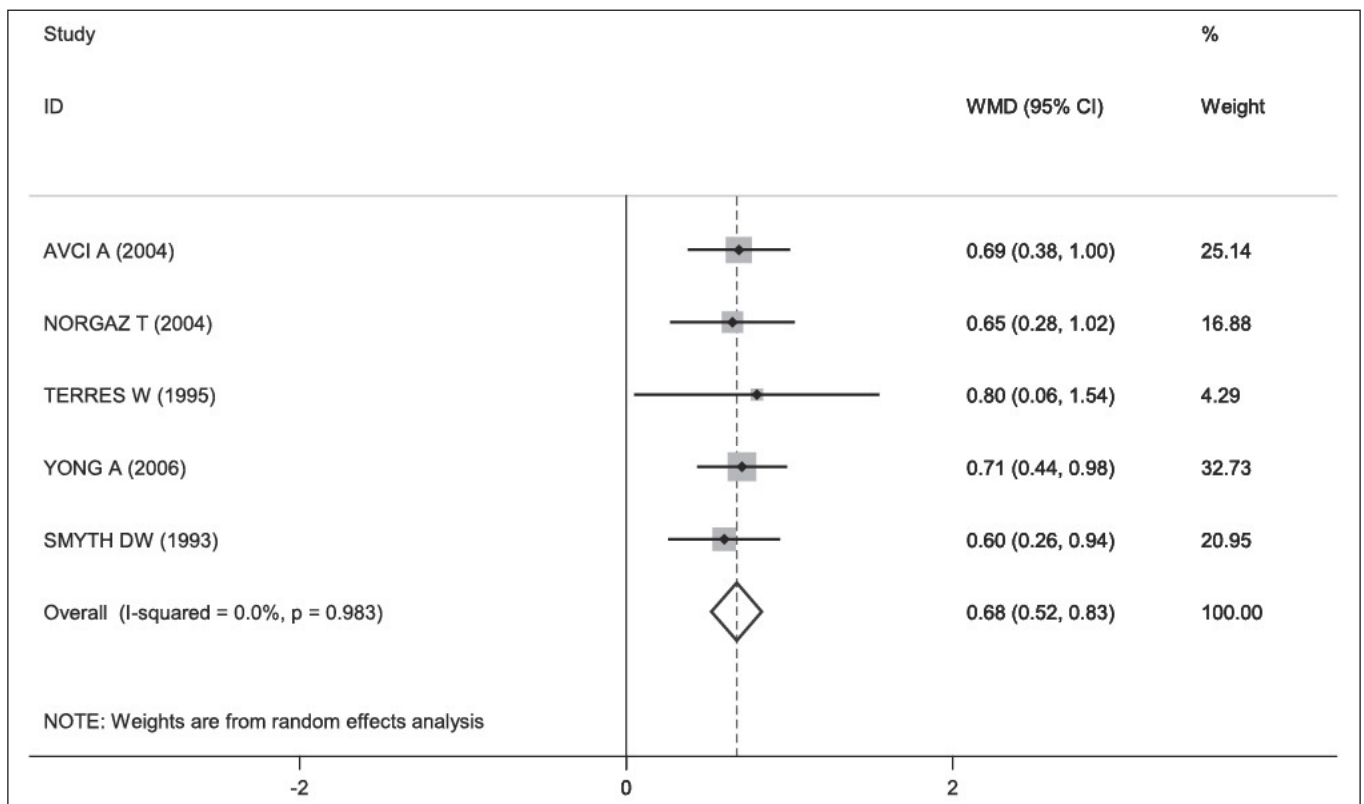

Figure 5: Pooling of weighted mean difference (WMD) among studies reporting MPV difference between patients with and without restenosis.

Pooling restenosis as outcome

Pooling mean differences

There were five studies that reported MPV in patients with and without restenosis (24, 25, 27, 39, 46). The meta-analysis showed a significant difference of MPV in patients with and without restenosis with the USMD of 0.68 fL (95 % CI= 0.52, 0.83) and no evidence of heterogeneity (Chi-square = 0.39, df = 4, p = 0.983, I^2 = 0 %), see ▶Figure 5.

Pooling relative risks

Three studies provided data for pooling of relative risks (15, 39, 46). Applying a meta-analysis for pooling RR showed a sign of association with a pooled RR of 1.79 (95 % CI 0.84–3.81) but this was not statistically significant. However, there was a large amount heterogeneity among studies (Chi-square = 29.59, df = 2, p <0.01, I^2 = 93.2 %) (see Suppl. Figure 7, available online at www.thrombosis-online.com).

Discussion

We performed a systematic review and meta-analysis of MPV effects on CVD progression. Our results indicate that the MPV was approximately 0.65 fL larger in patients who developed CVEs than non-CVE patients, particularly in those with MI and death, where the difference was about 0.80 fL. In addition, the risk of death or MI was approximately 17 % higher in high-MPV (i.e. >8.4 to 11.7 fL) patients than low-MPV patients.

Large platelets contain more dense granule, express more adhesion molecules, produce more thromboxane, and have more thrombotic potential than smaller platelets (12, 13). MPV is a simple marker that reflects platelet size and activity (47–49). A recent meta-analysis showed an association between MPV and CAD (50). Patients with CAD had higher MPV compared to non-CAD patients and the chance of having CAD in patients with high MPV was more than double compared with those who had low MPV. Furthermore, a dose response relationship was also detected in that meta-analysis; the mean difference of MPV in ACS patients was greater than in patients with stable angina.

However, the aforementioned meta-analysis did not examine the influence of MPV on disease progression or occurrence of CVEs in CAD patients. Previous evidence showed conflicting results, some cohort studies observed a risk effect of high MPV (14–16) on the development of CVEs, but some other studies did not (17–19). Our systematic review and meta-analysis therefore combined all cohort studies to fill the gap in knowledge regarding the effects of MPV on coronary artery disease progression. The findings from this meta-analysis support the possible role of MPV as a prognostic marker to predict future cardiovascular events, including MI and death, in CAD patients.

Our pooled estimates showed substantial heterogeneity. This can be explained by vast differences in: baseline characteristics of studied population (age, sex, comorbidity such as diabetes and hypertension, etc.), the subgroup of CAD (UA, NSTEMI, STEMI, CSA, etc.), the type of outcomes (death, MI, composite endpoints, etc.), timing of outcome measurement (in-hospital, 30 days, 6 months, 2 years, etc.) and the timing of measurement of MPV. The association between diabetes and MPV has been shown in many previous studies (51–53). Diabetic patients have higher MPV compared to non-diabetic patients. The similar association was also found between hypertension and MPV (54–56). The individual study included in our meta-anlaysis contained substantial variation in percentage of diabetes and hypertension. This could results in high heterogeneity of the meta-anlaysis. In addition, previous studies have revealed that platelets swell in blood sample analyser mediums such as EDTA and citrate (57, 58). Therefore, the difference in timing of MPV measurement after venipuncture might partly explain the heterogeneity seen in different studies included for pooling. Moreover, the type of analysate (EDTA vs citrate) itself as well as the model of automated machine have all been reported to cause significant differences in MPV measurement. Furthermore, there has been no consensus cut-off of MPV and the threshold used to classify patients into high and low MPV varies dramatically among trials included in our analysis. This may also be a source of heterogeneity. Sensitivity analysis and meta-regression could not clearly identify sources of heterogeneity. We suspect that multiple factors rather than one factor might play a role for the high heterogeneity found in this meta-analysis.

Of note is the study from Tekbas et al. (14) which showed much greater effects of MPV compared to other studies. We explored in detail the possible explanation of their results but could not identify the cause of such difference except for the very high prevalence of diabetes (>50 %) in their study population. The magnitude of MPV effects seen in their study is unprecedented (i.e. mean difference of MPV was 3.1 fL) and has not been confirmed in any other studies. However, the heterogeneity still remained high if this study was omitted but the magnitude of MPV effect decreased from 0.65 to 0.53 fL.

The possible mechanisms of increased CVEs in patients with high MPV include not only increase in platelet activity and aggregation in patients with high MPV but also increase in platelet turnover in those patients. Patients with high MPV have higher hemostatic properties which lead to increase platelet aggregation as discussed above. Furthermore, high MPV might reflect increase in platelet turnover. In high platelet turnover state, there is an increased release of young, large and reactive platelets from megakaryocytes in bone marrow which will result in increased in measurement of MPV. High platelet turnover has been reported to be associated with, soluble P-selectin, platelet activation marker, platelet aggregation (59) and inadequate response to antiplatelet drugs (60–62).

MPV can also indirectly affects CVEs as previous evidence has found an association between MPV and traditional cardiovascular risk factors such as age (63), sex (64), diabetes (52, 65), smoking (66, 67), and inflammation (68). Therefore, MPV itself may be directly associated with CVEs, or it may be mediated through known cardio-vascular risk factors such as diabetes.

In this meta-analysis, we performed a subgroup analysis and found MPV to have prognostic significance for predicting CVE only in ACS patients. In those patients with chronic stable angina or coronary stenosis and in post-PCI patients, the magnitude of MPV effects was lesser and did not reach statistical significance, but remained similar. The findings are in agreement with previous publication (69, 70). This may partly be explained by the more important role of platelets in pathophysiology of ACS. Platelet activation, adhesion and aggregation are the crucial steps in ACS and platelet reactivity has been shown to be associated with outcomes (10, 11). Furthermore, dual antiplatelet therapy has been shown to reduce CVE in ACS and is recommended by many guidelines (7, 9). Unlike ACS, patients with chronic stable angina are more stable with less activation of platelets. The current guidelines recommend only aspirin for secondary prevention and dual antiplatelet medications are not routinely recommended. Therefore, the role of MPV in predicting outcomes in such a subgroup of CAD patients may be less and did not reach statistical significance.

In post-PCI patients, platelet activation is less than in ACS patients. Furthermore, nearly all patients receive coronary stents and dual antiplatelet medications are routinely subscribed. This may overcome the effect that larger platelets with higher platelet reactivity might have on CV outcomes and could be the explanation for the negative finding observed in this subgroup of patients.

On the other hand, both CAD and post-PCI subgroup analyses contained fewer studies for pooling with a smaller number of patients included. The null effect might merely be due to the small sample size and the lack of power to detect any difference.

Given this finding future research should focus on ACS patients and the impact of aspirin, clopidogrel or dual antiplatelet medications on the effects of MPV.

Our meta-analysis also found that MPV is a predictor of death in CAD patients. Patients with a higher MPV had 12 % greater chance of death compared to those with low MPV. Furthermore, mean MPV is significantly larger in patients who died compared to those who survived.

Studies that have examined restenosis as the outcome have also been few. Our meta-analysis showed that all four studies reporting mean difference of MPV in patients with and without restenosis were homogenous (I^2 =0) between studies. The MPV in patients who developed restenosis was approximately 0.70 fL greater than that in patients with no restenosis. Patients with high MPV had 80 % more chance of having restenosis, but this did not reach statistical significance due to a small number of included studies. However, most studies were conducted many years ago using either bare-metal stent or balloon angioplasty with no use of stent as their angioplasty strategy. The management in those studies including type of medications and stents does not reflect the contemporary practice of present day angioplasty. It is uncertain if MPV can still be useful in patients receiving current standards medication as well as second or third generation drug-eluting stents. Large prospective studies are encouraged in order to provide the answer to this important research question.

Strength and limitation

Our meta-analysis has some strengths. To the best of our knowledge, it is the first meta-analysis assessing MPV effects on CAD progression. Only cohort studies, which were the best designs for assessing the prognostic effect of MPV on CVEs, were included. Subgroup analyses by individual outcomes and type of CAD were performed. The review was conducted following the standard recommended by PRISMA and MOOSE guidelines (see references).

Pooled estimates were affected by a high degree of heterogeneity which are likely due to differences in characteristics of the study populations, timing for measurement of MPV, and diagnosis of CAD (subgroup). Although efforts were made to explore the sources of heterogeneity, these could not be identified. Many of the pooled studies did not adjust for confounding variables and thus the MPV effect might be overestimated.

Clinical application and future research

MPV is a simple, inexpensive, and easy-to-interpret test that is a widely available in clinical practice. The results of our meta-analysis provide evidence of a possible role of MPV as a prognostic factor in patients with CAD. However, whether MPV itself is directly associated with CVEs, or it is indirectly associated with CVEs through other mediators such as diabetes is unknown.

We encourage more research to be carried out in order to both confirm our findings and to examine the clinical utility of MPV as prognostic marker in CAD patients. A large-scale cohort study that has collected information on all known cardiovascular risk factors with solid follow-up for CVEs would be useful to answer these questions. The cohort should be large enough to adjust for all known cardiovascular risk factors when assessing the effect of MPV. In addition, more advanced analysis, i. e. a mediation analysis may be needed to to determine the causal effect of MPV on CVEs.

What is known about this topic?
- Previous studies have reported conflicting results of mean platelet volume (MPV) as a prognostic marker in coronary artery disease (CAD) patients.

What does this paper add?
- We have performed a comprehensive systematic review and meta-analysis with aim of determining prognostic effect of MPV in CAD patients.
- Our findings suggest the association between MPV and the incidence of cardiovascular events (CVE) in CAD patients.
- CAD patients who developed cardiovascular events (CVE) had significantly higher MPV (0.65 fL) compared with those without CVE.
- The MPV difference appears to be larger in ACS patients than stable angina and post-PCI patients.
- CAD patients with high MPV had 17 % higher risk of having future CVE compared to patients with low MPV.

Abbreviations

ACS, Acute coronary syndrome; CAD, Coronary artery disease; CBC, Complete blood count; CI, Confidence interval; CS, Coronary artery stenosis; CSA, Chronic stable angina; CVE, Cardiovascular events; df, Degree of freedom; DM, Diabetes mellitus; MI, Myocardial infarction; MPV, Mean platelet volume; NA, Not available; NSTEMI, Non-ST elevation myocardial infarction; OR, Odds ratio; RR, Risk ratio; SD, Standard deviation; STEMI, ST elevation myocardial infarction; UA, Unstable angina; USMD, Unstandardised mean difference.

Our meta-analysis finds MPV to have prognostic value only in ACS patients. However, the number of studies and patients included in the subgroup of stable CAD and in post-PCI patients is small. More research should also be conducted in these CAD subgroups before ruling out a benefit of MPV in those subgroups of patients. Furthermore, the cut-off used to classify MPV as high or low in clinical practice is also unknown. A well-designed, large-scale cohort should give the answer regarding the recommended reference range or cut-off of MPV for risk stratification in different subgroups of CAD patients.

Moreover, if MPV could be used as an independent predictor of CVEs, it should be integrated into the known risk prediction calculators in order to improve the predictive performance of known risk score. This will lead to the better risk stratification of CAD patients.

Finally, if high MPV is associated with CVEs, it would be interesting to further explore the possible role of more intensive anti-platelet therapy in subgroups of patients with high MPV. This could provide very useful information for tailoring anti-platelet medications in each individual.

Conclusion

There appears to be an association between elevated MPV and CAD progression. Patients with CVEs including death, MI, and restenosis, had significantly higher MPV than non-CVE patients. In addition, CAD patients with high MPV had a higher risk of CVEs than those with low MPV. These findings suggest that MPV may be a useful prognostic marker in patients with CAD.

Conflicts of interest
None declared.

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