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SYSTEMATIC REVIEW

# Platelet Reactivity with MACE in Acute Coronary Syndrome Patients Post-PCI under Dual Antiplatelet Therapy: A Meta-Analysis

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## Abstract

**Aim/Background** Acute coronary syndrome (ACS), a condition characterized by acute cardiac ischemia, is among the major causes of death from cardiovascular diseases (CVD). However, whether there is a correlation between platelet reactivity and major adverse cardiovascular events (MACE) remains debatable, and whether platelet function tests should be tailored for ACS patients after percutaneous coronary intervention (PCI) is still under discussion. This study aims to investigate the relationship between platelet reactivity and the occurrence of MACE in ACS patients post-PCI and to discuss the implications of these findings.

**Methods** Clinical studies on 'PCI, ACS, dual antiplatelet therapy (DAPT), platelet reactivity, major adverse cardiovascular events (MACE)' up to 31 October 2023, were systematically collected from Embase, PubMed, and the Cochrane Library. Twelve articles meeting predefined criteria were selected. Meta-analysis was performed using Review Manager 5.4 (Cochrane, London, UK) and Stata 15.0 (StataCorp LLC, College Station, TX, USA) to compute pooled effect sizes, assess heterogeneity, explore sources of heterogeneity, and evaluate publication bias.

**Results** Twelve articles consisting of 9297 patients were included. The meta-analysis showed that ACS patients with high platelet reactivity (HPR) who received PCI and used DAPT for 1–2 years had a greater risk of MACE (risk ratio (RR) = 1.79, 95% confidence interval (CI): 1.30–2.46) compared to those with low platelet reactivity. Moreover, greater platelet reactivity was associated independently with all-cause mortality (RR = 2.26, 95% CI: 1.63–3.12), cardiac mortality (RR = 2.87, 95% CI: 2.16–3.8), myocardial infarction (RR = 1.98, 95% CI: 1.53–2.5), in-stent restenosis (RR = 1.87, 95% CI: 1.22–2.87), as well as stroke (RR = 1.62, 95% CI: 1.02–2.57), but not with coronary revascularization events (RR = 0.99, $p = 0.96$, 95% CI: 0.80–1.24). On the other hand, meta-regression revealed that region ($p = 0.99$), type of ACS patient ($p = 0.16$), drug regimen ($p = 0.48$), testing method ($p = 0.51$), sampling time ($p = 0.70$), follow-up time ($p = 0.45$), and PCI protocol ($p = 0.27$) were not sources of heterogeneity in the study.

**Conclusion** The meta-analysis outcomes indicate that in ACS patients receiving PCI and using dual antiplatelet therapy for 1–2 years, HPR was independently positively correlated with major adverse cardiovascular events, all-cause (or cardiac) mortality, recurrent myocardial infarction, in-stent restenosis, and stroke. This suggests that platelet reactivity testing has clinical and translational significance in predicting patients' risk of adverse cardiovascular events.

**Key words: acute coronary syndrome; platelet reactivity; major adverse cardiovascular events; dual antiplatelet therapy; meta-analysis**

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# Introduction

In recent years, the global number of individuals with cardiovascular disease (CVD) has surged from 271 million to 523 million (Roth et al, 2020), this disease has the highest mortality rate worldwide, with acute coronary syndrome (ACS) as the leading cause of death (Ralapanawa and Sivakanesan, 2021). ACS is an acute cardiac ischemic syndrome due to the erosion or rupture of unstable atherosclerotic plaques within the coronary arteries, thereby forming new thrombi (Libby, 2013). It encompasses ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), as well as unstable angina (UA), with NSTEMI and UA collectively known as non-ST elevation NSTE ACS (Ibanez et al, 2018).

The pathogenesis of ACS is tied to platelet activation after damage to the surface or the endothelial layer of atherosclerotic plaques in arteries. During activation, adenosine diphosphate (ADP) stored within platelets is released. It stimulates P2Y12 receptors, inducing platelet aggregation (Nurden, 2011) and a cascade that forms thrombi (Lv et al, 2020). Therefore, antiplatelet aggregation treatment is critical for ACS patients. Aspirin inhibits platelet aggregation by irreversibly acetylating cyclooxygenase-1 (COX-1), as well as thromboxane A2 (TXA2) (Soodi et al, 2020). Conversely, P2Y12 receptor inhibitors, including prasugrel, ticagrelor, and clopidogrel, can further inhibit platelet aggregation by suppressing ADP-mediated signal transduction (Kelemen et al, 2019; Wallentin et al, 2009). The 2002 Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial indicated that under dual antiplatelet therapy (DAPT) treatment, ACS patients have a 9-month period in which cardiovascular adverse events are significantly reduced compared to non-DAPT patients (9.3% vs. 11.4%) (Yusuf et al, 2001).

However, during DAPT, patients might still encounter adverse cardiovascular events. Müller et al (2003) reported that some post-percutaneous coronary intervention (PCI) patients treated with clopidogrel experienced suboptimal outcomes, including recurrence of thrombosis. Consequently, evaluating platelet reactivity has potential clinical significance in predicting patients' major adverse cardiovascular events (MACE) and guiding the adjustment of antiplatelet medication regimens. Nevertheless, the necessity of platelet function testing and how to apply test results to guide antiplatelet therapy for post-PCI ACS patients still requires further research (Valgimigli et al, 2017). This study aims to explore, through meta-analysis, the correlation between platelet reactivity and major adverse cardiovascular events within a 2-year period in ACS patients receiving DAPT post-PCI. We hope to provide a clinical reference for the prognostic assessment of post-PCI ACS patients.

# Methods

This meta-analysis followed the PRISMA 2020 guidelines (Page et al, 2021), with the checklist available in **Supplementary File 1**.

## Search Strategy

Through Embase, PubMed, and Cochrane Library databases, clinical studies concerning "PCI, ACS, DAPT, platelet reactivity, MACE" published up to 31 Octo-

ber 2023, were collected. The collected literature was screened according to inclusion and exclusion criteria. Correspondingly, articles meeting the inclusion criteria were selected for quality assessment, and finally, the clinical studies that met the requirements were included.

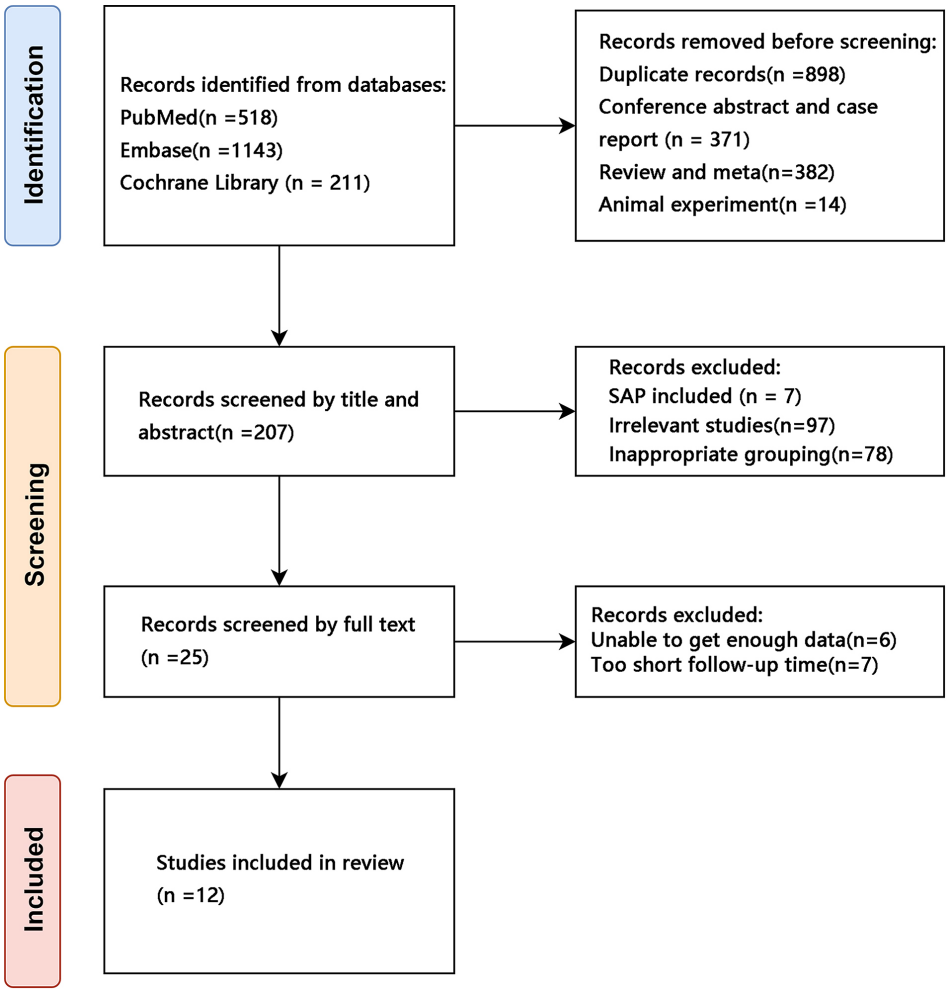


**Fig. 1. Flow chart for the study screening.** SAP, Stable Angina Pectoris.

## Search Terms and Logical Relationships

The following terms were used: "major adverse cardiovascular events", "blood platelets", "percutaneous coronary intervention", "platelet reactivity", "platelet aggregation", "antiplatelet resistance", and "acute coronary syndrome".

## Literature Inclusion and Exclusion Criteria

The literature was screened individually by two researchers. Discrepancies were resolved through discussion or a third party's decision. The criteria were whether the studies were retrospective or prospective cohort studies and whether the participants had received aspirin and clopidogrel (or ticagrelor) following PCI for ACS. Exclusions were made for irrelevant or incomplete data, follow-ups of less than 1 year, and duplicated studies.

**Table 1. Quality assessment of 12 cohort studies.**

| Study, year | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | Total score |
|---|---|---|---|---|---|---|---|---|---|
| Jin et al (2013) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Laine et al (2021) | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Lattuca et al (2019) | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Liu et al (2022) | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Marcucci et al (2009) | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Nishikawa et al (2020) | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Palmerini et al (2014) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Park et al (2013) | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Parodi et al (2011) | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Saia et al (2013) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| You et al (2020) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Vavuranakis et al (2014) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |

1 Selecting the exposed cohort; 2 Choosing the non-exposed cohort; 3 Ascertaining exposure; 4 Illustrating the outcome with regard to interest was absent at the initial stage of the research; 5 Comparing cohorts based on the analysis or design; 6 Assessing outcomes; 7 Following-up for long enough for outcomes to develop; 8 Competency of cohorts' follow up.

### Data Collection Process

We systematically reviewed and extracted data on patient characteristics (age, gender, disease type), treatment regimens (antiplatelet drugs and dosages), platelet reactivity testing methods (VerifyNow, vasodilator-stimulated phosphoprotein (VASP)), and MACE. Two researchers independently extracted the data, resolving discrepancies through discussion. We ensured reliability through double extraction, data verification, and quality assessment.

### Statistical Methods and Software

We used Review Manager 5.4 (Cochrane, London, UK) for effect size calculations and Stata 15.0 (StataCorp LLC, College Station, TX, USA) for heterogeneity and publication bias assessments. The combined effect size was expressed as risk ratio (RR) with 95% confidence interval (CI). $I^2$ statistics was used to assess inter-study heterogeneity, guiding fixed or random-effect model selection for combined analysis. Funnel plots and sensitivity analyses were used to assess publication bias. Meta-regression was conducted to determine the causes of heterogeneity.

## Results

### Study Screening

Twelve articles (Jin et al, 2013; Laine et al, 2021; Lattuca et al, 2019; Liu et al, 2022; Marcucci et al, 2009; Nishikawa et al, 2020; Palmerini et al, 2014; Park et al, 2013; Parodi et al, 2011; Saia et al, 2013; Vavuranakis et al, 2014; You et al, 2020) were considered (Fig. 1).

**Table 2. Basic information of the included literature.**

| Study, year | Design | Area | Patient profile | Drug and LD/MD (mg) | Testing method, cutoff for HPR | No. of patients | Exp/Ctrl | No. of patients | Age (mean ± SD) | Female n (%) | Follow-up (years) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Jin et al (2013) | Prospective | Asia | STEMI | Clopidogrel, 600/75 | VerifyNow, 282 | 181 | HPR | 54 | 63.3 ± 11.6 | 14 (26) | 1 |
| | | | | | | | NPR | 127 | 60.4 ± 12.3 | 16 (12) | |
| Laine et al (2021) | Prospective | Europe | ACS | Ticagrelor, 180/180 | VASP, 50% | 570 | HPR | 30 | NA | NA | 1 |
| | | | | | | | NPR | 540 | | | |
| Lattuca et al (2019) | Prospective | Europe | ACS | Clopidogrel/Ticagrelor, NA | VerifyNow, 235 | 1067 | HPR | 186 | 67 (58–75) | 45 (24) | 1 |
| | | | | | | | NPR | 881 | 62 (55–71) | 152 (7) | |
| Liu et al (2022) | Prospective | Asia | ACS | Clopidogrel, 300/75 | TEG, 47 mm | 474 | HPR | 124 | 61.1 ± 9.8 | 95 (76) | 2 |
| | | | | | | | NPR | 350 | NA | NA | |
| Marcucci et al (2009) | Prospective | Europe | ACS | Clopidogrel, 600/75 | VerifyNow, 240 | 683 | HPR | 219 | NA | 78 (36) | 1 |
| | | | | | | | NPR | 464 | | 88 (19) | |
| Nishikawa et al (2020) | Prospective | Asia | ACS | Clopidogrel, 300/75 | VerifyNow, 221 | 322 | HPR | 246 | NA | NA | 1 |
| | | | | | | | NPR | 76 | | | |
| Palmerini et al (2014) | Prospective | Europe | NSTEMI | Clopidogrel, 600/75 | VASP, 50% | 1007 | HPR | 413 | NA | NA | 1 |
| | | | | | | | NPR | 594 | | | |
| Park et al (2013) | Prospective | Asia | ACS | Clopidogrel, 600/75 | VerifyNow, 235 | 1095 | HPR | 682 | 62.1 ± 10.2 | 205 (30) | 1 |
| | | | | | | | NPR | 413 | 60.2 ± 10.4 | 94 (23) | |
| Parodi et al (2011) | Prospective | Europe | ACS | Clopidogrel, 600/75 | LTA, 70% | 1789 | HPR | 247 | 71.7 ± 11.3 | 120 (49) | 2 |
| | | | | | | | NPR | 1525 | 68.6 ± 11.8 | 988 (65) | |
| Saia et al (2013) | Prospective | Europe | NSTEMI | Clopidogrel, 600/75 | VerifyNow, 230 | 833 | HPR | 246 | 71.6 ± 10.5 | 69 (28) | 1 |
| | | | | | | | NPR | 569 | 65.8 ± 11.8 | 116 (20) | |
| Vavuranakis et al (2014) | Retrospective | Europe | STEMI | Clopidogrel, 600/75 | VerifyNow, 251.5 | 61 | HPR | 23 | 69.5 ± 9.4 | 7 (30) | 1 |
| | | | | | | | NPR | 38 | 57.6 ± 11.1 | 6 (16) | |
| You et al (2020) | Prospective | Asia | STEMI | Clopidogrel, 600/75 | VASP, 50% | 1215 | HPR | 195 | 68.6 ± 9.4 | 77 (39) | 1 |
| | | | | | | | NPR | 1020 | 67.5 ± 12.2 | 354 (35) | |

HPR, high on-treatment platelet reactivity; NPR, non-responsiveness to antiplatelet therapy; NA, not available; SD, standard deviation; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; ACS, acute coronary syndrome; VASP, vasodilator-stimulated phosphoprotein; LD/MD, Loading Dose/Maintenance Dose; LTA, light transmission aggregometry; Exp/Ctrl, Experimental group/Control group.

**Table 3. Extraction of literature data.**

| Study, year | MACE | | AVD | | CV | | MI | | TLR | | ISR | | Stroke | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | HPR | NPR | HPR | NPR | HPR | NPR | HPR | NPR | HPR | NPR | HPR | NPR | HPR | NPR |
| Jin et al (2013) | 11 | 5 | - | - | 6 | 4 | 4 | 1 | 5 | 4 | 3 | 3 | 1 | 1 |
| Laine et al (2021) | 5 | 74 | - | - | 1 | 13 | 1 | 15 | 4 | 66 | 1 | 6 | 0 | 1 |
| Lattuca et al (2019) | 11 | 53 | 3 | 14 | - | - | 5 | 17 | 2 | 33 | 1 | 6 | 1 | 3 |
| Liu et al (2022) | 11 | 45 | 1 | 6 | 1 | 6 | 3 | 7 | 8 | 31 | - | - | 0 | 4 |
| Marcucci et al (2009) | - | - | - | - | 13 | 11 | 16 | 11 | 16 | 24 | - | - | - | - |
| Nishikawa et al (2020) | 20 | 1 | 9 | 0 | 7 | 0 | 11 | 0 | 16 | 1 | 1 | 0 | 1 | 1 |
| Palmerini et al (2014) | 23 | 9 | 13 | 12 | 9 | 3 | 15 | 5 | - | - | 5 | 1 | - | - |
| Park et al (2013) | 68 | 23 | 1 | 0 | - | - | 62 | 23 | 35 | 19 | 0 | 0 | 7 | 1 |
| Parodi et al (2011) | 36 | 132 | - | - | 24 | 65 | 8 | 33 | 1 | 15 | 15 | 44 | 3 | 19 |
| Saia et al (2013) | - | - | 12 | 11 | - | - | 7 | 14 | 27 | 74 | 5 | 9 | 5 | 5 |
| You et al (2020) | 9 | 5 | - | - | 6 | 1 | 0 | 1 | 0 | 3 | - | - | 1 | 0 |
| Vavuranakis et al (2014) | 38 | 104 | 29 | 46 | 23 | 30 | 11 | 20 | 15 | 60 | 1 | 6 | 10 | 30 |

The numbers in the table represent the number of individuals with MACE events in the HPR group and the non-HPR group, respectively. MACE, major adverse cardiovascular events; AVD, all-cause mortality; CV, cardiovascular death; MI, myocardial infarction; TLR, target lesion revascularization; ISR, in-stent restenosis; HPR, high on-treatment platelet reactivity; NPR, non-responsiveness to antiplatelet therapy.

## Literature Quality Assessment

The quality assessment used the Newcastle-Ottawa Scale (NOS) scoring system (Wells et al, 2014). This meta-analysis comprised 11 prospective cohort studies and 1 retrospective study (Table 1).

## Basic Information of the Included Literature and Publication Bias Analysis

This meta-analysis included 12 studies, comprising 11 prospective cohort studies and 1 retrospective cohort study. The research regions were Asia (5 studies) and Europe (7 studies), with a total of 9297 patients. A total of 2665 individuals with elevated platelet reactivity and 6632 individuals without elevated platelet reactivity were enrolled. Patients' ages ranged from 45 to 85 years, with a higher percentage of male patients compared to female patients (Table 2). The follow-up duration was at least 1–2 years. The methods of platelet reactivity testing included VerifyNow (7 studies), VASP (3 studies), light transmission aggregometry(LTA) (1 study), and Thrombelastograghy (TEG) (1 study). The types of ACS patients encompassed ACS (7 studies), STEMI (3 studies), NSTEMI (1 study), and NSTEMI-ACS (1 study). PCI strategies included operator-selected procedures (5 studies), unspecified coronary stents (4 studies), and drug stents (3 studies). Various adverse endpoint events comprised MACE, all-cause mortality (AVD), cardiovascular death (CV), myocardial infarction (MI), target lesion revascularization (TLR), in-stent restenosis (ISR), and stroke (Table 3). No apparent publication bias was identified using Egger's test ($p = 0.984$), as well as the funnel plot construction method (Fig. 2).

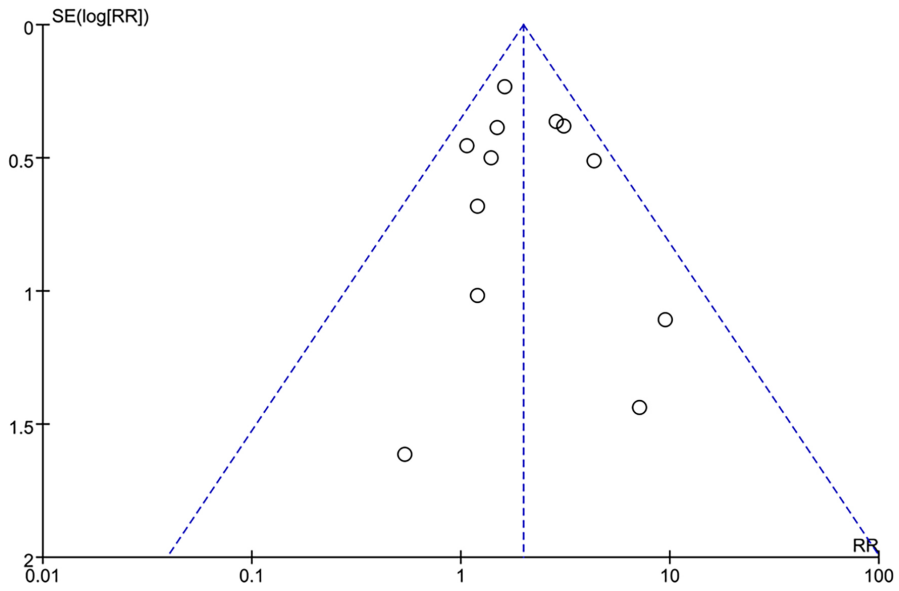


**Fig. 2. Funnel plot having pseudo 95% confidence limits.** RR, risk ratio; SE, Standard Error.

## Meta-Analysis

Based on the ten cohort studies (Jin et al, 2013; Laine et al, 2021; Lattuca et al, 2019; Liu et al, 2022; Nishikawa et al, 2020; Palmerini et al, 2014; Park et al, 2013;

Parodi et al, 2011; Vavuranakis et al, 2014; You et al, 2020) included, an analysis was conducted on the relationship between platelet reactivity and MACE in patients having ACS after PCI following long-term DAPT. The outcomes are illustrated in Fig. 3. The high platelet reactivity (HPR) group showed a higher risk of MACE compared to the non-responsiveness to antiplatelet therapy (NPR) group for post-PCI ACS patients receiving long-term DAPT (RR = 1.79; 95% CI: 1.30–2.46; $p$ = 0.0004, $I^2$ = 62%).

A sensitivity analysis using the one-by-one exclusion method revealed that excluding any single study did not significantly alter the pooled results (95% CI: 1.45–2.06) (Fig. 4), indicating the stability and robustness of the findings. Subsequently, multivariate meta-regression analysis was carried out for several factors (Table 4). None of the factors, including region ($p$ = 0.99), type of ACS patient ($p$ = 0.16), drug loading dose ($p$ = 0.48), assay method ($p$ = 0.51), sampling duration ($p$ = 0.70), follow-up time ($p$ = 0.45), and PCI strategy ($p$ = 0.27), were identified as sources of heterogeneity for MACE.

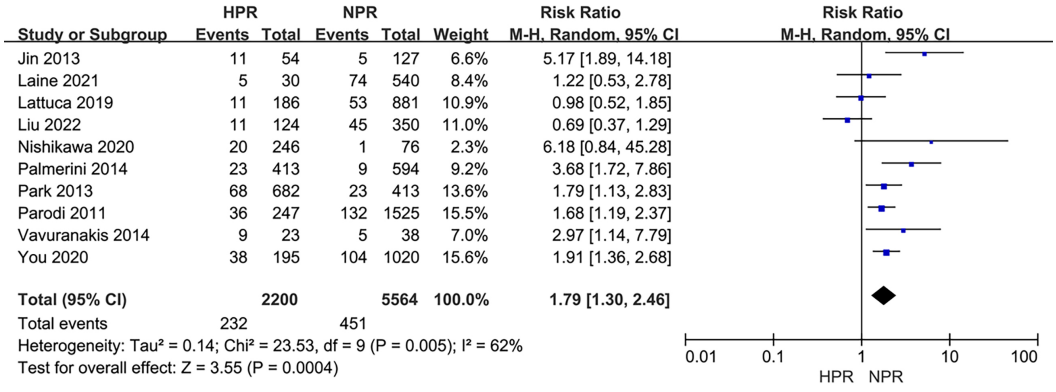


**Fig. 3. Forest plot for MACE.**

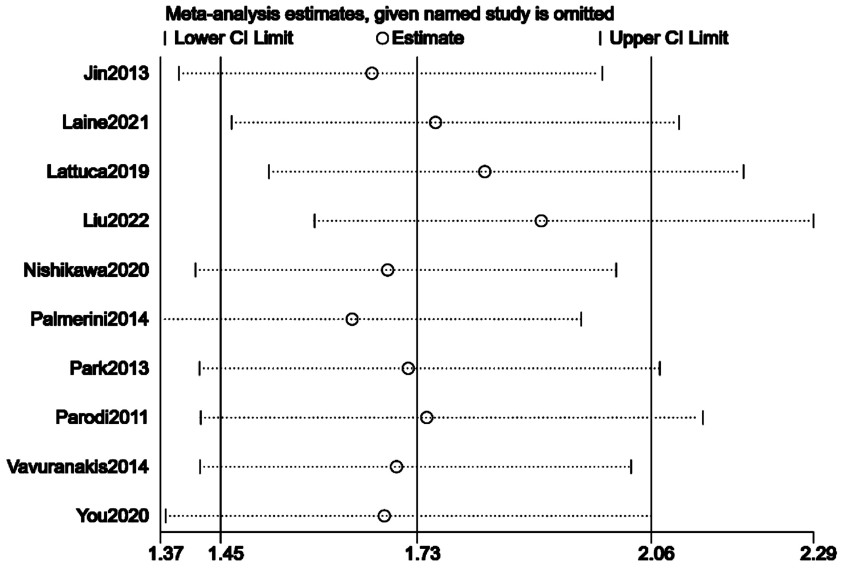


**Fig. 4. Sensitivity analysis for MACE.**

**Table 4. Biased factor regression analysis of MACE.**

| Bias factor | Coefficient | Stu. err. | *t* | *p* | 95% CI |
|---|---|---|---|---|---|
| Area | 0 | 0.52 | –0.01 | 0.99 | –6.60–6.59 |
| Patient profile | 1.28 | 0.33 | 3.92 | 0.16 | –2.87–5.43 |
| Drug | –0.47 | 0.44 | –0.17 | 0.48 | –6.10–5.14 |
| Testing methods | 0.68 | 0.70 | 0.97 | 0.51 | –8.21–9.57 |
| Sampling time | –0.29 | 0.59 | –0.50 | 0.70 | –7.77–7.18 |
| Follow-up | –0.29 | 0.45 | 1.18 | 0.45 | –5.16–6.20 |
| PCI selection | –2.22 | 0.99 | –2.24 | 0.27 | –14.80–10.36 |

"Stu. err." stands for "Standard Error". "*t*" stands for "*t*-value".

Here, the results from multiple studies were analyzed to determine the correlation between HPR and various clinical outcomes. Seven studies (Lattuca et al, 2019; Liu et al, 2022; Nishikawa et al, 2020; Palmerini et al, 2014; Park et al, 2013; Saia et al, 2013; You et al, 2020) demonstrated a significant correlation between HPR and all-cause mortality events (RR = 2.26, 95% CI: 1.63–3.12) (Fig. 5A), indicating a more than doubled risk. Nine studies (Jin et al, 2013; Laine et al, 2021; Liu et al, 2022; Marcucci et al, 2009; Nishikawa et al, 2020; Palmerini et al, 2014; Parodi et al, 2011; Vavuranakis et al, 2014; You et al, 2020) indicated a strong correlation with cardiovascular death events (RR = 2.87, 95% CI: 2.16–3.81) (Fig. 5B), suggesting that HPR significantly contributes to cardiovascular mortality. Twelve studies (Jin et al, 2013; Laine et al, 2021; Lattuca et al, 2019; Liu et al, 2022; Marcucci et al, 2009; Nishikawa et al, 2020; Palmerini et al, 2014; Park et al, 2013; Parodi et al, 2011; Saia et al, 2013; Vavuranakis et al, 2014; You et al, 2020) associated HPR with myocardial infarction (RR = 1.98, 95% CI: 1.53–2.56) (Fig. 5C), emphasizing the importance of monitoring HPR to prevent myocardial infarctions. Nine studies (Jin et al, 2013; Laine et al, 2021; Lattuca et al, 2019; Nishikawa et al, 2020; Palmerini et al, 2014; Park et al, 2013; Parodi et al, 2011; Saia et al, 2013; You et al, 2020) showed a significant association with in-stent restenosis events (RR = 1.87, 95% CI: 1.22–2.87) (Fig. 6A), indicating HPR could lead to stent failure. Ten studies (Jin et al, 2013; Laine et al, 2021; Lattuca et al, 2019; Liu et al, 2022; Nishikawa et al, 2020; Park et al, 2013; Parodi et al, 2011; Saia et al, 2013; Vavuranakis et al, 2014; You et al, 2020) reported a correlation with stroke events (RR = 1.62, 95% CI: 1.02–2.57) (Fig. 6B), highlighting the increased stroke risk. However, eleven studies (Jin et al, 2013; Laine et al, 2021; Lattuca et al, 2019; Liu et al, 2022; Marcucci et al, 2009; Nishikawa et al, 2020; Park et al, 2013; Parodi et al, 2011; Saia et al, 2013; Vavuranakis et al, 2014; You et al, 2020) showed no significant correlation with target lesion revascularization events (RR = 0.99, $p$ = 0.96, 95% CI: 0.80–1.24) (Fig. 6C).

## Discussion

To date, controversy surrounds the correlation between platelet reactivity and adverse events, with conflicting findings between studies by Jin et al (2013), Palmerini et al (2014), Parodi et al (2011), Lattuca et al (2019), and Liu et al (2022). A meta-

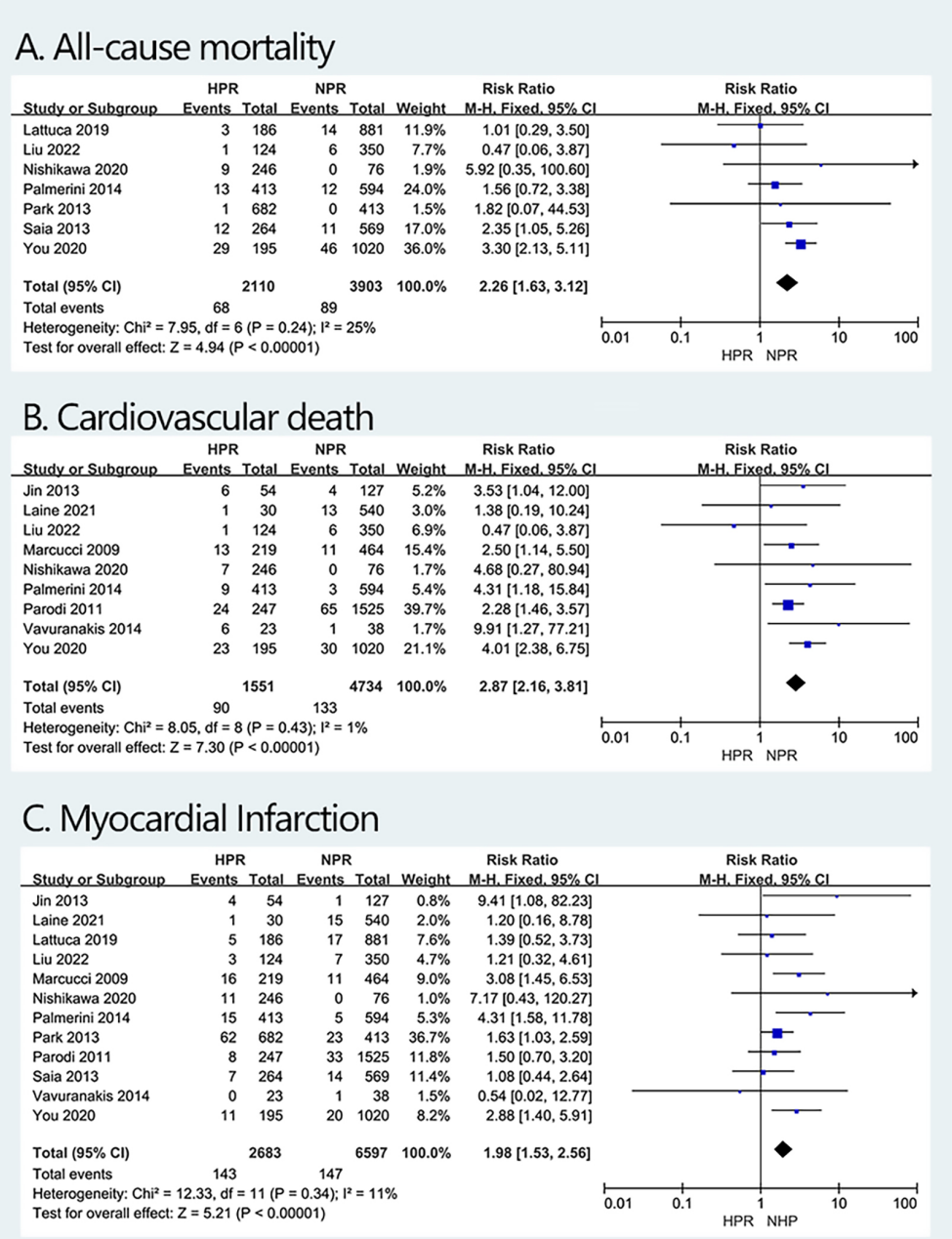


**Fig. 5. Forest plot for all-cause mortality (A), cardiovascular death (B) and myocardial infarction (C).**

analysis (Aradi et al, 2010) conducted in 2010, which examined the correlation between platelet activity levels and cardiovascular adverse events post-PCI under DAPT, suggested a relationship between platelet activity levels and adverse events. Nonetheless, the study included many stable angina patients without distinguishing between stable angina and ACS patients. Furthermore, there were significant disparities in follow-up duration (1 month, 1 year, or 2 years), and recent clinical research results by Laine et al (2021), and You et al (2020), were not included. This meta-analysis's findings included data from 12 cohort studies, showing that patients with ACS receiving 1–2 years of DAPT after PCI who have HPR are more likely to experience MACE than patients who do not. Higher platelet reactivity is not

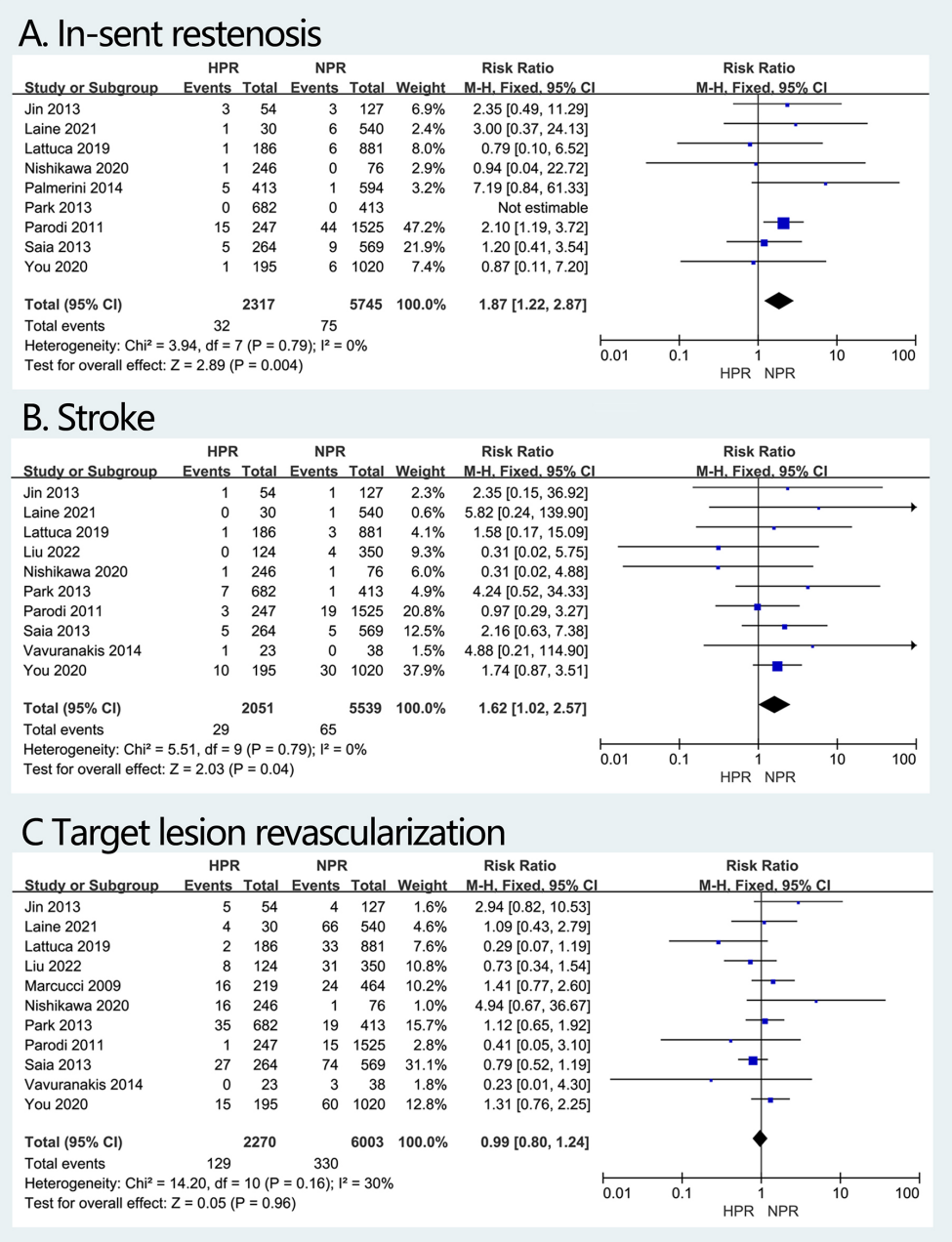


**Fig. 6. Forest plot for in-sent restenosis (A), stroke (B), and target lesion revascularization (C).**

linked to coronary revascularization events. However, it is independently related to myocardial infarction, in-stent restenosis, stroke, and all-cause mortality. HPR and MACE are associated with the same risk factors regardless of the location, kind of ACS patient, medication dosage, mode of testing, length of follow-up, or PCI approach.

The relationship between HPR and MACE may be related to the following mechanisms: (1) Increased platelet aggregation: HPR implies that platelets are more likely to aggregate when stimulated, increasing the risk of thrombus formation (Jackson et al, 2019). This could lead to myocardial ischemia, triggering myocardial infarction or unstable angina (Libby, 2013); (2) Exacerbated inflammatory response: Increasing evidence suggests that platelets are crucial in inflammatory

responses (Morrell et al, 2014). HPR may exacerbate inflammatory reactions, resulting in endothelial injury and atherosclerotic plaque formation (Libby, 2013); (3) Endothelial dysfunction: HPR may be related to endothelial dysfunction (Gkaliagkousi et al, 2015), leading to reduced vasodilation, increased inflammatory response, and enhanced coagulation activity (Gkaliagkousi et al, 2015); (4) Promotion of atherosclerotic plaque rupture: HPR may make atherosclerotic plaques more prone to rupture (Aradi et al, 2015b). Following rupture, platelet aggregation at the rupture site can lead to coronary artery obstruction (Schrottmaier et al, 2020); (5) Elevated risk of thrombus detachment: HPR may increase the likelihood of thrombus detachment, triggering myocardial ischemia and myocardial infarction, among other adverse events (Pettersen et al, 2015); (6) Promotion of coagulation factor activation: HPR may increase the activation of coagulation factors, enhancing the risk of thrombus formation (Jackson et al, 2019); and (7) Induction of vasospasm: A study indicates that platelet activation can induce smooth muscle cell contraction, leading to vasospasm (Kazimierczyk and Kamiński, 2018). These mechanisms can explain, to some extent, the correlation between HPR and MACE. In this study, no correlation was determined between HPR and coronary revascularization events. This is possibly due to the multiple factors involved in coronary revascularization. This includes endothelial dysfunction, alterations in coronary hemodynamics, migration, proliferation of vascular smooth muscle cells, enhanced matrix metalloproteinase activity, local inflammatory responses, and the action of endothelial progenitor cells (Libby et al, 2019).

With advances in medical technology, the tests for platelet reactivity have gradually become more straightforward, stable, and cost-effective, thus reducing the difficulties in clinical testing (Tantry et al, 2013). Among the literature included in our study, VerifyNow and VASP methods are the two most commonly used testing methods for platelet reactivity, accounting for 58.3% and 25% of all tests, respectively. Moreover, neither showed a significant impact on heterogeneity in the regression analysis. Both can be considered for evaluating the correlation between platelet reactivity and MACE. Both types of testing methods have a wide range of applications, high feasibility, and the potential to become clinical testing indicators. Other testing methods lacked sufficient evidence in this analysis, but one clinical study suggests that other methods can independently test platelet reactivity (Aradi et al, 2015a).

The correlation between platelet reactivity and the risk of CVD remains contentious. In the future, researchers should design larger-scale and longer-term prospective studies, standardizing factors such as the definition of MACE, materials used in PCI procedures, methods of testing for platelet reactivity, and cutoff points for platelet reactivity to assess the correlation between platelet reactivity and risk of CVD onset.

The advantages of this work include the comprehensive analysis of multiple studies, providing a robust understanding of the correlation between HPR and adverse cardiovascular events. This study also highlights the need for standardized definitions and methodologies in future research, which is important for improving the accuracy and reliability of the findings in this field. However, this study also

has several limitations: (1) The definition of MACE has not been unified to date (Cutlip et al, 2007; Hicks et al, 2018; Vranckx et al, 2010). Different studies and trials may have different definitions and standards. In some of the included studies, MACE might only encompass events such as death, myocardial infarction, revascularization, and stroke (Liu et al, 2022; Marcucci et al, 2009; Nishikawa et al, 2020; Vavuranakis et al, 2014; You et al, 2020). Meanwhile, another study also includes events like unstable angina, endovascular treatment, and heart failure (Hicks et al, 2018). The definition of MACE in the studies included in this meta-analysis varies. It introduces certain biases in the analysis of the correlation between platelet reactivity and adverse cardiovascular events, making quality control in this aspect challenging. (2) This meta-analysis lacks sufficient literature concerning other P2Y12 receptor antagonists. Hence, it is impossible to analyze whether there is a difference in adverse cardiovascular events in patients with HPR treated with aspirin as well as the clopidogrel combination or ticagrelor and other P2Y12 receptor antagonists. (3) It should be noted that the heterogeneity in the meta-analysis of adverse cardiovascular events is relatively high. Even after conducting regression on factors with potential bias, the source of heterogeneity was not identified.

## Conclusion

The meta-analysis outcomes indicate that in ACS patients receiving PCI and using dual antiplatelet therapy for 1–2 years, HPR was independently positively correlated with major adverse cardiovascular events, all-cause (or cardiac) mortality, recurrent myocardial infarction, in-stent restenosis, and stroke. This suggests that platelet reactivity testing has clinical and translational significance in predicting patients' risk with regard to adverse cardiovascular events.

### Key Points

- Acute coronary syndrome (ACS) is a condition characterized by acute cardiac ischemia.
- It is still debatable whether platelet function tests are necessary for ACS patients after percutaneous coronary intervention (PCI) and how the antiplatelet medication should be tailored.
- The meta-analysis showed that ACS patients with high platelet reactivity who received PCI and used dual antiplatelet therapy for 1–2 years, high platelet reactivity was independently positively correlated with major adverse cardiovascular events, all-cause (or cardiac) mortality, recurrent myocardial infarction, in-stent restenosis, and stroke.

## Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

## Author Contributions

JW and XS contributed to the conception of the study. MH contributed significantly to the data analysis and study preparation. LC and TL performed the data analyses and wrote the study. CW helped perform the analysis with constructive discussions. All authors revised the manuscript critically for important intellectual content and gave final approval of the version to be published. All authors participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be 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.

## Ethics Approval and Consent to Participate

Not applicable.

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## Conflict of Interest

The authors declare no conflict of interest.

## Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2024.0370.

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