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Comparison of P2Y12 inhibitors and aspirin in secondary prevention of coronary events: a meta-analysis of RCTs

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Abstract

Objective This systematic review and meta-analysis compared the efficacy and safety of P2Y12 inhibitors versus aspirin monotherapy for secondary prevention in patients with coronary heart disease (CAD), providing evidence for clinical decision-making.

Methods Following the PRISMA and AMSTAR2 guidelines, a comprehensive literature search was conducted in PubMed, EMBASE, Web of Science, and the Cochrane Library to identify randomized controlled trials (RCTs) comparing P2Y12 inhibitors and aspirin monotherapy in CAD patients. The inclusion criteria focused on RCTs comparing P2Y12 inhibitors (clopidogrel, ticagrelor, and prasugrel) with aspirin. Studies that were non-randomized, did not focus on monotherapies with these agents, involved patients under 18 years old, or included non-CAD patients were excluded. The primary outcomes included myocardial infarction (MI) and stroke, while secondary outcomes comprised gastrointestinal complications, major bleeding, and mortality. The Cochrane Risk of Bias tool was used to assess the risk of bias. A random-effects model was applied to calculate risk ratios (RR) with 95% confidence intervals (CI), and sensitivity analyses were conducted to evaluate the robustness of the findings.

Results A total of 31,956 patients were included in the meta-analysis. P2Y12 inhibitors significantly reduced the risk of myocardial infarction (RR: 0.77, 95% CI: 0.67 to 0.89, $I^2 = 0\%$, $P < 0.001$) and hemorrhagic stroke risk (RR: 0.53, 95% CI: 0.30 to 0.92, $I^2 = 20.2\%$, $P = 0.025$). No statistically significant difference was observed in major bleeding (RR: 0.96, 95% CI: 0.71 to 1.30, $I^2 = 63.8\%$, $P = 0.814$) or all-cause mortality (RR: 0.99, 95% CI: 0.85 to 1.15, $I^2 = 30.3\%$, $P = 0.877$). Heterogeneity was assessed, and sensitivity analysis confirmed the robustness of the primary findings.

Conclusions Compared with aspirin, P2Y12 inhibitors reduce risk of myocardial infarction and hemorrhagic stroke in the secondary prevention of CAD. However, there is no significant differences in major bleeding or all-cause mortality. Further research, including subgroup analyses and studies in diverse populations, is needed to validate these findings and explore genetic factors that may influence treatment outcomes.

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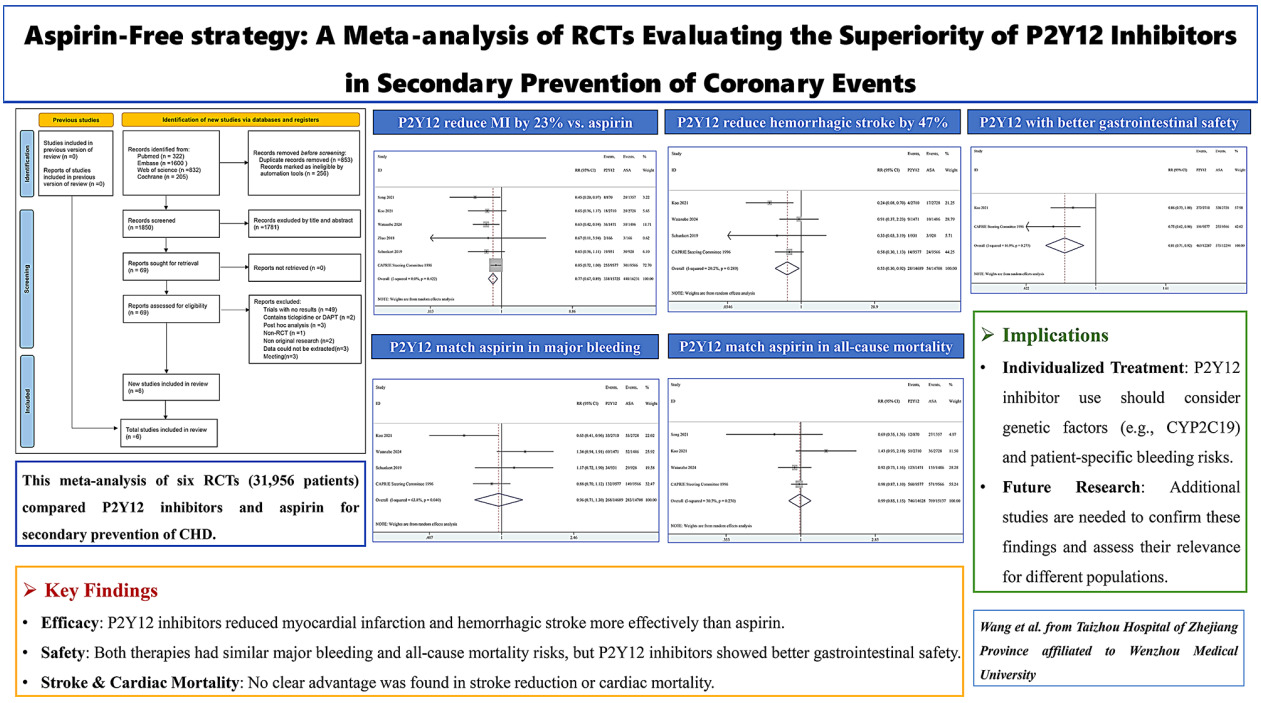
Graphical Abstract



Keywords Aspirin, P2Y12 inhibitors, Coronary heart disease, Complication, Meta-analysis

Introduction

Coronary heart disease (CAD), characterized by coronary artery narrowing or obstruction, remains a major global health concern. Platelet aggregation plays a crucial role in the development of atherosclerotic thrombosis [1], highlighting the importance of antiplatelet therapy in the management of CAD. The landmark CURE trial in 2001 [2] demonstrated that dual antiplatelet therapy (DAPT), combining aspirin with a P2Y12 inhibitor, reduces ischemic events in acute coronary syndrome (ACS). However, the long-term bleeding risk associated with DAPT has limited its use. As a results, monotherapy is typically introduced after one year of DAPT to mitigate bleeding risks [3].

Historically, aspirin has been the standard monotherapy for secondary prevention in CAD patients. However, emerging evidence suggests that P2Y12 inhibitors (such as clopidogrel, prasugrel, and ticagrelor) may offer superior protection against recurrent cardiovascular events in the long term. Recent trials, including GLOBAL LEADERS and TWILIGHT, suggest that P2Y12 inhibitors could outperform aspirin in reducing major adverse cardiovascular events (MACE), particularly in certain patient populations. However, these trials focus on studies comparing P2Y12 inhibitors verse aspirin monotherapy in patients who have undergone percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) [4–7].

The necessity of exploring an "aspirin-free" strategy in the management of CAD has become increasingly relevant due to concerns regarding the long-term bleeding risks associated with aspirin. This has led to active consideration of P2Y12 inhibitors in clinical guidelines as an alternative for secondary prevention [8]. Some studies suggest that P2Y12 inhibitors may offer an advantage in preventing recurrent cardiovascular events [9]. Particularly in populations with specific genetic characteristics, such as East Asians, CYP2C19 polymorphisms may lead to reduced metabolism of clopidogrel, thereby affecting the therapeutic efficacy of P2Y12 inhibitors [10]. Therefore, CYP2C19 genetic testing can be used to guide the selection of P2Y12 inhibitors in patients with acute coronary syndrome or those undergoing percutaneous coronary intervention, optimizing efficacy and reducing the incidence of ischemic events [11].

Recent studies suggest that patients undergoing complex PCI treated with P2Y12 inhibitors may have a reduced risk of major bleeding complications without an increase of ischemic events [12]. A study published by Oliva et al. (2023) demonstrated that in patients undergoing complex PCI, the use of P2Y12 inhibitors significantly reduced the incidence of major bleeding while

maintaining a low occurrence of ischemic events such as myocardial infarction or stroke [13]. This finding is particularly important because patients undergoing complex PCI are at a higher risk of both bleeding and ischemic complications. This study suggests that P2Y12 inhibitors may offer an optimal balance between efficacy and safety in this high-risk group, making them an important consideration in clinical practice. Therefore, this meta-analysis included studies focusing on patients undergoing PCI or CABG while excluding dual antiplatelet therapy (DAPT), which could confound the results.

The debate regarding the role of P2Y12 inhibitors as monotherapy for secondary prevention of CAD remains ongoing [14]. While some studies suggest that P2Y12 inhibitors may be superior to aspirin in preventing MACE, others have found comparable safety and efficacy between the two therapies across a broad patient population. This meta-analysis specifically excluded studies involving DAPT and instead focused on the direct comparison of P2Y12 inhibitors monotherapy versus aspirin monotherapy for secondary prevention after PCI or CABG.

This systematic review and meta-analysis aim to compare the efficacy and safety of P2Y12 inhibitors versus aspirin monotherapy for secondary prevention in CAD. By synthesizing data from randomized controlled trials (RCTs), this analysis seeks to provide evidence-based insights to optimize treatment strategies and guide clinical practice. Many of the studies included in this meta-analysis were conducted in East Asian populations, where genetic factors, including CYP2C19 polymorphisms, may influence drug responses. The East Asian Paradox refers to differences in pharmacodynamics and pharmacokinetics responses between East Asian and non-East Asian populations, which may impact the generalizability of our findings.

Methods

To ensure methodological transparency and rigor, this meta-analysis was conducted in accordance with PRISMA and AMSTAR2 guidelines [15, 16]. Prior to conducting the review, the study was registered on PROSPERO (Registration No: 42024559446).

Inclusion criteria

We included RCTs that investigated patients diagnosed with CAD. The intervention group must have received a P2Y12 inhibitors (clopidogrel, ticagrelor, or prasugrel), while the control group received aspirin monotherapy. The predefined primary outcomes, as specified in the PROSPERO registration, included myocardial infarction (MI), stroke (both ischemic and hemorrhagic), and gastrointestinal complications. The predefined secondary outcomes included major and minor bleeding events, all-cause mortality, cardiac death, revascularization procedures, and major adverse cardiovascular events (MACE). In addition to these predefined outcomes, we further analyzed the differences in ischemic stroke, hemorrhagic stroke, and other secondary complications, which were considered additional outcomes for this review.

Exclusion criteria

We excluded non-randomized controlled trials (non-RCTs), case reports, reviews, or republished studies. Trials involving dual therapy or those not focused exclusively on P2Y12 inhibitors or aspirin were excluded. Studies that lacked data on the specified outcomes or involved anticoagulation therapies unrelated to CAD were also excluded. We also excluded studies where DAPT was initially used but later transitioned to monotherapy, as this could have affected the outcomes related to monotherapy.

Search strategy

Two independent reviewers performed a search in PubMed, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials from the inception date to May 29, 2024, using the keywords "aspirin," "P2Y12," "clopidogrel," "ticagrelor," "prasugrel," combined with "coronary heart disease" and "myocardial infarction." No language restrictions were applied, and non-English studies were assessed and included when eligible. Additionally, no specific filters for RCTs were applied during the initial search process. However, studies were later filtered to include only RCTs in the screening process.

Study selection

Two researchers screened the retrieved literature strictly against inclusion and exclusion criteria. First, the documents that meet the inclusion criteria are read in full by reading the title and abstract, and the included papers are finally confirmed. If two researchers do not agree during the literature screening process, it will be left to the senior researcher. To assess inter-reviewer reliability, Cohen's kappa coefficient was calculated [17].

Data collection and risk of bias assessment

Two independent reviewers screened the retrieved studies according to the predefined inclusion and exclusion criteria. Data on sample size, patient demographics, interventions, outcomes, and study design were extracted independently by both reviewers. The risk of bias in individual studies was assessed using the Cochrane Risk of

Bias tool [18], considering factors such as randomization, allocation, performance, detection, attrition, reporting and orther bias.

Definition of major bleeding and Gastrointestinal complications

In this meta-analysis, major bleeding events were defined according to the Bleeding Academic Research Consortium (BARC) criteria, which classify bleeding events as major when they result in substantial morbidity, such as requiring transfusions or leading to death (BARC 3–5). Gastrointestinal (GI) complications included clinically significant adverse events such as upper gastrointestinal bleeding, peptic ulcers, and gastrointestinal hemorrhage, regardless of the need for hospitalization or surgical intervention.

Statistical analysis

Heterogeneity across studies was assessed using the Q test and I^2 statistic, with I^2 values categorized into four levels to evaluate its impact: low (0–25%), moderate (26–50%), substantial (51–75%), and considerable (>75%). The random effects model was chosen due to the anticipated clinical and methodological heterogeneity across the included studies. This approach allows for the variability both within and between studies, providing a more conservative estimate of the treatment effect when heterogeneity is present. Results for dichotomous outcomes were expressed as risk ratios (RR) with 95% confidence intervals (CI). A P value < 0.05 was considered statistically significant. In the figures of this manuscript, the p-values represent the results of heterogeneity tests, which primarily reflect the variability between individual studies (such as the Q test and I^2 statistic). These p-values are used to assess the differences across the studies. In contrast, the p-values presented in the text represent the overall statistical significance after pooling the data from all the included studies. These values reflect the significance of the combined results of the meta-analysis. Sensitivity analysis was conducted by systematically excluding each study one at a time to evaluate its influence on the overall findings. Additionally, odds ratios (OR) were used as an alternative effect measure to assess the robustness of the results. Potential publication bias was evaluated using funnel plots.

Results

After identifying 2,959 studies, 853 duplicates were removed, and 2,037 irrelevant studies were excluded based on titles and abstracts. The full text of 69 articles was assessed, with 63 exclusions: 49 trials with on results, two studies were excluded due to interventions involving ticlopidine or DAPT [19, 20]; three were post hoc analyses of the HOST-EXAM RCTs [21–23], one was a non-RCT study [24]; two were not original research [25, 26]; three had outcomes that differed from our target indicators, and the data could not be extracted [4, 27, 28]; and three were meeting abstracts. Ultimately, six RCTs involving 31,956 patients met the inclusion criteria and were included in the meta-analysis. The agreement between the two independent reviewers during the screening process was high, with a Cohen's kappa coefficient of 0.84, indicating substantial agreement. The literature screening process is shown in Fig. 1, and the key characteristics of the included studies are summarized in Table 1. The absolute event rates were provided in Table 2.

Risk of bias

A detailed assessment of bias for each included study is presented in Table 3. A study with low risk of bias [3]. Three studies exhibited some risk of bias due to insufficient methodological details [29–31], while two studies had a high risk of bias due to their open-label design [32, 33].

Primary outcomes

Bleeding events

All six studies considered bleeding events as the primary outcome [3, 29–33]. The pooled analysis showed no significant difference between the P2Y12 and aspirin groups (RR: 1.01, 95% CI: 0.82 to 1.25, I^2 = 61.3%, P = 0.929; Fig. 2A). The substantial heterogeneity (I^2 = 61.3%) suggests that variability in study populations, definitions of bleeding, and study methodologies could have contributed to difference in effect estimates. Due to the substantial heterogeneity (I^2 = 61.3%), we excluded the study by Watanabe et al. and found that the heterogeneity significantly decreased (I^2 = 38.7%, Fig. 2B).

Major bleeding events

Four studies assessed major bleeding events [3, 29, 30, 32]. Song et al. is a pooled analysis of the SMART DATE and SMART CHOICE trials, which did not directly compare P2Y12 inhibitor monotherapy versus aspirin monotherapy. Its inclusion was based on the relevant outcomes reported in the pooled data. The analysis showed no statistically significant difference between the two groups (RR: 0.96, 95% CI: 0.71 to 1.30, I^2 = 63.8%, P = 0.814; Fig. 3). The observed heterogeneity likely reflects differences in definitions of major bleeding and patient characteristics. Although no significant difference in major bleeding risk was observed, the heterogeneity warrants cautious interpretation.

All-cause mortality

Four studies evaluated all-cause mortality [3, 29, 31, 32]. The pooled analysis revealed no significant difference

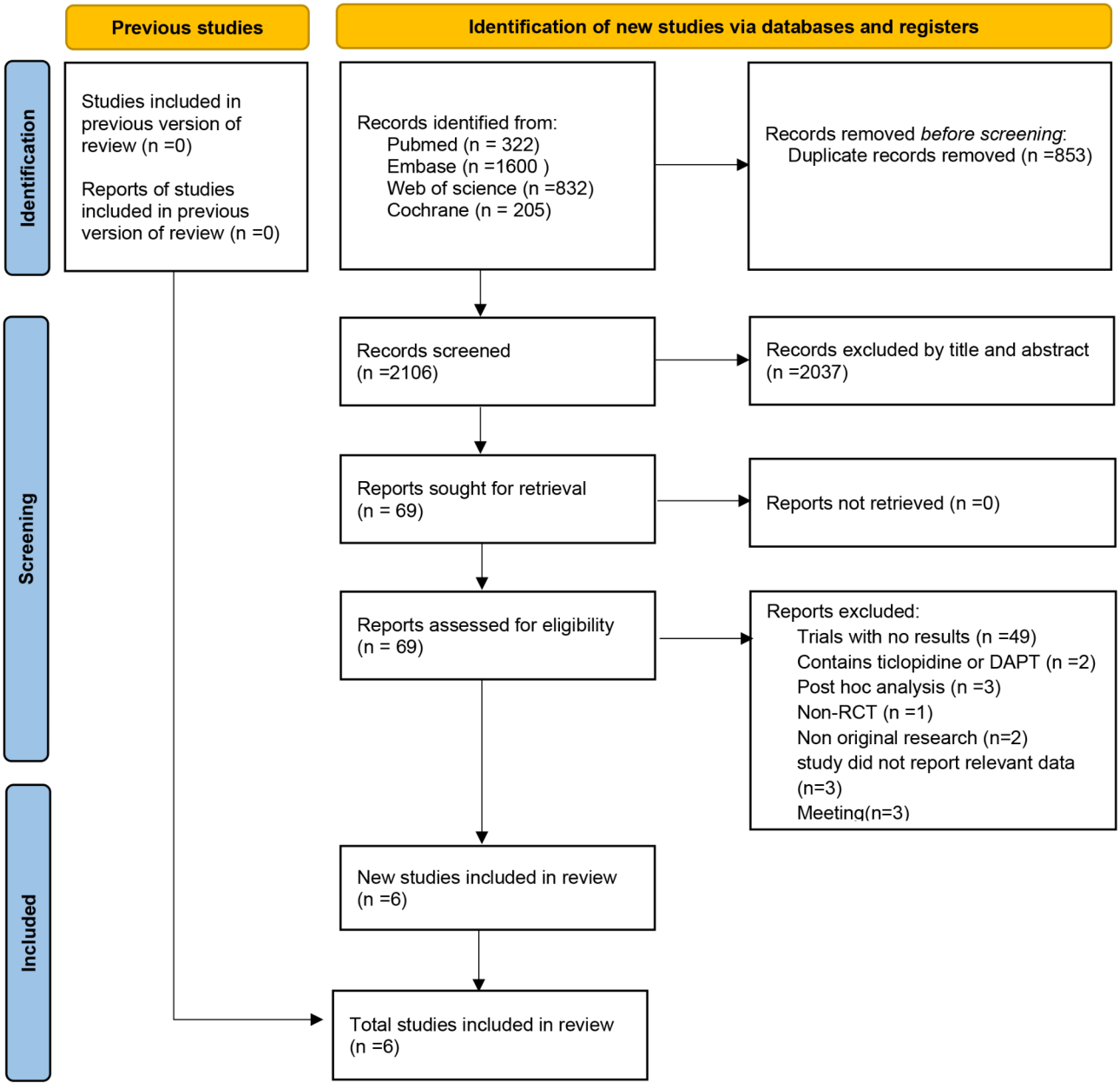


Fig. 1 Flow diagram for search and selection of included studies

between the two groups (RR: 0.99, 95% CI: 0.85 to 1.15, I^2 = 30.3%, P = 0.877; Fig. 4). Given the broad confidence interval, no clear advantage in terms of survival was identified, and further studies with larger sample sizes are needed to confirm this finding.

Cardiac mortality

Five studies reported cardiac mortality [3, 29, 30, 32, 33]. Although a trend toward reduced cardiac mortality was observed in the P2Y12 group (RR: 0.80, 95% CI: 0.62 to 1.02, I^2 = 0%, P = 0.076; Fig. 5), the difference did not reach statistical significance. This suggests that P2Y12 inhibitors may have a modest effect on cardiac mortality, but further trials with larger sample sizes are required to confirm these potential benefits.

Myocardial infarction

All six studies included myocardial infarction as an outcome [3, 29–33]. The results showed a significantly lower incidence of MI in the P2Y12 group compared to the aspirin group (RR: 0.77, 95% CI: 0.67 to 0.89, I^2 = 0%, P < 0.001; Fig. 6). The absence of heterogeneity supports the robustness of this finding, suggesting a clear benefit of P2Y12 inhibitors in reducing the risk of MI. This result is clinically significant, particularly for patients at high risk for recurrent myocardial events.

Table 1 The key characteristics of the included studies

Study	Nation	Participants	Intervention	Design	No.		Age		Gender(M/F)		DM		HBP		HLP		Smoke		CKD		MI		CVA		Outcomes
					P_2Y_{12}	ASA	P_2Y_{12}	ASA	P_2Y_{12}	ASA	P_2Y_{12}	ASA	P_2Y_{12}	ASA	P_2Y_{12}	ASA	P_2Y_{12}	ASA	P_2Y_{12}	ASA	P_2Y_{12}	ASA	P_2Y_{12}	ASA	
Song 2021	Korea	patients undergoing PCI for ACS	100 mg aspirin vs. clopidogrel 75 mg / prasugrel 10 mg / ticagrelor 90 mg	RCT	870	1357	64.4 ± 11.3	62.0 ± 11.5	629/241	1016/341	318	365	530	669	420	322	306	506	25	13	34	30	52	52	All-cause death, MI, stroke, bleeding at 12 months.
Koo 2021	Korea	6–18 months post-PCI	100 mg aspirin 75 mg clopidogrel	RCT	2710	2728	63.5 ± 10.7	63.4 ± 10.7	2015/695	2039/689	925	935	1664	1674	1884	1883	545	581	356	337	437	435	120	133	All-cause death, MI, stroke, Revascularization, gastrointestinal complications
Watanabe 2024	Japan	patients undergoing PCI	aspirin 81–200 mg vs.clopidogrel 75 mg/prasugrel 3.75 mg	RCT	1471	1486	68.1 ± 10.9	69.0 ± 10.4	1159/312	1138/348	571	567	1084	1100	1096	1115	387	308	509	516	202	197	77	104	Cardiac death, MI, definite stent thrombosis, stroke, bleeding events
Zhao 2018	China	patients undergoing CABG	100 mg aspirin vs. 90 mg ticagrelor	RCT	166	166	63.3 ± 8.3	64.0 ± 8.1	134/32	141/25	75	67	122	120	124	119	74	87	3	0	60	43	13	22	Cardiac death, MI, stroke, bleeding
Schunkert 2019	Germany	patients undergoing CABG	100 mg aspirin vs. 90 mg ticagrelor bid	RCT	931	928	66.4 ± 10.1	67.0 ± 10.2	794/137	785/143	338	330	836	836	765	754	200	187	59	72	218	204	83	82	Cardiac death, MI, stroke, revascularization, all-cause death, bleeding events.
CAPRIE 1996	Canada	patients with ischaemic stroke, MI, or atherosclerotic	325 mg aspirin vs. 75 mg clopidogrel	RCT	9577	9566	62.5 ± 11.1	62.5 ± 11.1	6911/2688	6901/2685	1915	1913	4980	4879	3927	3922	2777	2870			1628	1531	19	19	Stroke, MI, vascular death amputation, all-cause mortality.

Abbreviation: DM, diabetes mellitus; HBP, High blood pressure; HLP, hyperlipidaemia; CKD, Chronic kidney disease; MI, myocardial infarction; CVA, cerebrovascular accident; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ASA, aspirin;

ACS, acute coronary syndrome; CCS, chronic coronary syndrome

Table 2 Absolute event rates for each study

Study	N(P2Y12)	N(ASA)	Any Bleeding		Stroke		MI		Major Bleeding		Ischaemic Stroke		Hemorrhagic Stroke		All-Cause Death		Any minor gastrointestinal complications		Cardiac Death	
			P2Y12(%)	ASA(%)	P2Y12(%)	ASA(%)	P2Y12(%)	ASA(%)	P2Y12(%)	ASA(%)	P2Y12(%)	ASA(%)	P2Y12(%)	ASA(%)	P2Y12(%)	ASA(%)	P2Y12(%)	ASA(%)	P2Y12(%)	ASA(%)
Song 2021	870	1357	15 (1.72)	33(2.43)	6(0.69)	9(0.66)	8(0.92)	28(2.06)	/	/	/	/	/	/	12(1.38)	27(1.99)	/	/	/	/
Koo 2021	2710	2728	61(2.25)	87(3.19)	18(0.66)	43(1.58)	18(0.66)	28(1.03)	33(1.22)	53(1.94)	14(0.52)	26(0.95)	4(0.15)	17(0.62)	51(1.88)	36(1.32)	272(10.04)	320(11.73)	19(0.7)	14(0.51)
Watanabe 2024	1471	1486	103(7)	72(4.85)	30(2.04)	39(2.62)	36(2.45)	58(3.90)	69(4.69)	52(3.5)	21(1.43)	29(1.95)	9(0.61)	10(0.67)	123(8.36)	135(9.08)	/	/	28(1.90)	36(2.42)
Zhao 2018	166	166	21(12.65)	15(9.04)	2(1.20)	4(2.41)	2(1.20)	3(1.81)	/	/	/	/	/	/	/	/	/	/	0(0)	2(1.20)
Schunkert 2019	931	928	45(4.83)	44(4.74)	29(3.11)	24(2.59)	19(2.04)	19(2.05)	30(3.22)	34(3.66)	28(3.01)	21(2.62)	1(0.1)	3(0.32)	/	/	/	/	11(1.18)	13(1.40)
CAPRIE Steering	9577	9566	890(9.29)	890(9.30)	486(5.07)	528(5.51)	255(2.66)	301(3.15)	132(1.38)	149(1.56)	472(4.93)	504(5.27)	14(0.15)	24(0.25)	560(5.85)	571(5.97)	191(1.99)	255(2.67)	53(0.55)	75(0.78)

Stroke

Stroke was reported in six studies [3, 29–33]. Although the overall incidence of stroke was lower in the P2Y12 group (RR: 0.81, 95% CI: 0.61 to 1.08, I^2 = 47.6%, P = 0.155; Fig. 7), the difference was not statistically significant. While this trend suggests a potential benefit, it lacks the statistical significance required to definitively conclude that P2Y12 inhibitors are superior to aspirin in preventing stroke.

Ischemic stroke

Four studies reported ischemic stroke [3, 29, 30, 32]. No significant difference between groups was observed (RR: 0.89, 95% CI: 0.68 to 1.16, I^2 = 39.4%, P = 0.372; Fig. 8). This suggests that P2Y12 inhibitors do not offer a clear advantage in preventing ischemic stroke in patients with coronary heart disease.

Hemorrhagic stroke

Four studies analyzed hemorrhagic stroke [3, 29, 30, 32]. The pooled results showed a significantly lower incidence in the P2Y12 group (RR: 0.53, 95% CI: 0.30 to 0.92, I^2 = 20.2%, P = 0.025; Fig. 9), indicating a potential safety advantage for P2Y12 inhibitors regarding hemorrhagic stroke.

Secondary outcomes

Gastrointestinal complications

Two studies reported gastrointestinal complications [3, 29]. The pooled analysis showed a significantly lower incidence of gastrointestinal adverse events in the P2Y12 group compared to the aspirin group (RR: 0.81, 95% CI: 0.71 to 0.92, I^2 = 16.9%, P = 0.001; Fig. 10). This finding underscores the potential gastrointestinal safety benefits of P2Y12 inhibitors, which may be an important consideration for long-term use in patients with coronary heart disease.

Meta-regression and sensitivity analysis

Significant heterogeneity was observed in the analysis of bleeding events (I^2 = 61.3%) and major bleeding events (I^2 = 63.8%). This variability is likely due to differences in study designs, patient populations, definitions of bleeding, and follow-up durations. We performed meta-regression analyses on outcomes exhibiting high heterogeneity (I^2 >50%), specifically any bleeding and major bleeding events. The meta-regression analysis examined the effects of age and sex on bleeding events and major bleeding events (Table 4). Age was found to be a significant predictor for both bleeding events (coefficient = 0.060, 95% CI: 0.014 to 0.106, P = 0.014) and major bleeding events (coefficient = 0.082, 95% CI: 0.016 to 0.147, P = 0.015), indicating that an increase in age was associated with a higher risk of bleeding. In

Table 3 The risk of bias summary: review authors' judgements about each risk of bias item for each included study

Author	Bias from Randomization	Bias from Allocation	Bias from Performance	Bias from Detection	Bias from Attrition	Bias from Reporting	Bias from Other	Overall Risk of Bias
CAPRIE 1996	Low	Low	Low	Low	Low	Low	Low	Low
Koo 2021	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Some
Schunkert 2019	Low	Unclear	Low	Low	Low	Low	Low	Some
Song 2021	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Some
Watanabe 2024	Low	Unclear	High	Low	Low	Low	Low	High
Zhao 2018	Low	Low	High	Low	Low	Low	Low	High

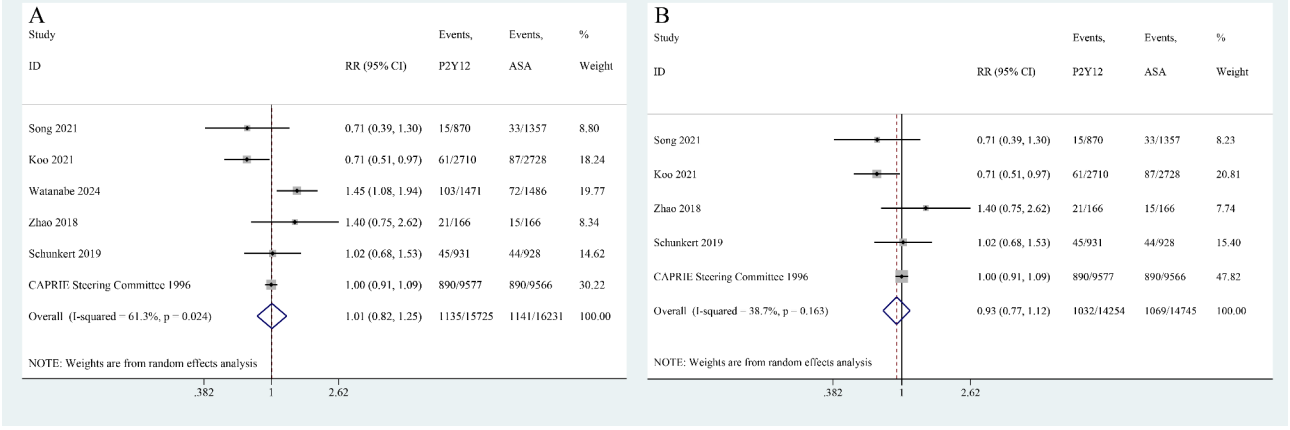


Fig. 2 Forest plot of comparison: P2Y12 vs. aspirin; outcome: Bleeding events. (A: all included trials; B: after excluding Watanabe et al.'s trial)

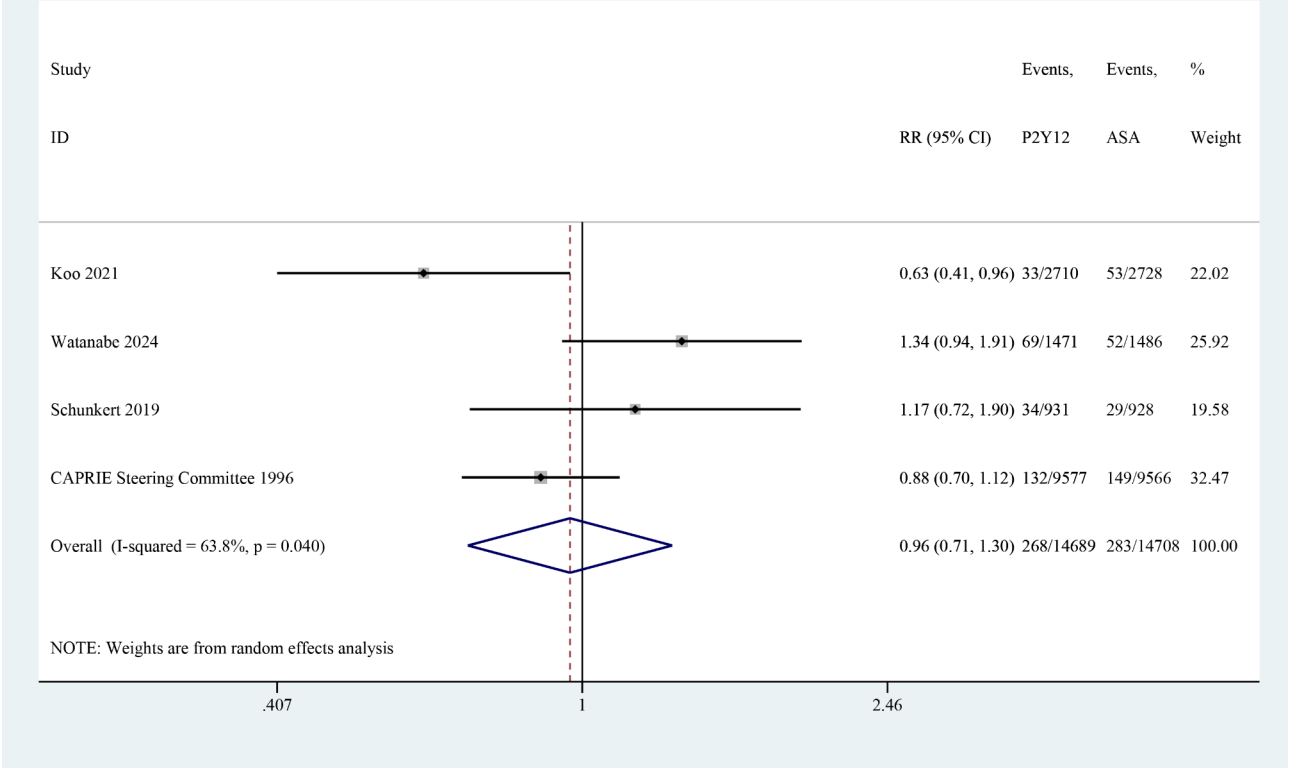


Fig. 3 Forest plot of comparison: P2Y12 vs. aspirin; outcome: Major bleeding events

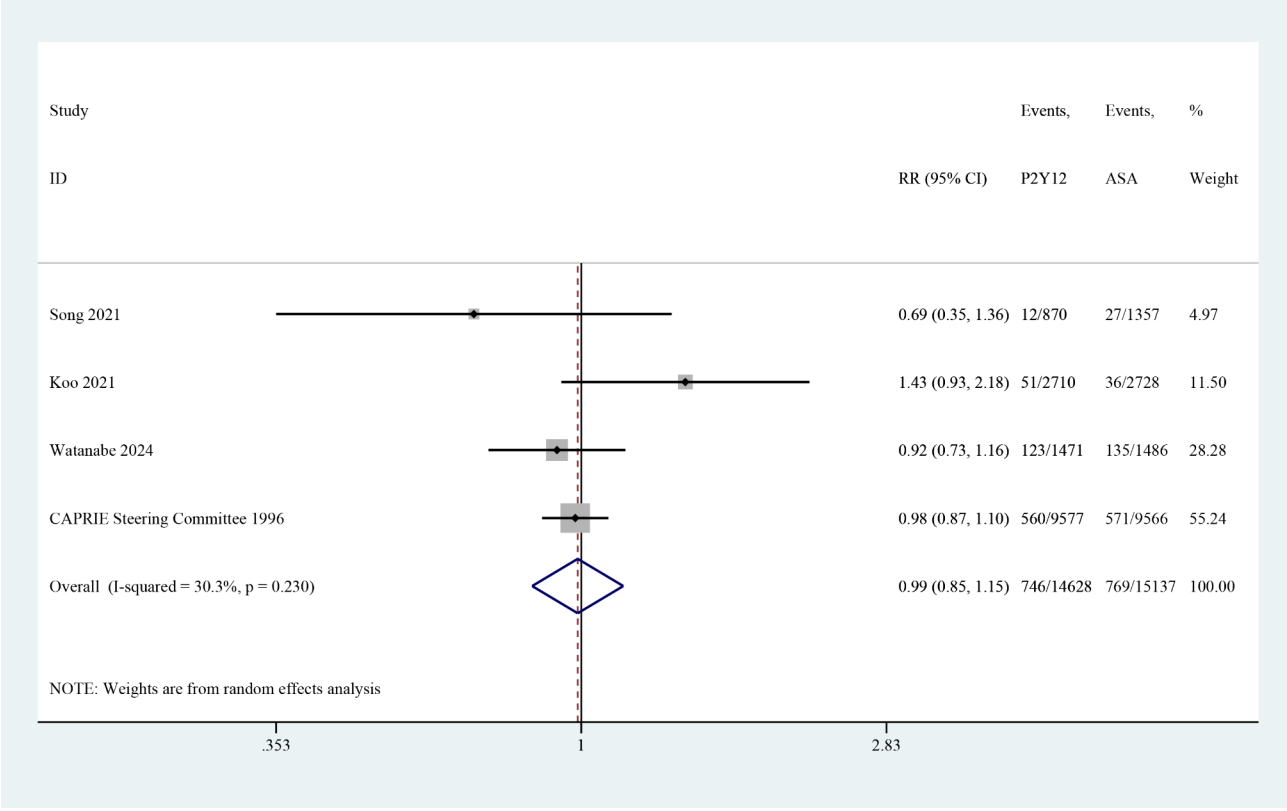


Fig. 4 Forest plot of comparison: P2Y12 vs. aspirin; outcome: All-cause death

contrast, sex did not show a statistically significant association with bleeding events (coefficient = 0.090, 95% CI: -0.142 to 0.322, $P = 0.446$) or major bleeding events (coefficient = 0.121, 95% CI: -0.157 to 0.399, $P = 0.394$). The remaining studies were combined when any individual study was excluded. No particular study had a significant impact on the results.

Publication bias

Because fewer than ten trials were included in the meta-analysis, a funnel plot was not performed (as funnel plot analyses are generally unreliable with such a small number of studies). We acknowledge that the limited number of studies may introduce publication bias as a potential concern, particularly given that our analysis relied exclusively on published data. While no statistical tests for publication bias were applied due to these limitations, we recognize that reporting bias may still exist. In future analyses, we recommend incorporating unpublished or grey literature to provide a more comprehensive and balanced assessment of the research landscape, thereby reducing the risk of publication bias.

Discussion

Our comprehensive literature search identified 2,959 articles, of which six studies involving 31,956 patients were included in this systematic review and meta-analysis. The evidence suggests that P2Y12 inhibitors, particularly clopidogrel, are associated with a reduced risk of MI and hemorrhagic stroke, without increasing major bleeding events or ischemic stroke compared to aspirin monotherapy. However, the lack of significant impact on major bleeding, mortality, or ischemic stroke suggests that P2Y12 inhibitors may provide selective benefits in certain outcomes, rather than being broadly superior to aspirin.

Recent trials, such as the DAPT-TR study, have further validated our findings. This trial, which was conducted in the Turkish population, compared a fixed-dose antiplatelet dual combination in patients with coronary artery disease, revealing similar outcomes for P2Y12 inhibitors in reducing adverse ischemic events and major bleeding risks, reinforcing the idea that P2Y12 inhibitors might offer a safer alternative to aspirin-based therapy for secondary prevention [34].

Current guidelines recommend aspirin as standard antiplatelet monotherapy beyond a year post-PCI or CABG [35, 36]. However, recent trials have suggest that P2Y12 inhibitors, such as clopidogrel, may be a better option, particularly in reducing bleeding events without

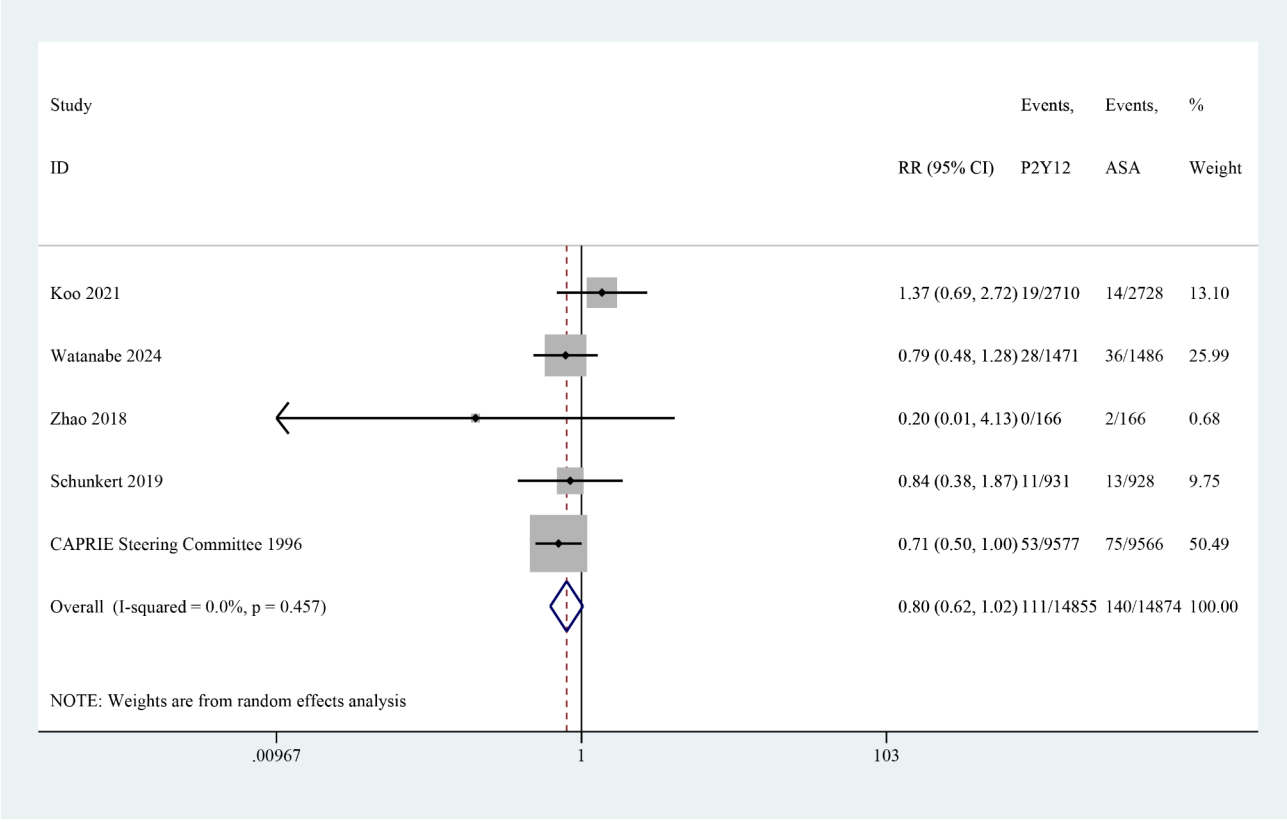


Fig. 5 Forest plot of comparison: P2Y12 vs. aspirin; outcome: Cardiac death

compromising cardiovascular outcomes [29]. Additionally, the 2020 update of the ESC guidelines on the management of chronic coronary syndromes emphasizes the importance of a personalized treatment strategies for CAD patients, considering both bleeding and ischemic risks [37]. Therefore, P2Y12 inhibitors may offer advantages in specific patient populations, but they should not be considered a one-size-fits-all alternative to aspirin. However, clopidogrel resistance in some patients may affect its efficacy, particularly in East Asian populations, where CYP2C19 polymorphisms have been shown to be closely associated with clopidogrel resistance [38]. Variants of this gene can lead to reduced levels of the active metabolite of clopidogrel, thereby decreasing its antiplatelet effect [39]. Given these findings, it is hypothesized that genetic factors, such as CYP2C19 polymorphisms, may influence the efficacy of P2Y12 inhibitors, particularly in East Asian populations. However, since genetic data were not analyzed in this meta-analysis, further research is needed to explore the impact of these genetic variations on treatment outcomes. This should be considered as a hypothesis for future investigation rather than a definitive conclusion. A 2020 meta-analysis published in The Lancet reviewed multiple studies and affirmed aspirin's efficacy in secondary prevention of atherosclerotic cardiovascular disease, finding no significant differences between aspirin and P2Y12 inhibitors in terms of ischemic events, hard endpoints (e.g., stroke, all-cause mortality, cardiovascular death), or bleeding events [40]. In contrast, our study suggests that while P2Y12 inhibitors may offer benefits in reducing myocardial infarction and hemorrhagic stroke, they do not show a clear advantage over aspirin in preventing mortality or major bleeding events.

Similarly, an American meta-analysis reported that long-term clopidogrel monotherapy post-PCI significantly reduced major adverse cardiovascular events (MACE) by 22%, stroke risk by 49%, and hemorrhagic stroke risk by 76%, compared to aspirin monotherapy [41]. These studies corroborate our results in that P2Y12 inhibitors, particularly clopidogrel, may provide effective prevention of recurrent ischemic events and stroke.

However, the lack of statistically significant differences in all-cause mortality and major bleeding events underscores the complexity of deciding between aspirin and P2Y12 inhibitors. While the observed reductions in MI and hemorrhagic stroke are promising, the absence of clear benefits in mortality and the lack of impact on major bleeding events suggest that P2Y12 inhibitors should not be considered a one-size-fits-all alternative to aspirin [30]. This highlights the necessity of identifying specific patient subgroups that would benefit most from

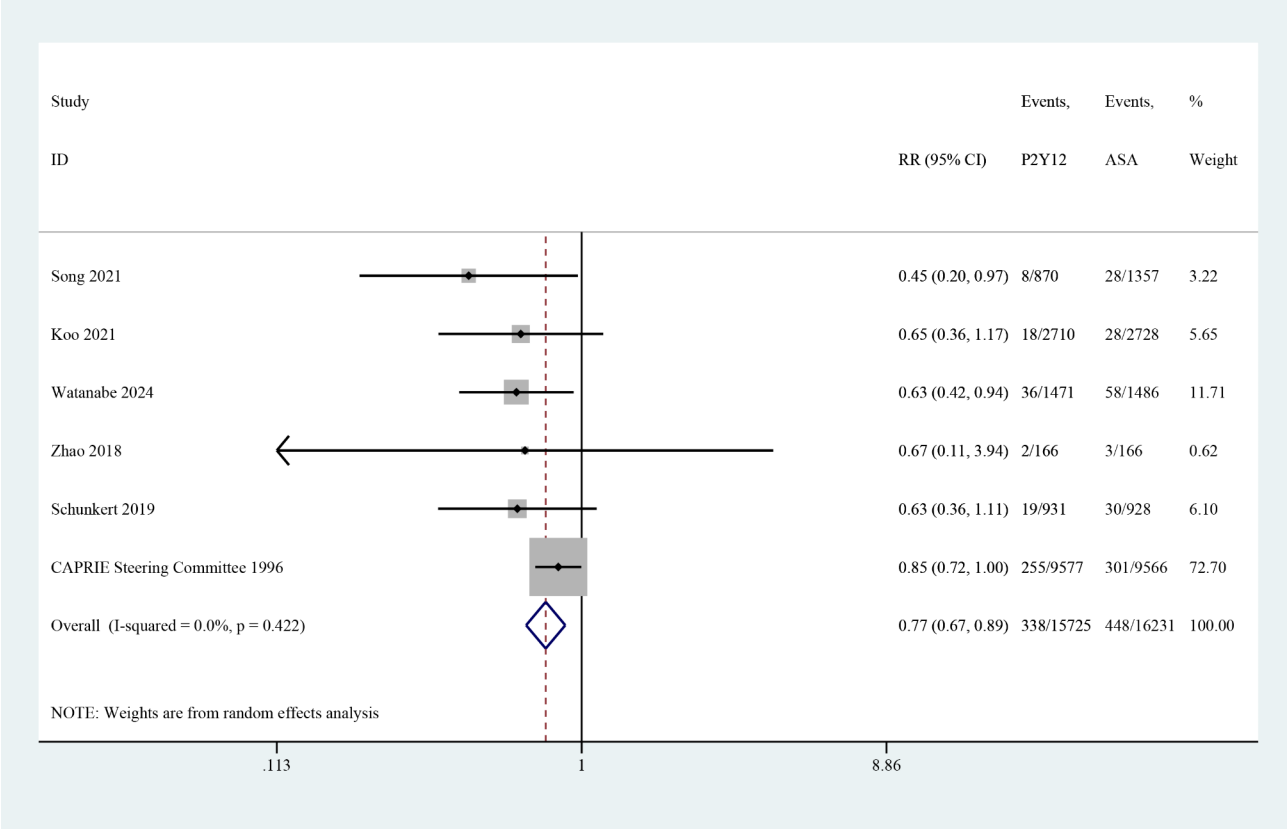


Fig. 6 Forest plot of comparison: P2Y12 vs. aspirin; outcome: Myocardial infraction

P2Y12 inhibitors. Factors such as genetic polymorphisms (e.g., CYP2C19) and individual bleeding risk may be critical in determining the optimal antiplatelet therapy for patients [42].

Our meta-analysis revealed substantial heterogeneity, particularly in bleeding events (I^2 = 61.3%) and major bleeding events (I^2 = 63.8%). This variability is likely due to differences in patient populations, study designs, and follow-up durations. For instance, the duration of dual antiplatelet therapy (DAPT) could influence both bleeding and ischemic event rates, especially since some studies included patients on prolonged DAPT regimens, which may have confounded the results [43]. While subgroup analyses based on study design and DAPT duration did not fully explain the observed heterogeneity, future research employing meta-regression or further subgroup analyses is needed to clarify the underlying factors contributing to this variability.

The results of this meta-analysis, which predominantly involved East Asian populations, provide important insights for clinical practice, particularly in the context of long-term antiplatelet monotherapy for patients with coronary heart disease. Our analysis shows that P2Y12 inhibitors significantly reduce the risk of MI, with no observed heterogeneity (I^2 = 0%), suggesting the robustness of this finding. The reduction in hemorrhagic stroke risk further supports the safety profile of P2Y12 inhibitors over aspirin, which has been associated with an increased risk of intracranial hemorrhage. However, the lack of significant differences in all-cause mortality and major bleeding events suggests that while P2Y12 inhibitors may offer certain advantages, they should not be viewed as a universal replacement for aspirin in all patients. Furthermore, given the predominance of East Asian participants in our analysis, the applicability of these findings to other populations, particularly those with different genetic backgrounds, remains uncertain and warrants further investigation.

The predominance of East Asian populations in the included studies suggests that the results may be particularly relevant to Asian populations. However, given the significant genetic differences between East Asian and other populations, such as those related to CYP2C19 polymorphisms, the generalizability of these findings to non-Asian populations is uncertain. Clopidogrel, in particular, is known to have variable efficacy due to CYP2C19 genetic variations, which are more prevalent in East Asian populations. Therefore, further studies involving more diverse ethnic groups are needed to confirm these findings and assess whether P2Y12 inhibitors

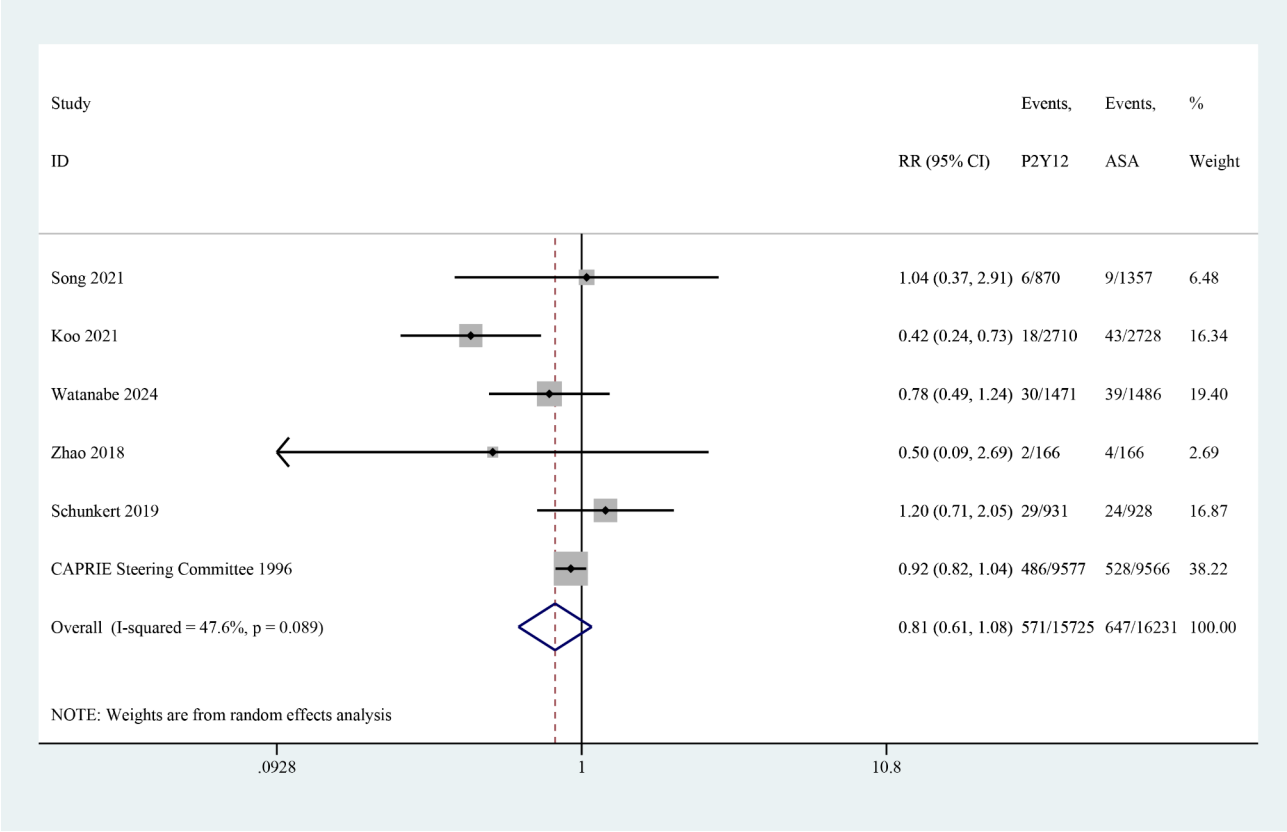


Fig. 7 Forest plot of comparison: P2Y12 vs. aspirin; outcome: Stroke

exhibit similar efficacy in populations with different genetic backgrounds.

Limitations

This study has several limitations. First, the small number of included trials (fewer than ten) limits the statistical power and reduces the reliability of the results. Publication bias is another concern, as the small sample size prevents funnel plot assessment. Dependence on published studies increases the risk of reporting bias, potentially overestimate treatment effects. Future research should incorporate unpublished data to mitigate this issue.

Additionally, most included studies were conducted in East Asian populations, limiting generalizability to other ethnic groups. Genetic factors, such as CYP2C19 polymorphisms, which affect clopidogrel efficacy and are more prevalent in East Asians, may influence the applicability of findings to other populations. Further studies in diverse cohorts are needed to confirm whether the observed benefits extend across different genetic backgrounds.

Some studies also had methodological limitations, including open-label designs and inadequate reporting, increasing the risk of bias. Future studies should adopt double-blind RCTs, with detailed methodology reporting to enhance reliability. While sensitivity analyses were conducted, potential biases in the included studies may still impact overall validity. Larger, well-designed RCTs with extended follow-up are essential to confirm the long-term safety and efficacy of P2Y12 inhibitors, particularly in diverse patient populations.

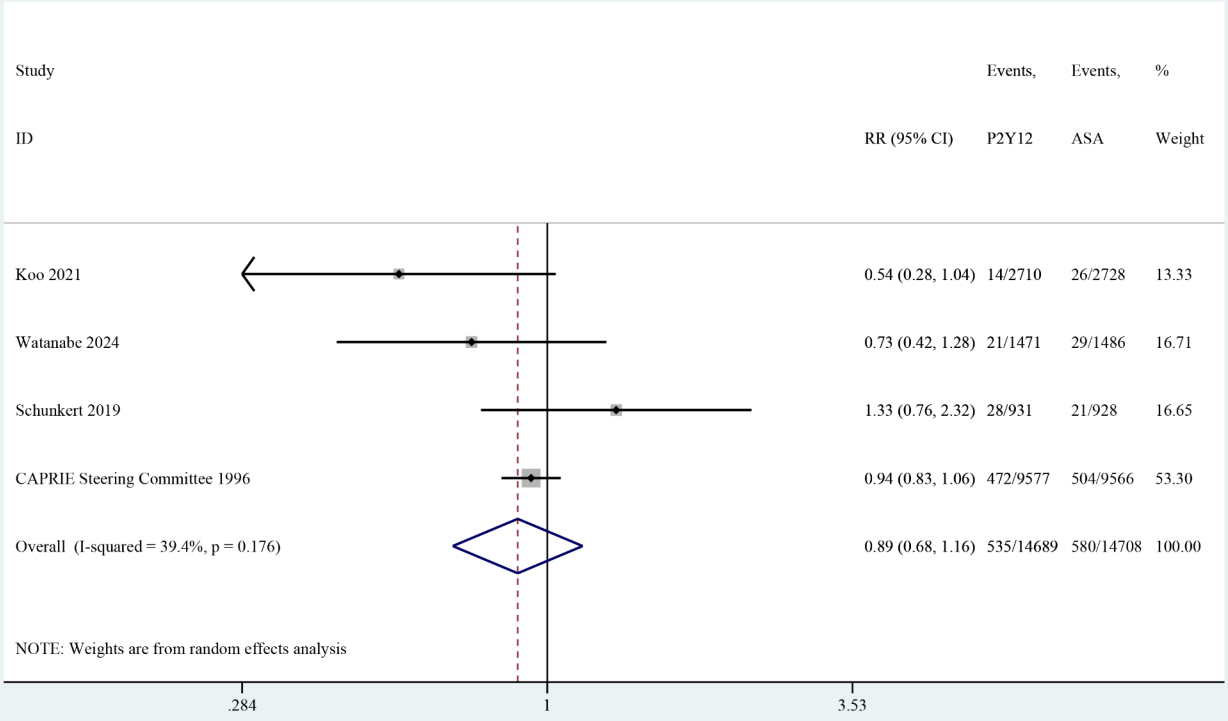


Fig. 8 Forest plot of comparison: P2Y12 vs. aspirin; outcome: Ischemic stroke

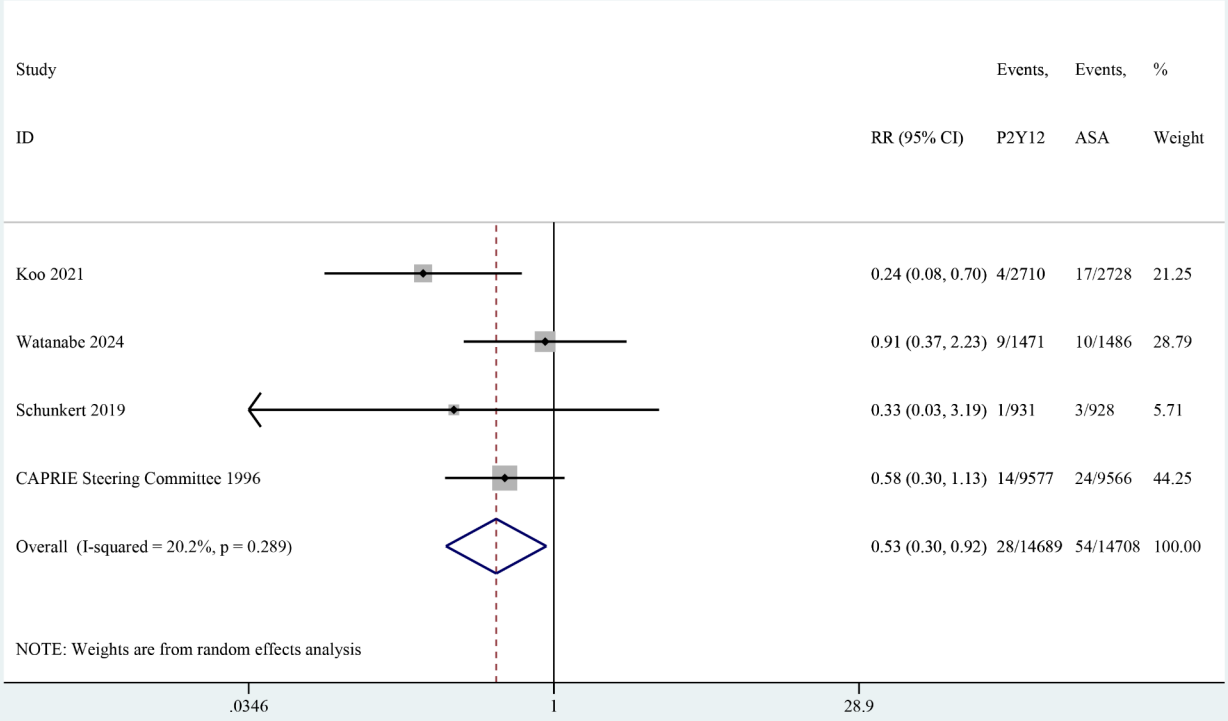


Fig. 9 Forest plot of comparison: P2Y12 vs. aspirin; outcome: Hemorrhagic stroke

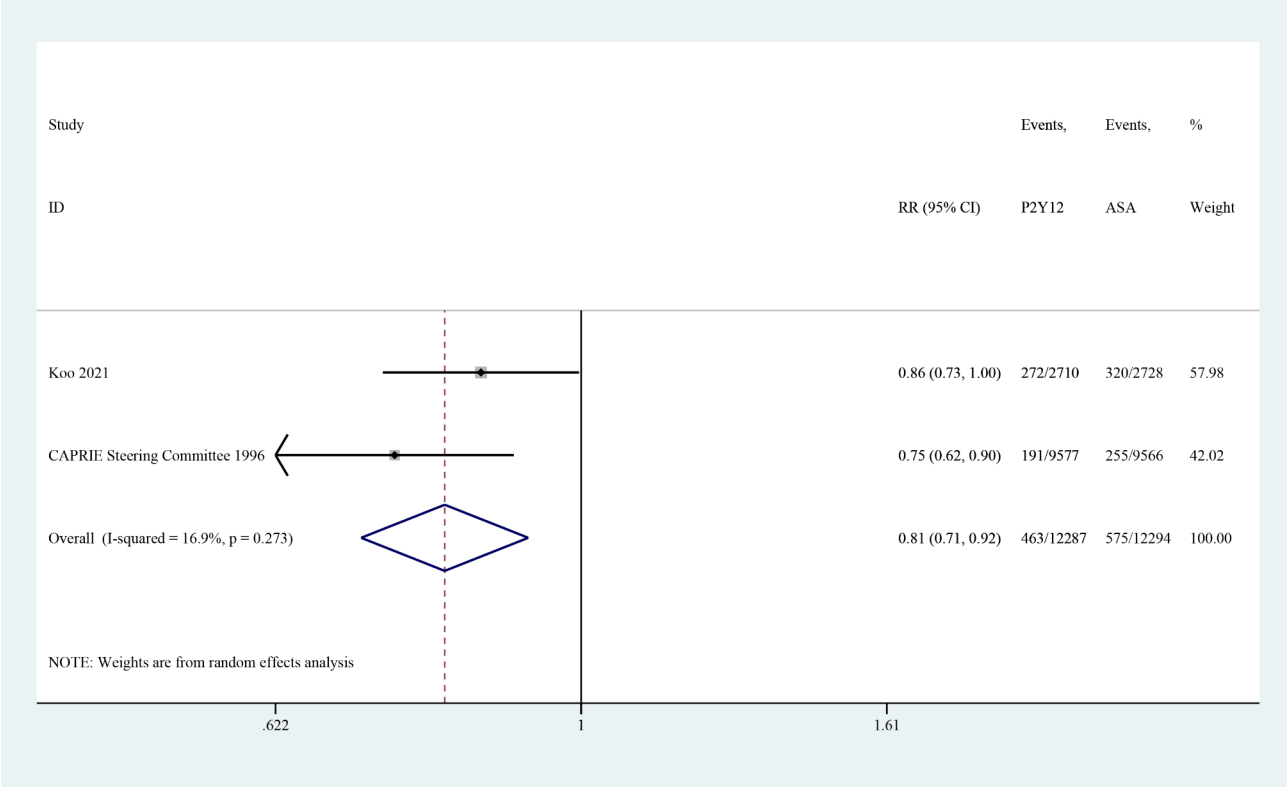


Fig. 10 Forest plot of comparison: P2Y12 vs. aspirin; outcome: Gastrointestinal complications

Table 4 Meta-Regression analysis of age and sex as a covariate on bleeding events and major bleeding events

Outcomes	Covariate	Coefficient	SE	Z	*P*	95% CI
Bleeding events	Age	0.060	0.023	0.011	0.014	0.014, 0.106
	Sex	0.090	0.118	0.76	0.446	-0.142, 0.322
Major bleeding events	Age	0.082	0.033	2.44	0.015	0.016, 0.147
	Sex	0.121	0.142	0.85	0.394	-0.157, 0.399

Conclusion

Compared to aspirin, P2Y12 inhibitors, particularly clopidogrel, reduce the risk of myocardial infarction and hemorrhagic stroke without increasing major bleeding. However, no significant differences were observed in all-cause mortality, major bleeding events, or cardiac death. These findings suggest that P2Y12 inhibitors should not universally replace aspirin, particularly in broader patient populations. Treatment decisions should be individualized, considering specific secondary outcomes and patient risk factors. While genetic factors like CYP2C19 polymorphisms may play a role, this study did not directly assess genetic data, warranting further research. Future studies should focus on identifying the patient subgroups that benefit most from P2Y12 inhibitors and evaluating their long-term effects in diverse populations.

Abbreviations

RCT Randomized Controlled Trials
CAD Coronary Heart Disease
MI Myocardial Infarction
RR Risk Ratios
CI Confidence Intervals
DAPT Dual Antiplatelet Therapy
ACS Acute Coronary Syndrome
MACE Major Adverse Cardiovascular Events
PCI Percutaneous Coronary Intervention
CABG Coronary Artery Bypass Grafting
BARC Bleeding Academic Research Consortium
GI Gastrointestinal
OR Odds Ratios

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Author contributions

ZW contributed to study design, data collection, statistical analysis, and manuscript drafting. SZ assisted in literature search, data extraction, statistical analysis, and manuscript revision. JZ contributed to data collection, quality assessment of included studies, and critical review of the manuscript. ZJ supervised the study, provided methodological guidance, and contributed to manuscript editing and final approval. YR provided clinical expertise, assisted in interpreting results, and contributed to manuscript revision and final approval.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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