

3 Original article

4 Aspirin versus clopidogrel monotherapy 5 after dual antiplatelet therapy in coronary 6 artery disease: a systematic review and 7 meta-analysis

8 Saud Ali Almutairi^{1*}, Yazeed Mohammed Alruwaili¹, Hussam Mohammed
9 Alwaily¹, Tariq Abdullah Alhafi¹, Hussam Yousef Altuwaijri¹, Mohammad
10 Abdulsamad Alhamoud¹, Saleh Abdulaziz Alghadeer²

11 ABSTRACT

12 **Background:** Aspirin has traditionally been the standard antiplatelet therapy after discontinuation of dual
13 antiplatelet therapy (DAPT) following percutaneous coronary intervention. However, emerging evidence sug-
14 gests that clopidogrel may offer comparable or potentially better outcomes. This study compared the efficacy
15 and safety of aspirin versus clopidogrel monotherapy in patients with coronary artery disease (CAD).

16 **Methods:** We performed a systematic review and meta-analysis in accordance with the Preferred Reporting
17 Items for Systematic Reviews and Meta-Analyses guidelines. The protocol was registered in the International
18 Prospective Register of Systematic Reviews (CRD420251101793). PubMed, Google Scholar, and the Cochrane
19 Library were searched from inception to August 2025 for randomized controlled trials and observational stud-
20 ies comparing aspirin with clopidogrel monotherapy after DAPT. Outcomes included myocardial infarction
21 (MI), stroke, major and minor bleeding, cardiovascular mortality, revascularization, and stent thrombosis. Risk
22 ratios (RRs) with 95% confidence intervals (CIs) were pooled using a random-effects model.

23 **Results:** Seven studies involving more than 15,000 patients were included. Aspirin was associated with a
24 significantly higher risk of stroke than clopidogrel (RR 1.51, 95% CI: 1.06-2.15, $p = 0.024$). No significant differ-
25 ences were observed in MI (RR 1.06, 95% CI: 0.74-1.53, $p = 0.738$), major bleeding (RR 1.16, 95% CI: 0.78-1.75,
26 $p = 0.463$), minor bleeding (RR 1.43, 95% CI: 0.72-2.82, $p = 0.304$), cardiovascular mortality (RR 1.14, 95% CI:
27 0.87-1.50, $p = 0.331$), revascularization (RR 1.07, 95% CI: 0.91-1.27, $p = 0.401$), or stent thrombosis (RR 1.53,
28 95% CI: 0.81-2.89, $p = 0.193$).

29 **Conclusion:** Clopidogrel and aspirin showed no significant differences in most evaluated outcomes after DAPT.
30 Clopidogrel was associated with a lower risk of stroke without a significant increase in major or minor bleed-
31 ing, supporting its use as an alternative to aspirin for long-term maintenance therapy.

32 **Keywords:** Coronary artery disease, clopidogrel, aspirin, percutaneous coronary intervention, dual antiplate-
33 let therapy.

34 Introduction

35 Coronary artery disease (CAD) remains a major cause
36 of morbidity and mortality worldwide, accounting for
37 ~17.9 million deaths annually [1]. Atherosclerotic plaque
38 formation and subsequent plaque rupture can trigger
39 platelet activation and coronary thrombosis, leading to
40 acute coronary syndromes, myocardial infarction (MI),
41 and sudden cardiac death [2,3].

Correspondence to: Saud Ali Almutairi

*College of Medicine, King Saud bin Abdulaziz University
for Health Sciences (KSAU-HS), Riyadh, Saudi Arabia.

Email: saudali2902@gmail.com

Full list of author information is available at the end of
the article.

Received: 27 August 2026 | Accepted: 08 October 2026



Antiplatelet therapy is central to the management of CAD, particularly after percutaneous coronary intervention (PCI) with stent implantation. Dual antiplatelet therapy (DAPT), typically consisting of aspirin and a P2Y12 inhibitor such as clopidogrel, reduces stent thrombosis and recurrent ischemic events [4,5]. However, prolonged DAPT may increase bleeding risk, requiring careful assessment of the balance between ischemic and bleeding risks [6].

Following DAPT, patients are commonly transitioned to single antiplatelet therapy for long-term secondary prevention [7]. Aspirin, an irreversible cyclooxygenase-1 inhibitor, has traditionally been used for this purpose because of its established efficacy, low cost, and availability [8]. However, long-term aspirin use is associated with gastrointestinal bleeding and, in some populations, intracranial hemorrhage [9]. Clopidogrel, a P2Y12 receptor antagonist, has emerged as an alternative to aspirin [10], with recent randomized evidence, including the SMART-CHOICE 3 trial, supporting its use as long-term monotherapy [11]. Previous meta-analyses have also suggested that clopidogrel may be an effective alternative to aspirin [12].

Current guidelines continue to support aspirin for long-term secondary prevention while recognizing clopidogrel as an alternative in selected patients [13,14]. Recent comparative evidence, however, has raised questions regarding the relative efficacy and safety of these two strategies after DAPT [11,12]. The evolving landscape of antiplatelet therapy following PCI has further emphasized the importance of individualized treatment strategies that balance ischemic protection against bleeding risk [15]. Therefore, this systematic review and meta-analysis compared aspirin and clopidogrel monotherapy following DAPT in patients with CAD, evaluating MI, stroke, major and minor bleeding, cardiovascular mortality, revascularization, and stent thrombosis.

Methods

Literature search strategy

This systematic review was prospectively registered in the International Prospective Register of Systematic Reviews (CRD420251101793) [16] and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17]. PubMed, Google Scholar, and the Cochrane Library were searched from inception to August 2025. Reference lists of relevant studies were also screened to identify additional eligible articles. The following search terms were used: (coronary artery disease OR CAD OR ischemic heart disease OR atherosclerosis) AND (clopidogrel OR Plavix) AND (aspirin OR acetylsalicylic acid) AND (monotherapy OR single antiplatelet therapy) AND (dual antiplatelet therapy OR DAPT) AND (secondary prevention OR cardiovascular events OR myocardial infarction OR stroke OR bleeding OR mortality).

Study eligibility criteria

Studies were eligible if they: (1) were published in English; (2) were randomized controlled trials (RCT) or observational studies; (3) compared clopidogrel with aspirin monotherapy following DAPT in adults with CAD; (4) included participants aged 18 years or older; and (5) reported cardiovascular outcomes, mortality, or adverse effects related to antiplatelet therapy. Studies were excluded if they: (1) were published in a language other than English; (2) were case reports, reviews, or editorials; (3) included pediatric populations; (4) were considered to have a high risk of bias or low methodological quality; or (5) did not evaluate aspirin or clopidogrel as monotherapy following DAPT.

Study selection and data extraction

Records identified through the database searches were imported into Rayyan for duplicate removal and screening [18]. Two reviewers independently screened titles and abstracts to identify potentially eligible studies. The full texts of potentially eligible articles were then independently assessed by two reviewers, with disagreements resolved by a third reviewer. Data were independently extracted by two reviewers and included study characteristics (authors, publication year, and study design); participant characteristics [sample size, treatment group, age, sex, and body mass index (BMI)]; clinical outcomes, including MI, stroke, major and minor bleeding, cardiovascular mortality, repeat revascularization, and stent thrombosis; follow-up duration; and comorbidities. Disagreements during data extraction were resolved by consensus.

Quality and risk-of-bias assessment

The Newcastle–Ottawa Scale was used to assess the methodological quality of observational studies [19]. Scores range from 0 to 9, with scores of 7–9 considered high quality with low risk of bias, 4–6 indicating moderate risk of bias, and 0–3 indicating high risk of bias. RCTs were assessed using the Cochrane Risk of Bias 2 tool [20]. The tool evaluates five domains of potential bias using signaling questions and assigns an overall judgment of low risk, some concerns, or high risk of bias. Risk-of-bias assessments were performed independently by two reviewers, with disagreements resolved through consensus after consultation with senior authors.

Statistical analysis

The meta-analysis was conducted using RStudio with the metafor package. Risk ratios (RR) with 95% confidence intervals (CIs) were calculated for all dichotomous outcomes. A random-effects model was applied using the inverse-variance method, with between-study variance (τ^2) estimated by restricted maximum likelihood. Heterogeneity was assessed using Cochran's Q test and quantified using the I^2 statistic. Forest plots were used to display pooled estimates, and publication bias was visually assessed using funnel plots. All analyses used a two-sided significance level of 0.05. Subgroup analyses by study design were not performed because of the limited number of studies within each category,

160 particularly RCTs, which could have produced unstable
161 and underpowered subgroup estimates.

162 Results

163 Seven studies comparing aspirin with clopidogrel
164 monotherapy following DAPT were included. Two
165 were large RCTs from South Korea, including 5,438
166 and 5,506 patients, respectively [11,21]. The remaining
167 five studies were observational and were conducted in
168 Korea, Japan, and China [22-26]. Sample sizes in the
169 observational studies ranged from 755 patients in the
170 Chinese retrospective study by Zhuang et al. [22] to
171 more than 3,000 patients in the Korean registry analysis
172 by Park et al. [26]. Clopidogrel groups were generally
173 smaller than aspirin groups, particularly in registry-based
174 studies [24,26] (Table 1).

175 Baseline demographic characteristics are presented in
176 Table 2. Mean or median ages ranged from the early 60s
177 to ~70 years. Sim et al. [24] reported mean ages of ~61
178 years in both treatment groups, whereas participants in
179 the Japanese observational study by Natsuaki et al. [23]
180 were older, with mean ages approaching 70 years.

181 Men represented the majority of participants in studies
182 reporting sex distribution [11,21]. Female representation
183 was lower but generally balanced between treatment
184 groups within individual studies. BMI was also
185 comparable between aspirin and clopidogrel groups and
186 was generally in the mid-20 kg/m² range [11,23,24].

187 Cardiovascular risk factors were common, particularly
188 hypertension, diabetes mellitus, dyslipidemia, and
189 chronic kidney disease [11,21,26]. Several cohorts also
190 included patients with a history of smoking, stroke,
191 atrial fibrillation, heart failure, or multivessel disease
192 [22,24,25]. Baseline renal function was comparable
193 between treatment groups, with creatinine values of
194 ~1.0 mg/dl or 80-90 µmol/l [11,21]. Prior MI was also
195 common, particularly in the larger studies [11,26] (Table
196 3).

197 As shown in Table 4, aspirin was administered at 100
198 mg once daily in studies reporting dosage. Clopidogrel
199 was predominantly administered at 75 mg once daily,
200 except in Zhuang et al. [22], which included both 25 and
201 75 mg/day regimens. Treatment duration ranged from 1
202 month in Natsuaki et al. [23] to 24 months in Sim et al.
203 [23], although most studies used a 12-month antiplatelet
204 strategy after DAPT [22,25,26]. Follow-up ranged from

Table 1. Characteristics of included studies comparing aspirin versus clopidogrel monotherapy after DAPT.

Author	Country	Study design	Aspirin (N)	Clopidogrel (N)	Total (N)
Koo et al. [21]	South Korea	RCT	2,728	2,710	5,438
Choi et al. [11]	South Korea	RCT	2,754	2,752	5,506
Zhuang et al. [22]	China	Retrospective observational	283	472	755
Natsuaki et al. [23]	Japan	Observational	1,339	1,480	2,819
Sim et al. [24]	South Korea	Prospective observational	1,286	533	1,819
Lan et al. [25]	China	Retrospective cohort observational	582	422	1,004
Park et al. [26]	South Korea	Observational registry (landmark analysis after DAPT)	2,472	771	3,243

Table 2. Baseline demographic characteristics of included studies.

Author (year)	Age (years)			Males (N)			Females (N)			BMI		
	Aspirin	Clopidogrel	Total	Aspirin	Clopidogrel	Total	Aspirin	Clopidogrel	Total	Aspirin	Clopidogrel	Total
Koo et al. [21]	63.4 ± 10.7	63.5 ± 10.7	NR	2,039	2,015	4,054	689	695	1,384	NR	NR	NR
Choi et al. [11]	65.0 (58.0-73.0)	66.0 (58.0-73.0)	NR	2,264	2,240	4,504	490	512	1,002	24.8 (23.1-26.9)	24.9 (23.0-27.0)	NR
Zhuang et al. [22]	68.3 ± 7.8	69.2 ± 5.7 (25 mg) 70.1 ± 6.2 (75 mg)	NR	NR	NR	NR	NR	NR	NR	24.9 ± 4.1	25.1 ± 3.2 (25 mg) 26.6 ± 4.7 (75 mg)	NR
Natsuaki et al. [23]	69.7 ± 10.7	68.1 ± 10.8	NR	973	1,170	2,143	366	310	676	24.1 ± 3.6	24.4 ± 3.5	NR
Sim et al. [24]	61.1 ± 11.7	60.9 ± 11.7	NR	1,006	418	1,424	280	115	395	24.1 ± 3.0	24.1 ± 3.3	NR
Lan et al. [25]	62.62 ± 12.44	66.38 ± 11.67	NR	453	321	774	129	101	230	24.96 ± 3.30	24.80 ± 3.77	NR
Park et al. [26]	62 (53-69)	64 (56-71)	NR	1,811	570	2,381	661	201	862	NR	NR	NR

Table 3. Baseline comorbidities, renal function, and prior MI across aspirin- and clopidogrel-treated cohorts.

Author (year)	Key comorbidities		Baseline creatinine	Prior MI		
	Aspirin	Clopidogrel		Aspirin	Clopidogrel	Total
Koo et al. [21]	DM: 935 HTN: 1,674 Dyslipidemia: 1,883 Current smoker: 581 CKD: 337	DM: 925 HTN: 1,664 Dyslipidemia: 1,884 Current smoker: 545 CKD: 356	1.0 ± 0.7 mg/d; (both)	435	437	872
Choi et al. [11]	Hypertension: 1,690 Diabetes: 1,128 Dyslipidaemia: 1,604 CKD: 260 Previous stroke: 66 PVD: 22 Current smoking: 488	Hypertension: 1,756 Diabetes: 1,119 Dyslipidaemia: 1,626 CKD: 242 Previous stroke: 76 PVD: 23 Current smoking: 448	86 ± 20 µmol/l (both)	1,269	1,283	2,552
Zhuang et al. [22]	Hypertension: 192 Stroke history: 73 Multivessel disease: 188 Prior MI: 47 CKD: 42	Hypertension: 149 Stroke history: 51 Multivessel disease: 153 Prior MI: 107 CKD: 33	NR	47	107	154
Natsuaki et al. [23]	Hypertension: 1,107 Diabetes mellitus: 522 Dyslipidemia: 1,069 CKD (all stages): 514	Hypertension: 1,090 Diabetes mellitus: 578 Dyslipidemia: 1,102 CKD (all stages): 621	NR	224	206	430
Sim et al. [24]	Hypertension: 592 Diabetes mellitus: 275 Dyslipidemia: 171 Smoking: 809 Prior MI: 38 Heart failure: 5	Hypertension: 244 Diabetes mellitus: 110 Dyslipidemia: 70 Smoking: 336 Prior MI: 15 Heart failure: 10	0.9 mg/dl	38	15	53
Lan et al. [25]	Hypertension: 335 Diabetes mellitus: 174 Hypertriglyceridemia: 107 CKD: 18 Atrial fibrillation: 24 MI history: 48 DES history: 94 Smoking: 339	Hypertension: 308 Diabetes mellitus: 129 Hypertriglyceridemia: 88 CKD: 21 Atrial fibrillation: 44 MI history: 43 DES history: 84 Smoking: 230	78-84 µmol/l	48	43	91
Park et al. [26]	Hypertension: 1,315 Diabetes mellitus: 834 Dyslipidemia: 705 CKD: 199 Prior MI: 469 Prior PCI: 243 Prior CABG: 63 Prior stroke: 79 Current smoking: 429	Hypertension: 497 Diabetes mellitus: 325 Dyslipidemia: 258 CKD: 79 Prior MI: 142 Prior PCI: 109 Prior CABG: 26 Prior stroke: 47 Current smoking: 174	NR	469	142	611

12 months to a median of 2.3 years, with some cohorts followed for 3 years or longer [22,26]. Concomitant cardiovascular therapy commonly included statins, beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers [11,21].

Risk of bias and quality assessment

Both RCTs were judged to have some concerns regarding overall risk of bias, mainly because of potential deviations from the intended interventions; the remaining domains were rated as low risk (Table 5). Among the five cohort studies, one had a Newcastle–Ottawa Scale score of 9, two scored 8, one scored 7, and one scored 6 (Table 6). Four cohort studies were therefore considered to have a low risk of bias, while one had a moderate risk of bias.

Meta-analysis of clinical outcomes

Aspirin was associated with a significantly higher risk of stroke than clopidogrel (RR 1.51, 95% CI: 1.06-2.15, $p = 0.024$), with low heterogeneity ($I^2 = 23.8\%$) (Figure

3). No significant difference was observed in MI (RR 1.06, 95% CI: 0.74-1.53, $p = 0.738$), with moderate heterogeneity ($I^2 = 51.1\%$) (Figure 2).

Major bleeding did not differ significantly between aspirin and clopidogrel (RR 1.16, 95% CI: 0.78-1.75, $p = 0.463$), with moderate heterogeneity ($I^2 = 43.2\%$) (Supplementary Figure 1). Similarly, there was no significant difference in minor bleeding (RR 1.43, 95% CI: 0.72-2.82, $p = 0.304$), although heterogeneity was substantial ($I^2 = 76.9\%$) (Supplementary Figure 2).

No significant difference was observed in cardiovascular mortality (RR 1.14, 95% CI: 0.87-1.50, $p = 0.331$), with low heterogeneity ($I^2 = 10.0\%$) (Figure 4). Revascularization was also comparable between the two groups (RR 1.07, 95% CI: 0.91-1.27, $p = 0.401$), with no observed heterogeneity ($I^2 = 0.0\%$) (Supplementary Figure 3). Similarly, stent thrombosis did not differ significantly between aspirin and clopidogrel (RR 1.53, 95% CI: 0.81-2.89, $p = 0.193$), with minimal heterogeneity ($I^2 = 3.1\%$) (Supplementary Figure 4).

Table 4. Antiplatelet therapy duration, dosing regimens, follow-up periods, and background cardiovascular medication use in included studies.

Author (year)	Duration of APT		Dosage		Follow-up	Previous medication use	
	Aspirin	Clopidogrel	Aspirin	Clopidogrel		Aspirin	Clopidogrel
Koo et al. [21]	6-18 mo	6-18 mo	100 mg once daily	75 mg once daily	12 and 24 mo	ASA + Clopi: 2,212 ASA + Tica: 268 ASA + Pras: 235 ASA + Clopi + Cilo: 13	ASA + Clopi: 2,218 ASA + Tica: 266 ASA + Pras: 212 ASA + Clopi + Cilo: 14
Choi et al. [11]	6-12 mo	6-12 mo	100 mg once daily	75 mg once daily	Median 2.3 yrs	Statin: 2,714 Eze: 1,730 BB: 1,565 ACEI/ARB: 1,762 GI med: 844 PPI: 589 P-CAB: 115 H2B/other: 150	Statin: 2,708 Eze: 1,717 BB: 1,524 ACEI/ARB: 1,755 GI med: 792 PPI: 545 P-CAB: 100 H2B/other: 153
Zhuang et al. [22]	12 mo	12 mo	100 mg once daily	25 or 75 mg/day	36 ± 2.4 mo	ACEI: 75 ARB: 139 BB: 231 Statin: 224	ACEI: 59 ARB: 108 BB: 185 Statin: 185
Natsuaki et al. [23]	3 mo	1 mo	100 mg once daily	75 mg once daily	12 mo	ASA: 100% Thieno: 99.9% Clopi: 1,325 Ticlo: 12 Statin: 1,077 BB: 506 ACEI/ARB: 823 CCB: 597 Nitrate: 192	ASA: 1,479 Thieno: 100% Clopi: 891 Ticlo: 2 Prasu: 587 Statin: 1301 BB: 664 ACEI/ARB: 921 CCB: 557 Nitrate: 176
Sim et al. [24]	24 mo	24 mo	100 mg once daily	75 mg once daily	24 mo	BB: 1,010 ACEI/ARB: 932 Statin: 1234	BB: 418 ACEI/ARB: 381 Statin: 508
Lan et al. [25]	12 mo	12 mo	100 mg once daily	75 mg once daily	25 ± 8 mo	ACEI/ARB: 460 BB: 456 Statin: 579	ACEI/ARB: 315 BB: 321 Statin: 419
Park et al. [26]	12 mo	12 mo	100 mg once daily	75 mg once daily	36 mo	NR	NR

Table 5. Risk of bias assessment of included studies.

	Randomization process	Deviations from intended intervention	Missing outcome Data	Measurement of the outcome	Selection of the reported result	Overall risk of bias
Koo et al. [21]	Low risk	Unclear risk	Low risk	Low risk	Low risk	Some concern
Choi et al. [11]	Low risk	Unclear risk	Low risk	Low risk	Low risk	Some concerns

Table 6. The Newcastle-Ottawa Scale for the included cohort prospective and retrospective studies.

	Selection				Comparability	Outcome			Quality Score	Risk of bias (0-3: high, 4-6: moderate, 7-9: low)
Article	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8		
Zhuang et al. [22]		★	★	★		★	★	★	Moderate Quality Study (6)	Moderate risk
Natsuaki et al. [23]		★	★	★	★	★	★	★	Good Quality Study (7)	Low risk
Sim et al. [24]	★	★	★	★	★★	★	★	★	Good Quality Study (9)	Low risk
Lan et al. [25]		★	★	★	★★	★	★	★	Good Quality Study (8)	Low risk
Park et al. [26]		★	★	★	★★	★	★	★	Good Quality Study (8)	Low risk

Selection: Q1. Representativeness of the exposure cohort? Q2. Selection of the non-exposure cohort? Q3. Ascertainment of exposure? Q4. Demonstration that the outcome of interest was not present at the start of the study?

Comparability: Q5. Comparability of cohort on the basis of the design or analysis?

Outcome: Q6. Assessment of outcome? Q7. Was follow-up long enough for outcomes to occur? Q8. Adequacy of follow-up of cohorts?

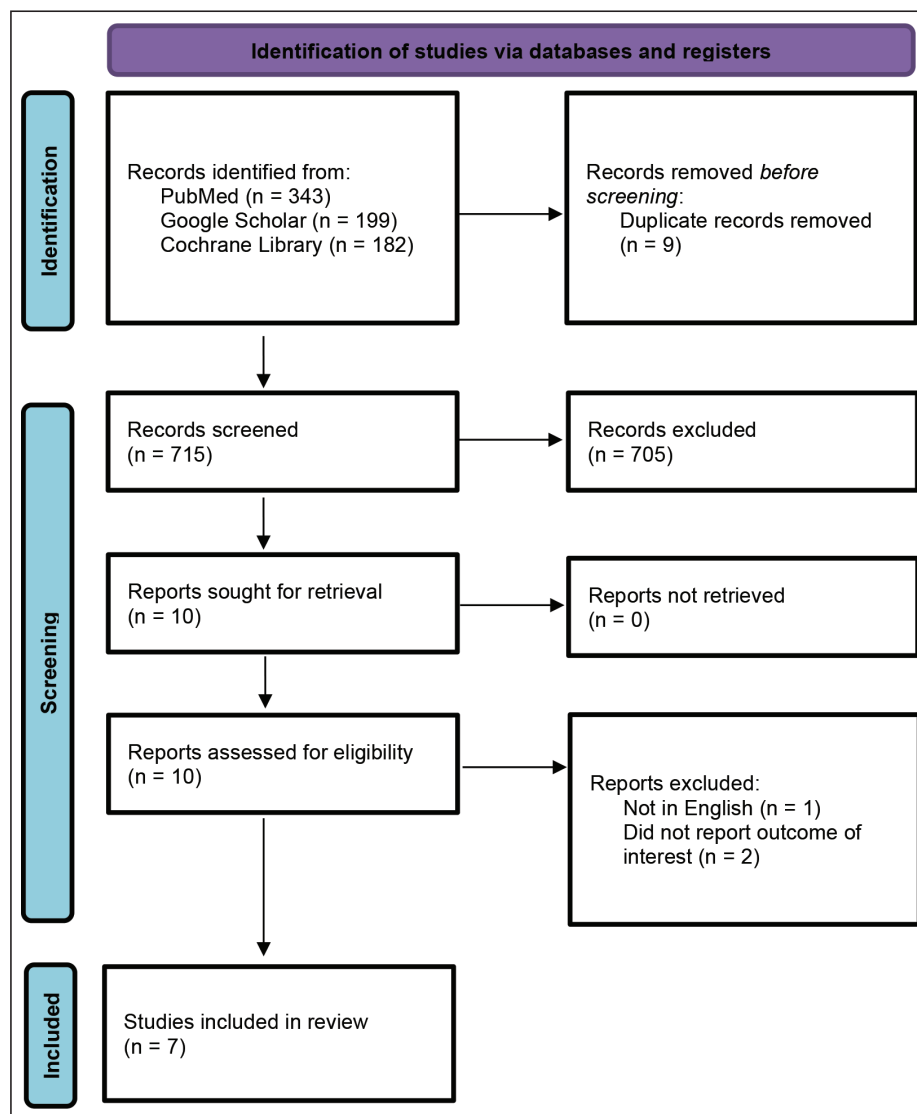


Figure 1. PRISMA 2020 flow diagram for new systematic reviews that included searches of databases and registers only.

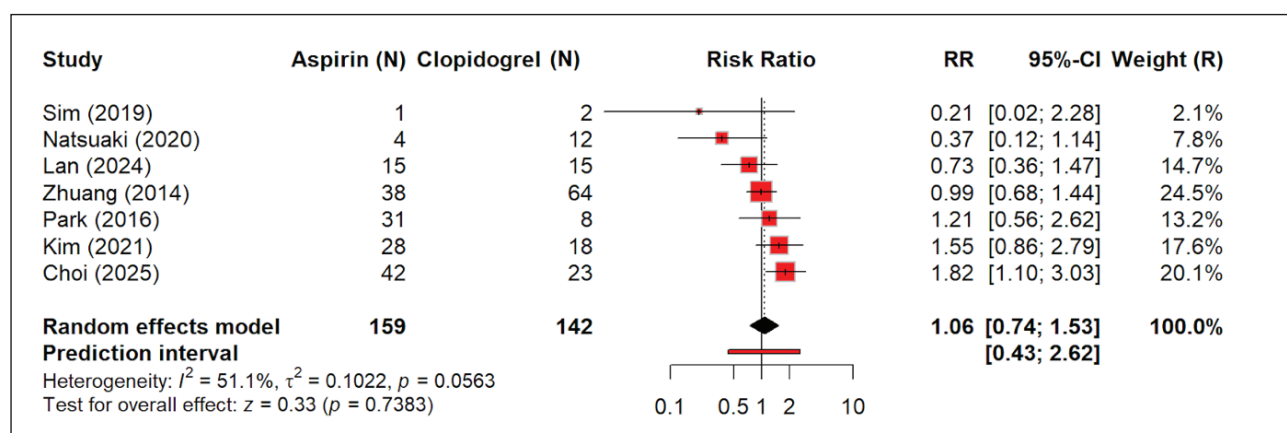


Figure 2. Risk of post-intervention MI between aspirin and clopidogrel.

Publication bias

Publication bias was visually assessed using a funnel plot (Supplementary Figure 5). The distribution of studies

was reasonably symmetrical around the pooled estimate, with no clear pattern of asymmetry suggesting substantial small-study effects.

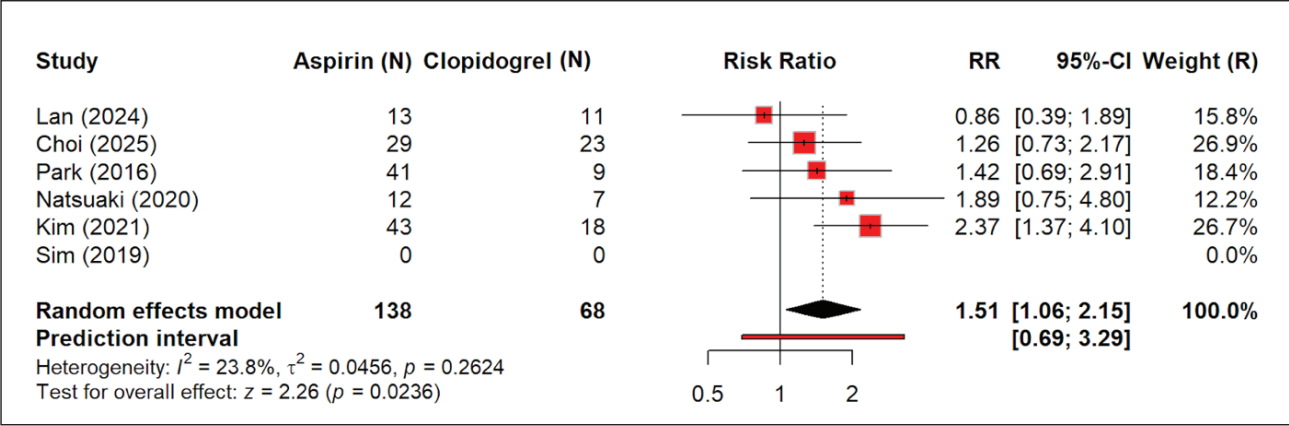


Figure 3. Risk of post-intervention stroke between aspirin and clopidogrel.

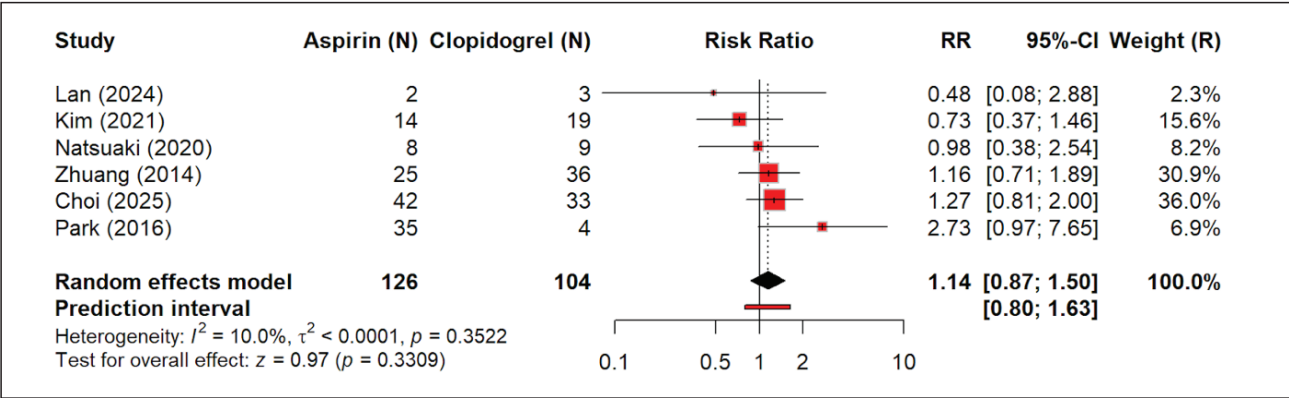


Figure 4. Risk of CVD mortality between aspirin and clopidogrel.

Discussion

This systematic review and meta-analysis found no significant differences between aspirin and clopidogrel monotherapy after DAPT in MI, major or minor bleeding, cardiovascular mortality, revascularization, or stent thrombosis. However, aspirin was associated with a significantly higher risk of stroke. The low heterogeneity for this outcome indicates that the direction of the stroke finding was generally consistent across the included studies.

Post-intervention stroke risk

The lower stroke risk with clopidogrel is consistent with previous post-PCI evidence, although some randomized studies have not found a significant difference between the two strategies [27,28]. Low event rates, shorter follow-up, and limited statistical power for stroke may partly explain this discrepancy. A possible explanation for our finding is the different platelet pathways targeted by the two drugs. Clopidogrel inhibits adenosine diphosphate-mediated platelet activation through the P2Y12 receptor, whereas aspirin primarily inhibits thromboxane production. Differences in these pathways and variability in individual platelet response could influence protection against thrombotic events across vascular beds. However, the present analysis cannot establish a causal mechanism for the observed reduction in stroke.

Recurrent MI

No significant difference in recurrent MI was observed between aspirin and clopidogrel, consistent with previous post-PCI meta-analyses after DAPT completion [27]. In contrast, SMART-CHOICE 3 reported a significantly lower risk of MI with clopidogrel among patients at high risk of recurrent ischemic events after PCI [11]. That trial specifically included patients with previous MI, medication-treated diabetes, or complex coronary lesions. Differences in baseline ischemic risk may therefore partly explain why its findings differ from our pooled estimate.

Bleeding risk

Major and minor bleeding did not differ significantly between the two monotherapy strategies, in line with previous post-PCI evidence [27]. Similarly, Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-3 reported comparable rates of major bleeding, defined as Bleeding Academic Research Consortium type 3 or 5 bleeding, between 1 month and 1 year after PCI [28]. Differences in bleeding definitions and baseline bleeding risk across the included populations may have contributed to variation in event rates and pooled estimates. <AQ3>

303	Cardiovascular mortality	359
304	Cardiovascular mortality was also similar between	360
305	aspirin and clopidogrel, consistent with previous post-	361
306	DAPT evidence [27]. Randomized post-PCI comparisons	
307	have likewise shown limited evidence of a mortality	
308	difference, although low event rates and relatively short	
309	follow-up may reduce the ability to detect one [28].	
310	Therefore, our findings do not support a cardiovascular	
311	mortality advantage for either monotherapy strategy.	
312	Revascularization	
313	No significant difference in revascularization was	
314	observed between aspirin and clopidogrel, consistent	
315	with previous evidence after DAPT completion [27].	
316	Based on the available data, revascularization does not	
317	appear to distinguish the two strategies during long-term	
318	maintenance therapy.	
319	Stent thrombosis	
320	Stent thrombosis did not differ significantly between	
321	aspirin and clopidogrel, consistent with previous post-	
322	PCI evidence [27,28]. The small number of stent	
323	thrombosis events may have limited the ability to detect	
324	modest differences between treatments. Procedural	
325	complexity and baseline ischemic risk may also have	
326	contributed to variation across studies [29]. The available	
327	evidence therefore does not show a clear advantage of	
328	either strategy for preventing stent thrombosis.	
329	Limitations	
330	A few limitations must be acknowledged. First, although	
331	this meta-analysis included two large contemporary	
332	RCTs, a proportion of the pooled data was derived	
333	from observational studies, which are inherently	
334	subject to residual confounding despite adjustment.	
335	Separate analyses according to study design were not	
336	performed because of the limited number of studies	
337	within each subgroup; therefore, the pooled estimates	
338	should be interpreted with caution. Second, the included	
339	populations were predominantly East Asian, which may	
340	limit generalizability to other ethnic groups with different	
341	ischemic and bleeding risk profiles. Finally, variability in	
342	antiplatelet duration and follow-up periods across studies	
343	may have contributed to moderate heterogeneity for some	
344	outcomes. Despite these limitations, the consistency of	
345	findings across multiple clinically relevant endpoints	
346	strengthens the overall conclusions.	
347	Conclusion	
348	After DAPT discontinuation, clopidogrel and aspirin	
349	monotherapy provide comparable protection against	
350	coronary ischemic events, bleeding, cardiovascular	
351	mortality, revascularization, and stent thrombosis.	
352	Clopidogrel is, however, associated with a lower risk of	
353	stroke without increased bleeding, indicating a potential	
354	cerebrovascular advantage during maintenance therapy.	
355	Accordingly, clopidogrel represents a reasonable	
356	alternative to aspirin in contemporary post-PCI care,	
357	particularly for patients at higher cerebrovascular risk.	
358	Future randomized studies with longer follow-up and	
	diverse populations are warranted to better define patient	359
	subgroups most likely to derive incremental benefit from	360
	P2Y12-based maintenance therapy.	361
	List of Abbreviations	362
	ACE Angiotensin-converting enzyme inhibitors	363
	ARB Angiotensin receptor blocker	364
	BMI Body mass index	365
	CAD Coronary artery disease	366
	DAPT Dual antiplatelet therapy	367
	MI Myocardial infarction	368
	PCI Percutaneous coronary intervention	369
	PPI Proton Pump Inhibitor	370
	PRISMA Preferred Reporting Items for Systematic Reviews	371
	and Meta-Analyses	372
	RCT Randomized controlled trial	373
	Conflict of interests	374
	The authors declare that there is no conflict of interest	375
	regarding the publication of this article.	376
	Funding	377
	None.	378
	Consent for participation	379
	Not applicable.	380
	Ethical approval	381
	Not applicable.	382
	Author details	383
	Saud Ali Alumtairi ¹ , Yazeed Mohammed Alruwaili ¹ , Hussam	384
	Mohammed Alwaili ¹ , Tariq Abdullah Alhafi ¹ , Hussam Yousef	385
	Altuwaijri ¹ , Mohammad Abdulsamad Alhamoud ¹ , Saleh	386
	Abdulaziz Alghadeer ²	387
	1. College of Medicine, King Saud bin Abdulaziz University	388
	for Health Sciences (KSAU-HS), Riyadh, Saudi Arabia	389
	2. Department of Cardiology, Ministry of National Guard	390
	Hospital, Riyadh, Saudi Arabia	391
	<i>Supplementary content (If any) is available online.</i>	392
	References	393
	1. World Health Organization. Cardiovascular diseases	394
	(CVDs). Geneva, Switzerland: WHO; 2024. Available from:	395
	https://www.who.int/news-room/fact-sheets/detail/	396
	cardiovascular-diseases-(cvds)	397
	2. Libby P, Buring JE, Badimon L, Hansson GK, Deanfield	398
	J, Bittencourt MS, et al. Atherosclerosis. Nat Rev Dis	399
	Primers. 2019;5(1):56. https://doi.org/10.1038/s41572-	400
	019-0106-z	401
	3. Jackson SP. Arterial thrombosis-insidious, unpredictable	402
	and deadly. Nat Med. 2011;17(11):1423–36. https://doi.	403
	org/10.1038/nm.2515	404
	4. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F,	405
	Jeppsson A, et al. 2021 ESC guidelines for cardiovascular	406
	revascularization. Eur Heart J. 2022;43(4):381–500.	407
	5. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk	408
	V, et al. 2014 ESC/EACTS Guidelines on myocardial	409
	revascularization. Eur Heart J. 2014;35(37):2541–619.	410
	https://doi.org/10.1093/eurheartj/ehu278	411
	6. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P,	412
	Cutlip DE, Steg PG, et al. Twelve or 30 months of dual	413
	antiplatelet therapy after drug-eluting stents. N Engl J	414

- Med. 2014;371(23):2155–66. <https://doi.org/10.1056/NEJMoa1409312>
7. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2016;68(10):1082–115. <https://doi.org/10.1016/j.jacc.2016.03.513>
8. Patrono C, Baigent C. Role of aspirin in secondary prevention of cardiovascular disease. *J Am Coll Cardiol.* 2019;74(12):1506–21.
9. Lanan A, Wu P, Medin J, Mills EJ. Low doses of acetylsalicylic acid increase risk of gastrointestinal bleeding: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2011;9(9):762–8.e6. <https://doi.org/10.1016/j.cgh.2011.05.020>
10. Gurbel PA, Bliden KP, DiChiara J, Tantry US. Clopidogrel for coronary artery disease: mechanism of action, variability, and clinical efficacy. *Thromb Haemost.* 2005;93(2):256–66.
11. Choi KH, Park YH, Lee JY, Jeong JO, Kim CJ, Yun KH, et al.; SMART-CHOICE 3 investigators. Efficacy and safety of clopidogrel versus aspirin monotherapy in patients at high risk of subsequent cardiovascular event after percutaneous coronary intervention (SMART-CHOICE 3): a randomised, open-label, multicentre trial. *Lancet.* 2025;405(10486):1252–63. [https://doi.org/10.1016/S0140-6736\(25\)00449-0](https://doi.org/10.1016/S0140-6736(25)00449-0)
12. Wani SA, Naveed MA, Azeem B, Ashraf S, Ali A, Ali T, et al. Comparative outcomes of clopidogrel vs aspirin monotherapy in post-PCI patients: an updated systematic review and meta-analysis. *Cardiovasc Revasc Med.* 2025;80:122–30. <https://doi.org/10.1016/j.carrev.2025.06.006>
13. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al.; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* 2021;42(14):1289–367. <https://doi.org/10.1093/eurheartj/ehaa602>
14. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, et al.; Writing Committee Members. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization. *J Am Coll Cardiol.* 2022;79(2):e21–129.
15. Capodanno D, Angiolillo DJ, Bhatt DL, Byrne RA, Collet JP, Dangas GD, et al. Antiplatelet therapy after percutaneous coronary intervention: contemporary clinical practice and future directions. *Eur Heart J.* 2022;43(34):3243–56.
16. Almutairi S, Alruwaili Y, Alwaili H, Alhafi T, Altuwaijri H, Alhamoud M, et al. Aspirin versus clopidogrel monotherapy after dual antiplatelet therapy in coronary artery disease: a systematic review and meta-analysis. PROSPERO. 2025. Registration No.: CRD420251101793. Available from: <https://www.crd.york.ac.uk/PROSPERO/>
17. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372(71):n71. <https://doi.org/10.1136/bmj.n71>
18. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan: a web and mobile app for systematic reviews. *Syst Rev.* 2016 5;5(1):210. <https://doi.org/10.1186/s13643-016-0384-4>
19. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol.* 2010;25(9):603–5. <https://doi.org/10.1007/s10654-010-9491-z>
20. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:l4898. <https://doi.org/10.1136/bmj.l4898>
21. Koo BK, Kang J, Park KW, Rhee TM, Yang HM, Won KB, et al.; HOST-EXAM investigators. Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicentre trial. *Lancet.* 2021;397(10293):2487–96.
22. Zhuang XD, Long M, Li CL, Hu CH, Du ZM, Liao XX. Efficacy and safety of low-dose clopidogrel after 12-month dual antiplatelet therapy for patients having drug-eluting stent implantation. *J Thorac Dis.* 2014;6(5):459–65.
23. Natsuaki M, Morimoto T, Watanabe H, Abe M, Kawai K, Nakao K, et al.; STOPDAPT-1 and STOPDAPT-2 Trial Investigators. Clopidogrel monotherapy vs aspirin monotherapy following short-term dual antiplatelet therapy in patients receiving everolimus-eluting coronary stent implantation. *Circ J.* 2020;84(9):1483–92. <https://doi.org/10.1253/circj.CJ-20-0298>
24. Sim DS, Jeong MH, Kim HS, Gwon HC, Seung KB, Rha SW, et al.; KAMIR-NIH registry investigators. Clopidogrel versus aspirin after dual antiplatelet therapy in acute myocardial infarction patients undergoing drug-eluting stenting. *Korean Circ J.* 2020;50(2):120–9. <https://doi.org/10.4070/kcj.2019.0166>
25. Lan K, Gao H, Gong H. A retrospective study of the safety and efficacy of clopidogrel versus aspirin monotherapy one year after coronary stent implantation. *BMC Pharmacol Toxicol.* 2024;25(1):67. <https://doi.org/10.1186/s40360-024-00796-w>
26. Park TK, Song YB, Ahn J, Carriere KC, Hahn JY, Yang JH, et al. Clopidogrel versus aspirin as an antiplatelet monotherapy after 12-month dual-antiplatelet therapy in the era of drug-eluting stents. *Circ Cardiovasc Interv.* 2016;9(1):e002816. <https://doi.org/10.1161/CIRCINTERVENTIONS.115.002816>
27. Tan BE, Wong PY, Baibhav B, Thakkar S, Azhar AZ, Rao M, et al. Clopidogrel vs aspirin monotherapy following dual antiplatelet therapy after percutaneous coronary intervention: a systematic review and meta-analysis. *Curr Probl Cardiol.* 2023;48(8):101174. <https://doi.org/10.1016/j.cpcardiol.2022.101174>
28. Watanabe H, Natsuaki M, Morimoto T, Yamamoto K, Obayashi Y, Nishikawa R, et al. Aspirin vs. clopidogrel monotherapy after percutaneous coronary intervention: 1-year follow-up of the STOPDAPT-3 trial. *Eur Heart J.* 2024;45(47):5042–54. <https://doi.org/10.1093/eurheartj/ehae617>
29. Domei T, Yamamoto K, Natsuaki M, Watanabe H, Morimoto T, Obayashi Y, et al. Aspirin vs. clopidogrel monotherapy beyond 1 month after complex percutaneous coronary intervention: a pre-specified subgroup analysis of the STOPDAPT-3 trial. *Eur Heart J Cardiovasc Pharmacother.* 2025;11(2):198–209. <https://doi.org/10.1093/ehjcvp/pvaf002>