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Intervention

Risk–Benefit Profile of Oral Antiplatelet Strategies After Percutaneous Coronary Intervention with a Drug-eluting Stent: A Contemporary Network Meta-analysis of Major Bleeding and Stent Thrombosis Outcomes

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Abstract

Background: Optimal antiplatelet therapy after percutaneous coronary intervention (PCI) with drug-eluting stents (DES) requires balancing thrombotic protection and bleeding risk, but the comparative effectiveness of current strategies remains uncertain. **Aims:** To evaluate the risk–benefit profile of oral antiplatelet strategies after PCI with DES, focusing on major bleeding and stent thrombosis. **Methods:** A network meta-analysis of randomised and observational studies was conducted. Strategies included standard or extended dual antiplatelet therapy (DAPT), shortened DAPT followed by monotherapy and P2Y12 inhibitor-based monotherapy. Outcomes were analysed using a random-effects model and ranked with p-scores. Evidence certainty was assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE). **Results:** Thirty studies involving 110,035 patients were included. Ticagrelor monotherapy ranked highest for reducing major bleeding, whereas extended DAPT provided the greatest protection against stent thrombosis, with clopidogrel-based therapy beyond 12 months ranking highest (RR 0.08; 95% CI [0.01–0.52]; p-score=0.94). Notably, clopidogrel monotherapy after prolonged DAPT demonstrated a relatively balanced profile across both outcomes. However, no strategy was consistently optimal and most estimates showed wide CIs. **Conclusion:** Antiplatelet strategies after PCI with DES involve a clear trade-off between bleeding and thrombotic risk. Clopidogrel monotherapy after prolonged DAPT may offer a balanced approach, although findings should be interpreted cautiously due to limited precision and consistency.

Keywords

Antiplatelet therapy, drug-eluting stents, trade-off

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Cardiovascular disease remains the leading cause of death and disability worldwide and its absolute burden continues to rise in parallel with population ageing and the persistence of modifiable risk factors.[1] Coronary artery disease constitutes a major component of this burden, with mortality patterns shaped by regional disparities in risk factor control and access to care.[1] Although several regions have achieved relative reductions in age-standardised mortality, the total number of cardiovascular deaths remains substantial, underscoring the enduring public health challenge.[2] Global initiatives such as the WHO 25 × 25 target and the UN's Sustainable Development Goal 3.4 have framed the reduction of premature cardiovascular mortality as a policy priority, yet progress varies considerably across countries and regions.[1,2] These disparities highlight the need for context-sensitive strategies in both prevention and interventional management of coronary artery disease.

Within contemporary revascularisation practice, percutaneous coronary intervention (PCI) with drug-eluting stents (DES) has become a cornerstone therapy for patients with obstructive coronary disease. DES consistently reduce restenosis and target lesion revascularisation compared with bare-metal stents, establishing PCI with DES as a standard approach in many clinical scenarios.[3] Advances in second-generation DES have further improved safety and efficacy profiles relative to first-generation devices.[3,4]

Nevertheless, the risk of stent thrombosis persists, particularly in the early phase following implantation, necessitating effective adjunctive antiplatelet therapy.[3] Decisions regarding revascularisation strategies, including the choice between PCI and alternative modalities, must integrate anatomical complexity, comorbid conditions and anticipated thrombotic risk.[5]

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor remains the foundation of pharmacological management after PCI with DES. International guidelines consistently recommend DAPT for up to 12 months in many acute coronary syndrome settings, with adaptations according to individual risk profiles for bleeding and ischaemia.[6,7] Over the past decade, however, an increasing body of evidence has supported strategies that shorten DAPT, de-escalating to less potent $P2Y_{12}$ inhibitors or a transition to $P2Y_{12}$ inhibitor monotherapy in selected patients.[8] These approaches aim to mitigate bleeding without compromising protection against thrombotic events, although concerns remain regarding stent thrombosis in specific subgroups or when de-escalation is implemented prematurely.[9]

The clinical dilemma underlying these evolving strategies lies in the trade-off between ischaemic protection and bleeding harm. Major bleeding is not a trivial adverse event, it is associated with increased transfusion requirements, prolonged hospitalisation, rehospitalisation and higher mortality.[10] Several analyses indicate that bleeding-related mortality may equal or even exceed that attributable to recurrent MI during certain follow-up periods.[10] Potent $P2Y_{12}$ inhibitors, such as prasugrel and ticagrelor, are consistently linked to higher bleeding rates compared with clopidogrel, particularly among patients with advanced age, chronic kidney disease, anaemia or other features that contribute to a high risk of bleeding.[11] Moreover, prolonged DAPT increases cumulative bleeding risk, reinforcing the need for individualised duration strategies.[10]

In the era of newer-generation DES, where device-related ischaemic complications have been reduced, bleeding events increasingly shape overall prognosis and net clinical benefit.[12] Despite numerous randomised trials and pairwise meta-analyses comparing specific regimens, uncertainty persists regarding the comparative major bleeding risk across the full spectrum of contemporary oral antiplatelet strategies following PCI with DES. Heterogeneity in patient populations, stent generations, antiplatelet intensity and treatment duration further complicates direct interpretation.

A comprehensive network meta-analysis that integrates evidence across decades and therapeutic strategies may provide a more precise hierarchy of major bleeding risk. Such an approach is essential to inform individualised decision-making in contemporary practice, where the prevention of thrombotic events must be carefully balanced against the potentially lethal consequences of bleeding.

Methods

This study was designed as a systematic review and network meta-analysis to evaluate the comparative risk of major bleeding associated with intensified oral antiplatelet strategies following PCI with DES. The conduct and reporting of this study adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) extension for network meta-analysis. A predefined protocol outlining the study objectives, eligibility criteria and analytical plan was registered prospectively in PROSPERO under ID CRD420261293529.

Search Strategy

A comprehensive literature search was undertaken across multiple electronic databases, including PubMed, Scopus, Web of Science, ScienceDirect, EBSCOhost and Semantic Scholar. The search strategy combined controlled vocabulary terms and free-text keywords. Boolean operators were used to enhance sensitivity and specificity and medical subject headings were applied when appropriate, resulting in the following keywords: (antiplatelet OR ticagrelor OR clopidogrel OR aspirin OR COX OR P2Y12 OR prasugrel OR DAPT) AND (DES OR "drug-eluting stent") AND (bleeding OR "major bleeding" OR BARC OR TIMI OR GUSTO OR "Stent thrombosis"). The publication year was restricted to 2016–2026.

Eligibility Criteria

Studies were eligible for inclusion if they enrolled adult patients (≥18 years) undergoing PCI exclusively with DES implantation and compared at least two oral antiplatelet strategies after the procedure. Eligible interventions included combinations or monotherapy using oral antiplatelet agents, encompassing P2Y12 receptor inhibitors, such as clopidogrel, prasugrel or ticagrelor, as well as cyclooxygenase inhibitors or other antiplatelet agents, such as indobufen. These strategies included, but were not limited to, DAPT with varying durations, short-duration combination therapy followed by antiplatelet monotherapy, P2Y12 inhibitor monotherapy after a brief or no combination therapy period, monotherapy with other oral antiplatelet agents, extended-duration combination therapy and switching or de-escalation strategies between oral antiplatelet agents. Studies were required to include clearly defined antiplatelet regimens that could be appropriately classified within the treatment network.

Eligible studies were required to report major bleeding events as the primary outcome, while stent thrombosis was analysed as a secondary outcome derived from the same set of studies. This approach was applied to ensure that both endpoints were evaluated in the same patient populations, thereby maintaining consistency and comparability of the results.

Major bleeding must be defined using established classification systems, including Thrombolysis in MI (TIMI), the bleeding classification from the GUSTO trials or the Bleeding Academic Research Consortium (BARC) criteria. Only clinically relevant major bleeding events were included, defined as TIMI Major Bleeding bleeding, severe or life-threatening bleeding by GUSTO or BARC type 3–5 bleeding. Stent thrombosis was preferably defined based on Academic Research Consortium (ARC) definitions – definite or probable stent thrombosis. Randomised controlled trials (RCTs) and comparative observational studies (prospective or retrospective) published in English were included.

Studies were excluded if they involved patients treated with bare-metal stents or mixed stent types without separately reported outcomes for DES, they evaluated IV antiplatelet agents or non-oral antithrombotic therapies or employed single-arm designs without a comparator group. Studies were also excluded if they were review articles, editorials, conference abstracts, study protocols or if bleeding outcomes were not reported using standardised definitions or could not be reliably extracted. In cases of overlapping study populations, the most comprehensive or most recent dataset was included to avoid duplication.

Study Selection Process

Study selection was conducted using Rayyan to facilitate blinded screening and reduce selection bias. After removal of duplicate records, titles and abstracts were independently screened by four reviewers to identify studies that met the predefined inclusion criteria. Full-text articles of potentially relevant studies were then assessed for eligibility. Disagreements at any stage of the selection process were resolved through discussion and consensus. When necessary, a senior reviewer (SS) was consulted to adjudicate unresolved discrepancies.

Data Extraction

Data extraction was performed independently by the reviewers using a standardised data collection form developed prior to analysis. Extracted information included study characteristics, publication year, study design, patient demographics, the drug in the DES, antiplatelet regimens and their administration, duration of follow-up and definitions of major bleeding. For each treatment arm, the number of bleeding events and total sample size were recorded. When studies reported multiple bleeding classifications, outcomes corresponding to major bleeding were preferentially extracted. All extracted data were cross-checked for accuracy and consistency before synthesis.

Quality Assessment

The methodological quality of included studies was assessed independently by all reviewers. RCTs were evaluated using the Risk of Bias 2.0 tool, which examines potential bias across five domains: the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result, leading to an overall judgement of low risk, some concerns or high risk of bias. Observational studies were appraised using the Newcastle-Ottawa Scale, which assesses selection, comparability and outcome domains. Studies achieving higher scores were considered to have a lower risk of bias. Any discrepancies in risk of bias assessment were resolved through consensus discussion. The impact of study quality on the overall certainty of evidence was subsequently incorporated into the analysis using the Confidence in Network Meta-Analysis (CINeMA) framework.

Data Synthesis

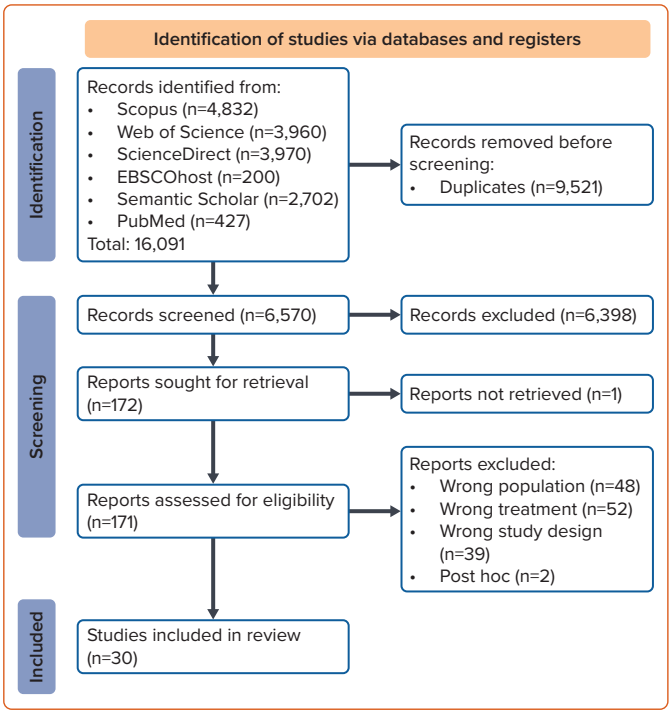
For data synthesis, a random-effects network meta-analysis model was employed to account for clinical and methodological heterogeneity across studies. Dichotomous outcomes were analysed and treatment effects were expressed as RR with 95% CI. When a large number of antiplatelet strategy models were identified, treatments were grouped according to both the type of oral antiplatelet agents, such as clopidogrel, prasugrel, ticagrelor or indobufen, and the therapeutic strategy, including duration and sequencing of therapy, such as short-duration dual therapy followed by monotherapy, extended dual therapy or initial-extended monotherapy, to ensure network coherence and clinically meaningful comparisons. Network meta-analysis was conducted using NMAstudio, and the certainty of evidence for each comparison was evaluated using CINeMA, considering within-study bias, indirectness, heterogeneity and inconsistency.[13,14] Treatment strategies were ranked according to their relative risk of major bleeding and also stent thrombosis. Graphical outputs, including forest plots and network diagrams, were generated to facilitate interpretation of comparative bleeding risks and stent thrombosis across antiplatelet strategies. Transitivity was conducted using any baseline characteristics that was provided by all included studies.

Results

Included Studies

A total of 16,091 records were initially identified through the database search, including Scopus (n=4,832), Web of Science (n=3,960), ScienceDirect (n=3,970), EBSCOhost (n=200), Semantic Scholar (n=2,702) and PubMed (n=427). After removal of 9,521 duplicate records, 6,570 unique studies remained and were subjected to title and abstract screening, of which 6,398 were excluded. The full texts of 172 reports were retrieved and assessed for eligibility, with 171 reports successfully obtained. Following full-text evaluation, 139 studies were excluded due to ineligible population (n=48), inappropriate treatment strategies (n=52), unsuitable study design (n=39) or post hoc studies (n=2). Ultimately, 30 studies met the inclusion criteria and were included in the final analysis (*Figure 1*).

Figure 1: PRISMA Flow Diagram



Characteristics and Transitivity Check

Thirty studies were included in the analysis (*Table 1*), comprising both RCTs and observational studies conducted across diverse geographical regions, predominantly in Asia, with additional contributions from Europe, Australia and the Middle East.[15–44] The pooled sample size across all studies was 110,035 participants, with individual study sizes ranging from fewer than 300 patients to large registry-based cohorts exceeding 10,000 participants. Most studies employed a two-arm design, although several included three treatment arms. The mean age of participants generally ranged from approximately 55 years to 75 years, reflecting a predominantly older adult population undergoing PCI (*Figure 2*), while BMI, when reported, was relatively consistent across studies, typically ranging from 23 to 28 kg/m^2.

Follow-up duration varied from 90 days to over 5 years, with most studies reporting outcomes at 12 months. Most studies used second-generation DES, including everolimus-, zotarolimus- and sirolimus-eluting stents. Definitions of major bleeding were largely standardised using BARC criteria (commonly type 3–5), although TIMI and GUSTO classifications were also applied in several studies. A broad range of oral antiplatelet strategies was evaluated, including conventional DAPT, intensified regimens with potent P2Y12 inhibitors, shortened DAPT followed by monotherapy, extended-duration DAPT and alternative combinations involving agents such as indobufen or cilostazol.

Network Among Antiplatelets

The network plot (*Figure 3*) illustrates the wide variation in antiplatelet strategies following DES implantation, with the most common approach involving different durations of DAPT prior to switching to monotherapy. To enable valid comparisons within the network meta-analysis, treatments were categorised based on DAPT duration to ensure connectivity across

Table 1: Characteristics of Included Studies

Study	Origin	Study Design	Antiplatelet	n	Mean age	Mean BMI	Follow-up	Drug on DES	Major Bleeding Criteria	Administration
Algazzar et al. 2024[15]	Egypt	Prospective observational	Arm 1: CPG-ASA Arm 2: TCG-ASA	Arm 1: 120 Arm 2: 135	Arm 1: 55.44 Arm 2: 54.3	Arm 1: 23.1 Arm 2: 24.1	12m	Sirolimus/ everolimus	BARC 3–5	• Arm 1: CPG 75 mg once daily + ASA 100 mg once daily. Arm 2: TCG 90 mg twice daily + ASA 100 mg once daily. Duration: 12 months post-PCI
Bacquelin et al. 2016[16]	France	Observational registry	Arm 1: CPG-ASA Arm 2: PSG-ASA	Arm 1: 505 Arm 2: 483	Arm 1: 62.7 Arm 2: 67.3	Arm 1: 26.3 Arm 2: 25.4	12m	Everolimus/ zotarolimus	BARC ≥3, TIMI	• Arm 1: CPG 75 mg once daily + ASA 100 mg once daily. • Arm 2: PSG LD 60 mg, then MD 10 mg once daily (5 mg if <60 kg or >75 yo) + ASA 75–160 mg once daily
Kim et al. 2020[17]	South Korea	RCT	Arm 1: TCG-3MDAPT Arm 2: TCG-ASA	Arm 1: 1,527 Arm 2: 1,529	Arm 1: 61 Arm 2: 61	Arm 1: 24.9 Arm 2: 24.9	12m	Sirolimus	BARC 3 or 5	• Arm 1: TCG 90 twice daily + ASA 100 mg for 3 months, then ASA discontinued, Arm 2: TCG 90 mg twice daily + ASA 100mg prolonged until 12 months
Hee et al. 2019[18]	Australia	Retrospective	Arm 1: TCG Arm 2: CPG	Arm 1: 423 Arm 2: 232	Arm 1: 64.5 Arm 2: 59.5	Arm 1: 27.8 Arm 2: 28.3	2.7y	Everolimus/ zotarolimus	BARC 3–5	• TCG: LD 180 mg, MD 90 mg twice daily + ASA 100 mg. CPG: LD 600 mg, MD 75 mg once daily + ASA 100 mg
Watanabe et al. 2024[19]	Japan	RCT	Arm 1: ASA-3MDAPT Arm 2: CPG-3MDAPT	Arm 1: 2,805 Arm 2: 2,810	Arm 1: 73 Arm 2: 73	Arm 1: 23.7 Arm 2: 23.5	12m	Everolimus/ zotarolimus/ sirolimus	BARC 3 or 5	• Arm 1: ASA 80-100mg +: CPG (LD 300 mg, MD 75 mg) for 3 months, then CPG discontinued. . • DAPT Arm 2: CPG 75 mg + ASA 80–100 mg for 3 months, then ASA discontinued.
Hong et al. 2024[20]	South Korea	RCT	Arm 1: TCG-1MDAPT Arm 2: TCG-ASA	Arm 1: 1,426 Arm 2: 1,424	Arm 1: 61 Arm 2: 61	Arm 1: 25.1 Arm 2: 25	12 m	Everolimus/ zotarolimus	BARC 3 or 5	• Arm 1: TCG 90 mg twice daily + ASA 100 mg) for <1 month (median 16 days), then ASA discontinued, Arm 2: TCG 90 mg twice daily + ASA 100 mg)
Kang et al. 2023[21]	South Korea	RCT	Arm 1: CPG-12MDAPT Arm 2: ASA-12MDAPT	Arm 1: 2,431 Arm 2: 2,286	Arm 1: 63.3 Arm 2: 63.3	Arm 1: 24.9 Arm 2: 24.9	5.8y	Everolimus/ zotarolimus/ sirolimus	BARC ≥3	• Maintenance: After 12 ± 6 months of event-free DAPT, patients switched to long-term CPG 75 mg once daily or ASA 100 mg once daily
Lan et al. 2024[22]	China	Retrospective	Arm 1: ASA-12MDAPT Arm 2: CPG-12MDAPT	Arm 1: 582 Arm 2: 422	Arm 1: 62.6 Arm 2: 66.3	Arm 1: 24.9 Arm 2: 24.8	25.7m	Everolimus/ sirolimus	BARC ≥3	• Maintenance after 12 months of DAPT, switch to either CPG 75 mg once daily or ASA 100 mg once daily monotherapy
Koo et al. 2021[23]	South Korea	RCT	Arm 1: CPG-18MDAPT Arm 2: ASA-18MDAPT	Arm 1: 2,710 Arm 2: 2,728	Arm 1: 63.5 Arm 2: 63.4	NA	24m	Everolimus/ zotarolimus/ sirolimus	BARC ≥3	• Maintenance: After 6–18 months of DAPT, randomised to CPG 75 mg once daily or ASA 100 mg once daily for 24 months
Lee et al. 2017[24]	South Korea	RCT	Arm 1: CTZ-CPG-ASA Arm 2: CPG-ASA	Arm 1: 202 Arm 2: 202	Arm 1: 61.9 Arm 2: 62.5	Arm 1: 25.4 Arm 2: 25.4	12m	Everolimus/ zotarolimus	TIMI Major Bleeding	• Arm 1: ASA 100 mg + CPG 75 mg + CTZ 100 mg twice daily until 12 months. Arm 2: ASA + CPG + placebo

Table 1 (cont)

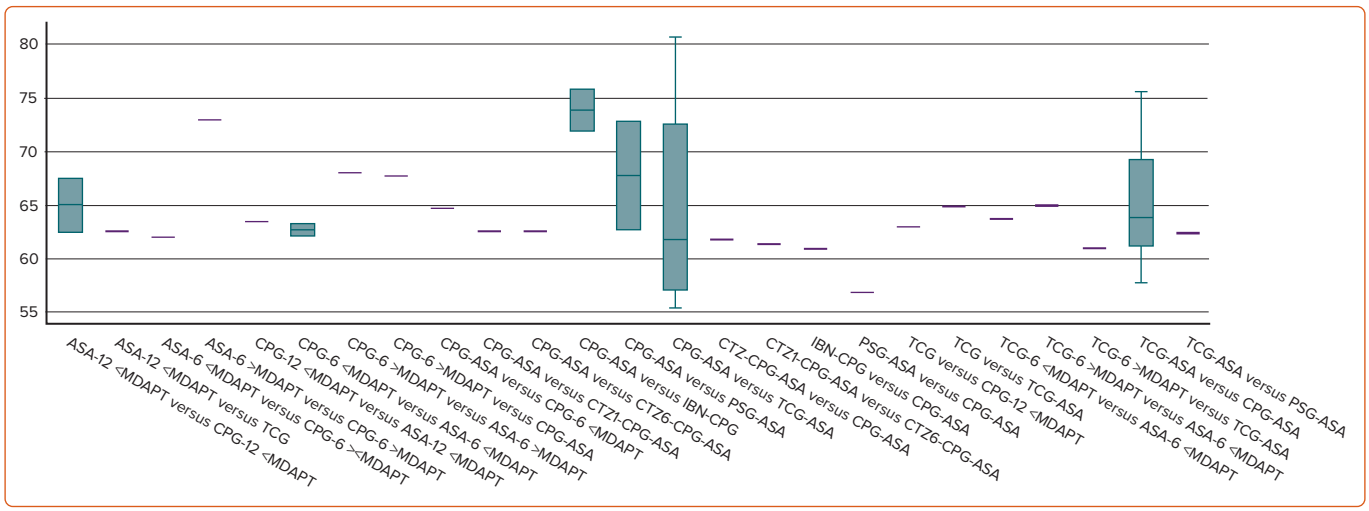
Study	Origin	Study Design	Antiplatelet	n	Mean age	Mean BMI	Follow-up	Drug on DES	Major Bleeding Criteria	Administration
Li et al. 2021[25]	China	Retrospective	Arm 1: TCG-ASA Arm 2: CPG-ASA	Arm 1: 1,321 Arm 2: 1,321	Arm 1: 57.8 Arm 2: 59.8	Arm 1: 25.9 Arm 2: 25.9	1 m	Everolimus/ zotarolimus	BARC ≥2	• Arm 1: 90 mg twice daily + ASA 100 mg. Arm 2: 75 mg once daily + ASA 100 mg. LDs given at PCI (TCG 180 mg / CPG 300–600 mg)
Loh et al. 2025[26]	Singapore	Observational registry	Arm 1: CPG-ASA Arm 2: TCG-ASA	Arm 1: 5,387 Arm 2: 5,387	Arm 1: 59.1 Arm 2: 59.9	NA	12 months	Everolimus / sirolimus/ zotarolimus	BARC 2, 3, 5	• Arm 1: CPG MD 75 mg once daily + ASA 75–100 mg. Duration: 12 months • Arm 2: TCG MD 90 mg twice daily + ASA 75–100 mg.
Ono et al. 2022[27]	Multicentre	RCT	Arm 1: TCG-12MDAPT Arm 2: ASA-12MDAPT	Arm 1: 5,308 Arm 2: 5,813	Arm 1: 63.7 Arm 2: 64.1	Arm 1: 28.2 Arm 2: 28.2	24 months	Biolimus A9	BARC 3 or 5	• Arm 1: TCG 90 mg twice daily + ASA 100 mg 1 month, then TCG 90 mg twice daily mono (23 months). Arm 2: DAPT (12 months), then ASA mono (12 months)
Natsuaki et al. 2020[28]	Japan	Observational registry	Arm 1: ASA-13MDAPT Arm 2: CPG	Arm 1: 2,984 Arm 2: 2,982	Arm 1: 71.8 Arm 2: 71.5	Arm 1: 23.9 Arm 2: 24.0	12 months	Everolimus	TIMI Major Bleeding	• Maintenance: post-short DAPT transition to CPG 75 mg QD versus ASA 80–100 mg once daily for chronic phase
Obayashi et al. 2022[29]	Japan	RCT	Arm 1: CPG-3MDAPT Arm 2: CPG-ASA	Arm 1: 2,993 Arm 2: 3,004	Arm 1: 67.7 Arm 2: 67.9	Arm 1: 24.3 Arm 2: 24.2	12 months	Everolimus	TIMI Major Bleeding	• Short DAPT: 1 month DAPT (ASA + CPG), then switch to CPG 75 mg once daily monotherapy until 12 months
Park et al. 2016[30]	South Korea	Observational registry	Arm 1: ASA-12MDAPT Arm 2: CPG-12MDAPT	Arm 1: 2,472 Arm 2: 771	Arm 1: 62 Arm 2: 64	NR	36 months	Sirolimus/ everolimus	TIMI Major Bleeding	• Maintenance: After 12 months of DAPT, transition to CPG 75 mg once daily or ASA 100 mg once daily monotherapy
Park et al. 2023[31]	South Korea	RCT	Arm 1: CTZ1-CPG-ASA Arm 2: CPG-ASA Arm 3: CTZ6-CPG-ASA	Arm 1: 320 Arm 2: 317 Arm 3: 311	Arm 1: 62.6 Arm 2: 61.4 Arm 3: 60.9	NR	12 months	Everolimus / tacrolimus	BARC ≥3	• Triple: ASA 100 mg + CPG 75 mg + CTZ 100 mg twice daily. Dual: ASA 100 mg + CPG 75 mg. Intensive phase 1 month
Shibata et al. 2021[32]	Japan	Retrospective	Arm 1: PSG-ASA Arm 2: CPG-ASA	Arm 1: 330 Arm 2: 204	Arm 1: 72.8 Arm 2: 63.9	Arm 1: 23.5 Arm 2: 24.7	90 days	Everolimus zotarolimus / sirolimus	GUSTO/TIMI	• Arm 1: PSG LD 20 mg, MD 3.75 mg once daily + ASA 80–100 mg. Arm 2: CPG LD 300 mg, MD 75 mg once daily + ASA 81–100 mg
Sim et al. 2020[33]	South Korea	Observational registry	Arm 1: TCG-ASA Arm 2: PSG-ASA Arm 3: CPG-ASA	Arm 1: 659 Arm 2: 242 Arm 3: 3,180	Arm 1: 62.4 Arm 2: 56.9 Arm 3: 65.7	NA	12 months	Everolimus zotarolimus/ sirolimus	BARC criteria	• Maintenance: after mandatory DAPT period (12 months), switch to CPG 75 mg or ASA 100 mg for long-term therapy
Sim et al. 2019[34]	South Korea	Observational registry	Arm 1: TCG or PSG-12MDAPT Arm 2: ASA-12MDAPT	Arm 1: 534 Arm 2: 1,285	Arm 1: 62.2 Arm 2: 60.7	Arm 1: 24 Arm 2: 24.2	12 months	Everolimus/ zotarolimus	BARC ≥3	• Potent: TCG 90 mg twice daily or PSG10 mg once daily + ASA. Standard: CPG 75 mg once daily + ASA. Duration: 12 months
Tian et al. 2021[35]	China	Retrospective	Arm 1: TCG Arm 2: TCG-ASA	Arm 1: 128 Arm 2: 141	Arm 1: 64.9 Arm 2: 65.3	Arm 1: 69.7 (weight) Arm 2: 68 (weight)	12 months	Everolimus/ zotarolimus	BARC 2, 3, 5	• Arm 1: TCG 90 mg twice daily monotherapy for 1 year. Arm 2: TCG 90 mg twice daily + ASA 100 mg once daily for 1 year

Table 1 (cont)

Study	Origin	Study Design	Antiplatelet	n	Mean age	Mean BMI	Follow-up	Drug on DES	Major Bleeding Criteria	Administration
Dai et al. 2024[36]	China	RCT	Arm 1: CPG-ASA Arm 2: IBN-CPG	Arm 1: 224 Arm 2: 224	Arm 1: 72 Arm 2: 72	NA	12 months	Everolimus/ zotarolimus	BARC/TIMI	• IBN strategy: IBN 100 mg twice daily + CPG 75 mg once daily. ASA strategy: ASA 100 mg once daily + CPG 75 mg once daily
Dai et al. 2025[37]	China	Retrospective	Arm 1: CPG-ASA Arm 2: IBN-CPG	Arm 1: 306 Arm 2: 306	Arm 1: 75.8 Arm 2: 75.7	NA	12 months	Everolimus zotarolimus / sirolimus	NACE/Bleed	• Elderly protocol: IBN 100 mg twice daily (replacing ASA) + CPG 75 mg once daily for 12 months in patients >75 years
Wu et al. 2023[38]	China	RCT	Arm 1: IBN-CPG Arm 2: CPG-ASA	Arm 1: 2,258 Arm 2: 2,293	Arm 1: 61 Arm 2: 61.2	Arm 1: 25 Arm 2: 25	12 months	Everolimus Zotarolimus / sirolimus	BARC ≥2	• IBN: 100 mg twice daily + CPG 75 mg once daily. ASA: 100 mg once daily + CPG 75 mg once daily. Duration: 12 months
Xu et al. 2022 [PLATO][39]	China	Retrospective	Arm 1: CPG-ASA Arm 2: TCG-ASA	Arm 1: 644 Arm 2: 264	Arm 1: 80.7 Arm 2: 79.1	NA	12 months	Everolimus / Zotarolimus	Major bleeding	• TCG: 90 mg twice daily+ ASA 100 mg. CPG: 75 mg once daily + ASA 100 mg. Duration: 12 months in elderly Chinese cohort
Yang et al. 2023[40]	South Korea	RCT (*Post-hoc*)	Arm 1: ASA-18MDAPT Arm 2: CPG-18MDAPT	Arm 1: 2,712 Arm 2: 2,691	Arm 1: 67.5 Arm 2: 68.5	NA	5.8 years	Everolimus/ zotarolimus / Sirolimus	BARC ≥3	• Maintenance: Long-term follow-up (median 5.8 years) of CPG 75 mg QD versus ASA 100 mg once daily after the initial DAPT phase
Yeh et al. 2023[41]	Taiwan	Retrospective	Arm 1: TCG-ASA Arm 2: CPG-ASA	Arm 1: 5,244 Arm 2: 9,635	Arm 1: 75.6 Arm 2: 75.3	NA	12 months	Everolimus / zotarolimus	Major bleeding	• TCG: 90 mg twice daily + ASA 100 mg. CPG: 75 mg once daily + ASA 100 mg. Duration: 12 months in elderly AMI patients
Zhao et al. 2024[42]	China	Observational propensity match	Arm 1: TCG-ASA Arm 2: CPG-ASA	Arm 1: 581 Arm 2: 593	Arm 1: 67 Arm 2: 67	NA	12 months	Everolimus/ zotarolimus/ sirolimus	BARC 2, 3, 5	• TCG: 90 mg twice daily + ASA 100 mg versus CPG: 75 mg once daily + ASA 100 mg. Duration: 12 months.
Zhang et al. 2025[43]	China	RCT	Arm 1: CPG-ASA Arm 2: CPG	Arm 1: 3,816 Arm 2: 3,806	Arm 1: 64.7 Arm 2: 64.75	Arm 1: 25.3 Arm 2: 25.4	9 m	Everolimus/ zotarolimus	BARC 2, 3, 5	• Following 9–12 months of DAPT, randomised to CPG 75 mg mono or prolonged DAPT (CPG + ASA) for 9 additional months
Zocca et al. 2017[44]	Netherlands	Observational	Arm 1: TCG-ASA Arm 2: CPG-ASA	Arm 1: 1,053 Arm 2: 1,009	Arm 1: 63.9 Arm 2: 62.9	Arm 1: 27.7 Arm 2: 27.4	12 months	Sirolimus/ zotarolimus/ everolimus	BARC criteria	• Switch protocol: Cohort 1: CPG 75 mg once daily + ASA 100 mg. Cohort 2: TCG 90 mg twice daily + ASA 100 mg. Duration: 12 months post-PCI

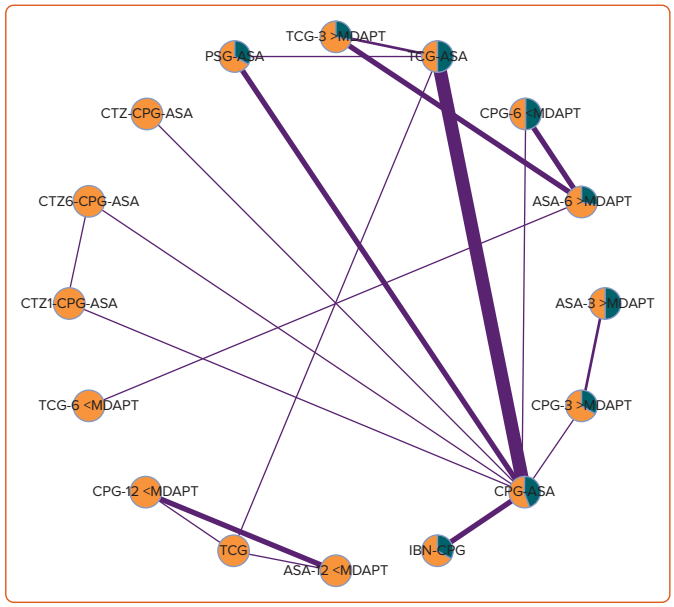
AMI = acute MI; ASA = aspirin; BARC = Bleeding Academic Research Consortium scoring system; CPG = clopidogrel; CTZ = cilostazol; CTZ1 = cilostazol 6 months; CTZ6 = cilostazol 6 months; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; GUSTO = Global Usage of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; IBN = indobufen; LD = loading dose; MD = maintenance dose; MDAPT = months after dual antiplatelet therapy; Mono = monotherapy; PSG = prasugrel; RCT = randomised controlled trial; TCG = ticagrelor; TIMI = Thrombolysis in MI.

Figure 2: Transitivity Check Towards Population Age



ASA = aspirin; CPG = clopidogrel; CTZ = cilostazol; CTZ6 = cilostazol 6 months; DAPT = dual antiplatelet therapy; IBN = indobufen; MDAPT = months after dual antiplatelet therapy; PSG = prasugrel; TCG = ticagrelor.

Figure 3: Network among Antiplatelet Strategies



ASA = aspirin; CPG = clopidogrel; CTZ = cilostazol; CTZ6 = cilostazol 6 months; DAPT = dual antiplatelet therapy; IBN = indobufen; MDAPT = months after dual antiplatelet therapy; PSG = prasugrel; TCG = ticagrelor.

studies, as at least one shared comparator is required to form indirect links between interventions. Accordingly, strategies were grouped into ≤6 months duration of DAPT (>6 months after DAPT [MDAPT]), 7–12 months duration (<6 MDAPT) and >12 months duration (>12 MDAPT) before transitioning to monotherapy. Refer to *Table 2* for the definitions of the included regimens.

Ranking

The network meta-analysis ranking based on p-scores demonstrated substantial variability across treatment strategies for both outcomes. For major bleeding (*Figure 4A*), ticagrelor monotherapy (TCG) achieved the highest ranking (p=0.93), followed by CPG-6 >MDAPT (p=0.8) and ASA-6 >MDAPT (p=0.73), indicating a higher probability of being among the most favourable strategies in reducing bleeding risk. TCG-6 >MDAPT (p=0.67), ASA−6 <MDAPT (p=0.64) and CPG-6 <MDAPT (p=0.63) occupied intermediate positions. The lowest p-scores, indicating a higher probability of being among the most favourable strategies in increasing bleeding risk, were noted in prasugrel PSG-ASA (p=0.25) and (CTZ6)-CPG-ASA (p=0.22).

In contrast, for stent thrombosis (*Figure 4b*), CPG-12 <MDAPT ranked highest (p= 0.94), followed by ASA-12 <MDAPT (p=0.85) and CTZ-CPG-ASA (p=0.76). Intermediate positions included CPG-ASA (p=0.49), TCG-ASA (p=0.49), indobufen (IBN)-CPG (p=0.47) and TCG-6 <MDAPT (p=0.38), whereas lower rankings were observed for TCG (p=0.18) and ASA-6 <MDAPT (p=0.19). Several notable patterns were observed in the ranking distribution across both outcomes. CPG-12 <MDAPT occupied a mid-to-upper position for major bleeding (p=0.52), while simultaneously achieving the highest ranking for reducing stent thrombosis risk (p=0.94). In addition, several extended DAPT strategies, including PSG-ASA, CPG-ASA, TCG-ASA and IBN-CPG, demonstrated progressively decreasing p-scores yet remained within the mid-to-upper range for stent thrombosis. Among these, only CPG-ASA and IBN-CPG also maintained intermediate positions in the major bleeding outcome, indicating an overlap within the mid-ranking range across both endpoints.

Forest Plot

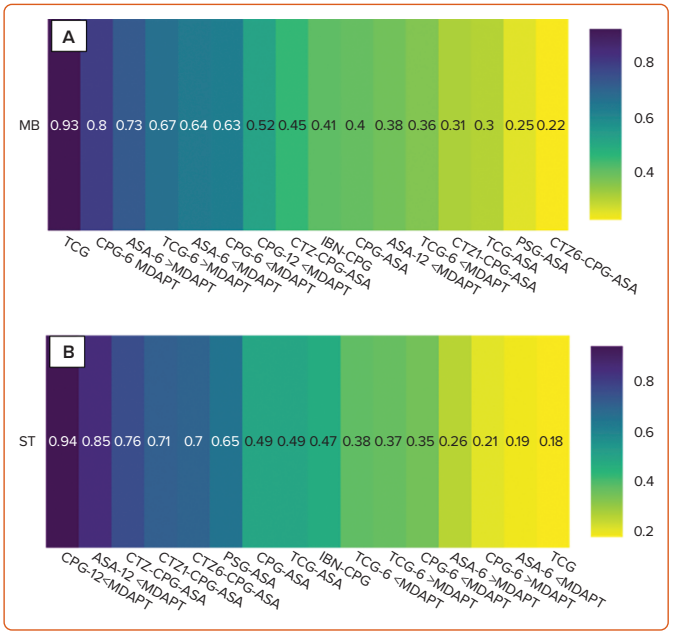
The forest plot analysis was conducted using TCG as the reference comparator, selected based on its central role in the network (*Figure 3*), where it demonstrated the highest number of direct connections with other interventions. Relative to CPG-ASA, TCG showed the lowest RR for major bleeding (RR 0.13; 95% CI [0.01–1.13]), while CPG-6 >MDAPT was the only strategy associated with a statistically significant reduction (RR 0.39; 95% CI [0.16–0.95]). In contrast, extended combination regimens, particularly CTZ6-CPG-ASA and CTZ1-CPG-ASA, were associated with higher RRs, although with wide CIs (RR 2.06; 95% CI [0.33–12.74] and RR 1.51; 95% CI [0.22–10.21]). For stent thrombosis, CPG–12 <MDAPT demonstrated the greatest reduction in risk relative to CPG-ASA (RR 0.08; 95% CI [0.01–0.52]), followed by ASA–12 <MDAPT (RR 0.13; 95% CI [0.02–0.85]), both showing statistically significant effects. Conversely, TCG was associated with a higher RR of stent thrombosis compared with CPG-ASA. Across both outcomes, most estimates were accompanied by wide CIs that frequently crossed unity, indicating limited precision in several comparisons (*Figure 5*).

Table 2: List of Antiplatelet Strategies

Arms	Definition
TCG	Ticagrelor monotherapy
CPG-6 >MDAPT	Clopidogrel monotherapy administered after DAPT with clopidogrel-aspirin (CPG-ASA) for less than 6 months (including 1 and 3 months)
ASA-6 >MDAPT	Aspirin monotherapy administered after DAPT with P2Y12 inhibitors-aspirin for less than 6 months (including 1 and 3 months)
TCG-6 >MDAPT	Ticagrelor monotherapy administered after DAPT with ticagrelor-aspirin (TCG-ASA) for less than 6 months (including 1 and 3 months)
CPG-6 <MDAPT	Clopidogrel monotherapy administered after DAPT with clopidogrel-aspirin (CPG-ASA) for more than 6 months (including 1 and 3 months)
ASA-6 <MDAPT	Aspirin monotherapy administered after DAPT with P2Y12 inhibitors-aspirin for more than 6 months (including 1 and 3 months)
TCG-6 <MDAPT	Ticagrelor monotherapy administered after DAPT with ticagrelor-aspirin (TCG-ASA) for more than 6 months (including 1 and 3 months)
CPG-12 <MDAPT	Clopidogrel monotherapy administered after DAPT with clopidogrel-aspirin (CPG-ASA) for more than 12 months (including 13, 18 and 24 months)
ASA-12 <MDAPT	Aspirin monotherapy administered after DAPT with P2Y12 inhibitors-aspirin for more than 12 months (including 13, 18 and 24 months)
CTZ-CPG-ASA	Triple therapy with cilostazol, clopidogrel and aspirin administered continuously from post-PCI through the follow-up period.
CTZ6-CPG-ASA	Triple therapy with clopidogrel-aspirin plus cilostazol for the first 6 months post-PCI, followed by clopidogrel-aspirin through the follow-up period.
CTZ1-CPG-ASA	Triple therapy with clopidogrel-aspirin plus cilostazol for the first month post-PCI followed by clopidogrel-aspirin through the follow-up period
TCG-ASA	Ticagrelor-aspirin administered continuously from post-PCI through the follow-up period
CPG-ASA	Clopidogrel-aspirin administered continuously from post-PCI through the follow-up period
IBN-CPG	Indobufen-clopidogrel administered continuously from post-PCI through the follow-up period
PSG-ASA	Prasugrel-aspirin administered continuously from post-PCI through the follow-up period

The inequality symbols (< and >) indicate DAPT duration relative to the reference duration (6 or 12 months). "<6 months" and "<12 months" denote DAPT durations shorter than the respective reference durations, whereas ">6 months" and ">12 months" denote DAPT durations longer than the respective reference durations. DAPT = dual antiplatelet therapy; MDAPT = monotherapy after dual antiplatelet therapy; PCI = percutaneous coronary intervention.

Figure 4: Heatmap Ranking (A) Major bleeding; (B) Stent thrombosis



Quality of Evidence

The risk of bias assessment across the studies demonstrated an overall moderate quality of evidence. Of the 33 studies included in the analysis, 11 were classified as having low risk of bias, while the remaining 22 studies were assessed as having a moderate risk of bias. Across pairwise comparisons, most treatment contrasts were predominantly informed by studies with moderate risk of bias, although a proportion of comparisons included contributions from low-risk studies. No studies were categorised as high risk of bias. Across the 33 included studies, the overall assessment of indirectness revealed that 24 comparisons were classified as low, six as moderate and three as high. Notably, the pairwise comparison between ASA–12 <MDAPT and CPG–12 <MDAPT demonstrated a particularly high degree of indirectness, representing a salient concern within the network. In contrast, the comparison of ASA-6 >MDAPT versus CPG-6 >MDAPT was characterised entirely by moderate indirectness. The detailed pairwise comparison risk of bias and indirectness can be seen in the supplementary material.

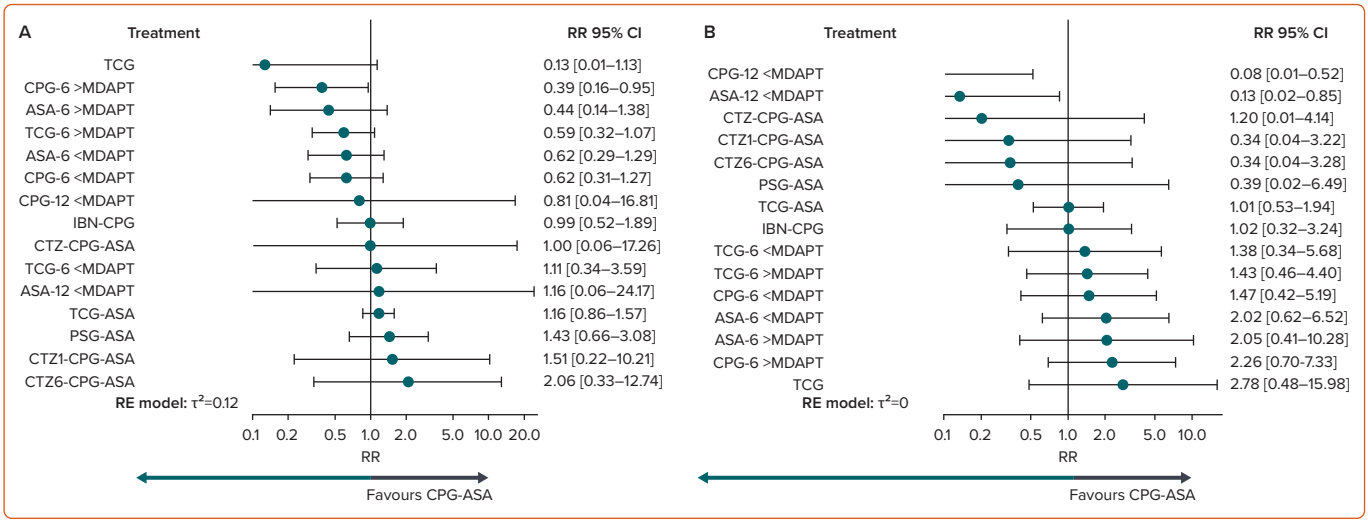
GRADE Assessment

The GRADE assessment (*Table 3*) indicated an overall moderate level of certainty across both outcomes, with some domain-specific limitations. For major bleeding, no significant inconsistency (p=0.085) or incoherence (p=0.100) was observed and heterogeneity was low (τ^2=0.12), while indirectness was rated as low. However, imprecision was judged as moderate to high, reflecting variability in the CI across comparisons. Similarly, for stent thrombosis, inconsistency (p=0.887) and incoherence (p=0.485) were not statistically significant, with no observed heterogeneity (τ^2=0.00) and low indirectness. Imprecision was likewise rated as moderate to high, indicating limited precision of effect estimates despite overall network consistency.

Discussion

This network meta-analysis demonstrates a clinically meaningful trade-off between bleeding and thrombotic outcomes across contemporary oral antiplatelet strategies after PCI with DES. Strategies ranked highest for reducing major bleeding were consistently those involving early de-escalation, including immediate ticagrelor monotherapy and shortened DAPT (≤6 months) followed by monotherapy with clopidogrel, aspirin or ticagrelor. However, these approaches were concurrently associated with relatively higher rankings for stent thrombosis. In contrast, the most favourable strategies for preventing stent thrombosis were dominated by prolonged or extended DAPT, including DAPT beyond 12 months followed by clopidogrel or aspirin monotherapy, as well as continued DAPT throughout follow-up and triple antiplatelet therapy (plus cilostazol).

Figure 5: Forest Plots for Major Bleeding and Stent Thrombosis



(A) Major bleeding. (B) Stent thrombosis. ASA = aspirin; CPG = clopidogrel; CTZ = cilostazol; CTZ6 = cilostazol 6 months; DAPT = dual antiplatelet therapy; IBN = indobufen; MDAPT = months after dual antiplatelet therapy; PSG = prasugrel; TCG = ticagrelor.

Table 3: GRADE Summary

	Inconsistency (p-value)	Incoherence (p-value)	Imprecision	Indirectness	Heterogeneity (τ^2)
Major bleeding	0.074	0.112	Moderate to high	Low to moderate	0.12
Stent thrombosis	0.820	0.476	Moderate to high	Low to moderate	0.00

Notably, no included studies evaluated prolonged ticagrelor-based DAPT beyond 12 months followed by ticagrelor monotherapy, which may limit the interpretation of this specific strategy. These findings reinforce the inverse relationship between bleeding reduction and thrombotic protection, highlighting the need for careful balancing of antiplatelet intensity and duration in clinical decision-making.

From a bleeding perspective, TCG achieved the highest ranking (p=0.93), followed by shortened DAPT strategies transitioning to monotherapy, such as CPG-6 >MDAPT. These findings align with the growing body of evidence suggesting that de-escalation strategies particularly early aspirin withdrawal significantly reduce bleeding risk without a proportional increase in ischaemic events.[45–47] Mechanistically, this can be explained by the reduction in cumulative antiplatelet intensity through removal of aspirin-mediated COX-1 inhibition while maintaining suppression of the adenosine diphosphate (ADP)-P2Y12 pathway, which remains central to thrombus propagation. The magnitude of bleeding reduction observed in this analysis is consistent with previous reports demonstrating relative reductions of approximately 40–60% with P2Y12 monotherapy following short DAPT.[48,49] Conversely, strategies involving prolonged DAPT demonstrated superior protection against stent thrombosis. In this analysis, CPG-12 <MDAPT showed the highest efficacy for reducing stent thrombosis (RR 0.08; 95% CI [0.01–0.53]; p=0.94), followed by ASA-12 <MDAPT. This reinforces the established paradigm that sustained dual pathway inhibition targeting both the thromboxane A_2 (TXA_2)-COX-1 and ADP-P2Y12 axes remains critical during periods of heightened thrombotic vulnerability, particularly in patients with high ischaemic risk.[50,51]

A more nuanced pattern emerges when examining the ranking distribution across both outcomes. CPG-12 <MDAPT occupied a mid-to-upper position for major bleeding (p=0.52), while simultaneously achieving the highest ranking for reducing stent thrombosis risk (p=0.94). In addition, several extended DAPT strategies, including PSG-ASA, CPG-ASA, TCG-ASA and IBN-CPG, demonstrated progressively decreasing p-scores yet remained within the mid-to-upper range for stent thrombosis. Among these, only CPG-ASA and IBN-CPG also maintained intermediate positions in the major bleeding outcome (both p=0.41), indicating overlap within the mid-ranking range across both endpoints. This pattern suggests that while most strategies diverge toward either bleeding reduction or thrombotic protection, a limited subset may offer a relatively balanced trade-off without achieving top ranking in either outcome.

Importantly, the observed divergence in rankings between bleeding and stent thrombosis highlights the central concept of net clinical benefit. Strategies that minimise bleeding, such as TCG, were associated with relatively lower rankings for stent thrombosis, whereas extended DAPT strategies demonstrated the opposite pattern. This inverse relationship reflects the underlying biological interplay between platelet inhibition intensity and haemostatic balance.[46] Another key observation is that not all intensified antiplatelet regimens confer additional benefit. Triple therapy strategies, such as CTZ-CPG-ASA, and potent DAPT combinations, such as PSG-ASA, were associated with a higher bleeding risk without clear superiority in thrombotic protection as reflected by their lower rankings in bleeding outcomes. This supports previous evidence that excessive platelet inhibition beyond dual-pathway targeting may disproportionately increase haemorrhagic complications without any meaningful ischaemic gain.[52]

The forest plot further reinforces these findings, showing that while several strategies demonstrated trends toward reduced bleeding or thrombosis, only a limited number reached statistical significance, and many comparisons were characterised by wide CIs. This imprecision likely reflects heterogeneity in study design, patient populations and treatment duration consistent with the moderate-to-high imprecision identified in the GRADE assessment. Taken together, these findings suggest that

contemporary antiplatelet management after PCI with DES should prioritise individualised strategies based on patient-specific bleeding and ischaemic risk profiles. Short DAPT followed by P2Y12 inhibitor monotherapy appears to offer a favourable bleeding profile in the era of newer-generation DES, whereas extended DAPT retains a role in patients with high thrombotic risk.

Strengths and Limitations

This study has several key strengths. First, the use of a network meta-analysis framework allowed simultaneous comparison of multiple antiplatelet strategies, including various DAPT durations and P2Y12 inhibitor-based regimens, providing a comprehensive hierarchy of treatment effects beyond conventional pairwise comparisons. Second, the analysis reflects contemporary clinical practice by focusing on PCI with newer-generation DES and incorporating modern strategies such as short DAPT followed by P2Y12 monotherapy. Third, the inclusion of both major bleeding and stent thrombosis as assessed outcomes enhances clinical relevance by directly addressing the central trade-off underlying antiplatelet therapy and enabling assessment of net clinical benefit.

The observed imprecision in this network meta-analysis is likely attributable to several methodological and clinical factors. First, key outcomes such as stent thrombosis are relatively rare events, resulting in sparse data and wide CIs across multiple comparisons. Second, despite a large overall sample size, several treatment nodes were informed by a limited number of studies or small sample subsets, increasing reliance on indirect estimates within the network. Third, the inclusion of both RCTs and observational studies may have introduced additional variability due to differences in study design and residual confounding. Furthermore, heterogeneity in outcome definitions, particularly the use of different bleeding classifications, such as BARC, TIMI and GUSTO, and substantial variation in follow-up durations across studies may have contributed to inconsistent event rates. Differences in treatment protocols, including DAPT duration, timing of de-escalation and clinical profile of patients, also pose challenges to the assumption of transitivity. Additionally, several comparisons were characterised by limited direct head-to-head evidence, increasing dependence on indirect comparisons and further reducing precision. Finally, the absence of individual patient-level data precluded stratified analyses based on bleeding and ischaemic risk, which may have masked differential treatment effects across clinically relevant subgroups. Together, these factors are likely to have contributed to the moderate-to-high imprecision observed in the certainty of evidence.

Clinical Implications and Future Directions

The findings of this network meta-analysis support a risk-adapted approach to antiplatelet therapy following PCI with DES, consistent with current guideline recommendations. Early de-escalation strategies, including immediate TCG or shortened DAPT (≤6 months) followed by monotherapy, were most effective in reducing major bleeding and are therefore preferable in patients with a high bleeding risk. In contrast, prolonged or extended DAPT, particularly clopidogrel-based regimens beyond 12 months, provided superior protection against stent thrombosis, supporting their use in patients with elevated ischaemic risk. Notably, clopidogrel monotherapy after extended DAPT demonstrated a relatively balanced profile across both outcomes, suggesting a pragmatic long-term maintenance option.

These findings highlight the importance of individualised, strategy-based decision-making that integrates both treatment intensity and duration rather than relying solely on fixed-duration models. Future research should focus on defining the optimal timing of de-escalation, particularly the role and safety window of early aspirin withdrawal across different risk profiles. In addition, the lack of evidence on prolonged TCG-based DAPT followed by monotherapy represents an important gap. Further studies incorporating individual patient-level data, standardised outcome definitions and targeted subgroup analyses, such as high bleeding risk, diabetes and complex PCI, are needed to refine treatment selection. The integration of precision-based approaches, such as genotype-guided therapy and platelet function testing, may further enhance alignment between antiplatelet strategies and patient-specific risk, ultimately improving net clinical benefit.

Conclusion

This network meta-analysis highlights the importance of risk-adapted antiplatelet strategies following PCI with DES. In patients at high risk of major bleeding, early de-escalation strategies are favoured to minimise bleeding complications. Conversely, in patients at high risk of stent thrombosis, prolonged or extended DAPT appears to provide greater thrombotic protection. For patients with concomitant high bleeding and ischaemic risks, an individualised approach is warranted, including stepwise de-escalation or tailored DAPT duration. Notably, clopidogrel monotherapy administered after more than 12 months of DAPT demonstrated a relatively balanced profile, maintaining a mid-to-upper ranking for major bleeding while achieving the highest efficacy in reducing stent thrombosis. Given the moderate-to-high imprecision across several comparisons, these findings should be interpreted cautiously. Further high-quality studies incorporating patient-level data are needed to better define optimal, risk-tailored antiplatelet strategies. ❑

Clinical Perspective

- Antiplatelet therapy after percutaneous coronary intervention with drug-eluting-stent should be guided by individual patient risk, given the clear trade-off between bleeding and thrombotic outcomes.
- Early de-escalation strategies are favoured in patients at high bleeding risk to minimise haemorrhagic complications.
- Extended dual antiplatelet therapy (DAPT) provides greater protection against stent thrombosis and remains important in patients with high ischaemic risk.
- In patients with concurrent high bleeding and ischaemic risks, a tailored approach such as stepwise de-escalation or individualised DAPT duration is essential.
- Clopidogrel monotherapy after prolonged DAPT may offer a relatively balanced strategy, although findings should be interpreted cautiously due to limited precision and warrant further high-quality studies.

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