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Indobufen-Based Dual Antiplatelet Therapy After Percutaneous Coronary Intervention: A Systematic Review and Network Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 9 August 2026 and was last updated on 9 August 2026.

INTRODUCTION

Review question / Objective To evaluate the safety and efficacy of indobufen-based dual antiplatelet therapy (DAPT) relative to contemporary oral antiplatelet strategies in patients undergoing percutaneous coronary intervention (PCI) with drug-eluting stents.

Specifically, the study aims to:

Quantify relative effects: Estimate the comparative impact of indobufen-based DAPT against six alternative antiplatelet strategies on major bleeding (BARC type 3/5) and individual ischemic outcomes (myocardial infarction, stent thrombosis, all-cause death, and stroke) using aspirin plus clopidogrel as the reference.

Rank treatment strategies: Order competing antiplatelet regimens using frequentist P-scores across safety and efficacy outcomes where evidence permits.

Characterize network limitations: Explicitly evaluate the structural connectivity, transitivity, and limitations of the network—including reliance on single bridging trials and the absence of closed loops.

Inform clinical decision-making: Provide evidence to guide individualized antiplatelet regimens for patients post-PCI based on specific bleeding and ischemic risk profiles.

Rationale Bleeding Trade-off Post-PCI: DAPT reduces ischemic risk following PCI with drug-eluting stents, but it causes bleeding that independently increases morbidity and mortality. Fragmented Evidence: Existing bleeding-reduction approaches (shortened DAPT, P2Y_{12} monotherapy, de-escalation) have mostly been tested in isolated pairwise trials with varied endpoints, leaving their comparative hierarchy uncertain. Indobufen Rationale: Indobufen is a reversible COX-1 inhibitor with better gastric tolerance and prostacyclin preservation than aspirin. While trials like OPTION showed lower

bleeding with indobufen-based DAPT compared to aspirin plus clopidogrel, indobufen has never been directly compared against other contemporary strategies. Uncertain Standing: It is unknown where indobufen-based DAPT ranks relative to potent-P2Y_{12} DAPT, ticagrelor monotherapy, or clopidogrel monotherapy. Need for Network Synthesis: A network meta-analysis is required to integrate direct and indirect trial data, evaluating indobufen's relative safety and efficacy across the broader post-PCI therapeutic landscape.

Condition being studied Condition Being Studied: Coronary Artery Disease Requiring Percutaneous Coronary Intervention (PCI)Health Condition & Clinical Context: Coronary artery disease (CAD) occurs when atherosclerotic plaque builds up within the coronary arteries, restricting blood flow to the myocardium. It manifests across a spectrum of clinical presentations, ranging from chronic stable angina to acute coronary syndromes (ACS), such as unstable angina and myocardial infarction. Interventional Treatment: Patients with significant coronary stenosis frequently undergo percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation to restore vessel patency and cardiac perfusion. Therapeutic Challenge: Following PCI, stent implantation creates a transiently pro-thrombotic intravascular environment, making dual antiplatelet therapy (DAPT)—typically combining aspirin with a P2Y_{12} receptor inhibitor—essential to prevent stent thrombosis and recurrent ischemic events. However, antiplatelet therapy inherently increases the risk of major and minor bleeding. Post-PCI bleeding is an independent predictor of adverse clinical outcomes, long-term mortality, and treatment discontinuation. Focus of Interest: The central condition of interest encompasses post-PCI patients across both acute and stable clinical presentations who require an optimal balance between reducing ischemic complications (e.g., stent thrombosis, myocardial infarction, stroke) and minimizing therapy-induced bleeding.

METHODS

Participant or population The participants addressed in this review are adults undergoing percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation across the full clinical spectrum of coronary artery disease, including both acute coronary syndrome (ACS) and stable chronic coronary disease. Enrolled patients encompassed diverse clinical profiles ranging from elective, troponin-negative stable CAD to high-risk ACS presentations, reflecting variable baseline risks for both ischemic events and bleeding complications.

Intervention The interventions evaluated in this network meta-analysis comprise seven pre-specified oral antiplatelet strategies administered following percutaneous coronary intervention (PCI) with drug-eluting stents: the principal experimental regimen of indobufen plus clopidogrel (IC); standard dual antiplatelet therapy consisting of aspirin plus clopidogrel (AC, serving as the reference); aspirin combined with a potent P2Y 12 inhibitor like ticagrelor or prasugrel (AT); ticagrelor monotherapy initiated after abbreviated dual antiplatelet therapy (TM); clopidogrel monotherapy initiated after short-course dual therapy or for chronic maintenance (CM); aspirin monotherapy for chronic maintenance (AM); and potent P2Y 12 inhibitor monotherapy (predominantly prasugrel) paired with immediate, early withdrawal of aspirin (PM).

Comparator The primary comparative intervention applied to the target population is conventional dual antiplatelet therapy consisting of aspirin plus clopidogrel (AC), which serves as the pre-specified reference node across all outcome networks. The other active comparative strategies evaluated against both aspirin plus clopidogrel and indobufen plus clopidogrel include aspirin combined with a potent P2Y 12 inhibitor (ticagrelor or prasugrel), ticagrelor monotherapy initiated after an abbreviated course of dual antiplatelet therapy, clopidogrel monotherapy following short-course dual therapy or for chronic maintenance, aspirin monotherapy for chronic maintenance, and potent P2Y 12 inhibitor monotherapy paired with immediate early aspirin withdrawal.

Study designs to be included The primary study designs included to address the objectives of this systematic review and network meta-analysis are randomized controlled trials (RCTs). Additionally, prospective propensity-matched observational cohort studies comparing indobufen- and aspirin-based dual antiplatelet therapies were eligible and included strictly for pre-specified sensitivity analyses. Non-randomized studies outside of these prospective propensity-matched cohorts, single-arm studies, and conference abstracts lacking full publication were excluded.

Eligibility criteria Inclusion Criteria: Studies were required to report extractable, per-arm crude event counts for at least one of the pre-specified primary or secondary outcomes. Additionally, both arms of a study had to map directly onto one of the defined treatment nodes.

Exclusion Criteria: Studies were excluded if they were non-randomized designs (other than the prospective propensity-matched cohorts reserved for sensitivity analysis), single-arm trials, or conference abstracts without full publications. Studies reporting exclusively surrogate platelet-function endpoints or composite endpoints without extractable component counts were also excluded.

Information sources PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) were systematically searched from inception through May 2026.

Main outcome(s) The primary safety outcome evaluated in the network meta-analysis was major bleeding defined as Bleeding Academic Research Consortium (BARC) type 3/5, with BARC type 2–5 bleeding examined via direct pairwise comparisons due to network disconnection. Secondary efficacy outcomes were evaluated per individual component—comprising myocardial infarction, definite or probable stent thrombosis, all-cause death, and stroke—rather than as a reconstructed composite endpoint to avoid double-counting patients. All outcomes were measured at the longest follow-up reported by each included trial, which ranged from 12 to 24 months post-percutaneous coronary intervention. Treatment effects across all safety and efficacy outcomes were quantified within a frequentist random-effects model using summary odds ratios (ORs) with corresponding 95% confidence intervals (CIs), complemented by frequentist P-scores to order relative strategy rankings.

Quality assessment / Risk of bias analysis Quality and risk of bias in primary studies were assessed independently by two reviewers, with disagreements resolved by consensus. Included randomized controlled trials were evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool across five standard domains—randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result—following standard algorithms. Prospective propensity-matched cohort studies included for sensitivity analysis were appraised using the ROBINS-I tool. Additionally, certainty of evidence for each network contrast was evaluated using the Confidence in Network Meta-Analysis (CINeMA) framework across six domains, including within-study bias, indirectness, imprecision, and incoherence.

Strategy of data synthesis Quantitative synthesis was conducted within a frequentist random-effects framework using the graph-theoretical network meta-analysis model implemented in R's netmeta package. Binary safety and efficacy outcomes were synthesized using crude per-arm event counts and total denominators to derive summary odds ratios (ORs) with 95% confidence intervals (CIs) relative to aspirin plus clopidogrel, retaining a binomial likelihood model without continuity corrections to account for sparse event counts. Network connectivity was evaluated for each outcome prior to estimation, and relative strategy hierarchies were quantified using frequentist P-scores. Common between-study variance tau^2 was calculated using the DerSimonian-Laird method alongside I^2 statistics. Transitivity was evaluated by examining clinical and methodological effect modifiers across contrasts, while robustness was tested through pre-specified sensitivity analyses that excluded bridging trials, omitted proxy bleeding definitions, and incorporated propensity-matched cohort data.

Subgroup analysis Subgroup analyses could not be conducted in this network meta-analysis due to the structural constraints of the evidence base. Specifically, every contrast across the network was informed by a single trial design, which precluded formal subgroup evaluations or network meta-regressions to explore potential effect modifiers such as clinical presentation or patient demographics.

Sensitivity analysis The robustness of the network model was rigorously evaluated through multiple pre-specified sensitivity analyses. First, a bridge-dependency analysis was performed by removing the single bridging trial (GLOBAL LEADERS), which confirmed that all cross-cluster comparisons depended entirely on that single study as its removal fragmented every network into disconnected components. Second, a major-bleeding sensitivity analysis was conducted excluding the two trials whose bleeding outcomes were mapped from the TIMI scale to BARC 3/5 definitions; this analysis confirmed that the direction, magnitude, and statistical significance of the principal estimates remained unchanged. Finally, incorporating data from three prospective propensity-matched observational cohorts yielded indobufen-versus-aspirin safety and efficacy estimates that were fully concordant with the main trial-only analysis.

Country(ies) involved Afghanistan - Kabul Medical Univeristy, Kabul, Afghanistan. India, South Korea, United States, United Kingdom, Serbia, Haiti, Austria, Ethiopia, Kenya, Afghanistan, Pakistan, China, Italy, India.

Keywords indobufen, dual antiplatelet therapy, percutaneous coronary intervention, network meta-analysis, aspirin, clopidogrel, P2Y12 inhibitors, major bleeding, antiplatelet de-escalation, drug-eluting stents.

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