

Catheterization and Cardiovascular Interventions

Review

Comparative Safety and Efficacy of Indobufen versus Aspirin-based Dual Antiplatelet Therapy in Patients Undergoing Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis of Randomized Trials and Observational Cohort Studies

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Comparative Safety and Efficacy of Indobufen versus Aspirin-based Dual Antiplatelet Therapy in Patients Undergoing Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis of Randomized Trials and Observational Cohort Studies

Running head: Indobufen vs Aspirin in PCI

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Authors Contribution:

Amarsimha Yerrajonna, Mirza Muhammad Hadeed Khawar, and Elham Shenawa were responsible for the conceptualization and methodology of the study. **Mirza Muhammad Hadeed Khawar and Elham Shenawa** further provided supervision and project administration. **Tawfiq Turjman** contributed to the methodology, formal analysis, and the review and editing of the manuscript. **Jungwook Heo, Afifa Fatima, and Riyazuddin Mohd** handled software, data curation, and visualization. The formal analysis was conducted by **Jungwook Heo, Afifa Fatima, Amarsimha Yerrajonna, and Tawfiq Turjman**. **Hannah George, Uchechi Blessing Azuwike, Dany Pierre Clitandre Bien-Aimé, and Jean Antoni Sebastien Lefevre** were involved in validation and investigation. **Aparna Gopinath, Lavinia Rech, Mihret Derbie Asfaw, and Joy Rita Ekumba** contributed to investigation and resource acquisition. All authors participated in the investigation and the writing of the original draft, while **Mirza Muhammad Hadeed Khawar, Elham Shenawa, Amarsimha Yerrajonna, and Tawfiq Turjman** performed the final review and editing

Abstract

Background: Dual antiplatelet therapy (DAPT) with aspirin and a P2Y₁₂ inhibitor is standard care following percutaneous coronary intervention (PCI), but bleeding complications remain a major limitation. Indobufen, a reversible cyclooxygenase-1 inhibitor, has been proposed as a safer alternative to aspirin.

Methods: We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) and observational cohort studies comparing indobufen- versus aspirin-based DAPT in PCI patients. Six studies (three RCTs, three cohorts) including 7,426 participants were analyzed. Outcomes included Bleeding Academic Research Consortium (BARC) bleeding, net adverse clinical events (NACE), major adverse cardiovascular and cerebrovascular events (MACCE), myocardial infarction, stent thrombosis, and target lesion revascularization (TLR). Risk of bias was assessed using RoB 2.0 and ROBINS-I, and certainty of evidence was graded using GRADE.

Results: Indobufen significantly reduced BARC type 2–5 bleeding compared with aspirin (RR = 1.03, 95% CI: 1.00–1.06; $p = 0.03$), with consistent benefit in RCTs (RR = 1.02, 95% CI: 1.01–1.03; $p = 0.0006$). NACE reduction was significant in RCTs (RR = 0.74, 95% CI: 0.58–0.94; $p = 0.02$), though not overall. No differences were observed for MACCE, myocardial infarction, or stent thrombosis. A borderline reduction in TLR was noted (RR = 0.77, 95% CI: 0.59–1.01; $p = 0.06$). Evidence certainty ranged from moderate (MACCE) to very low (stent thrombosis).

Conclusions: Indobufen-based DAPT offers superior safety with reduced bleeding risk compared to aspirin-based regimens, without compromising ischemic protection. These findings support indobufen as a promising alternative for post-PCI management, particularly in patients at high bleeding risk.

Keywords: Indobufen; Aspirin; Dual Antiplatelet Therapy (DAPT); Percutaneous Coronary Intervention (PCI); Bleeding Academic Research Consortium (BARC); Net Adverse Clinical Events (NACE); Major Adverse Cardiovascular and Cerebrovascular Events (MACCE); Target Lesion Revascularization (TLR); Stent Thrombosis

Introduction

Dual antiplatelet therapy (DAPT), typically comprising aspirin and a $P2Y_{12}$ receptor inhibitor, serves as the cornerstone of pharmacological management for patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) [1, 2]. While this regimen effectively reduces the incidence of major adverse cardiovascular and cerebrovascular events (MACCE), such as stent thrombosis and myocardial infarction, it is inherently associated with an increased risk of bleeding complications [3]. Bleeding events, particularly those classified by the Bleeding Academic Research Consortium (BARC), are independently linked to increased mortality and a significant economic burden on healthcare systems [4, 5]. Consequently, identifying alternative antiplatelet strategies that maintain ischemic protection while minimizing bleeding risks remains a critical clinical priority.

Indobufen, a reversible inhibitor of the cyclooxygenase-1 (COX-1) enzyme, has emerged as a potential alternative to aspirin [6]. Unlike aspirin, which irreversibly inhibits platelet aggregation, indobufen's reversible nature may offer a more favorable safety profile, particularly concerning gastrointestinal and major bleeding events [6, 7]. Recent clinical evidence, including the large-scale OPTION trial, has suggested that indobufen-based DAPT is non-inferior to aspirin-based DAPT in terms of ischemic protection while significantly reducing the risk of BARC-defined bleeding in patients undergoing PCI [7]. However, findings across individual randomized controlled trials (RCTs) and observational cohort studies have shown some variability, particularly regarding net adverse clinical events (NACE) and specific ischemic endpoints like target lesion revascularization (TLR) [8].

Despite the growing body of literature, a comprehensive synthesis of both experimental and real-world evidence is necessary to establish the definitive clinical role of indobufen in the post-PCI

setting. Previous analyses have often been limited by smaller sample sizes or the exclusion of high-quality observational data that reflect real-world clinical practice. Therefore, this systematic review and meta-analysis aims to evaluate the comparative safety and efficacy of indobufen versus aspirin as a component of DAPT in patients undergoing PCI, utilizing the most recent data from both randomized trials and cohort studies to provide a robust foundation for clinical decision-making.

Methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [9]. Eligibility criteria were defined using the PICOS framework, targeting patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI). The intervention group consisted of patients receiving indobufen-based dual antiplatelet therapy (DAPT), while the control group received conventional aspirin-based DAPT. Clinical outcomes included safety measures such as BARC bleeding and NACE, and efficacy measures including MACCE, myocardial infarction, stent thrombosis, and target lesion revascularization. A systematic search was conducted across PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL), supplemented by trial registries to ensure a comprehensive literature search.

Quality assessment was conducted using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool for randomized controlled trials and the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool for observational cohort studies. Statistical synthesis was performed using Review Manager (RevMan) software. For dichotomous outcomes, the Mantel-Haenszel method was used to calculate pooled Risk Ratios (RR) with 95% confidence intervals (CI). For time-to-

event outcomes, the generic inverse variance method was employed to pool Hazard Ratios (HR) and their corresponding 95% CIs.

Statistical heterogeneity was assessed using the I^2 statistic; a fixed-effects model was applied for outcomes with low heterogeneity ($I^2 < 50\%$), while a random-effects model was utilized when significant heterogeneity was observed ($I^2 \geq 50$). Subgroup analyses were stratified by study design (RCT vs. Cohort) to investigate the consistency of effects across different clinical evidence levels. Finally, the certainty of evidence for each outcome was evaluated according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.

Results

Study Selection

A systematic search conducted through December 2025 across PubMed, ScienceDirect, Embase, and ClinicalTrials.gov yielded 467 records. After removing 55 duplicates, 412 records were screened, with 315 excluded based on title and abstract. Of the 97 reports assessed for full-text eligibility, 91 were excluded because they were protocols, utilized indobufen as monotherapy, or lacked an aspirin-based control group. Ultimately, 6 [7, 10-14] studies (3 randomized controlled trials and 3 observational cohort studies) involving 7,426 patients were included in this meta-analysis (**Figure 1**).

Baseline Characteristics

The baseline clinical and demographic characteristics of the participants included in the six studies are summarized in the table 1, showing well-balanced profiles across the indobufen and

aspirin treatment groups. The mean age of the study populations ranged from approximately 59.5 to 75.8 years, with a notable proportion of elderly patients included in recent cohorts. Male participants were predominant in most trials, representing between 52.5% and 83.5% of the total cohorts. The mean Body Mass Index (BMI) remained relatively consistent across the groups, ranging from 23.6 to 25.6 kg/m².

High-risk cardiovascular comorbidities were highly prevalent among the patients. Hypertension affected between 55.5% and 78.1% of the participants, while diabetes mellitus prevalence ranged from 18.3% to 42.5%. Mean Low-Density Lipoprotein (LDL) levels were reported between 2.34 and 2.94 mmol/L in the studies where data was available. A significant portion of the population had a history of prior ischemic events, with prior myocardial infarction or acute coronary syndrome (ACS) ranging from 6.0% to as high as 60.9% in specialized cohorts. History of prior percutaneous coronary intervention (PCI) and stroke were reported in up to 26.1% and 19.0% of patients, respectively. Additionally, current or former smoking status was reported for 16.5% to 54.0% of the participants. Most studies focused on a 12-month follow-up period, though one study extended follow-up to 2.1 years (**Table 1**).

Risk of Bias Assessment

The risk of bias in the RCTs was evaluated using the Cochrane RoB 2.0 tool [15]. Wu 2023 (the OPTION trial) and Jiang 2025 were judged to be at low risk of bias due to robust randomization and blinded outcome adjudication. Wu 2024 was rated as having some concerns primarily due to higher attrition rates and a lack of outcome assessor blinding for subjective endpoints (**Figure 5**). For the three non-randomized studies, the ROBINS-I tool indicated a moderate risk of bias [16]; while these studies employed propensity score matching (PSM) or inverse probability of

treatment weighting (IPTW) to mitigate confounding, the inherent risk of residual unmeasured variables remained (**Figure 6**).

Safety Outcomes

- **BARC Type 2, 3, or 5 Bleeding:** Indobufen demonstrated a statistically significant reduction in bleeding risk compared to aspirin, with an overall Risk Ratio (RR) for "non-events" of 1.03 (95% CI: 1.00–1.06; $P = 0.03$). This benefit was highly consistent in the RCT subgroup (RR = 1.02, 95% CI: 1.01–1.03; $P = 0.0006$) with no heterogeneity ($I^2 = 0\%$). (**Figure 2a**)
- **Net Adverse Clinical Events (NACE):** While the overall pooled effect for NACE did not reach statistical significance (RR = 0.81, 95% CI: 0.61–1.08; $P = 0.15$), a significant advantage for indobufen was observed within the RCT subgroup (RR = 0.74, 95% CI: 0.58–0.94; $P = 0.02$). High overall heterogeneity ($I^2 = 68\%$) was noted, primarily driven by variations in the cohort study results (**Figure 2b**).

Efficacy Outcomes

- **MACCE:** No significant difference was observed between the indobufen and aspirin groups for the composite outcome of Major Adverse Cardiovascular and Cerebrovascular Events (RR = 1.03, 95% CI: 0.84–1.26; $P = 0.77$). Results were consistent across studies with zero heterogeneity ($I^2 = 0\%$) (**Figure 3a**)
- **Myocardial Infarction and Stent Thrombosis:** The risk of recurrent/non-fatal myocardial infarction was comparable between groups (RR = 0.91, 95% CI: 0.56–1.49; $P = 0.72$), as was the risk of definite or probable stent thrombosis (RR = 0.91, 95% CI: 0.47–1.75; $P = 0.77$) (**Figure 3b and 3c**)

- **Target Lesion Revascularization (TLR):** Indobufen-based DAPT showed a trend toward reducing TLR compared to aspirin (RR = 0.77, 95% CI: 0.59–1.01; P = 0.06), although this did not reach formal statistical significance (**Figure 4**).

Certainty of Evidence (GRADE)

Based on the GRADE framework, the certainty of evidence was moderate for the MACCE outcome due to high consistency and narrow confidence intervals. The certainty was rated as low for BARC bleeding, NACE, myocardial infarction, and TLR, primarily due to serious inconsistency or imprecision. The evidence for stent thrombosis was rated as very low due to very serious imprecision resulting from extremely low event rates across the included trials (**Table 2**).

Discussion

This systematic review and meta-analysis, incorporating data from 7,426 patients across three randomized controlled trials and three observational cohort studies, provides a comprehensive evaluation of the safety and efficacy of indobufen versus aspirin in patients undergoing percutaneous coronary intervention (PCI). The primary finding is that indobufen-based dual antiplatelet therapy (DAPT) is associated with a statistically significant reduction in the risk of BARC type 2, 3, or 5 bleeding events compared to aspirin-based DAPT, a benefit that was particularly pronounced and consistent within the randomized trial subgroup [7, 10]. Importantly, this safety advantage was achieved without compromising antithrombotic efficacy; there were no significant differences between the two treatment groups regarding the incidence of Major Adverse Cardiovascular and Cerebrovascular Events (MACCE), recurrent myocardial infarction,

or stent thrombosis. Additionally, a borderline significant trend toward reduced Target Lesion Revascularization (TLR) was observed in the indobufen arm [13, 17].

The superior safety profile of indobufen observed in this analysis can largely be attributed to its pharmacological mechanism as a reversible inhibitor of cyclooxygenase-1 (COX-1). Unlike aspirin, which permanently acetylates COX-1 and inhibits platelet function for the entire lifespan of the platelet, indobufen suppresses thromboxane B2 production reversibly. This reversible inhibition allows for a faster recovery of platelet function upon discontinuation and may result in less profound suppression of gastrointestinal mucosal protective factors, thereby reducing bleeding risks [18]. The finding that indobufen significantly reduced Net Adverse Clinical Events (NACE) in the RCT subgroup suggests that in a controlled setting, the reduction in bleeding events drives an overall net clinical benefit, even if the reduction in ischemic events is not statistically superior. The heterogeneity observed in the bleeding outcomes among cohort studies likely reflects the variability in real-world clinical practice, where baseline bleeding risks and adherence to gastroprotective agents may differ more widely than in structured trial environments [7].

Our findings align with and extend the results of the pivotal OPTION trial [7], which established the non-inferiority of indobufen to aspirin in a broad PCI population. While the OPTION trial primarily drove the weight of the RCT evidence, this meta-analysis incorporates recent data from specific high-risk populations, such as elderly patients in the Wu et al. (2024) [14] and Dai et al. (2025) [11] studies, and patients with acute myocardial infarction in the Wen-Bo Dai 2024 cohort. Unlike previous reviews that may have relied on older data or smaller sample sizes, our inclusion of the Jiang et al. (2025) trial [12] adds contemporary evidence regarding the use of indobufen following drug-eluting balloon (DEB) angioplasty, confirming that the safety benefits

persist across different PCI modalities. Furthermore, the consistency of the MACCE results across both randomized and observational studies ($I^2=0\%$) reinforces the external validity of indobufen as a potent alternative to aspirin for ischemic protection.

This study has several limitations that merit consideration. First, the inclusion of both RCTs and observational cohort studies introduces potential sources of bias; while the cohort studies employed propensity score matching or weighting to mitigate confounding, residual unmeasured confounders cannot be entirely ruled out. Second, there was significant heterogeneity in the safety outcomes (bleeding and NACE) within the cohort subgroup, likely due to differences in definitions of bleeding or data collection methods in retrospective registries compared to adjudicated trials. Third, the follow-up duration varied across studies, with the Jiang 2025 trial reporting only short-term (1-month) outcomes, which limits our ability to fully assess long-term safety and stent thrombosis risks for that specific subset. Finally, the majority of included studies were conducted in East Asian populations, which may limit the generalizability of the findings to other ethnic groups with different thrombotic and bleeding risk profiles.

The results of this meta-analysis have immediate clinical implications, suggesting that indobufen is a viable and potentially safer alternative to aspirin for DAPT, particularly for patients at high risk of bleeding or those with aspirin intolerance. The significant reduction in BARC bleeding without an increase in ischemic events supports the consideration of indobufen in personalized antiplatelet strategies, especially for elderly patients or those with a history of gastrointestinal bleeding. Future research should focus on large-scale, multi-center RCTs with longer follow-up periods to confirm the long-term durability of these benefits. Additionally, studies investigating the cost-effectiveness of indobufen compared to aspirin, as well as its efficacy in diverse non-

Asian populations, would be valuable to support broader adoption in international clinical guidelines.

Conclusion

In conclusion, this meta-analysis demonstrates that indobufen-based DAPT is associated with a significantly lower risk of bleeding complications compared to conventional aspirin-based DAPT in patients undergoing PCI, while providing comparable protection against major ischemic cardiovascular events. The favorable safety profile, particularly evident in randomized trials, positions indobufen as a promising therapeutic option for optimizing the balance between ischemia and bleeding. While further research is needed to validate these findings globally, current evidence supports the use of indobufen as an effective alternative to aspirin in post-PCI management.

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Table 1: Baseline Clinical and Demographic Characteristics of Patients in the Included Studies

STUDY ID	Study Design	Follow up period	Age (Mean ± SD)		Male/Female (%)		BMI (Mean ± SD)		Hypertension(%)		Diabetes mellitus(%)		LDL(mmol /L)		Prior myocardial infarction (MI)/ACS (%)		Prior PCI(%)		Prior stroke / Cerebrovascular disease(%)		Current or former smoker(%)	
			Indobufen	Aspirin	Indobufen	Aspirin	Indobufen	Aspirin	Indobufen	Aspirin	Indobufen	Aspirin	Indobufen	Aspirin	Indobufen	Aspirin	Indobufen	Aspirin	Indobufen	Aspirin	Indobufen	Aspirin
Dai 2024	Retrospective cohort		66+/-9.4	66+/-10.5	72.2/27.8	70.8/29.2	24.8+/-3.3	24.8+/-3.5	66	64	33.4	33.5	NA	NA	13.4	13.7	25.4	24.2	7.7	6.6	17.7	16.5
Dai 2025	Retrospective cohort	1 year	75.8 ± 6.54	75.7 ± 7.05	49/51	48.7/51.3	NA	NA	77.1	78.1	35	36.3	2.88 ± 0.94	2.83 ± 0.88	11.4	11.4	23.9	26.1	17	19	28.4	27.1
Wen-Bo Dai 2024	retrospective cohort	2.1 years	72 ± 11	72 ± 10	62.9/37.1	67/33	NA	NA	75	73.7	39.7	41..5	2.86 ± 0.92	2.94 ± 0.86	12.9	13.8	19.2	16.5	20.5	24.1	36.7	35.7
Wu 2023	Randomised clinical trial	1 year	61.0±8.3	61.2±8.4	67.4/32.6	63.1/36.9	25.0±3.3	25.0±3.2	67.2	67.2	35.5	33.5	2.53±0.95	2.55±0.99	6.1	6	NA	NA	6.5	4.7	25.9	23.6
Wu 2024	Randomised clinical trial	1 year	73.9+/-5.6	73+/-5.5	70.9/29.1	79.4/20.6	24.6+/-3.5	25.2+/-2.6	69.1	66	34.5	27.7	NA	NA	NA	NA	NA	NA	9.1	12.8	32.7	38.3
Jiang et al. (2025)	Randomised clinical trial	1 year	68.5 ± 12.2	69.7 ± 10.2	52.5/47.5	56.7/43.3	23.9 ± 3.2	23.6 ± 2.7	55.5	59.2	18.3	20.8	2.34 (1.78, 2.80)	2.41 (1.79, 2.97)	60.9	58.2	NA	NA	NA	NA	NA	NA

Table 2: GRADE Summary of Findings and Certainty of Evidence for Clinical Outcomes

Outcome	Risk Ratio (95% CI)	Subgroups Included	Heterogeneity (I ²)	GRADE Certainty
MACCE	1.03 (0.84, 1.26)	Cohort & RCT	0%	Moderate ⊕⊕⊕⊖
BARC 2, 3, 5 Bleeding	1.03 (1.00, 1.06)*	Cohort & RCT	80%	Low ⊕⊕⊖⊖
NACE	0.81 (0.61, 1.08)	Cohort & RCT	68%	Low ⊕⊕⊖⊖
Recurrent/Non-fatal MI	0.91 (0.56, 1.49)	Cohort & RCT	0%	Low ⊕⊕⊖⊖
TLR	0.77 (0.59, 1.01)	Cohort & RCT	0%	Low ⊕⊕⊖⊖
Stent Thrombosis	0.91 (0.47, 1.75)	Cohort & RCT	0%	Very Low ⊕⊖⊖⊖

Note:

- **High Certainty (⊕⊕⊕⊕):** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate Certainty (⊕⊕⊕⊖):** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low Certainty (⊕⊕⊖⊖):** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Very Low Certainty (⊕⊖⊖⊖):** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

MACCE: Major Adverse Cardiovascular and Cerebrovascular Events; **BARC:** Bleeding Academic Research Consortium; **NACE:** Net Adverse Clinical Events; **MI:** Myocardial Infarction; **TLR:** Target Lesion Revascularization

Figure 1. PRISMA flowchart outlining the literature screening process, study selection, and exclusion criteria

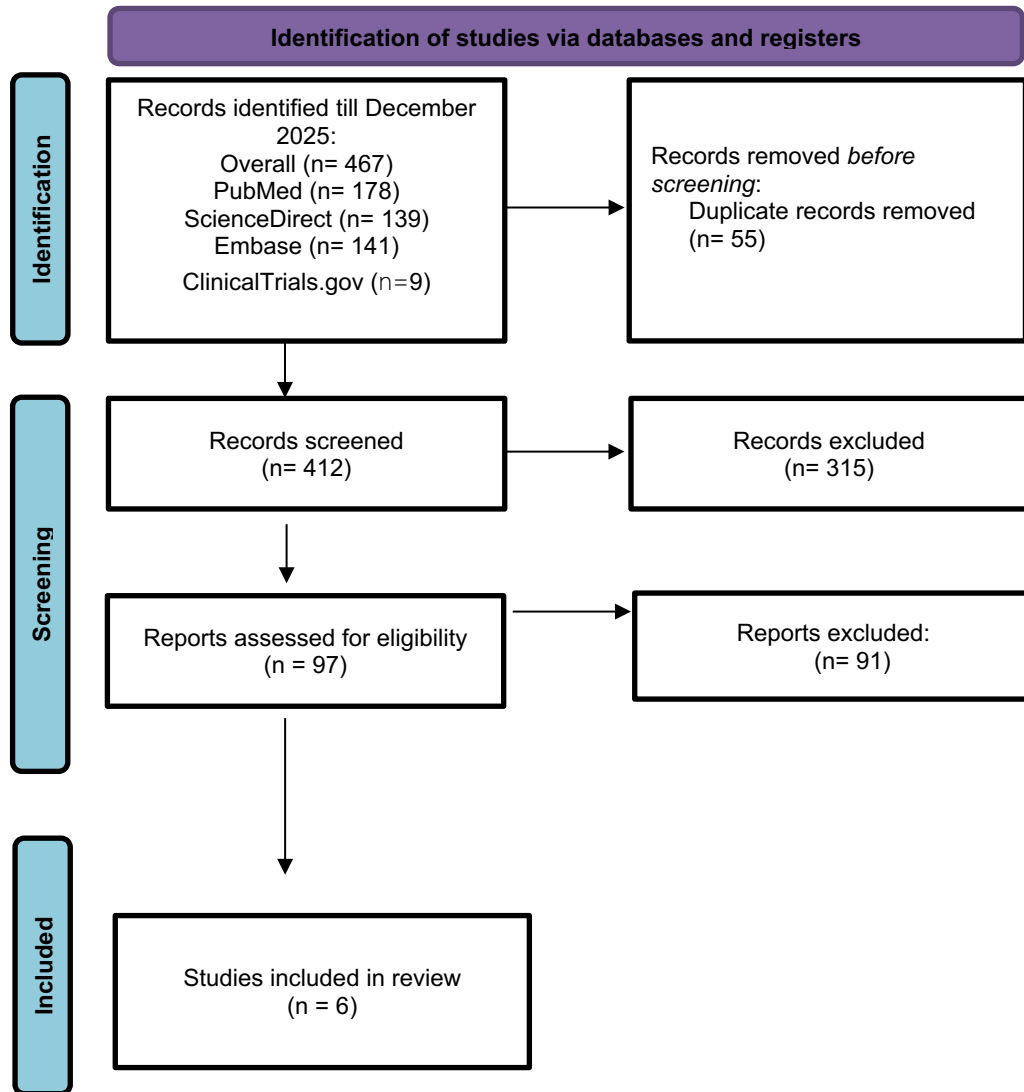
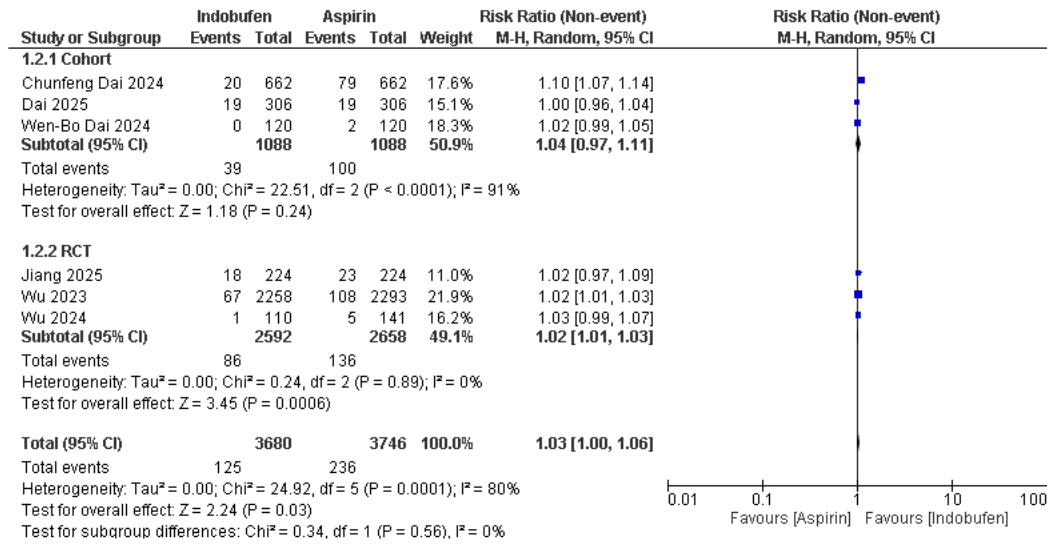


Figure 2: Forest Plots Comparing Safety Outcomes (BARC Bleeding and NACE) Between Indobufen and Aspirin Groups

a) BARC type 2, 3 or 5 bleeding



b) Net adverse clinical events (NACE)

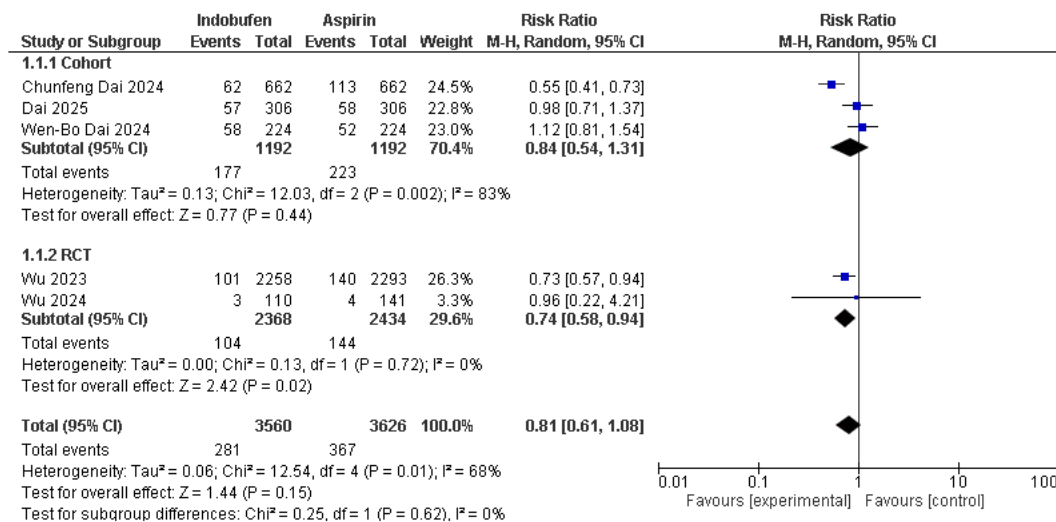
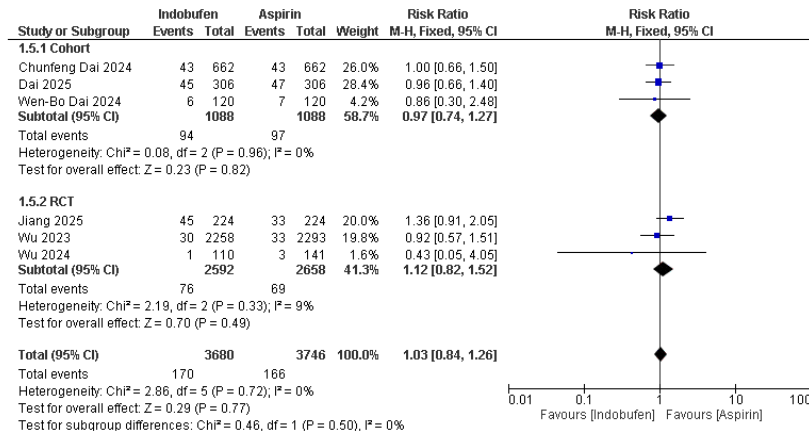
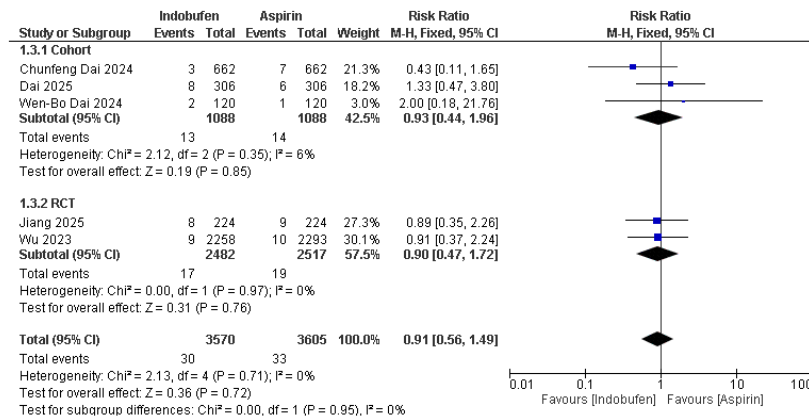


Figure 3: Forest Plots Comparing Efficacy Outcomes (MACCE, Myocardial Infarction, and Stent Thrombosis) Between Treatment Groups

a) Major Adverse Cardiovascular and Cerebrovascular Events (MACCE)



b) Recurrent/non-fatal myocardial infarction



c) Stent Thrombosis

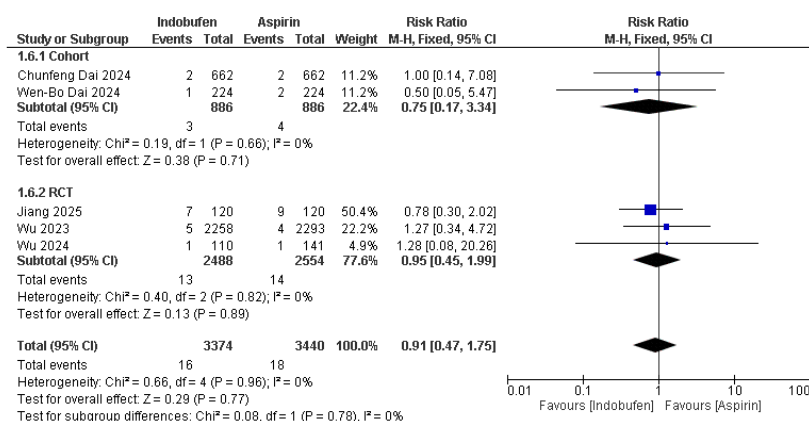


Figure 4: Forest Plot of Target Lesion Revascularization (TLR) Incidence in Indobufen versus

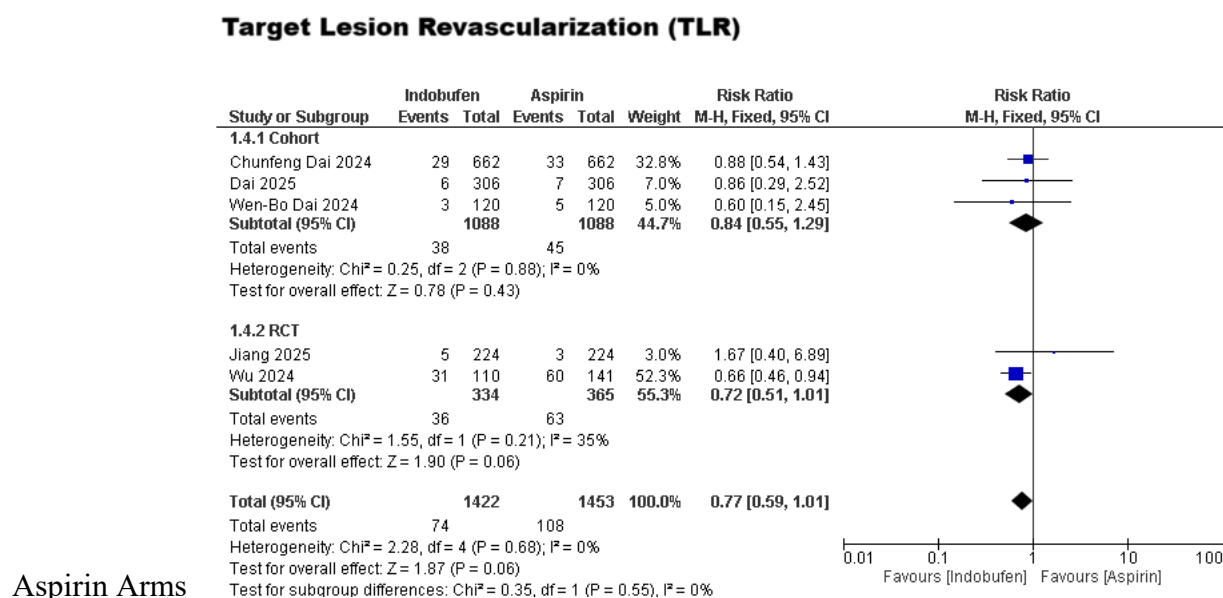


Figure 5: Risk of Bias Assessment for Randomized Controlled Trials Using the Cochrane RoB 2.0 Tool

		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
Study	Wu 2023	+	+	+	+	+	+
	Wu 2024	+	-	-	-	+	-
	Jiang 2025	+	+	+	+	+	+

Domains:

D1: Bias arising from the randomization process.

D2: Bias due to deviations from intended intervention.

D3: Bias due to missing outcome data.

D4: Bias in measurement of the outcome.

D5: Bias in selection of the reported result.

Judgement

-

Some concerns

+

Low

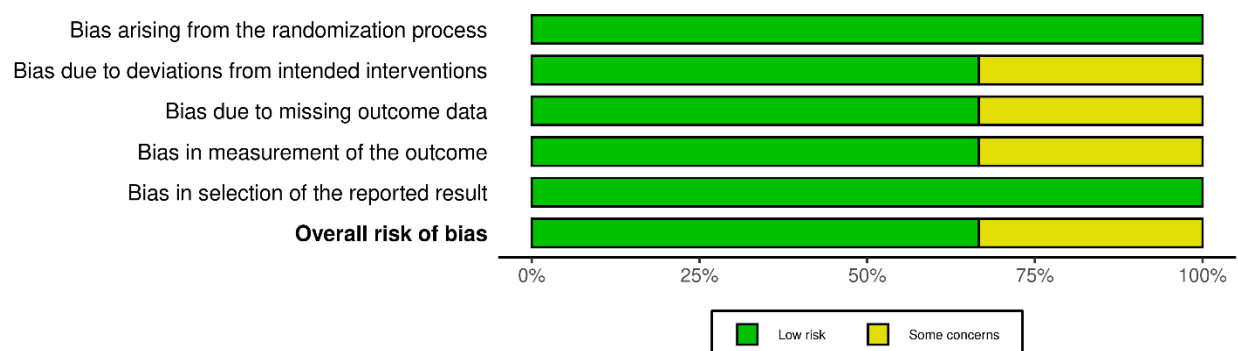


Figure 6: Risk of Bias Assessment for Observational Cohort Studies Using the ROBINS-I Tool

