

Safety and efficacy of aspirin and indobufen in the treatment of arteriosclerotic cardiovascular disease: a systematic review and meta-analysis

Wenhao Pan, Linger Guan, Haicheng Zhang

Submitted to: Interactive Journal of Medical Research
on: April 01, 2025

Disclaimer: © The authors. All rights reserved. This is a privileged document currently under peer-review/community review. Authors have provided JMIR Publications with an exclusive license to publish this preprint on its website for review purposes only. While the final peer-reviewed paper may be licensed under a CC BY license on publication, at this stage authors and publisher expressly prohibit redistribution of this draft paper other than for review purposes.

Table of Contents

Original Manuscript..... 4

Supplementary Files..... 22

 Figures 23

 Figure 1..... 24

 Figure 2..... 25

Safety and efficacy of aspirin and indobufen in the treatment of arteriosclerotic cardiovascular disease: a systematic review and meta-analysis

Wenhao Pan^{1*}; Linger Guan^{1*}; Haicheng Zhang¹

¹ Peking University People's Hospital Beijing CN

*these authors contributed equally

Corresponding Author:

Haicheng Zhang

Peking University People's Hospital

Peking University People's Hospital, Zhanzhan Road Street, Xicheng District, Bei

Beijing

CN

Abstract

Background: The pathogenesis of atherosclerotic thrombosis primarily involves platelet activation and aggregation, making antiplatelet therapy the cornerstone of treatment for such diseases.

Objective: This meta-analysis aimed to compare the safety and efficacy of aspirin and indobufen in antiplatelet therapy for patients with arteriosclerotic cardiovascular disease.

Methods: We searched the Cochrane Library, PubMed, EMBASE, Web of Science, and the Chinese Wanfang databases. The literature was screened according to predefined inclusion and exclusion criteria. Relative risk (RR) was used to assess the magnitude of risk associated with exposure.

Results: Eighteen clinical trials with a total of 12981 patients were included in this study. Compared with aspirin, indobufen reduced the risk of (1) bleeding events (RR 0.54; 95% CI: 0.41–0.71; $P < 0.0001$), (2) BARC 2/3/5 bleeding (RR 0.50; 95% CI: 0.26–0.94; $P = 0.03$), (3) adverse cardiovascular events (RR 0.43; 95% CI: 0.30–0.61; $P < 0.00001$), and (4) myocardial infarction (RR 0.60; 95% CI: 0.41–0.89; $P = 0.01$). However, there were no significant differences between the two groups in terms of MACCEs, stroke, or cardiovascular mortality.

Conclusions: Compared to aspirin, indobufen demonstrated better safety and was not inferior to aspirin in terms of efficacy, with superior results in some aspects. Further studies with larger sample sizes or longer follow-up periods may provide additional evidence. Clinical Trial: This study is registered with PROSPERO (CRD42024588250) and was conducted in accordance with the 2020 version of the PRISMA statement

(JMIR Preprints 01/04/2025:75363)

DOI: <https://doi.org/10.2196/preprints.75363>

Preprint Settings

1) Would you like to publish your submitted manuscript as preprint?

✓ **Please make my preprint PDF available to anyone at any time (recommended).**

Please make my preprint PDF available only to logged-in users; I understand that my title and abstract will remain visible to all users.

Only make the preprint title and abstract visible.

No, I do not wish to publish my submitted manuscript as a preprint.

2) If accepted for publication in a JMIR journal, would you like the PDF to be visible to the public?

✓ **Yes, please make my accepted manuscript PDF available to anyone at any time (Recommended).**

Yes, but please make my accepted manuscript PDF available only to logged-in users; I understand that the title and abstract will remain visible to all users.

Yes, but only make the title and abstract visible (see Important note, above). I understand that if I later pay to participate in a peer-reviewed journal, I will be able to make the full manuscript available to all users.

No. Please do not make my accepted manuscript PDF available to anyone.

Original Manuscript

Safety and efficacy of aspirin and indobufen in the treatment of arteriosclerotic cardiovascular disease: a systematic review and meta-analysis

Wenhao Pan^{†a}, Linger Guan^{†a}, Haicheng Zhang^{*a}

Abstract:

Introduction: The pathogenesis of atherosclerotic thrombosis primarily involves platelet activation and aggregation, making antiplatelet therapy the cornerstone of treatment for such diseases. This meta-analysis aimed to compare the safety and efficacy of aspirin and indobufen in antiplatelet therapy for patients with arteriosclerotic cardiovascular disease.

Methods: We searched the Cochrane Library, PubMed, EMBASE, Web of Science, and the Chinese Wanfang databases. The literature was screened according to predefined inclusion and exclusion criteria. Relative risk (RR) was used to assess the magnitude of risk associated with exposure.

Results: Eighteen clinical trials with a total of 12981 patients were included in this study. Compared with aspirin, indobufen reduced the risk of (1) bleeding events (RR 0.54; 95% CI: 0.41–0.71; $P < 0.0001$), (2) BARC 2/3/5 bleeding (RR 0.50; 95% CI: 0.26–0.94; $P = 0.03$), (3) adverse cardiovascular events (RR 0.43; 95% CI: 0.30–0.61; $P < 0.00001$), and (4) myocardial infarction (RR 0.60; 95% CI: 0.41–0.89; $P = 0.01$). However, there were no significant differences between the two groups in terms of MACCEs, stroke, or cardiovascular mortality.

Conclusion: Compared to aspirin, indobufen demonstrated better safety and was not inferior to aspirin in terms of efficacy, with superior results in some aspects. Further studies with larger sample sizes or longer follow-up periods may provide additional evidence.

This study is registered with PROSPERO (CRD42024588250) and was conducted in accordance with the 2020 version of the PRISMA statement

Keywords: arteriosclerotic cardiovascular disease, antiplatelet therapy, aspirin, indobufen

[†] Pan Wenhao and Guan Linger contributed equally to this work and should be considered co-first authors.

Email: Pan Wenhao: pwh000702@163.com; ORCID: [0009-0006-3542-5780](https://orcid.org/0009-0006-3542-5780)

Guan Linger: gleyyfoya@163.com

^aDepartment of Cardiology, Peking University People's Hospital, Beijing, China

^{*} Corresponding author¹: Department of Cardiology, Peking University People's Hospital, Beijing; zip code: 100044; E-mail: Zhang Haicheng: haichengzhang@bjmu.edu.cn; ORCID: [0000-0001-9655-9578](https://orcid.org/0000-0001-9655-9578)

¹ This study is supported by major projects of the National Social Science Fund (18ZDA086-4).

1. Introduction

Atherosclerotic diseases include a variety of conditions caused by the buildup of plaque within arteries, leading to their narrowing and hardening^[1]. This type of plaque is primarily composed of cholesterol, lipids, and other substances, which progressively restrict blood flow to key organs. Common manifestations include coronary atherosclerosis, intracranial atherosclerosis, and carotid artery and peripheral artery atherosclerotic disease. They increase the risk of cardiovascular events such as heart attacks and strokes. Major risk factors include elevated cholesterol, hypertension, diabetes, smoking, and obesity^[2].

The pathogenesis of atherothrombosis is mainly the activation and aggregation of platelets, and platelet reactivity might be associated with the severity of atherosclerosis^[3]. Therefore, antiplatelet therapy is the cornerstone of treatment. This activation triggers the release of various signaling molecules, including thromboxane A₂ (TXA₂), which is synthesized from arachidonic acid via the cyclooxygenase-1 (COX-1) enzyme^[4]. TXA₂ plays a critical role in amplifying the platelet activation process by promoting the recruitment of additional platelets to the injury site, thereby increasing platelet aggregation^[5]. The importance of the COX-1 enzyme in platelet activation is evident in the mechanism of antiplatelet drugs such as aspirin and indobufen^[6,7]. This disruption in the TXA₂ pathway significantly lowers the risk of thrombus formation, making COX-1 inhibitors essential for the prevention and treatment of atherosclerotic cardiovascular events. In summary, the COX-1/TXA₂ pathway is central to platelet aggregation, and its inhibition is a key therapeutic strategy for managing atherosclerotic diseases^[8].

In patients with atherosclerotic disease, the primary benefit of antiplatelet therapy is the reduction in adverse cardiovascular events related to arterial stenosis, ischemia, and occlusion^[9]. The main adverse reaction, however, is mucosal bleeding caused by platelet aggregation inhibition^[10]. Given that aspirin has a greater risk of intracranial and gastrointestinal bleeding than other antiplatelet agents do and that some patients may develop resistance, recent studies have focused on alternatives to aspirin^[11,12]. Currently, Chinese guidelines acknowledge the feasibility of indobufen as an antiplatelet agent but do not consider it a replacement for aspirin^[13]. In contrast, indobufen is less frequently mentioned as a treatment option for patients in the European and American guidelines.

In the evaluation of the efficacy and safety of antiplatelet therapy for patients with atherosclerotic disease, commonly assessed outcomes include the incidence of major adverse cardiovascular and cerebrovascular events (MACCEs)^[14,15]. MACCE is a composite endpoint comprising cardiovascular death, nonfatal myocardial infarction, clinically driven repeated revascularization, definite or probable stent thrombosis, and nonfatal ischemic stroke. Moreover, safety can be evaluated on the basis of the incidence of bleeding events. The Bleeding Academic Research Consortium (BARC) defines the primary safety endpoint as type 2, 3, or 5 bleeding, also known as major bleeding^[16]. Another safety outcome is any bleeding, including mild to severe bleeding.

This article comprehensively reviewed clinical trials and cohort studies on the efficacy and safety of indobufen in the treatment of atherosclerotic diseases such as stroke and coronary heart disease (CHD), with aspirin as the control. Through meta-analysis, we aimed to integrate existing clinical studies to explore the incidence of MACCEs during the treatment of the aforementioned disease population with indobufen, evaluate its efficacy, and assess the safety of the drug through the incidence of mucosal bleeding to provide a reference for the clinical application of indobufen and emphasize the necessity of further large-sample prospective studies.

2. Materials and methods

2.1. Literature review design

This study is registered with PROSPERO (CRD42024588250) and was conducted in accordance with the 2020 version of the PRISMA statement^[17].

2.2. Literature search

Four English databases (the Cochrane Library, PubMed, EMBASE, and Web of Science) and one Chinese database (Wanfang) were searched, and the publication deadline for the literature was October 1, 2024. We

searched each database to identify Medical Subject Headings (MeSH) (e.g., 'aspirin', 'indobufen', 'clinical trial') and related free terms (e.g., aAcetylsalicylic Acid*, Acetysal*, Acylpyrin*, Aloxiaprimum*, Colfarit*, Ibustrin*, controlled trial*, Trial*). The search strategy was developed via a combination of MeSH terms and related free terms. The full search strategy can be found in Supplementary Material 1. Moreover, the references of all included studies were browsed and screened to complement the eligible literature not retrieved. Owing to the limited number of randomized controlled trials in the relevant field, we also included eligible cohort studies in our analysis.

2.3. Study selection

For inclusion in the systematic review and meta-analysis, we selected clinical trials that investigated the antiplatelet impact of indobufen and aspirin and their safety in human subjects. The following inclusion criteria were applied: (1) the study population was adults (aged ≥ 18 years) with CHD caused by coronary artery atherosclerosis or stroke caused by intracranial atherosclerosis; (2) the intervention was represented by indobufen in the study groups versus aspirin in the control groups; (3) the primary outcome: the literature reported the incidence of MACCE or any bleeding or BARC 2/3/5 bleeding; (4) secondary outcome: 1) cardiovascular death, myocardial infarction, and ischemic stroke; 2) adverse cardiovascular events: coronary thrombus reformation, heart failure, myocardial infarction, stroke, angina pectoris, cardiovascular death; 3) stroke; 4) myocardial infarction; and 5) cardiovascular death. (5) Study design: randomized clinical trials with either crossover or parallel designs or prospective observational trials. Our exclusion criteria were as follows: 1) lack of control group studies; 2) no studies reporting cardiovascular or cerebrovascular events or bleeding during the follow-up or research group period; 3) follow-up time of less than 6 months or no mention of follow-up time; and 4) case control studies, cross-sectional studies, ecological studies, case reports, and other descriptive studies. Reviews, conference abstracts, and commentaries were also excluded.

2.4. Data extraction

Two authors evaluated the potentially relevant publications for eligibility. The investigators independently completed their searches and selected the studies eligible for inclusion in our analysis. Moreover, we resolved disagreements between the investigators by discussion. We extracted the following characteristics from the trials via a standardized data extraction form: year of publication, lead author, country of publication, total sample size of the trial in the case and control groups, duration of follow-up (months), age at entry, participants' sex percentage, drug dosage (mg/day) and sample size for the occurrence of outcome indicators.

2.5. Statistical analysis

Our data were managed via Excel, and we used Review Manager 5.3 (The Cochrane Collaboration, Oxford, England) and Stata SE 18.0 (Stata Corp LLC, College Station, TX) to combine and analyze outcomes from the selected trials. All the data were pooled to calculate the risk ratio (RR) and 95% confidence intervals via a fixed-effects model. Between-trial heterogeneity was assessed by using an I^2 test, and a value $> 50\%$ was regarded as considerable heterogeneity. If heterogeneity was high, we used a random effects model. Statistical significance was defined as a p value < 0.05 . If the number of pooled studies was greater than ten, publication bias was surveyed by visual inspection of the funnel plot and Egger's test.

2.6. Assessment of risk of bias and sensitivity analysis

We divided all the included studies into randomized controlled trials and non-RCT trials. Two researchers (WH Pan and LE Guan) independently assessed the quality of random control trials on the basis of the Cochrane risk-of-bias criteria according to the following criteria^[18]: 1) allocation concealment, 2) random sequence generation, 3) blinding of participants and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, 6) selective reporting, and 7) other probable sources of bias. The Newcastle–Ottawa Scale (NOS) was used to evaluate bias risk for non-RCTs across domains such as selection, intervention classification and comparability, missing data, outcome measurement, and result reporting^[19]. Studies with a score ≥ 7 were considered high-quality studies. We performed leave-one-out sensitivity analyses to test the robustness of the results.

3. Results

3.1. Results of the literature search

As reported in Figure 1, 307 articles from the English database were initially retrieved. A total of 86 duplicate studies were removed. Among the remaining 221 articles, 173 were excluded after the titles and abstracts were carefully screened. In the next step, 48 trials were further examined, and 41 additional trials were excluded for the following reasons: the population studied in 3 articles did not meet the inclusion criteria, the intervention methods used in 5 articles did not meet the requirements, 4 studies did not report the required outcome measures, 18 studies did not provide a proper comparison with aspirin, 1 study's design method did not meet the criteria, 4 articles had a follow-up time of less than 6 months or did not mention the follow-up time, and 6 articles did not retrieve the results. Finally, 7 studies (Bai 2022^[20], Dai CF 2024^[14], Dai WB 2024^[21], Pan YS 2024^[22], Shi QP 2022^[23], Wu HY 2022^[15], Yu R 2024^[24]) were included in our meta-analysis. An additional 11 studies (Chen B 2024^[25], Chen YC 2023^[26], Lin F 2020^[27], Liu XW 2020^[28], Ma K 2022^[29], Tu ZT 2021^[30], Wen JL 2012^[31], Wu YQ 2020^[32], Yang S 2019^[33], Rui SH 2024^[34], and Zhou CY 2023^[35]) from the Chinese database WanFang were included in the study. A total of 12981 patients were included in this analysis.

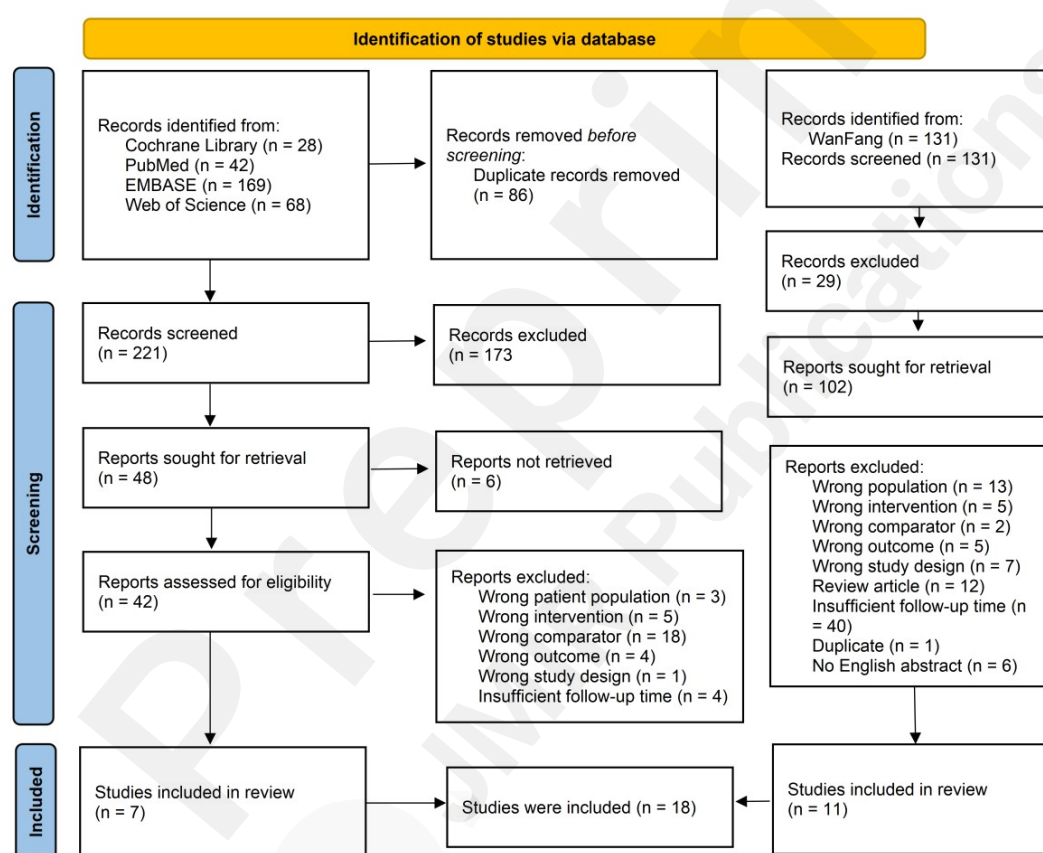


Fig. 1 Flow diagram for the search and selection of included studies

3.2. Trial characteristics

The mean age of the participants varied from 47.20 to 72 years. The sample sizes of the eligible studies ranged from 19 to 2723 participants. All the studies were performed in China. The literature we have included has focused primarily on populations with ischemic stroke caused by cerebral vascular atherosclerosis and CHD, which includes stable angina pectoris, acute coronary syndrome, and coronary artery stent implantation or coronary artery bypass grafting (CABG) due to CHD. The dose of indobufen given to these subjects ranged from 100 mg daily to 100 mg twice a day, and the daily dose of aspirin was 100 mg. The characteristics of the included studies are

summarized in Table 1. Figure 2 and Table 2 provide information regarding the quality assessment for the risk of bias for each study included in the meta-analysis.

Study	Follow-up	Population	Group	Sample Size (n)	Age (Mean $\pm$ SD)	Male (%)	Drug & Dose	Type
Bai 2022	1 year	CABG	Intervention group	76	60.3 $\pm$ 6.6	75.0 0%	Indobufen 100mg/day + Clopidogrel 75mg/day	RCT
			Control group	76	59.7 $\pm$ 7.2	81.6 0%	Aspirin 100mg/day + Clopidogrel 75mg/day	
Chen B 2024	1 year	CHD	Intervention group	34	66.34 $\pm$ 1.48	64.7 0%	Indobufen 100mg twice a day + Clopidogrel 75mg/day	RCT
			Control group	37	66.39 $\pm$ 1.47	64.9 0%	Aspirin 100mg/day + Clopidogrel 75mg/day	
Chen YC 2023	6 months	CHD	Intervention group	42	48.10 $\pm$ 12.70	38.1 0%	Indobufen 100mg twice a day + Clopidogrel 75mg/day	RCT
			Control group	42	47.20 $\pm$ 15.10	40.4 8%	Aspirin 100mg/day + Clopidogrel 75mg/day	
Dai CF 2024	1 year	PCI	Intervention group	662	66 $\pm$ 9.4	72.2 0%	Indobufen 100mg twice a day + P2Y12 receptor antagonist	Cohort study
			Control group	662	66 $\pm$ 10.5	70.8 0%	Aspirin 100mg/day + P2Y12 receptor antagonist	
Dai WB 2024	1 year	PCI(AMI)	Intervention group	224	72 $\pm$ 11	62.9 0%	Indobufen 100mg twice a day + Clopidogrel 75mg/day	Cohort study
			Control group	224	72 $\pm$ 10	67.0 0%	Aspirin 100mg/day + Clopidogrel 75mg/day	
Lin F 2020	1 year	CCS	Intervention group	37	71.56 $\pm$ 2.19	54.1 0%	Indobufen 200mg/day + Clopidogrel 75mg/day	Cohort study
			Control group	37	71.66 $\pm$ 2.45	59.5 0%	Aspirin 100mg/day + Clopidogrel 75mg/day	
Liu XW 2020	1 year	PCI	Intervention group	30	58.5 (53.5 - 66.5)	80.0 0%	Indobufen 100mg twice a day + Clopidogrel 75mg/day	RCT
			Control group	30	60 (56 - 64.25)	73.3 0%	Aspirin 100mg/day + Clopidogrel 75mg/day	
Ma K 2022	6 months	PCI(Unstable angina)	Intervention group	41	71.76 $\pm$ 5.85	68.3 0%	Indobufen 100mg twice a day + Clopidogrel 75mg/day	RCT
			Control group	41	70.51 $\pm$ 7.55	65.9 0%	Aspirin 100mg/day + Clopidogrel 75mg/day	
Pan YS 2024	1 year	Stroke	Intervention group	2715	64.7 (56.3 - 70.9)	64.5 0%	Indobufen 100mg twice a day + placebo	RCT
			Control group	2723	63.8 (56.0 - 70.3)	64.9 0%	Aspirin 100mg/day + placebo	
Rui SH 2024	1 year	ACS	Intervention group	78	68.42 $\pm$ 4.29	50.0 0%	Indobufen + Clopidogrel	Control study
			Control group	78	68.73 $\pm$ 4.75	51.3 0%	Aspirin + Clopidogrel	
Shi QP 2022	1 year	PCI(CCS)	Intervention group	52	63.07 $\pm$ 6.46	96.4 3%	Indobufen 100mg twice a day	Crossover study
			Control group	52	63.07 $\pm$ 6.46	96.4 3%	Aspirin 100mg/day	
Tu ZT 2021	6 months	STEMI	Intervention group	53	65.3 $\pm$ 9.8	56.6 0%	Indobufen 100mg twice a day + Ticagrelor 90mg twice a day	RCT
			Control group	53	64.8 $\pm$ 10.2	58.4 9%	Aspirin 100mg/day + Ticagrelor 90mg twice a day	
Wen J 2012	6 months	PCI	Intervention group	32	58 $\pm$ 7	81.2 5%	Indobufen 100mg twice a day + Clopidogrel 75mg/day	RCT
			Control group	32	57 $\pm$ 9	75%	Aspirin 100mg/day + Clopidogrel 75mg/day	
WU HY 2022	1 year	PCI	Intervention group	2258	61.0 $\pm$ 8.3	67.4 0%	Indobufen 100mg twice a day + Clopidogrel 75mg/day	RCT
			Control group	2293	61.2 $\pm$ 8.4	63.1 0%	Aspirin 100mg/day + Clopidogrel 75mg/day	
Wu YQ	6 months	ACS	Intervention group	34	69.88 $\pm$ 4.31	47.0 6%	Indobufen 100mg twice a day + Clopidogrel 75mg/day	RCT

2020	hs		Control group	34	69.68 ± 4.26	47.0 6%	Aspirin 100mg/day + Clopidogrel 75mg/day	
Yang S 2019	1 year	ACS	Intervention group	38	70.34 ± 3.44	65.7 0%	Indobufen 100mg twice a day + Clopidogrel 75mg/day	RCT
			Control group	38	71.03 ± 2.92	65.7 0%	Aspirin 100mg/day + Clopidogrel 75mg/day	
Yu R 2024	18 mont hs	CAB G	Intervention group	19	63.84 ± 7.99	78.9 5%	Indobufen 100mg twice a day + Clopidogrel 75mg/day	Retros pective cohort study
			Control group	20	64.60 ± 6.72	80.0 0%	Aspirin 100mg/day + Clopidogrel 75mg/day	
Zhou CY 2023	1 year	CAB G	Intervention group	34	57.63 ± 2.31	52.9 4%	Indobufen 0.2g/day, Clopidogrel 75mg/day	Retros pective cohort study
			Control group	50	57.54 ± 2.28	52%	Aspirin 100mg/day, Clopidogrel 75mg/day	

Table 1 Characteristics of included studies

Abbreviations: CABG, coronary artery bypass grafting; RCT, randomized control trial; CHD, coronary heart disease; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; ACS, acute coronary syndromes; CCS, chronic coronary syndromes; STEMI, ST-segment elevation myocardial infarction.

Data are presented as means ± SDs and median (IQR).

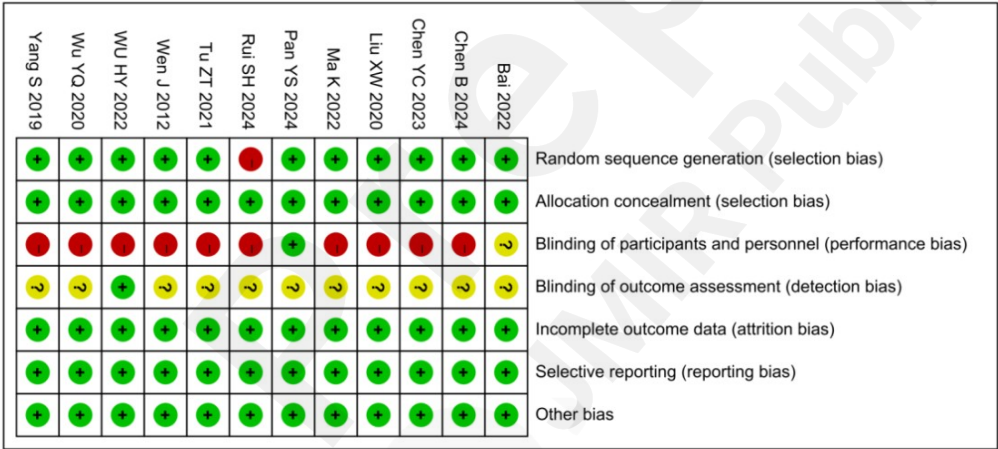


Fig. 2 Risk of bias summary: review authors' judgments about each risk of bias item for RCTs

Study	Selection				Comparability		Results			Total Score
	S1	S2	S3	S4	C1	C2	R1	R2	R3	
Dai CF 2024	★	★	★	★	★		★	★	★	8
Dai WB	★	★	★	★	★		★	★	★	8

2024										
Lin F 2020	★	★	★	★	★		★	★	7	
Shi QP 2022	★	★	★	★	★		★	★	7	
Yu R 2024	★	★	★	★	★		★	★	★	8
Zhou CY 2023	★	★	★	★	★		★	★		7

Table 2 Quality assessment of non-RCT according to NOS

3.3. Meta-analysis results

3.3.1. Major adverse cardiovascular and cerebrovascular events

Five studies reported major adverse cardiovascular and cerebrovascular events (MACCEs) (Bai 2022, Dai CF 2024, Dai WB 2024, Wu HY 2022). The pooled results revealed no significant difference in MACCE with indobufen compared with aspirin (RR: 1.12, 95% CI: 0.98–1.28, I² = 0%, P =0.09; Figure 3a).

3.3.2. Any bleeding

Seventeen studies reported any bleeding (Bai 2022, Chen B 2024, Chen YC 2023, Dai CF 2024, Dai WB 2024, Lin F 2020, Liu XW 2020, Ma K 2022, Pan YS 2024, Rui SH 2024, Shi QP 2022, Tu ZT 2021, Wen J 2012, Wu HY 2022, Yang S 2019, Yu R 2024, Zhou CY 2023). However, one study was excluded because there were no outcome events in either the experimental group or the control group. The combined results revealed a significant reduction in any bleeding with indobufen compared with aspirin (RR: 0.54, 95% CI: 0.41–0.71, I² = 51%, P < 0.0001; Figure 3b).

3.3.3. BARC 2/3/5 bleeding

Five studies reported BARC type 2, 3, or 5 bleeding (BARC 2/3/5 bleeding) (Dai CF 2024, Dai WB 2024, Liu XW 2020, Shi QP 2022, Wu HY 2022). Two studies were excluded from the pooled meta-analysis because both groups in these studies reported zero events. The heterogeneity (I² = 84%, p = 0.002) was high, so we used a random effects model to assess the outcome. The combined results revealed a reduction in BARC 2/3/5 bleeding with indobufen compared with aspirin (RR: 0.50, 95% CI: 0.26–0.94, I² = 84%, P =0.03; Figure 3c).

3.3.4. Adverse cardiovascular events

Thirteen studies reported adverse cardiovascular events (Bai 2022, Chen B 2024, Chen YC 2023, Lin F 2020, Liu XW 2020, Ma K 2022, Rui SH 2024, Tu ZT 2021, Wen J 2012, Wu YQ 2020, Yang S 2019, Yu R 2024, Zhou CY 2023). The pooled results revealed a significant decrease in adverse cardiovascular events with indobufen compared with aspirin (RR: 0.43, 95% CI: 0.30–0.61, I² = 0%, P < 0.00001; Figure 3d).

3.3.5. Stroke

Seventeen studies reported stroke (Bai 2022, Chen B 2024, Chen YC 2023, Dai CF 2024, Dai WB 2024, Lin F 2020, Liu XW 2020, Ma K 2022, Pan YS 2024, Rui SH 2024, Tu ZT 2021, Wen J 2012, Wu HY 2022, Wu YQ 2020, Yang S 2019, Yu R 2024, Zhou CY 2023). Five studies were excluded because of zero events. The pooled

results revealed no significant difference in the incidence of stroke between patients treated with indobufen and those treated with aspirin (RR: 1.07, 95% CI: 0.92–1.25, $I^2 = 0\%$, $P = 0.37$; Figure 3e).

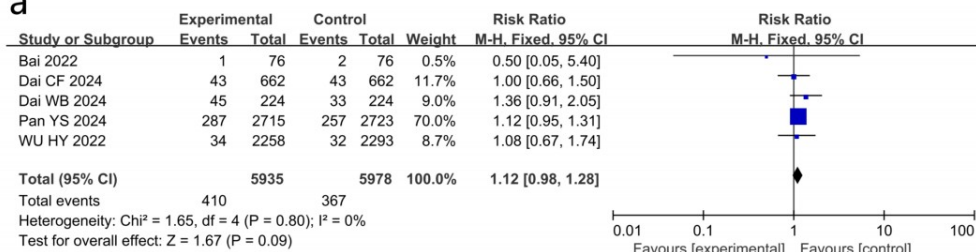
3.3.6. Myocardial Infarction

Seventeen studies reported myocardial infarction (MI) (Bai 2022, Chen B 2024, Chen YC 2023, Dai CF 2024, Dai WB 2024, Lin F 2020, Liu XW 2020, Ma K 2022, Pan YS 2024, Rui SH 2024, Tu ZT 2021, Wen J 2012, Wu HY 2022, Wu YQ 2020, Yang S 2019, Yu R 2024, Zhou CY 2023). Four studies were excluded because of zero events. The pooled results revealed a significant decrease in MI with indobufen compared with aspirin (RR: 0.60, 95% CI: 0.41–0.89, $I^2 = 0\%$, $P = 0.01$; Figure 3f).

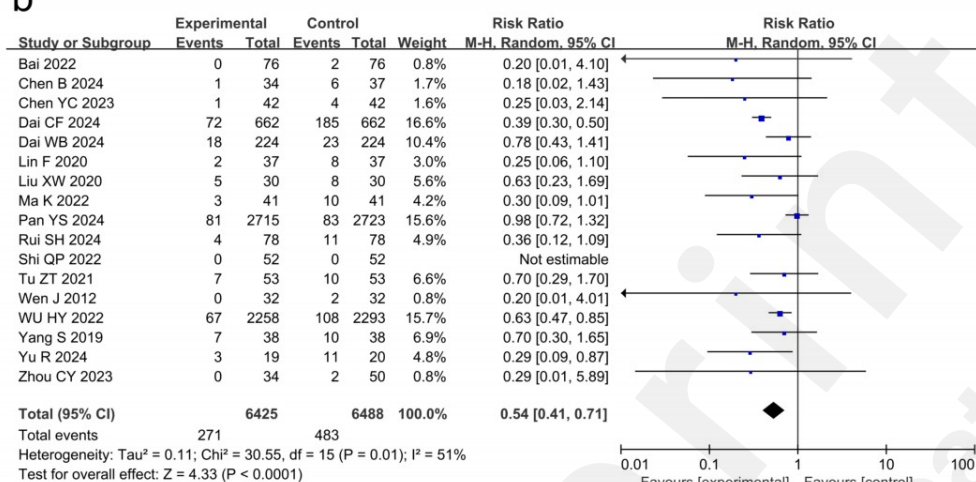
3.3.7. Cardiovascular death

Sixteen studies reported cardiovascular death (Bai 2022, Chen B 2024, Chen YC 2023, Dai CF 2024, Dai WB 2024, Lin F 2020, Liu XW 2020, Ma K 2022, Pan YS 2024, Rui SH 2024, Tu ZT 2021, Wen J 2012, Wu HY 2022, Wu YQ 2020, Yang S 2019, Zhou CY 2023). Eight studies were excluded because of zero events. The pooled results revealed no significant difference in cardiovascular death between indobufen and aspirin (RR: 1.13, 95% CI: 0.71–1.79, $I^2 = 0\%$, $P = 0.61$; Figure 3g).

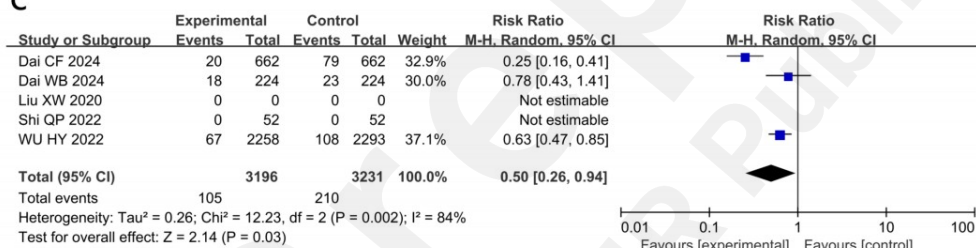
a



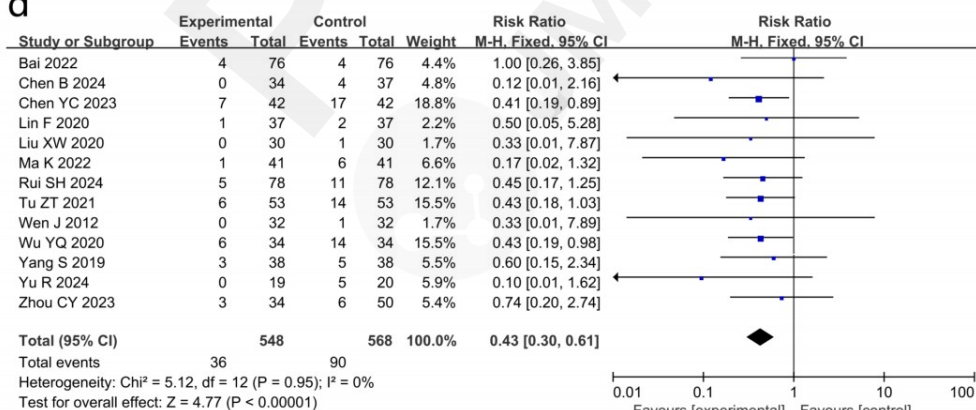
b



c



d



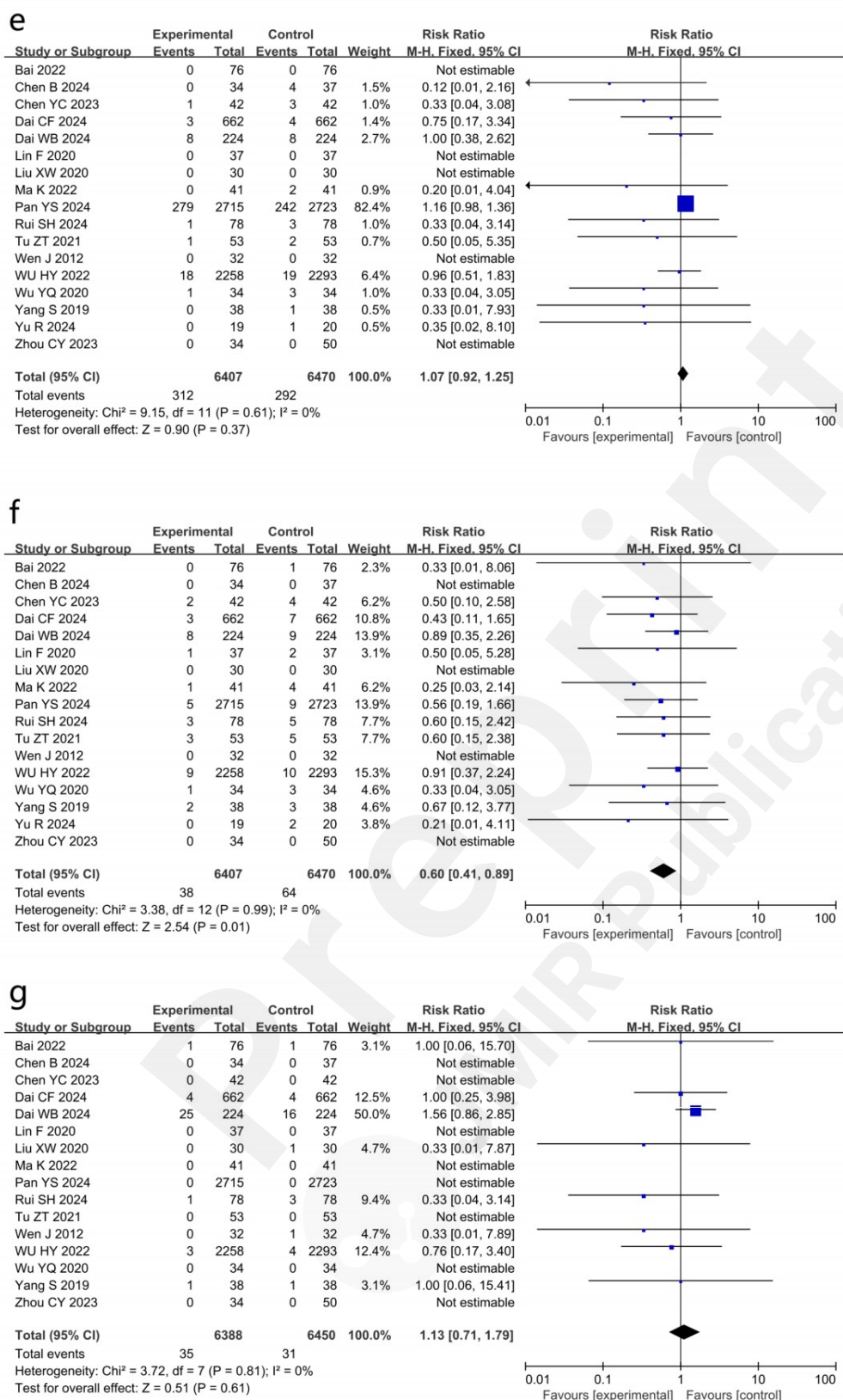


Fig. 3 Forest plots for the outcomes

(a) MACCE (RR 1.12; CI 0.98–1.28; $P = 0.09$); (b) Any bleeding events (RR 0.54; CI 0.41–0.71; $P < 0.0001$); (c) BARC 2/3/5/5 bleeding (RR 0.50; CI 0.26–0.94; $P = 0.03$); (d) Adverse cardiovascular events (RR 0.43; CI 0.30–0.61; $P < 0.00001$); (e) Stroke events (RR: 1.07; CI 0.92–1.25; $P = 0.37$); (f) Myocardial infarction events

(RR 0.60; CI 0.41–0.89; $P = 0.01$); (g) Cardiovascular death associated with the use of indobufen and aspirin (RR 1.13; CI 0.71–1.79; $P = 0.61$). Abbreviations: RR, risk ratio; CI, confidence interval.

3.4. Sensitivity analysis

In this meta-analysis, the results of any bleeding and BARC studies revealed a high level of heterogeneity, with I^2 values of 51% and 84%, indicating substantial heterogeneity, possibly due to the small sample size. To further explore the source of this heterogeneity, we conducted a sensitivity analysis. This involved sequentially excluding individual studies to assess their influence on the overall pooled estimate. Although the limited number of studies restricts the depth of the analysis, the results showed that the pooled effect estimate remained stable, indicating relative robustness (Figure 4 and Figure 5). However, variations in heterogeneity were observed when individual studies were excluded, suggesting that one or more studies might have contributed to the observed heterogeneity.

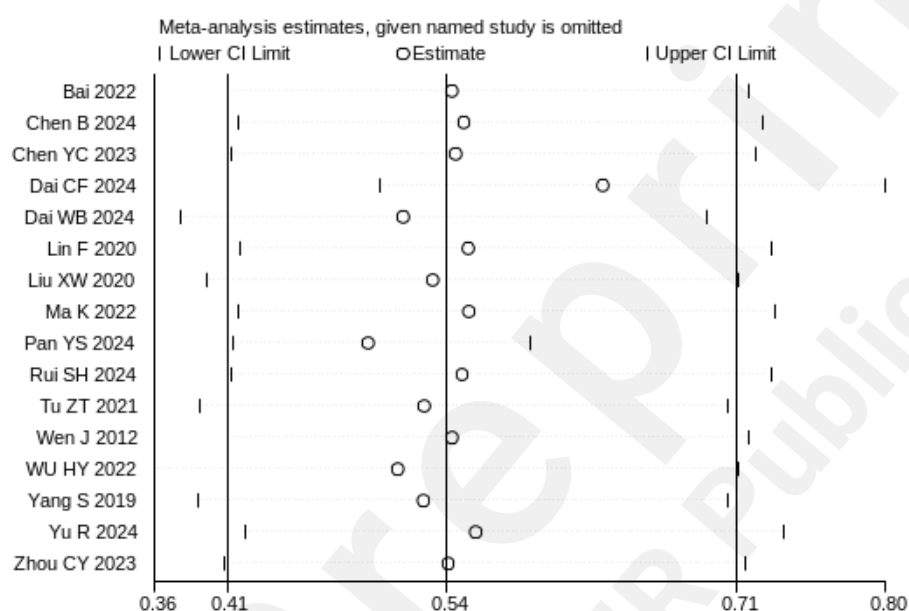


Fig. 4 Sensitivity analysis of any bleeding

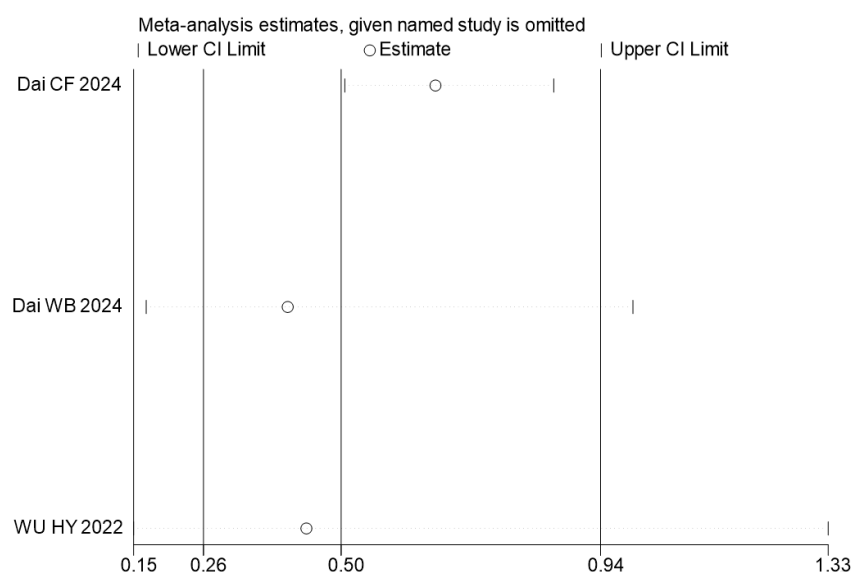


Fig. 5 Sensitivity analysis of BARC 2/3/5 bleeding

3.5. Publication bias

For outcomes with more than 10 articles included in the literature, we plotted funnel plots and performed Egger tests. The P values of the Egger tests for any bleeding or adverse cardiovascular events were 0.249 and 0.235, respectively, both of which are greater than 0.05. We believe that the publication bias is small, but the P values of the Egger tests for stroke, myocardial infarction, and cardiovascular death were 0.000, 0.001 and 0.006, indicating a certain degree of publication bias. All funnel plots are included in Supplementary Material 2.

4. Discussion

In this systematic review and meta-analysis involving 18 clinical trials and 12981 patients, we compared antiplatelet therapy involving indobufen with that involving aspirin. Although we did not impose any language restrictions for the included studies, all the clinical trials ultimately retrieved were conducted in China. This may be because indobufen is not widely approved as a routine antiplatelet agent in Europe and the Americas and is only used as a reference drug in specific studies^[36]. These results suggest that, compared with aspirin, indobufen can effectively reduce the incidence of mucosal bleeding (including both major and minor bleeding) in patients with cardiovascular and cerebrovascular atherosclerosis. Additionally, on the basis of the studies included in our analysis, indobufen was shown to reduce the incidence of adverse cardiovascular events (a composite outcome of coronary thrombus reformation, heart failure, myocardial infarction, stroke, angina pectoris, and cardiovascular death) as well as myocardial infarction. However, MACCEs, stroke, and cardiovascular death rates were similar between the two groups, which may be related to the limited follow-up time. The heterogeneity for any bleeding and BARC 2/3/5 bleeding was high, but the sensitivity analysis revealed no difference in outcomes. There was significant publication bias for stroke, myocardial infarction and cardiovascular death. The effects of indobufen on MACCEs, stroke, and cardiovascular death were similar to those of aspirin, demonstrating no inferiority in efficacy.

Antiplatelet therapy in patients with atherosclerosis remains a topic of considerable debate. Current guidelines recommend aspirin for secondary prevention in patients with coronary atherosclerotic heart disease, and dual antiplatelet therapy (DAPT) is advised for patients with a high risk of thrombosis and a low risk of bleeding or those undergoing interventional treatment^[37]. For patients who require DAPT but are intolerant to aspirin, indobufen is being investigated as a potential alternative to aspirin^[38, 39].

The antiplatelet effect of aspirin is achieved by irreversibly inhibiting and permanently blocking COX-1 in platelets, thereby preventing the formation of thromboxane A₂ (TXA₂)^[40]. This effect lasts for the lifespan of the

platelet (7–10 days)^[41]. In contrast, indobufen is a reversible COX-1 inhibitor, meaning that it temporarily inhibits the enzyme but does not cause persistent inhibition^[42]. This reversible action allows for shorter-term effects on platelet function than does aspirin^[43]. The inhibitory effects of indobufen on platelet function returned to baseline within 24 hours after discontinuation. Additionally, indobufen does not substantially impact prostacyclin, potentially minimizing the risk of aspirin-gastric side effects^[25]. While both drugs seek to reduce platelet aggregation and associated basis, the irreversible inhibition of aspirin leads to protracted platelet inhibition, whereas indobufen offers a reversible and potentially safer alternative, particularly in patients at greater risk for bleeding.

Aspirin's first-line status in the prevention and treatment of cardiovascular and cerebrovascular diseases is supported by a large body of evidence-based research^[10, 44, 45]. In comparison, although the clinical application of indobufen has evolved, it remains very limited at present. Initially, owing to its reversible inhibition of COX, it was not recommended, as it was considered insufficient to effectively inhibit platelet aggregation in vivo^[46]. However, subsequent clinical trials have led some meta-analyses to consider indobufen similarly to aspirin. Cataldo G et al., in their combined analysis of two multicenter CABG studies, concluded that indobufen is as effective as aspirin and dipyridamole in preventing graft occlusion^[47]. Bhana N et al., in their review, suggested that indobufen may be an effective alternative to aspirin for patients with nonrheumatic atrial fibrillation who have contraindications to anticoagulation or a greater risk of bleeding^[48]. In a meta-analysis of nine clinical studies, Zhang Xiaochen et al. reported that indobufen had fewer gastrointestinal reactions, a lower risk of bleeding, and could be a viable option for patients at high risk of bleeding or with gastrointestinal ulcers^[49].

The strengths of our study include the following: compared with previous studies, our meta-analysis incorporated a larger number of clinical trials and patients, with homogeneous outcome definitions and a large patient population, making the results more generalizable to the broader population. Additionally, the follow-up duration in all the included studies exceeded six months, enhancing the credibility of our findings. We also conducted publication bias and sensitivity analyses to further emphasize the reliability of this meta-analysis.

There are several limitations to this study. All the studies included focused on Chinese populations, which may limit the generalizability of our findings to other regions of the world. Additionally, because antiplatelet therapy is a long-term treatment requiring good patient adherence, the included trials were open-label, which might raise concerns about potential bias, although none of the studies carried a high risk of bias. Owing to the lack of available data, we were unable to perform subgroup analyses on the basis of individual patient characteristics, and the efficacy and safety of indobufen in specific populations require further investigation.

Our meta-analysis indicates that, compared with aspirin, indobufen offers a safer profile for antiplatelet therapy in patients with cardiovascular and cerebrovascular atherosclerosis, as it reduces the incidence of mucosal bleeding. In terms of efficacy, indobufen is associated with a lower incidence of adverse cardiovascular events and myocardial infarction, while its impact on MACCE and cardiovascular mortality is similar to that of aspirin. Indobufen demonstrated no overall inferiority in effectiveness, with superior results in some aspects. This provides additional robust evidence supporting the feasibility of using indobufen as an alternative antiplatelet therapy, particularly in patients who are intolerant to aspirin.

Acknowledgments: Not applicable.

Disclosure:

Data Availability: The original contributions presented in the study are included in the article/Supporting Information Material, further inquiries can be directed to the corresponding authors.

Code Availability: Not applicable.

Ethics Approval: Not applicable.

Consent to Participate: Not applicable.

Consent for Publication: Not applicable.

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions: Zhang Haicheng designed the systematic review plan; Pan Wenhao and Guan Linger conducted research screening, as well as data extraction and statistical analysis; Pan Wenhao wrote the manuscript. All authors contributed to the critical revision of the manuscript draft.

Reference:



- ¹[] Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes (2). *N Engl J Med* 1992;326(5):310-8.
- ²[] Pasternak RC, Criqui MH, Benjamin EJ, Fowkes FGR, Isselbacher EM, McCullough PA, et al. Atherosclerotic Vascular Disease Conference. *Circulation* 2004;109(21):2605-12.
- ³[] Yun KH, Mintz GS, Witenbichler B, Inaba S, Shimizu T, Metzger DC, et al. Relationship Between Platelet Reactivity and Culprit Lesion Morphology: An Assessment From the ADAPT-DES Intravascular Ultrasound Substudy. *JACC Cardiovasc Imaging* 2016;9(7):849-54.
- ⁴[] Kirkby NS, Lundberg MH, Harrington LS, Leadbeater PD, Milne GL, Potter CM, et al. Cyclooxygenase-1, not cyclooxygenase-2, is responsible for physiological production of prostacyclin in the cardiovascular system. *Proc Natl Acad Sci U S A* 2012;109(43):17597-602.
- ⁵[] Angiolillo DJ. The evolution of antiplatelet therapy in the treatment of acute coronary syndromes: from aspirin to the present day. *Drugs* 2012;72(16):2087-116.
- ⁶[] Smith JB, Araki H, Lefer AM. Thromboxane A₂, prostacyclin and aspirin: effects on vascular tone and platelet aggregation. *Circulation* 1980;62(6 Pt 2):V19-25.
- ⁷[] Liu X, Lv X, Peng Y, Wang J, Lei J, Tang C, et al. Clopidogrel with indobufen or aspirin in minor ischemic stroke or high-risk transient ischemic attack: a randomized controlled clinical study. *BMC Neurol* 2024;24(1):81.
- ⁸[] Bunimov N, Laneuville O. Cyclooxygenase inhibitors: instrumental drugs to understand cardiovascular homeostasis and arterial thrombosis. *Cardiovasc Hematol Disord Drug Targets* 2008;8(4):268-77.
- ⁹[] Hennekens CH. Update on aspirin in the treatment and prevention of cardiovascular disease. *Am J Manag Care* 2002;8(22 Suppl):S691-700.
- ¹⁰[] Zusman RM, Chesebro JH, Comerota A, Hartmann JR, Massin EK, Raps E, et al. Antiplatelet therapy in the prevention of ischemic vascular events: literature review and evidence-based guidelines for drug selection. *Clin Cardiol* 1999;22(9):559-73.
- ¹¹[] Davidson KW, Barry MJ, Mangione CM, Cabana M, Chelmow D, Coker TR, et al. Aspirin Use to Prevent Cardiovascular Disease: US Preventive Services Task Force Recommendation Statement. *Jama* 2022;327(16):1577-84.
- ¹²[] Horiuchi H. Recent advance in antiplatelet therapy: the mechanisms, evidence and approach to the problems. *Ann Med* 2006;38(3):162-72.
- ¹³[] [Chinese guidelines for the diagnosis and management of patients with chronic coronary syndrome]. *Zhonghua Xin Xue Guan Bing Za Zhi* 2024;52(6):589-614.
- ¹⁴[] Dai C, Liu M, Yang Z, Li Y, Zhou Y, Lu D, et al. Real-world performance of indobufen versus aspirin after percutaneous coronary intervention: insights from the ASPIRATION registry. *BMC Med* 2024;22(1):148.
- ¹⁵[] Wu H, Xu L, Zhao X, Zhang H, Cheng K, Wang X, et al. Indobufen or Aspirin on Top of Clopidogrel After Coronary Drug-Eluting Stent Implantation (OPTION): A Randomized, Open-Label, End Point-Blinded, Noninferiority Trial. *Circulation* 2023;147(3):212-22.
- ¹⁶[] Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011;123(23):2736-47.
- ¹⁷[] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* n71. 10.1136/bmj.n71
- ¹⁸[] Higgins JPT. et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.5 (updated August 2024). Cochrane. Available from www.training.cochrane.org/handbook (2024).
- ¹⁹[] Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute. 2011;2(1):1-12.
- ²⁰[] Bai C, Li JX, Yu Y, Liu R, Gao MX, Zhang F, et al. [A randomized controlled trial of indobufen versus aspirin in the prevention of bridging restenosis after coronary artery bypass grafting]. *Zhonghua Xin Xue Guan Bing Za Zhi* 2022;50(5):466-70.
- ²¹[] Dai WB, Ren JY, Hu ST, Zhang YK, Gu TS, Wu X, et al. The safety and efficacy of indobufen or aspirin combined with clopidogrel in patients with acute myocardial infarction after percutaneous coronary intervention. *Platelets* 2024;35(1):2364748.
- ²²[] Pan Y, Meng X, Yuan B, Johnston SC, Li H, Bath PM, et al. Indobufen versus aspirin in patients with acute ischaemic stroke in China (INSURE): a randomised, double-blind, double-dummy, active control, non-inferiority trial.

Lancet Neurol 2023;22(6):485-93.

- ²³[] Shi QP, Luo XY, Zhang B, Wang XG, Zhao J, Xie QF, et al. Effect of indobufen vs. aspirin on platelet accumulation in patients with stable coronary heart disease after percutaneous coronary intervention: An open-label crossover study. *Front Pharmacol* 2022;13:950719.
- ²⁴[] Ren Y, Zhu Y, Yan Q, Jin H, Luo H. Multicenter retrospective cohort study demonstrates superior safety profile of indobufen over aspirin for Post-CABG antiplatelet therapy. *Front Pharmacol* 2024;15:1474150.
- ²⁵[] Chen B, Yang YJ, Song JJ. Observation on the Effect of Indobufen in the Treatment of Coronary Heart Disease Combined with Non valvular Atrial Fibrillation[J]. *Technology and Health* 2024;3(11):45-48.
- ²⁶[] Chen YC. The Effect of Indobufen combined with Clopidogrel on myocardial Perfusion, NT-proBNP, and MACE in Patients with coronary Heart Disease after PCI[J]. *Clinical Research* 2023;31(10):53-56.
- ²⁷[] Lin F, Huang DS, Fu MW. The effect of clopidogrel and indobufen dual antiplatelet therapy on patients with stable coronary heart disease after coronary stenting[J]. *China Prac Med* 2020;15(31):95-97.
- ²⁸[] Liu XW. Indobufen versus aspirin combined with clopidogrel used for dual antiplatelet therapy after drug-eluting stent implantation: randomized controlled study[D]. Inner Mongolia Medical University 2020.
- ²⁹[] Ma K. Efficacy and safety study of indobufen combined with clopidogrel in patients with unstable angina pectoris after PCI[D]. Hebei Medical University 2022.
- ³⁰[] Tu ZT, Pei F, Yu CQ. Effect of ticagrelor combined with indobufen on clinical efficacy and prognosis of patients with acute ST-segment elevation myocardial infarction[J]. *Chongqing Medicine* 2021;50(21):3660-3663,3668.
- ³¹[] Wen JL, Cui XY. To explore the prevention effect of indobufen on PCI patients with coronary artery restenosis[J]. *Journal of TCM Univ of Hunan* 2012;32(10):29-30,32.
- ³²[] WU YQ. Clinical Comparison of Indobufen and Aspirin Combined with Clopidogrel in the Treatment of Acute Coronary Syndrome[J]. *Chinese and Foreign Medical Research* 2020, 18(32):40-42.
- ³³[] Yang S. Efficacy and safety of indobufen plus clopidogrel for postoperative PCI in patients with ACS who are at high risk for gastrointestinal bleeding[D]. Hebei Medical University 2019.
- ³⁴[] Rui SH, Wang CF, Li YH. Application of indobufen combined with clopidogrel in patients with ACS after PCI[J]. *Chin J Health Care Med* 2024;26(3):270-273.
- ³⁵[] Zhou CY, Su GB, Liu XC. Clinical efficacy and safety of indobufen combined with clopidogrel in preventing vascular restenosis in saphenous vein grafts following coronary artery bypass grafting[J]. *CHINESE JOURNAL OF RATIONAL DRUG USE* 2023;20(5):122-126.
- ³⁶[] Bianco M, Biolè C, Spirito A, Destefanis P, Luciano A, Montagna L, et al. [Management of ST-elevation myocardial infarction in a patient with aspirin hypersensitivity without oral P2Y₁₂ inhibitors]. *G Ital Cardiol (Rome)* 2022;23(1):75-7.
- ³⁷[] Virani SS, Newby LK, Arnold SV, Bittner V, Brewer LC, Demeter SH, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2023;82(9):833-955.
- ³⁸[] Wiseman LR, Fitton A, Buckley MM. Indobufen. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in cerebral, peripheral and coronary vascular disease. *Drugs* 1992;44(3):445-64.
- ³⁹[] Latib A, Ielasi A, Ferri L, Chieffo A, Godino C, Carlino M, et al. Aspirin intolerance and the need for dual antiplatelet therapy after stent implantation: a proposed alternative regimen. *Int J Cardiol* 2013;165(3):444-7.
- ⁴⁰[] Catella-Lawson F, Reilly MP, Kapoor SC, Cucchiara AJ, DeMarco S, Tournier B, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med* 2001;345(25):1809-17.
- ⁴¹[] Burch JW, Stanford N, Majerus PW. Inhibition of platelet prostaglandin synthetase by oral aspirin. *J Clin Invest* 1978;61(2):314-9.
- ⁴²[] Liu J, Sun P, Qi X. Reversible and Non-Competitive Inhibition of Cyclooxygenase by Indobufen for Efficient Antiplatelet Action and Relief of Gastrointestinal Irritation. *Pharmaceutics* 2023;15(8).
- ⁴³[] Tamassia V, Corvi G, Fuccella LM, Moro E, Tosolini G, Tremoli E. Indobufen (K 3920), a new inhibitor of platelet aggregation: effect of food on bioavailability, pharmacokinetic and pharmacodynamic study during repeated oral administration to man. *Eur J Clin Pharmacol* 1979;15(5):329-33.
- ⁴⁴[] Gaziano JM, Brotons C, Coppolecchia R, Cricelli C, Darius H, Gorelick PB, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *Lancet* 2018;392(10152):1036-46.
- ⁴⁵[] Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, et al. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. *N Engl J Med* 2016;375(1):35-43.
- ⁴⁶[] Yang M, Ye Z, Mei L, Ullah I, Tan C, Wang G, et al. Pharmacodynamic effects of indobufen compared with

aspirin in patients with coronary atherosclerosis. *Eur J Clin Pharmacol* 2021;77(12):1815-23.

⁴⁷ [] Cataldo G, Heiman F, Lavezzari M, Marubini E. Indobufen compared with aspirin and dipyridamole on graft patency after coronary artery bypass surgery: results of a combined analysis. *Coron Artery Dis* 1998;9(4):217-22.

⁴⁸ [] Bhana N, McClellan KJ. Indobufen: an updated review of its use in the management of atherothrombosis. *Drugs Aging* 2001;18(5):369-88.

⁴⁹ [] Zhang X, Yan Q, Jiang J, Luo H, Ren Y. Safety and efficacy of aspirin and indobufen in the treatment of coronary heart disease: a systematic review and meta-analysis. *Front Cardiovasc Med* 2024;11:1412944.

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

Fig. 2 Risk of bias summary: review authors' judgments about each risk of bias item for RCTs

Fig. 3 Forest plots for the outcomes

(a) MACCE (RR 1.12; CI 0.98–1.28; $P = 0.09$); (b) Any bleeding events (RR 0.54; CI 0.41–0.71; $P < 0.0001$); (c) BARC 2/3/5 bleeding (RR 0.50; CI 0.26–0.94; $P = 0.03$); (d) Adverse cardiovascular events (RR 0.43; CI 0.30–0.61; $P < 0.00001$); (e) Stroke events (RR: 1.07; CI 0.92–1.25; $P = 0.37$); (f) Myocardial infarction events (RR 0.60; CI 0.41–0.89; $P = 0.01$); (g) Cardiovascular death associated with the use of indobufen and aspirin (RR 1.13; CI 0.71–1.79; $P = 0.61$). Abbreviations: RR, risk ratio; CI, confidence interval.

Fig. 4 Sensitivity analysis of any bleeding

Fig. 5 Sensitivity analysis of BARC 2/3/5 bleeding

Table 1 Characteristics of included studies

Abbreviations: CABG, coronary artery bypass grafting; RCT, randomized control trial; CHD, coronary heart disease; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; ACS, acute coronary syndromes; CCS, chronic coronary syndromes; STEMI, ST-segment elevation myocardial infarction.

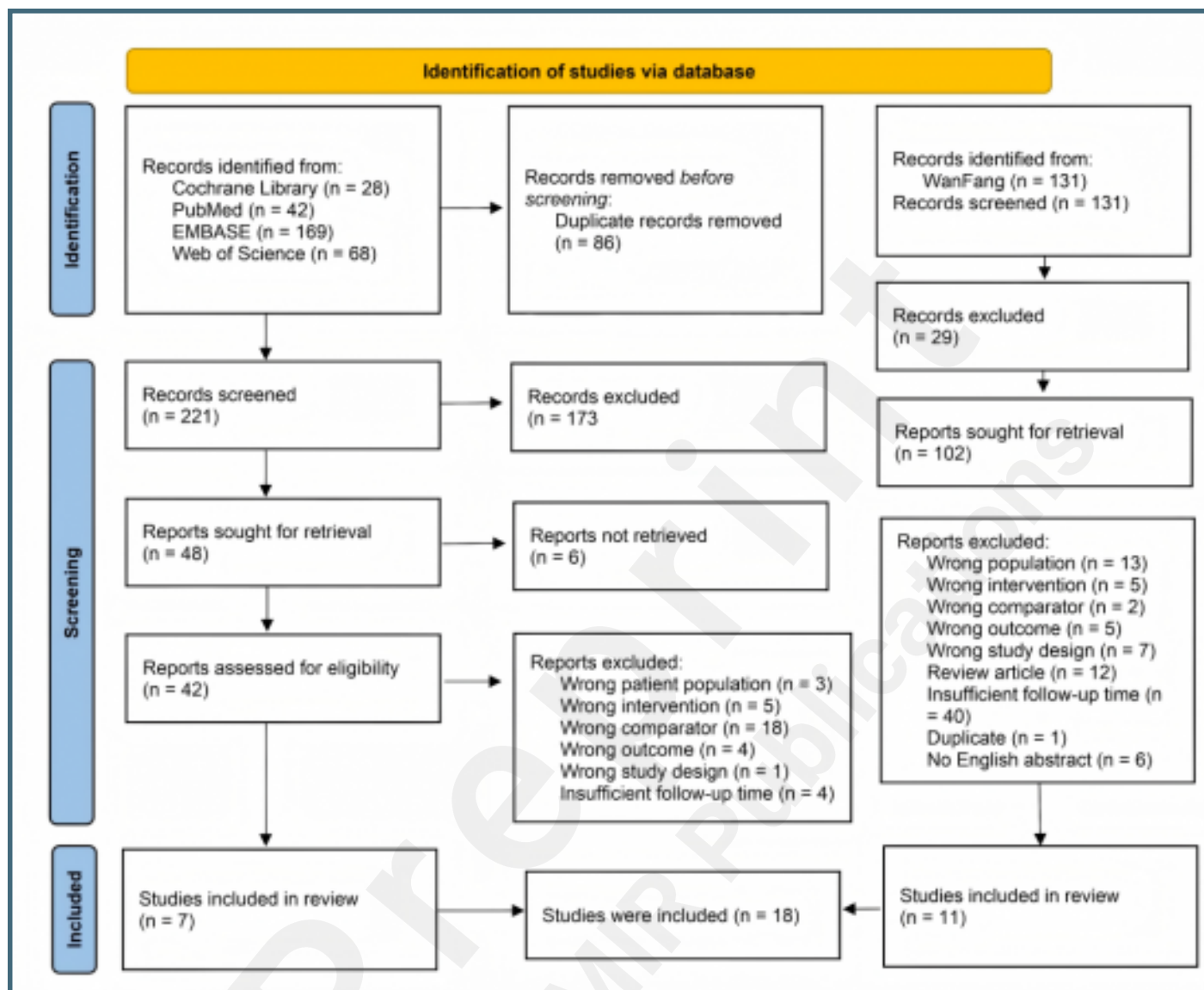
Data are presented as means $\pm$ SDs and median (IQR).

Table 2 Quality assessment of non-RCT according to NOS

Supplementary Files

Figures

Flow diagram for the search and selection of included studies.



Risk of bias summary: review authors' judgments about each risk of bias item for RCTs.

	Bai 2022	Chen B 2024	Chen YC 2023	Liu XW 2020	Ma K 2022	Pan YS 2024	Rui SH 2024	Tu ZT 2021	Wen J 2012	WU HY 2022	Wu YQ 2020	Yang S 2019
Random sequence generation (selection bias)	+	+	+	+	+	+	+	+	+	+	+	+
Allocation concealment (selection bias)	+	+	+	+	+	+	+	+	+	+	+	+
Blinding of participants and personnel (performance bias)	?	+	+	+	+	+	+	+	+	+	+	+
Blinding of outcome assessment (detection bias)	?	+	+	+	+	+	+	+	+	+	+	+
Incomplete outcome data (attrition bias)	+	+	+	+	+	+	+	+	+	+	+	+
Selective reporting (reporting bias)	+	+	+	+	+	+	+	+	+	+	+	+
Other bias	+	+	+	+	+	+	+	+	+	+	+	+