# Association of Aspirin Therapy with Prognosis in Patients with Nonobstructive Coronary Artery Disease: A Systematic Review and Meta-Analysis

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## Abstract

Purpose

The effect of aspirin therapy in patients with nonobstructive coronary artery disease (CAD) remains controversial. This study aimed to investigate the association between aspirin therapy and prognosis in nonobstructive CAD.

Methods

We searched for observational cohort studies on Pubmed, Embase, the Cochrane Library and Web of Science. Studies were included that compared the endpoint differences in patients with nonobstructive CAD who were treated with aspirin or not. The primary endpoint was a composite of major adverse cardiovascular events (MACEs). Secondary endpoints included all-cause death, cardiovascular death and myocardial infarction (MI). The pooled effect size was estimated as hazard ratio (HR) with 95% confidence interval (CI), which was measured by a random effect model using the generic inverse variance method.

Results

Thirteen published studies with 34,463 patients were included. Pooled data showed that aspirin therapy was not associated with the risk of MACEs (HR 1.10; 95% CI 0.85–1.41; $P = 0.47$, $I^2 = 57\%$). Similar results were observed in cardiovascular death (HR 1.12; 95% CI 0.73–1.73; $P = 0.60$, $I^2 = 0\%$) and MI (HR 0.53; 95% CI 0.09–3.20; $P = 0.49$, $I^2 = 68\%$), except all-cause death (HR 0.77; 95% CI 0.63–0.95; $P = 0.02$, $I^2 = 25\%$). Subgroup analyses showed that there were no associations between aspirin therapy and MACEs in all subsets.

Conclusions

Routine aspirin therapy might not improve prognosis in patients with nonobstructive CAD. Aspirin therapy in non-obstructive CAD should be better investigated and future research is needed. A personalized antiplatelet regimen might contribute to reduction in ischemic cardiovascular events in patients with non-obstructive CAD.

Registration: PROSPERO (CRD42021281706).


## Introduction

Nonobstructive coronary artery disease (CAD) is characterized by symptoms of suspected myocardial ischemia with stenosis of < 50% on angiography[1]. Nonobstructive CAD accounts for 67% of patients with stable angina and 13% of patients with non-ST-segment elevation acute coronary syndrome[2]. Nonobstructive CAD, a heterogeneous disease with limited atherosclerosis, is closely related to multiple conditions, including vulnerable plaque, thrombus, coronary artery spasm (CAS), microvascular dysfunction, myocarditis, inflammation, and cardiomyopathy[1, 3–5]. The prognosis of patients with nonobstructive CAD varies substantially depending on their underlying causes[6–9]. Overall, increasing evidence reveals that the presence of nonobstructive CAD contributes to higher risks of mortality[10–12], myocardial infarction (MI)[11, 12], re-hospitalization for angina[12], and economic burden[13].

Currently, the detection of nonobstructive CAD increases the prescription of cardiovascular preventive medical therapies, including aspirin[14–17]. Aspirin, a cornerstone agent, significantly reduces the risk of ischemic events in patients with obstructive CAD[18]. However, the prognosis of aspirin therapy in patients with nonobstructive CAD remains controversial, and there are no randomized controlled trials or systematic reviews regarding this topic. Hwang et al. reported that aspirin therapy was associated with a decreased risk of all-cause death, but with no effect on cardiovascular events[19], whereas another study found that aspirin failed to reduce the risk of all-cause death or cardiovascular events[20]. Furthermore, a few studies with smaller sample sizes lack adequately statistical power to determine the effect of aspirin on the outcomes of nonobstructive CAD[21–23].

Given these uncertainties, we aimed to clarify the efficacy and safety of aspirin therapy in patients with nonobstructive CAD, through a systematic review and meta-analysis of observational studies.

## Methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[24]. The protocol for this study was revised on October 30, 2021, and November 10, 2021; the search words were amended, and additional statistical analyses were performed according to the Cochrane handbook suggestions[25]. The protocol was registered on PROSPERO (registration number: CRD42021281706). Ethical approval was not required, because the participants' personal information was not included in this study.

# Inclusion And Exclusion Criteria

Patients with suspected myocardial ischemia with < 50% coronary stenosis on angiography were included in the study. The intervention and control groups included patients who received aspirin therapy and those who did not, respectively. Hazard ratios (HRs) of endpoints were the outcome indicators. We included prospective and retrospective cohort studies. Studies were excluded as per the following criteria: (1) reviews, (2) duplicate reports, (3) prior revascularization, (4) case reports, and (5) detailed antiplatelet regimens unavailable.

## Data Sources

We searched Pubmed, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science core collection (from 1985 to January 3, 2022) without language limitations. The detailed search strategies for each database are shown in Supplementary Table S1. The references of relevant reviews and included studies were manually searched.

## Study Selection And Data Extraction

We screened the title and abstracts and identified potentially eligible studies. Of these, the included studies were identified after reading the full texts. The reasons for exclusion were recorded in detail. The following data were extracted from the included studies: information about first author name, study name, publication year, location, study design, demographics and baseline characteristics, pathophysiological mechanisms, antiplatelet strategies, sample size, follow-up duration, cardiovascular events, titles, and notable labels. If propensity score-matched data or adjusted data were available, these were preferentially extracted because outcomes might be masked or overstated by these confounding factors. Two investigators independently conducted the above processes, and the discrepancies were resolved through discussion with a third investigator.

## Endpoint Definition

The primary endpoint was defined as a composite of major adverse cardiovascular events (MACEs), including all-cause or cardiovascular death, MI, and hospitalization for angina, heart failure, or stroke. The secondary endpoints included all-cause death, cardiovascular death and MI. The safety endpoint was bleeding risk, as defined in the original study.

## Individual Study Quality Assessment And Publication Bias

Two authors independently assessed the bias risk of each study using the Newcastle–Ottawa Scale (NOS)[26], which includes three aspects: population selection, comparability and outcome assessment. Semi-quantification of NOS was assessed using the following scores: low, 0–3; medium, 4–6; high quality, 7–9. Publication bias was visually described using funnel plots and quantitatively analyzed by Egger's tests when more than 10 studies were included. Statistical significance was set at a *P*-value of < 0.05.

## Statistical analysis

The pooled effect size with the 95% confidence interval (CI) was analyzed using RevMan (version 5.3; Nordic Cochrane Center, Cochrane Collaboration). The variability of effect size among studies was assessed using the $I^2$ statistical magnitude and *P*-value for heterogeneity. $I^2$ of > 50% or *P*-value of < 0.05 indicated wide heterogeneity[27]. Heterogeneity was inevitable because of the variations in sample size, follow-up duration, baseline MI, and pathophysiological mechanisms. Therefore, pooled HR was measured with a random effect model utilizing the generic inverse variance method. Sensitivity analysis was conducted by excluding individual studies to explore the sources of heterogeneity. In addition, predefined subgroup analyses were performed based on study design (prospective vs. retrospective), follow-up duration (> 36 months vs. ≤36 months), baseline MI (positive vs. negative), CAS (definite vs. indefinite), sample size (≤ 600 vs. >600) and adjustment (yes vs. no). Statistical significance was set at a *P*-value of < 0.05.

### Results

## Study selection and baseline characteristics

A total of 4694 studies were identified from the four databases, and two additional studies were selected by manually searching the references (Fig. 1). Thirteen published studies[19–23, 28–35] with 34,463 patients were enrolled in our meta-analysis. The median follow-up duration was 36 months (range, 12–98 months). A history of baseline MI was reported in five studies[21, 30–32, 35], and a potential pathophysiological mechanism associated with CAS was published in four studies[22, 23, 29, 30]. The prescription rate of aspirin in these studies ranged from 29.0–90.1% (Table 1).

Table 1
Baseline characteristics of the included studies.

| Source | Study design | Total | Age (years) | Male (%) | Mechanisms | Baseline MI | Coronary stenosis | Antiplatelet strategy (%) | | Statin (%) | Follow-up (months) | Outcom |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Aspirin | DAPT | | | |
| Vicente-Ibarra[35] 2021 (Spain) | Retrospective | 120 | 59 | 64.2 | Indefinite | Positive | < 50% | 60.0 | 18.3 | 59.2 | 35 | All-caus MI, stro hospita for CV c |
| Olesen 2021[20] (Denmark) | Retrospective | 4124 | 60 | 50.3 | Indefinite | Negative | < 50% | 60.0 | NR | 70.7 | 59 | All-caus death, M bleedin |
| Gu 2021[33] (China) | Retrospective | 757 | 53 | 61.2 | Indefinite | Negative | 1–49% | 44.4 | NR | 46.1 | 59 | CV deat revascu |
| Ciliberti 2021[32] (Italy) | Retrospective | 621 | 65 | 44.6 | Indefinite | Positive | < 50% | 87.9 | 58.8 | 81.0 | 90 | All-caus ACS, hospita for hea stroke |
| Paolisso 2020[21] (Italy) | Prospective | 88 | 67 | 37.5 | Indefinite | Positive | < 50% | 85.2 | 56.8 | 75.0 | 19 | All-caus MI, stro |
| Lee 2018[22] (South Korea) | Retrospective | 154 | 51 | 74.7 | Definite | Negative | < 50% | 50.0 | NR | NR | 36 | Death, I angina hospita |
| SWEDEHEART[31] 2017(Sweden) | Retrospective | 8118 | 65 | 39 | Indefinite | Positive | < 50% | 90.1 | 66.4 | 84.5 | 12 | All-caus death, hospita for MI, h failure a stroke |
| Conte 2017[34] (Italy) | Retrospective | 245 | 63 | 69.8 | Indefinite | Negative | 1–49% | 29 | NR | 22.9 | 98 | All-caus death, A revascu |
| KAMIR 2016[30] (South Korea) | Retrospective | 501 | 58 | 69.3 | Definite | Positive | < 50% | 77.3 | NR | 58.3 | 12 | All-caus MI, revascu |
| Ishii 2016[23] (Japan) | Retrospective | 224 | 67 | 58.0 | Definite | Negative | ≤ 50% | 50.0 | NR | 34.8 | 60 | CV deat |
| Lim 2016[29] (South Korea) | Retrospective | 721 | 56 | 83.5 | Definite | Negative | ≤ 50% | 60.2 | NR | 40.9 | 52 | All-caus death, A revascu |
| Hwang 2015[19] (South Korea) | Retrospective | 8372 | 61 | 70.3 | Indefinite | Negative | 1–49% | 44.8 | NR | 23.7 | 28 | All-caus revascu |
| CONFIRM[28] 2015(Canada) | Prospective | 10418 | 57 | 52.7 | Indefinite | Negative | < 50% | 37.7 | NR | 33.3 | 27 | All-caus |

MI, myocardial infarction; ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; CV, cardiovascular; NR, not reported.

## Quality Assessment Of Individual Study

The NOS score of one study[30] was five, indicating medium quality, and all the other studies were of high quality. Another study[20] recruited participants with diabetes mellitus only, which might contribute to bias risk regarding representativeness of the population (Table 2).

Table 2
Bias risk of individual studies using the Newcastle-Ottawa Scale.

| Study | Selection | | | | Comparability | Outcome | | | Total score |
|---|---|---|---|---|---|---|---|---|---|
| | Representativeness of the exposed | Selection of the non-exposed | Ascertainment of exposure | Demonstration | | Assessment of outcome | Follow-up length | Adequacy of follow-up | |
| Vicente-Ibarra 2021[35] | ★ | ★ | ★ | ★ | | ★ | ★ | ★ | 7 |
| Olesen 2021[20] | | ★ | ★ | ★ | ★★ | ★ | ★ | ★ | 8 |
| Gu 2021[33] | | ★ | ★ | ★ | ★★ | ★ | ★ | ★ | 8 |
| Ciliberti 2021[32] | ★ | ★ | ★ | ★ | ★★ | ★ | ★ | | 8 |
| Paolisso 2020[21] | ★ | ★ | ★ | ★ | | ★ | ★ | ★ | 7 |
| Lee 2018[22] | | ★ | ★ | ★ | ★★ | ★ | ★ | | 7 |
| SWEDEHEART 2017[31] | ★ | ★ | ★ | ★ | ★★ | ★ | ★ | ★ | 9 |
| Conte 2017[34] | ★ | ★ | ★ | ★ | | ★ | ★ | ★ | 7 |
| KAMIR 2016[30] | | ★ | ★ | ★ | | ★ | ★ | | 5 |
| Ishii 2016[23] | | ★ | ★ | ★ | ★★ | ★ | ★ | | 7 |
| Lim 2016[29] | | ★ | ★ | ★ | ★★ | ★ | ★ | ★ | 8 |
| Hwang 2015[19] | ★ | ★ | ★ | ★ | ★★ | ★ | ★ | | 8 |
| CONFIRM 2015[28] | ★ | ★ | ★ | ★ | ★★ | ★ | ★ | ★ | 9 |

# Primary Endpoint

Eleven studies[19–23, 28–30, 32–35] compared the risk of MACEs in patients treated with aspirin or not. Pooled data showed that aspirin therapy was not associated with the risk of MACEs (HR 1.10; 95% CI 0.85–1.41; $P = 0.47$); however, the results had a large heterogeneity ($I^2 = 57\%$) (Fig. 2). A small sample study[22] with extreme values might be the main source of heterogeneity, as excluding this study reversed the large heterogeneity (Supplementary Fig. S1a). In addition, after excluding the study with diabetes mellitus only [20] and another one with medium quality[30], the changes in heterogeneity were not obvious, which suggested that they were not the main sources of heterogeneity (Supplementary Fig. S1b,c). To further explore the source of heterogeneity, predefined subgroup analyses were performed. The interactions for all subgroups were not significant, except the follow-up duration (> 36 vs. ≤36 months), and aspirin use was not associated with the risk of MACEs in all subsets (Table 3). Similarly, dual antiplatelet therapy was not associated with the risk of MACEs (HR 0.86; 95% CI 0.63–1.18; $P = 0.35$, $I^2 = 21\%$) among the four studies that enrolled subjects with myocardial infarction with nonobstructive coronary arteries (MINOCA) (Supplementary Fig. S2)[21, 31, 32, 35].

Table 3
Subgroup analyses for major adverse cardiovascular events.

| Subgroup | No. of studies | No. of patients | HR | 95% CI | $I^2$ | *P* | *P* for interaction |
|---|---|---|---|---|---|---|---|
| Follow-up | | | | | | | |
| ≤ 36months | 5 | 9235 | 0.80 | 0.51–1.27 | 49% | 0.34 | 0.08 |
| > 36months | 6 | 6692 | 1.31 | 0.97–1.76 | 49% | 0.07 | |
| Study design | | | | | | | |
| Prospective | 1 | 88 | 0.80 | 0.23–2.81 | | 0.73 | 0.62 |
| Retrospective | 10 | 15839 | 1.11 | 0.86–1.44 | 61% | 0.43 | |
| CAS | | | | | | | |
| Definite | 4 | 1600 | 0.95 | 0.41–2.20 | 74% | 0.90 | 0.78 |
| Indefinite | 7 | 14327 | 1.07 | 0.85–1.36 | 43% | 0.55 | |
| Baseline MI | | | | | | | |
| Positive | 4 | 1330 | 1.45 | 0.93–2.26 | 0% | 0.10 | 0.20 |
| Negative | 7 | 14597 | 1.02 | 0.77–1.36 | 67% | 0.88 | |
| Sample size | | | | | | | |
| ≤ 600 | 6 | 1332 | 1.03 | 0.57–1.86 | 59% | 0.91 | 0.86 |
| > 600 | 5 | 14595 | 1.10 | 0.84–1.44 | 64% | 0.50 | |
| Adjustment | | | | | | | |
| Yes | 7 | 14973 | 1.03 | 0.76–1.39 | 69% | 0.85 | 0.24 |
| No | 4 | 954 | 1.41 | 0.92–2.15 | 0% | 0.11 | |

HR, hazard ratio; CI, confidence interval; CAS, coronary artery spasm; MI, myocardial infarction.

## Secondary Endpoints

Five studies[19–21, 28, 29] compared the risk of all-cause death in nonobstructive CAD patients treated with aspirin or not. Pooled data showed that aspirin use reduced the risk of all-cause death by 23% (HR 0.77; 95% CI 0.63–0.95; $P = 0.02$, $I^2 = 25\%$) (Fig. 3). Post-hoc sensitivity analysis was performed to confirm the effect of individual studies on the pooled data. The result was no longer statistically significant after excluding the study by Hwang et al. (Supplementary Fig. S3)[19]. Two [20, 29] and three studies[21, 22, 29] compared the risk of cardiovascular death and MI in patients treated with or without aspirin, respectively. As shown in Fig. 3, aspirin use was not associated with the risk of cardiovascular death (HR 1.12; 95% CI 0.73–1.73; $P = 0.60$, $I^2 = 0\%$) and MI (HR 0.53; 95% CI 0.09–3.20; $P = 0.49$, $I^2 = 68\%$).

## Safety Endpoint

Only one study[20] reported the adverse effects of aspirin on bleeding risk. No difference in bleeding risk was found in nonobstructive CAD patients who received aspirin or not (HR 0.95; 95% CI 0.73–1.23; $P = 0.70$).

## Publication bias

Publication bias for MACEs across studies was evaluated using funnel plot and Egger's tests. The funnel plot was symmetrical and the Egger's value was $P = 0.517$, suggesting that there was no publication bias (Fig. 4).

## Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to investigate the association between aspirin use and the prognosis of nonobstructive CAD. Based on the pooled data from thirteen studies with 34,463 participants, this study revealed that routine aspirin therapy did not decrease the risk of MACEs, cardiovascular death and MI, but reduced the risk of all-cause death.

The benefit of aspirin therapy is well established for secondary prevention in patients with atherosclerotic diseases, and a low-dose of aspirin is recommended by the guidelines of the European Society of Cardiology[36]. Unfortunately, in contrast to previous randomized trials that majorly recruited patients with obstructive CAD, few randomized trials have probed the association between routine aspirin use and cardiovascular events in patients with nonobstructive CAD. Increasing evidence indicates that patients with nonobstructive CAD already develop slight atherosclerotic alterations with a higher risk of cardiovascular events[10, 11]. As a result, more aggressive management might be needed for these patients. At present, the recommendations of guidelines for aspirin

therapy in patients with nonobstructive CAD are ambiguous. Indeed, the extreme variation in aspirin prescription rates (29.0–90.1%) in our study corroborated the dilemma of aspirin use in nonobstructive CAD. Therefore, evidence from our study that aspirin therapy failed to improve the prognosis of nonobstructive CAD might shed light on the management of this disease with aspirin in the future.

Several studies have assessed the impact of antiplatelet therapy on cardiovascular events in patients with nonobstructive CAD. In patients diagnosed with MINOCA, an observational study reported that aspirin use was not associated with a significantly reduced risk of the composite of adverse cardiovascular events (odds ratio 0.601; 95% CI 0.305–1.183) during 2-year follow-up[37]. Similarly, another study with a 3-year follow-up showed that antiplatelet agents did not improve the prognosis of nonobstructive CAD (HR 1.089; 95% CI 0.642–1.847)[38]. Because of the different effect sizes and lack of detailed antiplatelet regimens, these two studies were excluded from our meta-analysis. Another two studies that enrolled participants without a medical history of MI also found that aspirin therapy had no beneficial effect[20, 28], which was consistent with our findings. However, these studies were insufficiently representative, as participants with MI were either included or excluded. Our combined data showed that aspirin therapy did not improve the prognosis of patients with nonobstructive CAD regardless of whether they suffered from baseline MI or not, which was first reported (Table 3).

Of note, according to current guidelines, once a diagnosis of MI is confirmed, aspirin as well as P2Y12 receptor antagonists should be routinely administered[36, 39]. However, there is a debate as to whether antiplatelet agents should be routinely prescribed to patients with MINOCA. Luis et al. reported that insufficient secondary prevention medications (e.g., aspirin) were responsible for the poor outcome among MINOCA patients with “normal” cardiac magnetic resonance images[40]. On the contrary, a post-hoc analysis of the CURRENT-OASIS 7 trial showed that potent antiplatelet therapy might increase the risk of cardiovascular events[41]. The pooled data from our study indicated that aspirin therapy was not associated with improved prognosis in patients with nonobstructive CAD. Consistently, the results of dual antiplatelet therapy data from four studies could further strengthen this conclusion.

Our study showed that aspirin use reduced the risk of all-cause death in patients with nonobstructive CAD, with no effects on cardiovascular death or MI. Post-hoc sensitivity analyses of all-cause death indicated a reversible result after excluding the study by Hwang et al (Supplementary Fig. S3)[19]. In their study, more than half of aspirin users did not receive statin therapy, which suggested that the beneficial effects of aspirin on all-cause death might be influenced by a lower prescription rate of statins (23.7%). Currently, statins are widely available at a low price, and the effect of statins is superior to that of aspirin in primary prevention[18]. Multiple studies have shown that statins can perform well in the management of patients with nonobstructive CAD[20, 23, 28, 30, 31]. The efficacy of aspirin is likely to be attenuated or covered because of the gradually increasing prescription rate of statins[18]. Hence, the association between routine aspirin therapy and all-cause death remains unclear in patients with nonobstructive CAD under the comprehensive management of risk factors, such as smoking, diabetes, dyslipidemia, and hypertension, which requires further investigation.

Nonobstructive CAD is a heterogeneous disease with multiple potential underlying conditions, including vulnerable plaque, CAS, microvascular dysfunction and myocarditis, which may explain why aspirin use was not associated with improved outcomes.

First, critical findings might be ignored when evaluating coronary stenosis with coronary angiography alone. Intravascular imaging showed that vulnerable plaques, such as plaque rupture and plaque erosion, were detected in a few patients with nonobstructive CAD, which could eventually develop into thrombi[42, 43]. It was reasonable to prescribe antiplatelet agents to patients with thrombi. Although antiplatelet therapy based on intravascular imaging should be the target, in actual clinical practice it is not readily available due to the cost–benefit ratio. Additionally, it was showed that plaque burden, rather than vulnerable plaque, was a stronger predictor for patients with nonobstructive CAD[44]. The plaque burden was also associated with similar ischemic events, regardless of the presence or absence of obstructive CAD[45]. Indeed, coronary stenosis is positively correlated with plaque burden[45]. Overall, patients with nonobstructive CAD had a lower plaque burden than those with obstructive CAD[45]. This might explain why aspirin therapy was not as effective as expected in patients with nonobstructive CAD. On the other hand, those with a higher plaque burden may benefit from antiplatelet therapy. For example, two studies showed that only patients with a coronary artery calcium score of $\geq 100$ were likely to benefit from aspirin therapy in the primary prevention of atherosclerotic disease[46, 47]. Therefore, future research is needed to support our hypothesis that a personalized antiplatelet regimen based on plaque burden might contribute to reduction in ischemic cardiovascular events in patients with nonobstructive CAD.

Second, a previous study showed that CAS accounted for approximately 60% of patients with stable angina, indicating that it is a common condition in patients with nonobstructive CAD[48]. Similarly, a systematic review revealed that approximately 30% of MINOCA might be induced by CAS[4]. The presence of CAS was associated with poor outcomes in these patients[8, 49]. However, limited evidence is available regarding the effects of aspirin therapy on CAS. A high dose of aspirin (> 325mg daily) was considered as a potential inducer of coronary spasm[50], whereas a low dose of aspirin had the opposite effect[51]. Conversely, another study found that aspirin therapy might lead to CAS even at a low dose[52]. Hence, the impact of aspirin therapy on the prognosis of CAS was under ongoing debate. A recent meta-analysis showed that there was no significant association between aspirin use and clinical outcomes among patients with vasospastic angina without organic stenosis[53]. In the present study, pooled data based on a subset of CAS also indicated that aspirin use was not associated with the risk of cardiovascular events (Table 3). Of note, this finding should be interpreted with caution because of the post-hoc nature of subgroup analysis.

Third, recent studies indicated that patients with nonobstructive CAD could present with angina-like chest pain, but there was no evidence of myocardial ischemia[54]. Several non-ischemic diseases, including myocarditis, cardiomyopathy, and Takotsubo syndrome, can mimic MI in patients with MINOCA. Previous studies have shown that routine aspirin use does not reduce the risk of cardiovascular events in non-ischemia settings[55, 56]. In addition, a meta-analysis reported that aspirin therapy might worsen the long-term prognosis of patients with Takotsubo syndrome without any benefit[57].

There are several limitations of our study. First, the definitions of the primary endpoint differed slightly between the studies, which might be a potential source of heterogeneity in our results. Second, our results were extracted from observational cohort studies, most of which were retrospective. In addition, a small amount of the extracted data was unadjusted. Although subgroup analyses based on study design and adjustment revealed no interaction effects, our results might still be affected by potential confounding factors. Third, the lack of reported haemorrhagic events might affect the outcome in patients on aspirin

therapy. Finally, only published studies were included in the meta-analysis. The results might be corrected by unpublished studies, despite no evidence of publication bias. Currently, a prospective, multicenter, randomized trial is in progress, in which 4422 women suspected of myocardial ischemia with nonobstructive CAD have been recruited[58]. This trial may provide additional information about the efficacy of aspirin therapy (NCT03417388).

## Conclusion

Routine aspirin therapy might not improve prognosis in patients with nonobstructive CAD. A personalized antiplatelet regimen might contribute to reduction in ischemic cardiovascular events in patients with non-obstructive CAD.

## Declarations

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**Declaration of interest:**

None

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**Author contribution:**

Hua-ping Fan:Conceptualization, methodology, data curation and extraction, writing-original draft preparation
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Yu Zhou: Software

Jun Jin: Conceptualization,supervision, reviewing and editing

Quan-you Zheng:Funding acquisition, conceptualization, supervision, reviewing and editing

**Data availability:**

All data generated or analyzed during this study are available from the first or corresponding author upon reasonable request.

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## Figures

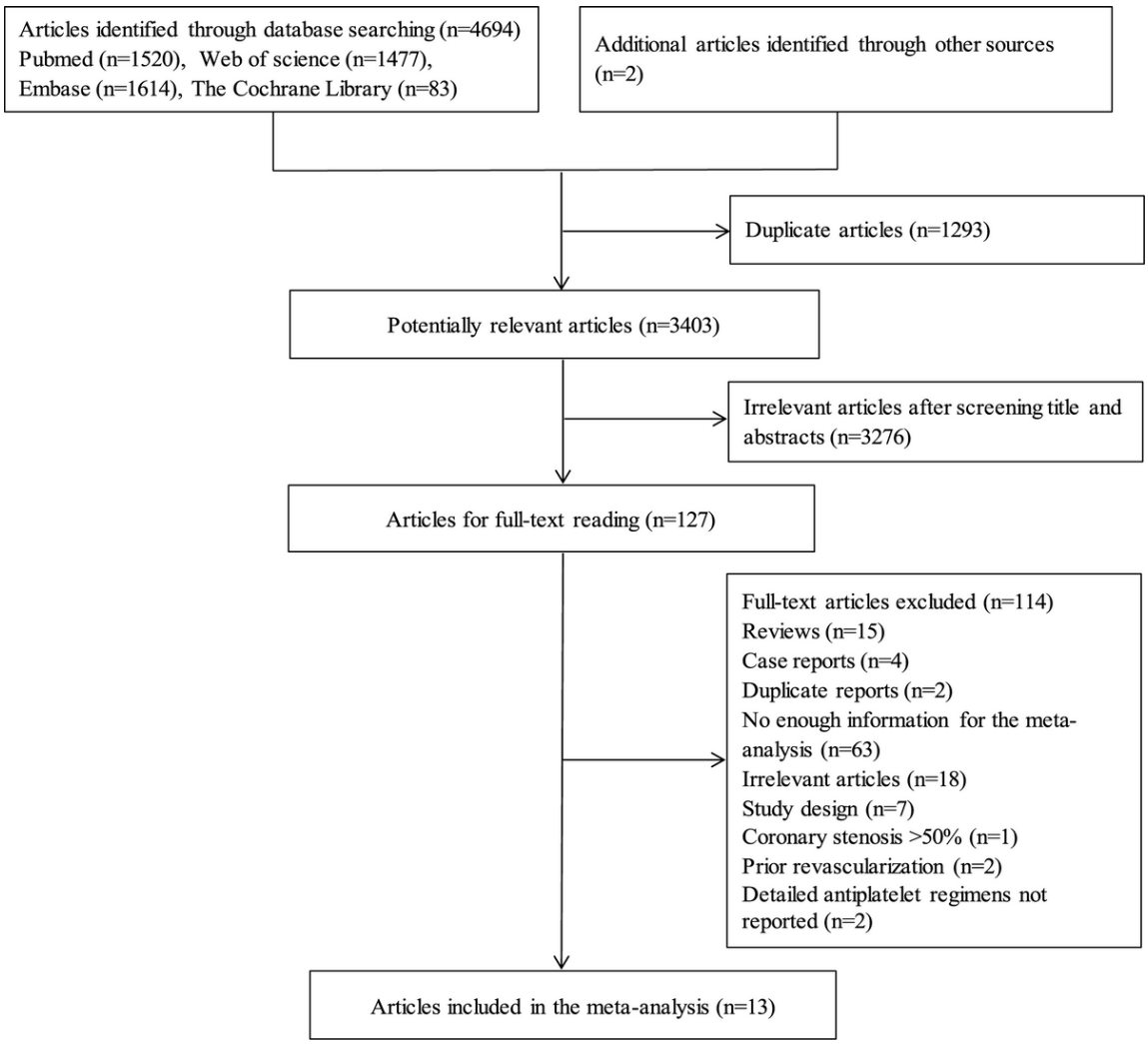


**Figure 1**

Flowchart of study enrollment in meta-analysis.

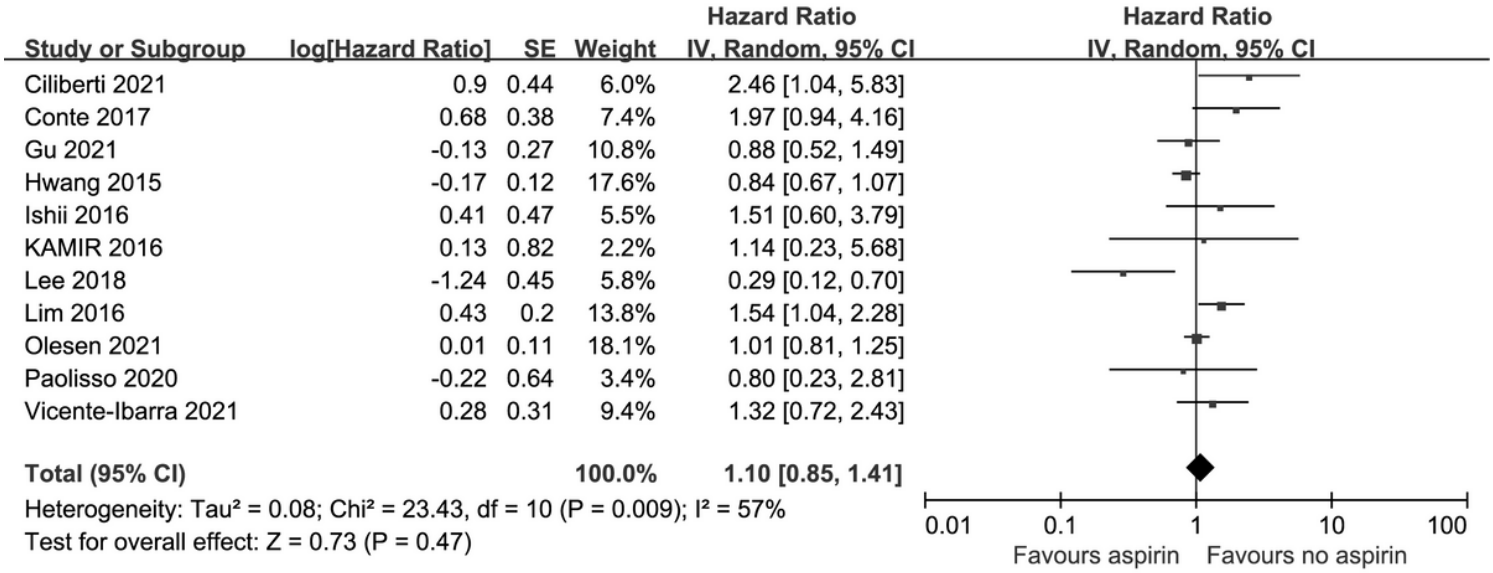


**Figure 2**

Forest plot of major adverse cardiovascular events.

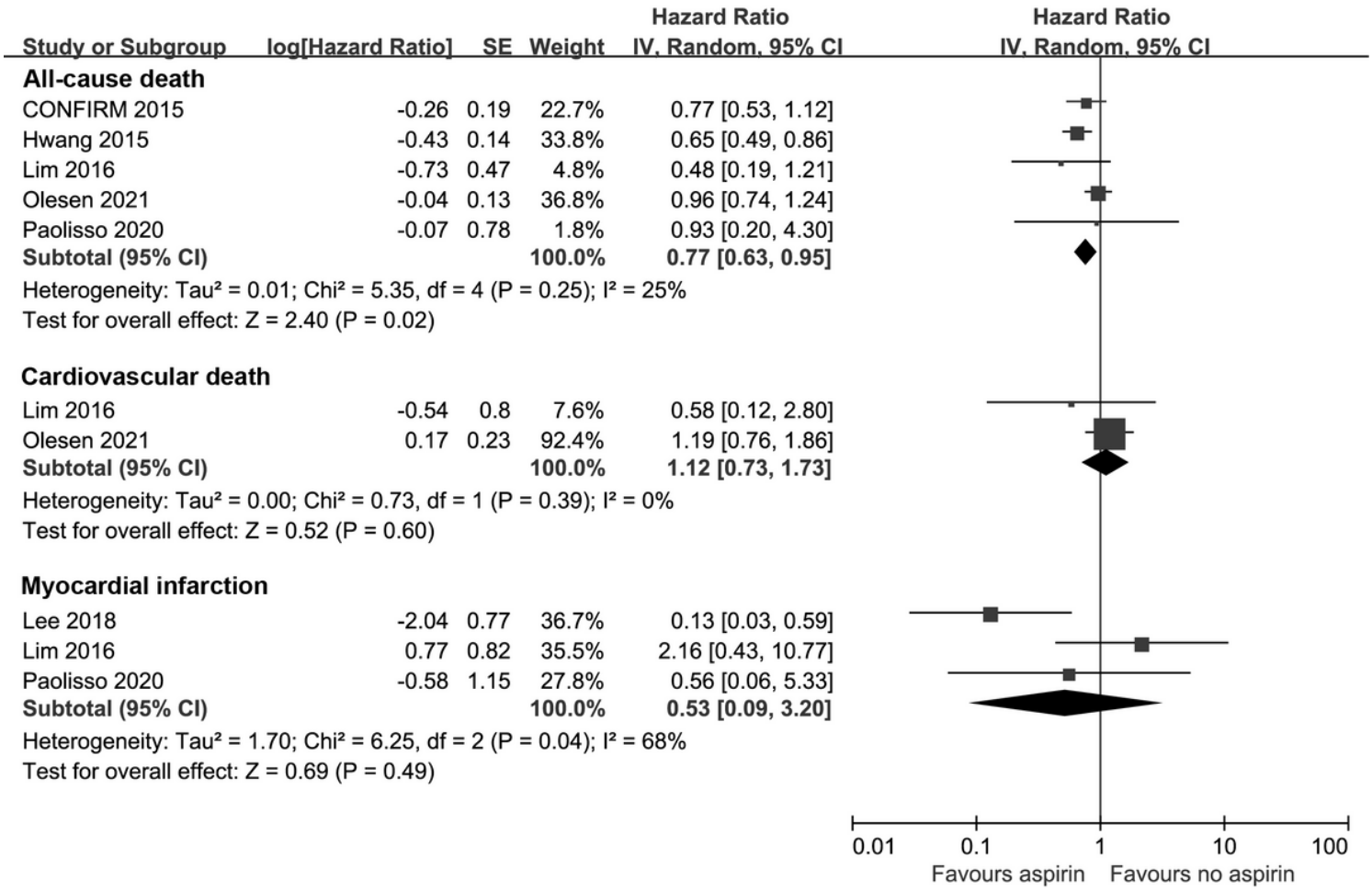


Figure 3

Forest plot of secondary endpoints.

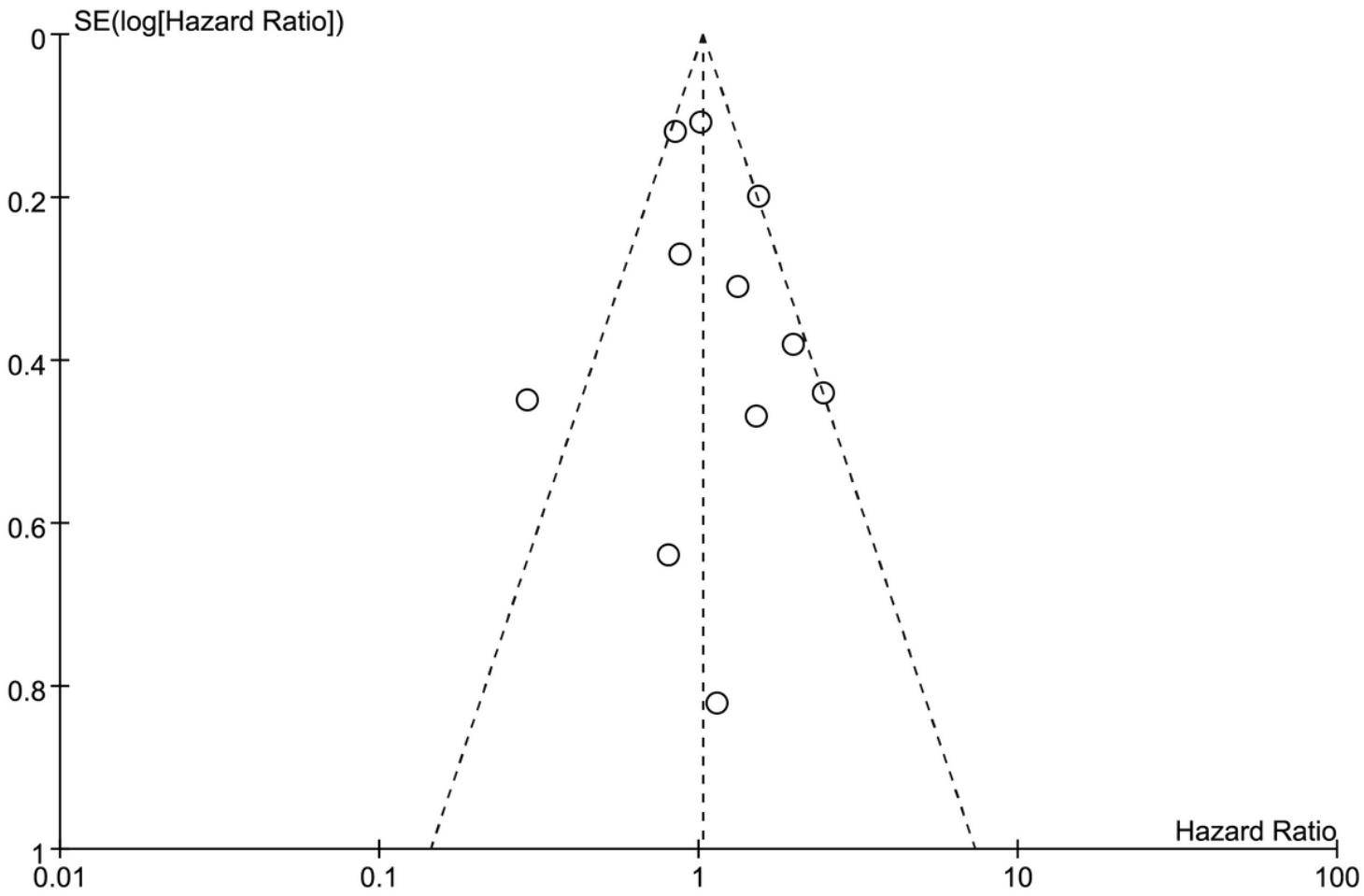


**Figure 4**

Funnel plot of major adverse cardiovascular events and aspirin therapy.

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