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Impact of aspirin use on clinical outcomes in patients with vasospastic angina: a systematic review and meta-analysis

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ABSTRACT

Objectives The use of aspirin to prevent cardiovascular disease in vasospastic angina (VSA) patients without significant stenosis has yet to be investigated. This study aimed to investigate the efficacy of aspirin use among VSA patients.

Design Systematic review and meta-analysis.

Data sources PubMed, Web of Science and Cochrane Central Register of Controlled Trials were searched for relevant information prior to October 2020.

Eligibility criteria for selecting studies Aspirin use versus no aspirin use (placebo or no treatment) among VSA patients without significant stenosis.

Data extraction and synthesis Two investigators extracted the study data. ORs and 95% CIs were calculated and graphed as forest plots. The Newcastle-Ottawa Quality Assessment Scale tool and Begg's funnel plot were used to assess risk of bias.

Results Four propensity-matched cohorts, one retrospective analysis and one prospective multicentre cohort, in total comprising 3661 patients (aspirin use group, n=1695; no aspirin use group, n=1966) were included in this meta-analysis. Aspirin use and the incidence of major cardiovascular adverse events with follow-up of 1–5 years were not significantly correlated (combined OR=0.90, 95% CI: 0.55 to 1.68, p=0.829, I^2=82.2%; subgroup analysis: OR=1.09, 95% CI: 0.81 to 1.47, I^2=0%). No significant difference was found between aspirin use and the incidence of myocardial infarction (OR=0.62, 95% CI: 0.09 to 4.36, p=0.615, I^2=73.8%) or cardiac death (OR=1.73, 95% CI: 0.61 to 4.94, p=0.444, I^2=0%) during follow-up.

Conclusion Aspirin use may not reduce the risk of future cardiovascular events in VSA patients without significant stenosis.

PROSPERO registration number CRD42020214891.

Strengths and limitations of this study

- ► This is the first meta-analysis to evaluate the impact of aspirin use on clinical outcomes in patients with vasospastic angina.
- ► The therapeutic drug used in the study by Mori (2020) is an antiplatelet drug that includes aspirin and P2Y12 inhibitors.
- ► The limitations inherent to multicentre observational studies performed in both retrospective and prospective manners may have affected data analysis.
- ► The conclusions of this study should be verified with randomised controlled trials with a larger sample size.

INTRODUCTION

Coronary spasm characterised by vasospastic angina (VSA) is one cause of ischaemia in a non-obstructive coronary artery.[1 2] VSA patients who also suffer from endothelial dysfunction or coronary atherosclerosis commonly use aspirin,[3 4] as per the guidelines of the European Society of Cardiology, for the management of chronic stable angina and acute coronary syndromes.[5 6]

The ASCEND study showed that the use of low-dose aspirin leads to a lower risk of serious vascular events (8.5% vs 9.6%; p=0.01) compared with placebo among persons with diabetes in primary treatment, but the absolute benefits of aspirin are largely counterbalanced by the bleeding hazard (4.1% vs 3.2%; p=0.003).[7] The ARRIVE study also suggested that aspirin use may result in a higher incidence of gastrointestinal bleeding (0.97% vs 0.46%; p=0.0007) or overall incidence of treatment-related adverse events (16.75% vs 13.54%; p<0.0001) compared with control groups.[8] Owing to the latest controversy and reduced usage of aspirin in preventing cardiovascular events,[9 10] aspirin's efficiency in VSA patients without significant stenosis has not yet been reported.[11–16] Therefore, this meta-analysis was designed to assess the correlation between aspirin use and cardiovascular events and cardiac death among VSA patients during long-term follow-up.

MATERIALS AND METHODS

Search strategy

A comprehensive search of PubMed, Web of Science and Cochrane Central Register of Controlled Trials databases for related research articles conducted before October 2020 was conducted to gather data. The keywords were 'vasospastic angina', 'coronary vasospasms', 'vasospasm', 'variant angina', 'Prinzmetal's variant angina', 'spastic coronary angina', 'coronary artery spasm,' as well as 'aspirin' and 'antiplatelet therapy'. Certain additional-related publications, such as review articles and editorials, were also assessed.

Patient and public involvement

Study participants met the eligibility criteria as outlined above. All included patients were diagnosed with epicardial coronary vasospasms by provocation test. Participants and other members of the public were not involved in the recruitment, design, conduct, reporting, or dissemination of this study.

Study selection and data extraction

The patient inclusion criteria were as follows: (i) diagnosed with VSA on provocation test, (ii) absence of significant stenosis (≤50%), (iii) the treatment group was administered oral aspirin and the control group received no aspirin or placebo and (iv) articles published in English. The exclusion criteria were as follows: significant stenosis (≥50%), intravenous aspirin, case report and case series. The study data were independently extracted by two investigators, namely Lin and Chen, using predefined extraction forms; any conflict was resolved by a third reviewer.

Data analysis and risk of bias assessment

Major cardiovascular adverse events (MACE) were the primary endpoints, while myocardial infarction (MI) and cardiac death during follow-up were the secondary endpoints. MACE have been described as cardiac death, acute coronary syndrome and hospitalisation due to unstable angina, percutaneous coronary intervention, symptomatic arrhythmia, appropriate implantable cardioverter defibrillator and shock. The Newcastle-Ottawa Quality Assessment Scale (NOS) tool was utilised to assess the risk of bias, and Begg's funnel plot was used to evaluated publication bias.

Statistical analysis

STATA software (V.14.0; StataCorp, College Station, TX, USA) was used for the meta-analysis. MACE (primary endpoints) and MI and cardiac death (secondary endpoints) were evaluated as combined ORs with 95% CIs. Heterogeneity between studies was derived using the I^2 statistic. If I^2>50%, the random effect model was used to assess heterogeneity; if I^2<50%, the fixed effect model was utilised to evaluate heterogeneity. Subgroups were studied to reduce the heterogeneity if I^2>50%. P values<0.05 were considered statistically significant.

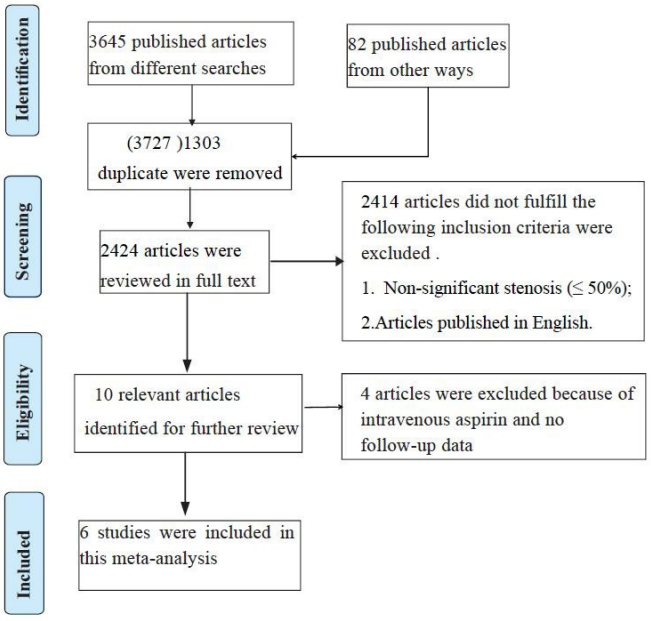

Figure 1 Flow diagram for identification processes.

RESULTS

Characteristics of included studies

The search engines were reviewed to identify 3645 related studies, among which 1303 articles were duplicates and 2414 articles did not fulfil the inclusion criteria and were excluded from the study. After removing these studies, four propensity-matched cohorts,[11 13 14 16] one retrospective analysis[12] and one prospective multicentre cohort[15] (figure 1), including a total of 3661 patients (aspirin group, n=1695; no aspirin group, n=1966, table 1) were included in the study. Four studies underwent coronary provocation test, except for one study (Seong-Sik Cho, 2019) that used the electrocardiograph provocation test. All studies provided a primary endpoint, with follow-up durations ranging from 1 to 5 years (table 2).

Primary and secondary endpoints

No significant correlation was recorded between aspirin use and MACE incidence within the follow-up of 1–5 years (combined OR=0.90, 95% CI: 0.55 to 1.68, p=0.829, I^2=82.2% (figure 2); subgroup analysis: OR=0.89, 95% CI: 0.40 to 2.02, I^2=86.9% and OR=1.09, 95% CI: 0.81 to 1.47, I^2=0% (figure 3A,B)).

MI was reported in four studies, and cardiac death was reported in five studies for the secondary endpoint. No significant difference was found between aspirin use and the incidence of MI (OR=0.62, 95% CI: 0.09 to 4.36, p=0.615, I^2=73.8%) or cardiac death (OR=1.73, 95% CI: 0.61 to 4.94, p=0.444, I^2=0%) during the follow-up (figure 4).

Risk of bias assessment and heterogeneity analysis

The NOS scores for study quality assessment of the included studies ranged from 7 to 9 (table 3). Publication bias is presented by asymmetry in the funnel plot (figure 5). Between-study heterogeneity in MACE-related

Table 1 Clinical characteristics of patients in included studies

Characteristics aspirin vs no	Kim[12]	Ishii[14]	Lim[13]	Lee[11]	Cho[15]	Mori[16]
Age (year)	/	66.0±9.5 vs 67.0±8.4, p=0.428	49.0–62.0 vs 49.0–62.5, p=0.61	51.3±6.7 vs . 50.8±7.5, p=0.70	57.2±11.2 vs 53.5±11.3, p=0.001	65.4±9.9 vs 66.7±10.3, p=0.07
Males, n (%)	/	47 (42.0) vs 47 (42.0), p=1.000	359 (82.7) vs 243 (84.7), p=0.49	60 (78) vs 55 (71), p=0.354	412 (64.3) vs 590 (58.4), p=0.055	247 (73.7%) vs 253 (75.5%), p=0.66
Hypertension, n (%)	/	52 (46.4) vs 57 (50.9), p=0.504	156 (36.0) vs 104 (36.2), p=0.96	22 (29) vs 20 (26), p=0.717	294 (45.9) vs 320 (31.7), p=0.001	158 (47.2%) vs 166 (49.6%), p=0.59
Diabetes mellitus, n (%)	/	26 (23.2) vs 27 (24.1), p=0.875	98 (22.6) vs 66 (23.0), p=0.91	17 (22) vs 16 (19), p=0.547	73 (11.4) vs 83 (8.2), p=0.037	56 (16.7%) vs 56 (16.7%), p=1.00
Smoking, n (%)	/	59 (52.7) vs 52 (46.4), p=0.350	127 (29.3) vs 87 (30.3), p=0.78	55 (71) vs 57 (74), p=0.717	183 (28.9) vs 250 (24.7), p=0.005	202 (60.3%) vs 202 (60.3%), p=1.00
Dyslipidaemia, n (%)	/	62 (55.4) vs 60 (53.6), p=0.788	91 (21.0) vs 62 (21.6), p=0.84	/	98 (15.4) vs160 (15.8), p=0.800	156 (46.6%) vs 142 (42.4%), p=0.31
Ca channel blocker, n (%)	/	104 (92.9) vs 101 (90.2), p=0.472	420 (96.9) vs 275 (95.8), p=0.46	50 (65) vs 48 (62), p=0.738	152 (24.2) vs 162 (16.12), p=0.001	316 (94.3%) vs 313 (93.4%), p=0.75
Statin, n (%)	/	38 (33.9) vs 40 (35.7), p=0.779	182 (42.0) vs 113 (39.4), p=0.49	/	123 (19.7) vs 119 (11.9), p=0.001	103 (30.7%) vs 95 (28.4%), p=0.55
ACEI/ARB, n (%)	/	33 (29.5) vs 25 (22.3), p=0.288	69 (15.9) vs 43 (15.0), p=0.74	/	152 (24.3) vs 126 (12.6), p=0.001	73 (21.8%) vs 71 (21.2%), p=0.93
Beta-blocker, n (%)	/	6 (5.4) vs 7 (6.3), p=0.775	1 (0.2) vs 0 (0.0), p=0.48	17 (22) vs 23 (30), p=0.270	54 (8.65) vs 59 (5.88), p=0.065	/

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

research was 82.2% and 86.9%. Therefore, the outcome of subgroup analyses of I^2 was 0%, indicating low publication bias (figure 3). The between-study heterogeneities in MI and cardiac death-related studies were 73.8% and 0%, respectively, indicating the occurrence of high publication bias for the MI endpoint (figure 4).

DISCUSSION

Our meta-analysis showed that aspirin had no significant effect on reducing MACE, MI and cardiac death in VSA patients without significant stenosis.

Coronary artery spasm (CAS) has been reported to play a significant role in the pathogenesis of ischaemic heart disease, including acute coronary syndrome and chronic coronary syndrome.[17] A common mechanism by which MI or MINOCA manifests is platelet aggregation, which leads to coronary thrombus formation. Aspirin inhibits cyclooxygenase-1 by reducing the production of thromboxane A2 and therefore has been extensively used in primary or secondary prevention of thrombosis among patients with atherosclerosis or coronary artery disease.[18 19] However, the benefit of low dosage aspirin in primary prevention was counterbalanced by higher rates of treatment-related adverse events.[7 8] Earlier studies have shown that aspirin use can aggravate CAS due to the lowered production of thromboxane A2 and increased MACE incidence in VSA patients.[20 21] Thus, the use of aspirin in VSA patients remains controversial.

MACE incidence in patients administered low-dose aspirin was significantly higher than that among patients

Table 2 Baseline characteristics of included studies

Study	Year	Design	Participants	Total	Aspirin	Without aspirin	Dosage of aspirin (mg)	MACE definition	MACE	Myocardial infarction	Cardiac death	All cause death	Follow-up
Kim[12]	2013	Retrospective analysis	Vasospastic angina (stenosis ≤70%)	240	96	144	100	Readmission rate associated with recurrent angina, cardiac death, percutaneous coronary intervention	20 (20.8) vs 29 (20.1)	/	1 (1.0) vs 1 (0.7)	/	1 year
Ishii[14]	2016	Retrospective analysis, propensity score matched analysis	Vasospastic angina (stenosis ≤50%)	224	112	112	81–100	Cardiac death, non-fatal acute myocardial infarction and unstable angina	4 (3.6) vs 6 (5.4)	0 vs 0	2 (1.8) vs 0 (0)	/	1 year
Lim[13]	2016	Retrospective analysis, propensity score matched analysis	Coronary artery spasm (stenosis ≤50%)	721	434	287	100	Cardiac death, acute myocardial infarction, revascularisation or rehospitalisation due to recurrent angina	100 (23.0) vs 34 (11.8)	9 (2.1) vs 2 (0.7)	4 (0.9) vs 3 (1.0), p=0.5	10 (2.2) vs 9 (1.5)	5 year
Lee[11]	2018	Retrospective study, propensity score-matched analysis	Coronary artery spasm (stenosis ≤50%)	154	77	77	100	Chest pain recurrence, myocardial infarction and cardiac death	9 (11.7) vs 33 (42.9)	2 (3) vs 13 (17)	0 vs 0	0 vs 0	4 year
Cho[15]	2019	Prospective multicentre cohort	Coronary artery spasm (stenosis ≤50%)	1652	641	1011	100	All cause death, acute coronary syndrome and symptomatic arrhythmia	29 (4.5) vs 44 (4.4)	/	/	3 (0.5) vs 7 (0.7)	3 year
Mori[16]	2020	Retrospective study, propensity score-matched analysis	Coronary artery spasm (stenosis ≤50%)	670	335	335	Aspirin 100 and P2Y12 inhibitors.	Cardiac death, non-fatal myocardial infarction, hospitalisation due to unstable angina pectoris and appropriate ICD shock	19 (5.7) vs 12 (3.6)	1 (0.3) vs 2 (0.6)	2 (0.6) vs 0 (0.0)	2 (0.6) vs 6 (1.8)	32 months

ICD, implantable cardioverter defibrillator; MACE, major cardiovascular adverse events.

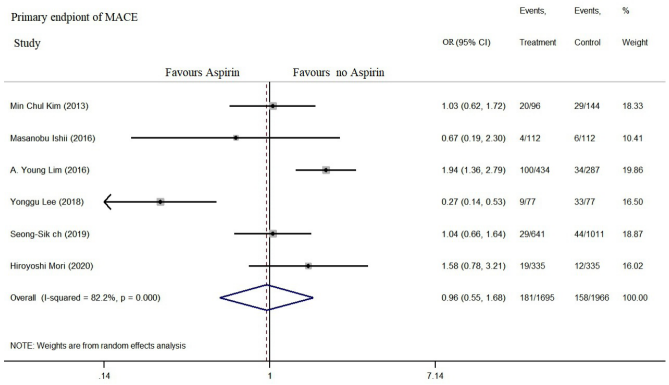

Figure 2 Aspirin use is not associated with a low incidence of MACE in patients with VSA. MACE, major cardiovascular adverse events; VSA, vasospastic angina.

not administered aspirin (HR (HR)=1.54; CI: 1.04 to 2.28; p=0.037) during a 52-month median follow-up period.[13] In contrast, MI (HR=0.13; CI: 0.03 to 0.61; p=0.014) and chest pain recurrence (HR=0.29; CI: 0.12 to 0.71; p=0.006) were observed by Lee *et al* to have been significantly reduced by aspirin use among VSA patients during follow-up.[11] Lee *et al* showed that acute intimal tears and erosion identified by optical coherence tomography are susceptible to thrombosis leading to MI. Therefore, aspirin was evidenced to reduce adverse events in VSA patients with a greater number of thrombotic intracoronary lesions. Nevertheless, aspirin use was not significantly correlated with the occurrence of cardiovascular events among VSA patients with non-significant stenosis during a

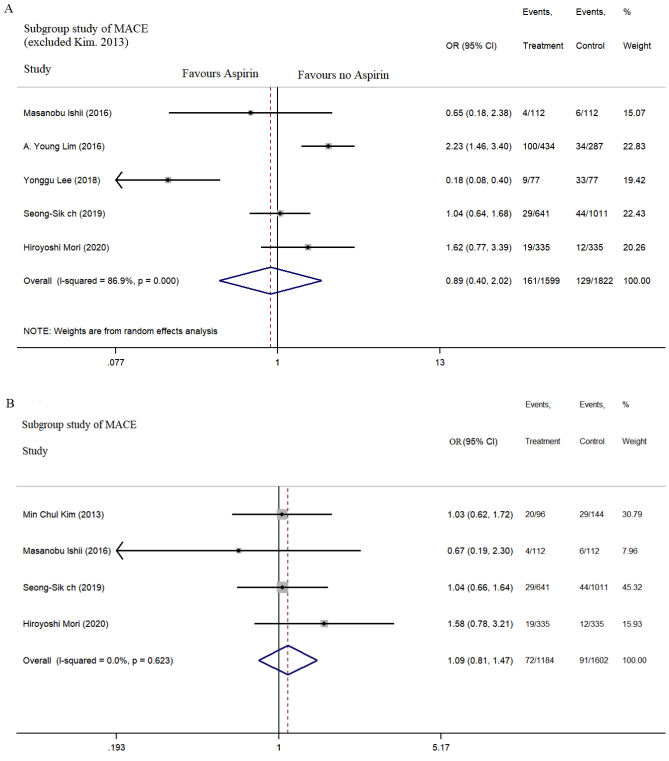

Figure 3 Subgroup analysis of MACE with aspirin use in patients with VSA. MACE, major cardiovascular adverse events; VSA, vasospastic angina.

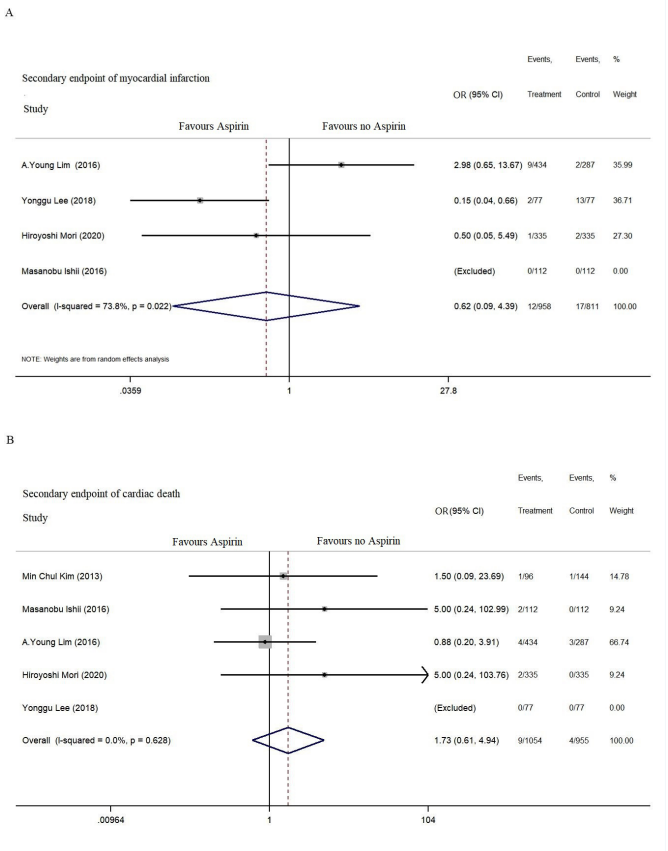

Figure 4 Secondary endpoints including myocardial infarction, cardiac death and all-cause death during 1–5 years of follow-up.

49-month mean follow-up period (p=0.541).[14] Moreover, the aspirin-treated group exhibited a similar MACE incidence compared with the non-antiplatelet agent group (HR=0.96; CI: 0.59 to 1.55, p=0.872) as reported by Cho *et al*.[15] Antiplatelet therapy was recently shown by Mori *et al* to have no beneficial effects on MACE (5.7% vs 3.6%, p=0.20) among VSA patients during a 32-month median follow-up period.[16]

Our meta-analysis indicates that aspirin use may not be linked to a lower risk of MACE and cardiac death. The subgroup analysis of MACE indicated that the studies by Lee[11] and Lim[13] were heterogeneous. The origin of heterogeneity in these studies may be attributable to chest pain recurrence in the MACE, which results in an entirely different outcome due to the definition. The following may potentially explain the lack of beneficial effects of aspirin use: (i) Aspirin use is known to damage the gastric mucosal barrier and increase risk of erosions, ulcers and bleeding by inhibiting cyclooxygenase-1 enzyme activity.[22] Several meta-analyses have indicated that aspirin's efficacy in primary prevention of cardiovascular disease should be weighed against any increase in major bleeding.[23–25] (ii) The adverse effects of asthma and dyspnoea may lead to CAS and increase the occurrence of MACE or cardiogenic death with aspirin use.[26 27] (iii) The synthesis of prostacyclin, a well-known vasodilator released by endothelial cells, is inhibited by aspirin[28] and CAS is induced

Table 3 Newcastle-Ottawa Quality Assessment Scale (NOS) for included studies

Study	Selection				Comparability	Outcome			
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total scores
Kim[12]	★	★	★	★	☆★	★	★	★	8
Ishii[14]	★	☆	★	★	★★	★	★	★	8
Lim[13]	★	★	★	★	☆★	★	★	★	8
Lee[11]	★	★	★	★	★★	★	★	★	9
Cho[15]	★	★	★	★	☆★	★	★	★	8
Mori[16]	☆	★	★	★	☆★	★	★	★	7

The bold star = 1 score. The hollow star = 0 score.

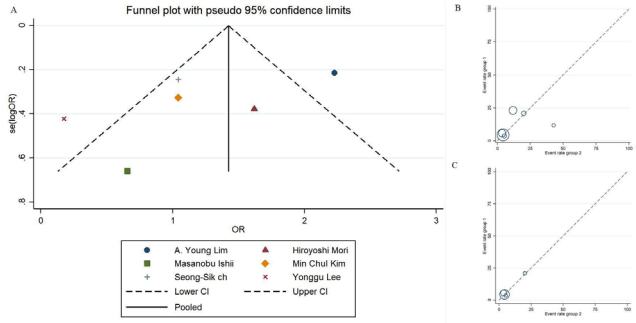

Figure 5 Assessment of bias risk of the studies.

by aspirin. This could, in turn, cause recurrent angina leading to rehospitalisation, MI, and cardiac death.

We found that aspirin use may have a protective effect against MI, which may be explained by aspirin's pharmacological mechanism. However, there was high heterogeneity in the study, which may be attributed to the lack of related studies and a different definition of MI used by Mori *et al*.[16] Aspirin use in CAS patients can be both advantageous and disadvantageous. Further investigation is necessary to determine when to recommend aspirin use.

Several potential limitations should be considered in this meta-analysis. First, MACE and MI were defined differently in the included articles. Due to the lack of original data, no standard definition of MACE was accessible in this meta-analysis. Second, one study by Mori *et al*[16] showed that an antiplatelet drug containing both aspirin and P2Y12 inhibitors was used as the treatment strategy. Third, the sample size in this analysis is too small; only a few studies conducted propensity matching analysis to balance baseline characteristics. The limitations inherent to multicentre observational studies performed in both retrospective and prospective manners could not be avoided in this analysis. Fourth, patients with 40% stenosis are considered to have VSA without coronary stenosis but might benefit from aspirin. Subgroup analysis should be performed in the next study. Finally, the major bleeding outcome was excluded from this study, which is essential for understanding the advantages of antiplatelet therapy. Despite these limitations, the merit of this study is that it is the first to evaluate the prognosis of VSA patients using low-dose aspirin.

CONCLUSIONS

Aspirin use may not reduce the risk of cardiovascular events in VSA patients without significant stenosis. Owing to its potential adverse effects, regular use of aspirin in VSA patients without significant stenosis should involve a thoughtful discussion.

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Contributors YL, QC and HYQ conceived, designed and led the study. YL, YC, JY and SD investigated, conducted the study and collected data. YL, SD and QC wrote, revised and edited the manuscript. All authors supervised the study and approved the final version of the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The institutional review board at the Shenzhen People's Hospital approved the study protocol.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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