BMJ Open

Impact of Aspirin Use on Clinical Outcomes in Patients With Vasospastic Angina: A Systematic Review and Meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-048719
Article Type:	Original research
Date Submitted by the Author:	05-Jan-2021
Complete List of Authors:	lin, yaowang; Shenzhen People's Hospital, Department of Cardiology yuan, jie; Shenzhen People's Hospital, Department of Cardiology chen, qiuling; Shenzhen People's Hospital, Department of Pharmacy dong, shaohong; Shenzhen People's Hospital, Department of Cardiology Qin, Haiyan; Shenzhen People's Hospital, Department of Emergency chen, yang; Guangdong Medical University, School of Pharmacy
Keywords:	Coronary heart disease < CARDIOLOGY, Myocardial infarction < CARDIOLOGY, Vascular medicine < INTERNAL MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Impact of Aspirin Use on Clinical Outcomes in Patients With Vasospastic Angina: A Systematic Review and Meta-analysis

Yaowang Lin[1,4], MD; Jie Yuan[1,4], MD; Qiuling Chen[3,4], MD; Shaohong Dong[1,4], MD; Haiyan Qin[2,4], MD; Yang Chen[5], MD

Author's Affiliation:

[1]Department of Cardiology; [2]Department of Emergency; [3]Department of Pharmacy; [4]Shenzhen People's Hospital, Second Clinical Medical College of Jinan University, first affiliated Hospital of South University of Science and Technology, Shenzhen, Guangdong. No. 1017, Dongmen Northern Road, 518020, Shenzhen, Guangdong, PR China.

[5]School of Pharmacy, Guangdong Medical University, Dongguan 523808, Guangdong, China

Correspondence should be addressed to Haiyan Qin and Yang Chen

Haiyan Qin, MD, e-mail: lgqinhaiyan@yeah.net and Yang Chen, MD, e-mail: ychan227@163.com.

ABSTRACT

Objectives: The use of aspirin to prevent cardiovascular disease in vasospastic angina (VSA) patients without significant stenosis is yet to be investigated. The efficacy of aspirin use among VSA patients has been investigated in this study.

Design: Databases recorded prior to October 2020 were searched for relevant information. Major adverse cardiovascular events (MACE) were the primary endpoint, and myocardial infarction and cardiac death during follow-up were secondary endpoints.

Participants: Aspirin use against no aspirin (placebo or no treatment) among VSA patients in the absence of significant stenosis.

Results: Four propensity-matched cohorts, one retrospective analysis, and one prospective multicenter cohort, totally comprising 3661 patients (aspirin use group, *n* = 1,695; no aspirin use group, *n* = 1,966) were included in this meta-analysis. Aspirin use and the incidence of MACE with follow-up of 1–5 years were not found to be

significantly correlated (combined odds ratio [OR] = 0.90, 95% confidence interval [CI]: 0.55–1.68, p = 0.829, I^2 = 82.2%; subgroup analysis: OR = 1.09, 95% CI: 0.81–1.47, I^2 = 0%). Aspirin use was found to be linked with a lower of incidence of myocardial infarction (OR = 0.62, 95% CI: 0.09–4.36, p = 0.615, I^2 = 73.8%) and higher tendency of incidence of cardiac death during follow-up, but no significant difference (OR = 1.73, 95% CI: 0.61–4.94, p = 0.444, I^2 = 0%).

Conclusion: Aspirin use is not likely to reduce future cardiovascular events in VSA patients without significant stenosis.

Keywords: aspirin, vasospastic angina, MACE, cardiac death, myocardial infarction, longtime follow-up

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 VSA.

► Aspirin use was found to have no significant effect on reducing MACE, myocardial infarction, and cardiac death in VSA patients without significant stenosis, as per the outcomes of this meta-analysis. A tendency of higher risk of MACE and cardiac death was recognized, but not that of myocardial infarction.

► Owing to the increased MACE, routine use of aspirin use in VSA patients without significant stenosis should be avoided.

► The conclusions should be confirmed by further randomized controlled trials with larger sample size.

INTRODUCTION

Coronary spasm characterized by vasospastic angina (VSA) is one of the causes of myocardial infarction with non-obstructive coronary arteries (MINOCA) and ischemia and non-obstructive coronary arteries (INOCA) [1-2]. VSA patients who parallelly suffer from endothelial dysfunction or coronary atherosclerosis commonly use aspirin [3-4] as per the guidelines of the European Society of Cardiology (ESC) for the management of chronic stable angina and acute coronary syndromes [5-6]

Owing to the latest controversy and reduced key usage of aspirin in preventing cardiovascular events [7-8], the aspirin's efficiency in VSA patients without

significant stenosis has not yet been explained [9-14]. Therefore, this meta-analysis was planned 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 related research articles conducted before October 2020in various search engines such as PubMed, web of science, and Cochrane Central Register of Controlled Trials was carried out for gathering 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, antiplatelet therapy." Certain additional related publications, such as review articles and editorials, were also assessed. This study was registered with PROSPERO (CRD42020214891).

Patient and public involvement

Study participants who met the eligibility criteria as outlined above. Participants and other members of public were not involved in the recruitment, design, conduct, reporting or dissemination plans.

Study selection and data extraction

Following are the inclusion criteria: (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 no aspirin or placebo, and (iv) articles published in English. The exclusion criteria included significant stenosis (≥ 50%), intravenous aspirin, case report, and case series. Two investigators, namely, Lin and Chen, extracted the study data, which have been presented in Table 1

Data analysis and subgroup study

Major cardiovascular adverse event (MACE) was the primary endpoint, while myocardial infarction and cardiac death during follow-up were the secondary endpoints. MACE has been described as cardiac death, acute coronary syndrome, and hospitalization due to unstable angina, percutaneous coronary intervention, symptomatic arrhythmia in heart failure, appropriate implantable cardioverter-defibrillator (ICD), and shock. The Cochrane Collaboration tool was utilized to assess the risk of bias in the included studies. If $I^2 > 50\%$, the random effect model was used to assess heterogeneity, whereas if $I^2 < 50\%$, the fixed effect model was utilized to evaluate heterogeneity. In the case of high heterogeneity ($I^2 > 50\%$), subgroup analysis was carried out.

Statistical analysis

STATA software (version 14.0; StataCorp, College Station, TX, USA) was utilized to perform the meta-analysis. MACE, the primary endpoint, and myocardial infarction and cardiac death, the secondary endpoints, were evaluated as combined odds ratios with 95% confidence intervals (CIs). Heterogeneity between studies was derived with the help of I^2 statistic. Subgroups were studied to reduce the heterogeneity if $I^2 > 50\%$.

Publication bias was evaluated with the help of Begg's funnel plots. *P* values < 0.05 were considered to be statistically significant.

RESULTS

Characteristics of included studies

Various search engines mentioned hereinbefore were scanned to identify about 3,645 related studies, among which 1,303 articles were duplicated whereas 2,414 articles did not fulfill the inclusion criteria and were thus expelled from the study. Therefore, four propensity-matched cohorts, one retrospective analysis, and one prospective multicenter cohort (Figure 1), including a total of 3,661 patients (aspirin group, n = 1,695; no aspirin group, n = 1,966, Table 2) eventually formed part of the study. All studies except five studies provided the secondary endpoint, with follow-up durations ranging from 1 to 5 years (Table 1).

Primary and secondary endpoints

No significant correlation was recorded between aspirin use and MACE incidence with follow-up of 1–5 years (combined odds ratio [OR] = 0.90, 95% confidence interval [CI]: 0.55–1.68, p = 0.829, I^2 = 82.2% [Figure 2]; subgroup analysis: OR = 1.09, 95% CI: 0.81–1.47, I^2 = 0%, [Figure 3]).

Myocardial infarction was reported in four studies, and cardiac death was reported in five studies for the secondary endpoint. Moreover, aspirin use was tended to be linked to a lower incidence of myocardial infarction (OR = 0.62, 95% CI: 0.09–4.36, p = 0.615, I^2 = 73.8%) and a higher incidence of cardiac death during follow-up (OR

= 1.73, 95% CI: 0.61–4.94, $p = 0.444$, $I^2 = 0\%$), but statistical difference was lacking between the two groups (Figure 4).

Risk of bias assessment and publication bias

A high risk of bias was exhibited in selective outcome reporting and assessment by all included studies. Publication bias with the studies of Lee and Lim was presented by an asymmetry in the funnel plot (Figure 5). Between-studies heterogeneity on MACE related research was 82.2%. Therefore, the outcome of subgroup analyses of I^2 was 0%, indicating low publication bias (Figure 3). The between-studies heterogeneities on myocardial infarction and cardiac death related studies were found to be 73.8% and 0%, respectively, indicating the occurrence of high publication bias regarding studies on myocardial infarction (Figure 4).

DISCUSSION

Aspirin use was found to have no significant effect on reducing MACE, myocardial infarction, and cardiac death in VSA patients without significant stenosis, as per the outcomes of this meta-analysis. A tendency of higher risk of MACE and cardiac death was recognized, but not that of myocardial infarction.

Coronary artery spasm (CAS) appeared to play a significant role in the pathogenesis of ischemic heart disease, besides acute coronary syndromes (ACS) or chronic coronary syndromes (CCS) [15]. A common mechanism by which myocardial infarction (MI) or MINOCA manifests by 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 [16-17], yet being controversial in VSA patients. Earlier studies have evidenced aspirin use to aggravate CAS due to the lowered production of thromboxane A2 and increase MACE incidence in VSA patients [18-19].

MACE incidence exhibited by patients administered low-dose aspirin was reported to be significantly higher than that among patients not administered aspirin (hazard ratio [HR] = 1.54; CI: 1.04-2.28; p = 0.037) with a 52-months median follow-up period [11]. On the contrary, MI (HR = 0.13; CI: 0.03–0.61; p = 0.014) and chest pain recurrence (HR = 0.29; CI: 0.12–0.71; p = 0.006) were observed by Lee et al. to have been significantly reduced by aspirin use among VSA patients during follow-up [9]. Acute intimal tears and erosion identified by Optical coherence tomography (OCT) are susceptible to thrombosis leading to MI as per Lee's findings. Therefore, aspirin was thus 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 nonsignificant stenosis during a 49-months mean follow-up period (p = 0.541) Ishi et al. [12]. Moreover, the aspirin-treated group exhibited a similar MACE compared with the no-antiplatelet agent group (HR 0.96, CI: 0.59–1.55, p = 0.872) as reported by Cho. S.S et al. [13]. Antiplatelet therapy was recently shown by Mori et al. to exert no beneficial effects on MACE (5.7% vs. 3.6%, p = 0.20) among VSA patients during a 32-months median follow-up period [14].

A systematic analysis of the available studies investigating the effects of aspirin use among VSA patients was conducted. Aspirin use was not linked to a lower risk of MACE and cardiac death as per this meta-analysis. The subgroup analysis for MACE indicated that the study by Lee[9] and Lim [11] is quite heterogeneous. The origin of heterogeneity in these studies may be attributable to chest pain recurrence in the MACE, which gives an entirely different outcome due to the inclusion of other literature. Following may be the possible reasons for no beneficial effects of aspirin use: (i) aspirin use is known to damage the gastric mucosal barrier and increase the risk of erosions, ulcers, and bleeding by way of inhibiting cyclooxygenase-1 enzyme activity [20]. Several meta-analyses have indicated that aspirin's efficacy in primary prevention of cardiovascular disease needs to be weighed against any increase in major bleeding [21-23]; (ii) attributable to adverse effects of causing asthma and dyspnea, aspirin is likely to cause CAS and increase the occurrence of MACE or cardiogenic death [24-25]; (iii) the synthesis of prostacyclin, a well-known vasodilator released by endothelial cells is inhibited by aspirin [26] and CAS induced by aspirin, which could, in turn, cause recurrent angina leading to rehospitalization, myocardial infarction, and cardiac death.

In addition, aspirin use has been found in this analysis to have a possible protective effect on MI. The pharmacological mechanism easily explains the aspirin's beneficial effects on MI. But there is great heterogeneity, which may be attributable to the lack of related studies and a different definition of myocardial infarction by Mori in his study[14]. Aspirin use in CAS patients is both advantageous as well as

disadvantageous. Further investigations are necessary for the analysis of beneficial effects to determine whether to recommend.

Several potential limitations should also be considered in the case of this meta-analysis. First, MACE and MI have been defined differently in the included articles. Second, in one of the studies by Mori (2020), not aspirin but an antiplatelet drug comprising aspirin and P2Y12 inhibitors have been used as the therapeutic drug. Third, the sample size in the included studies is too small; only a few studies have conducted propensity matching analysis to balance baseline characteristics. The limitations inherent to multicenter observational studies performed in both retrospective and prospective manners could not be avoided in this analysis. Finally, the major bleeding outcome was excluded from this study, which is essential for understanding the advantages of antiplatelet therapy. Considering that this study evaluated the prognosis of VSA patients using low-dose aspirin is the first of its kind, it has its merits.

CONCLUSIONS

Aspirin use may not lessen cardiovascular events among VSA patients without significant stenosis. Owing to its potential adverse effects, regular use of aspirin in VSA patients without significant stenosis is best avoided.

Acknowledgments

None

Contributors

YW, YC and YJ conceived, designed and led the study. YW, YJ, SH, XL and QL investigated, conducted the study and collected data. YW, YJ and YC wrote, revised and edited the manuscript. All authors supervised the study and approved of the final version submitted.

Funding

This study was supported by a grant from the Shenzhen Key Medical Discipline Construction Fund (no. SZXK059) and Shenzhen Foundation (SZLY2017025 and JCYJ20170307100512856).

Conflict of interest

No conflict of interest

Patient consent for publication

Not required

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data are available upon reasonable request. Data are available upon request.

ORCID iD

Yaowang Lin: https://orcid.org/0000-0002-4075-4259

References

1. Montone RA, Niccoli G, Fracassi F, et al. Patients with acute myocardial infarction and non-obstructive coronary arteries: safety and prognostic relevance of invasive coronary provocative tests. Eur Heart J. 2018; 39(2): 91-8.

2. Kunadian V, Chieffo A, Camici PG, et al. An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. Eur Heart J. 2020; 41(37): 3504-20.

3. Lee BK, Lim HS, Fearon WF, et al. Invasive evaluation of patients with angina in the absence of obstructive coronary artery disease. Circulation. 2015; 131(12): 1054-60.

4. Khuddus MA, Pepine CJ, Handberg EM, et al. An intravascular ultrasound analysis in women experiencing chest pain in the absence of obstructive coronary artery disease: a substudy from the National Heart, Lung and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). J Interv Cardiol. 2010; 23(6): 511-9.

5. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020; 41(3): 407-77.

6. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without per sistent ST-segment elevation. Eur Heart J. 2020.

7. Guirguis-Blake JM, Evans CV, Senger CA, O'Connor EA, Whitlock EP. Aspirin for the Primary Prevention of Cardiovascular Events: A Systematic Evidence Review for the U.S. Preventive Services Task Force. Ann Intern Med. 2016; 164(12): 804-13.

8. Zheng SL, Roddick AJ. Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events: A S ystematic Review and Meta-analysis. Jama. 2019; 321(3): 277-87.

9. Lee Y, Park HC, Shin J. Clinical efficacy of aspirin with identification of intimal morphology by optical coherence tomography in preventing event recurrence in patients with vasospasm-induced acute coronary syndrome. Int J Cardiovasc Imaging. 2018; 34(11): 1697-706.

10. Kim MC, Ahn Y, Park KH, et al. Clinical outcomes of low-dose aspirin administration in patients with variant angina pectoris. Int J Cardiol. 2013; 167(5): 2333-4.

11. Lim AY, Park TK, Cho SW, et al. Clinical implications of low-dose aspirin on vasospastic angina patients without significant coronary artery stenosis; a propensity score-matched analysis. Int J Cardiol. 2016; 221: 161-6.

12. Ishii M, Kaikita K, Sato K, et al. Impact of aspirin on the prognosis in patients

with coronary spasm without significant atherosclerotic stenosis. Int J Cardiol. 2016; 220: 328-32.

13. Cho SS, Jo SH, Han SH, et al. Clopidogrel plus Aspirin Use is Associated with Worse Long-Term Outcomes, but Aspirin Use Alone is Safe in Patients with Vasospastic Angina: Results from the VA-Korea Registry, A Prospective Multi-Center Cohort. Sci Rep. 2019; 9(1): 17783.

14. Mori H, Takahashi J, Sato K, et al. The impact of antiplatelet therapy on patients with vasospastic angina: A multicenter registry study of the Japanese Coronary Spasm Association. Int J Cardiol Heart Vasc. 2020; 29: 100561.

15. Yasue H, Mizuno Y, Harada E. Coronary artery spasm - Clinical features, pathogenesis and treatment. Proc Jpn Acad Ser B Phys Biol Sci. 2019; 95(2): 53-66.

16. Capodanno D, Alfonso F, Levine GN, Valgimigli M, Angiolillo DJ. ACC/AHA Versus ESC Guidelines on Dual Antiplatelet Therapy: JACC Guideline Comparison. J Am Coll Cardiol. 2018; 72(23 Pt A): 2915-31.

17. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018; 39(3): 213-60.

18. Picard F, Sayah N, Spagnoli V, Adjedj J, Varenne O. Vasospastic angina: A

literature review of current evidence. Arch Cardiovasc Dis. 2019; 112(1): 44-55.

19. Miwa K, Kambara H, Kawai C. Effect of aspirin in large doses on attacks of variant angina. Am Heart J. 1983; 105(2): 351-5.

20. Iwamoto J, Saito Y, Honda A, Matsuzaki Y. Clinical features of gastroduodenal injury associated with long-term low-dose aspirin therapy. World J Gastroenterol. 2013; 19(11): 1673-82.

21. Antithrombotic Trialists C, Baigent C, Blackwell L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009; 373(9678): 1849-60.

22. Xie W, Luo Y, Liang X, Lin Z, Wang Z, Liu M. The Efficacy And Safety Of Aspirin As The Primary Prevention Of Cardiovascular Disease: An Updated Meta-Analysis. Ther Clin Risk Manag. 2019; 15: 1129-40.

23. Whitlock EP, Burda BU, Williams SB, Guirguis-Blake JM, Evans CV. Bleeding Risks With Aspirin Use for Primary Prevention in Adults: A Systematic Review for the U.S. Pr eventive Services Task Force. Ann Intern Med. 2016; 164(12): 826-35.

24. Hangouche AJE, Lamliki O, Oukerraj L, et al. Kounis syndrome induced by oral intake of aspirin: case report and literature review. Pan Afr Med J. 2018; 30: 301.

25. Shah NH, Schneider TR, DeFaria Yeh D, Cahill KN, Laidlaw TM. Eosinophilia-Associated Coronary Artery Vasospasm in Patients with Aspirin-Exacerbated Respiratory Disease. J Allergy Clin Immunol Pract. 2016; 4(6):

1215-9.

26. Bates ER, Lau WC. Controversies in antiplatelet therapy for patients with cardiovascular disease. Circulation. 2005; 111(17): e267-71.

Figure 1. Flow diagram fo identification process

Figure 2. Aspirin use is not associated with low incidence of MACE in patients with VSA.

Figure 3. Subgroub analysis of MACE of aspirin use in patients with VSA.

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

Figure 5. Assess of bias risk of the studies.

Table 1. 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
Min Chul Kim	2013	Retrospective analysis	Vasospastic angina (stenosis≤50%)	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
Masanobu Ishii	2016	Retrospective analysis, propensity score matched analysis	Vasospastic angina (stenosis≤50%)	224	112	112	81–100	Cardiac death, nonfatal acute myocardial infarction, and unstable angina	4 (3.6) vs. 6 (5.4)	0 vs. 0	2 (1.8) vs. 0 (0)	/	1-year
A.Young Lim	2016	Retrospective analysis, propensity score matched analysis	Coronary artery spasm (stenosis≤50%)	721	434	287	100	Cardiac death, acute myocardial infarction, revascularization, or rehospitalization 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
Yonggu Lee	2018	Retrospective study, propensity score-matched	Coronary artery spasm	154	77	77	100	Chest pain recurrence, myocardial infarction, cardiac	9 (11.7) vs. 33	2 (3) vs.13 (17)	0 vs. 0	0 vs. 0	4-year

		analysis	(stenosis≤50%)					death	(42.9)				
Seong-Sik cho	2019	Prospective multicenter 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
Hiroyoshi Mori	2020	Retrospective study, propensity score-matched analysis	Coronary artery spasm (stenosis≤50%)	670	335	335	Aspirin 100 and P2Y12 inhibitors.	cardiac death, nonfatal myocardial infarction, hospitalization due to unstable angina pectoris, heart failure, 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

Table 2. Clinical characteristics of patients in icluded studies.

Characteristics aspirin vs. no	Min Chul Kim 2013	Masanobu Ishii 2016	A. Young Lim 2016	Yonggu Lee 2018	Seong-Sik cho 2019	Hiroyoshi Mori 2020
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
Diabete 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
Dyslipidemia, n (%)	/	62 (55.4) vs. 60 (53.6) , p = 0.788	91 (21.0) vs. 62 (21.6), p = 0.84	/	98 (15.4) vs.160(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

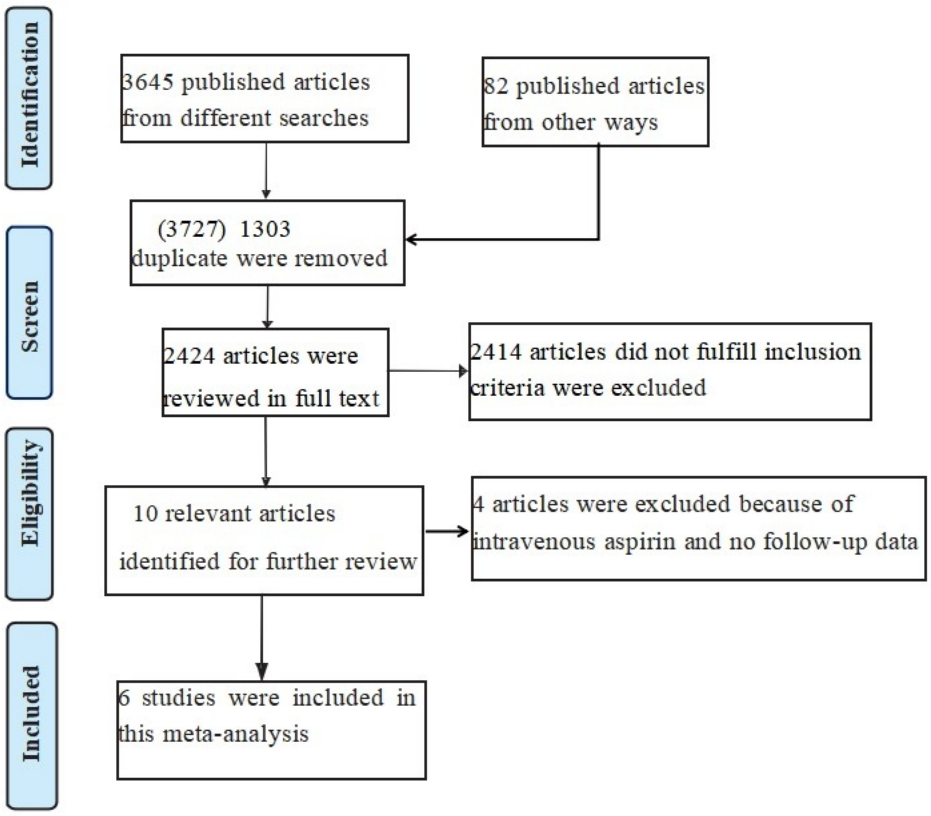

Figure 1. Flow diagram fo identification process

132x119mm (144 x 144 DPI)

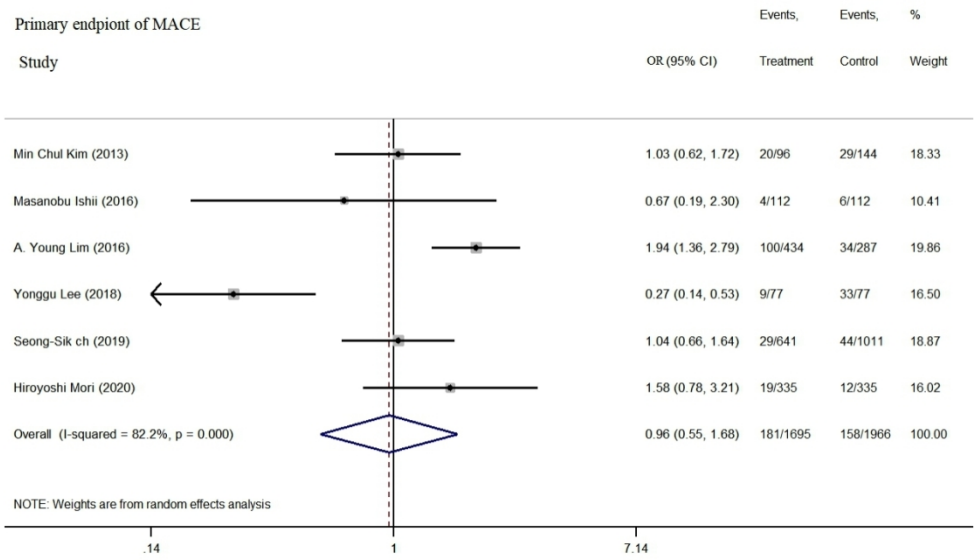

Figure 2. Aspirin use is not associated with low incidence of MACE in patients with VSA.

231x135mm (144 x 144 DPI)

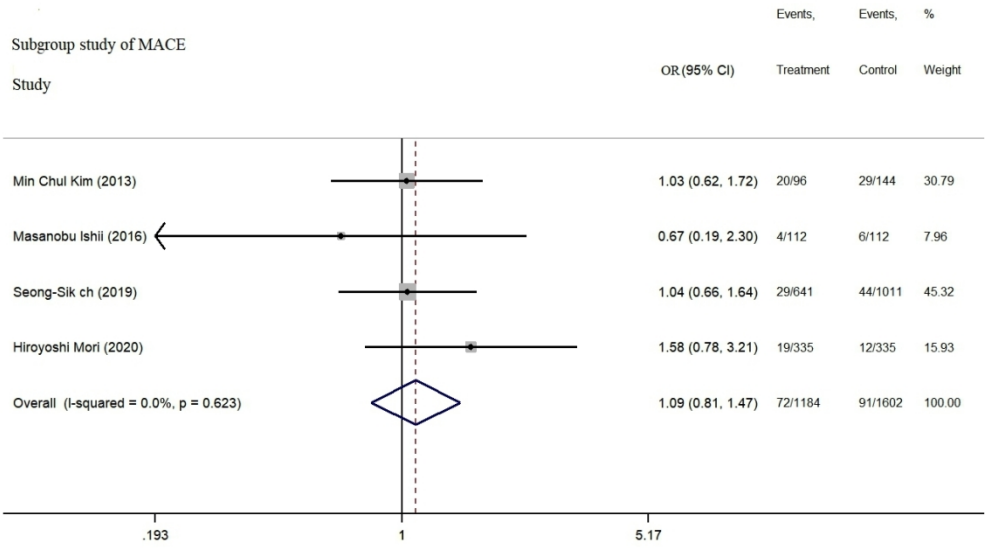

Figure 3. Subgroub analysis of MACE of aspirin use in patients with VSA.

233x136mm (144 x 144 DPI)

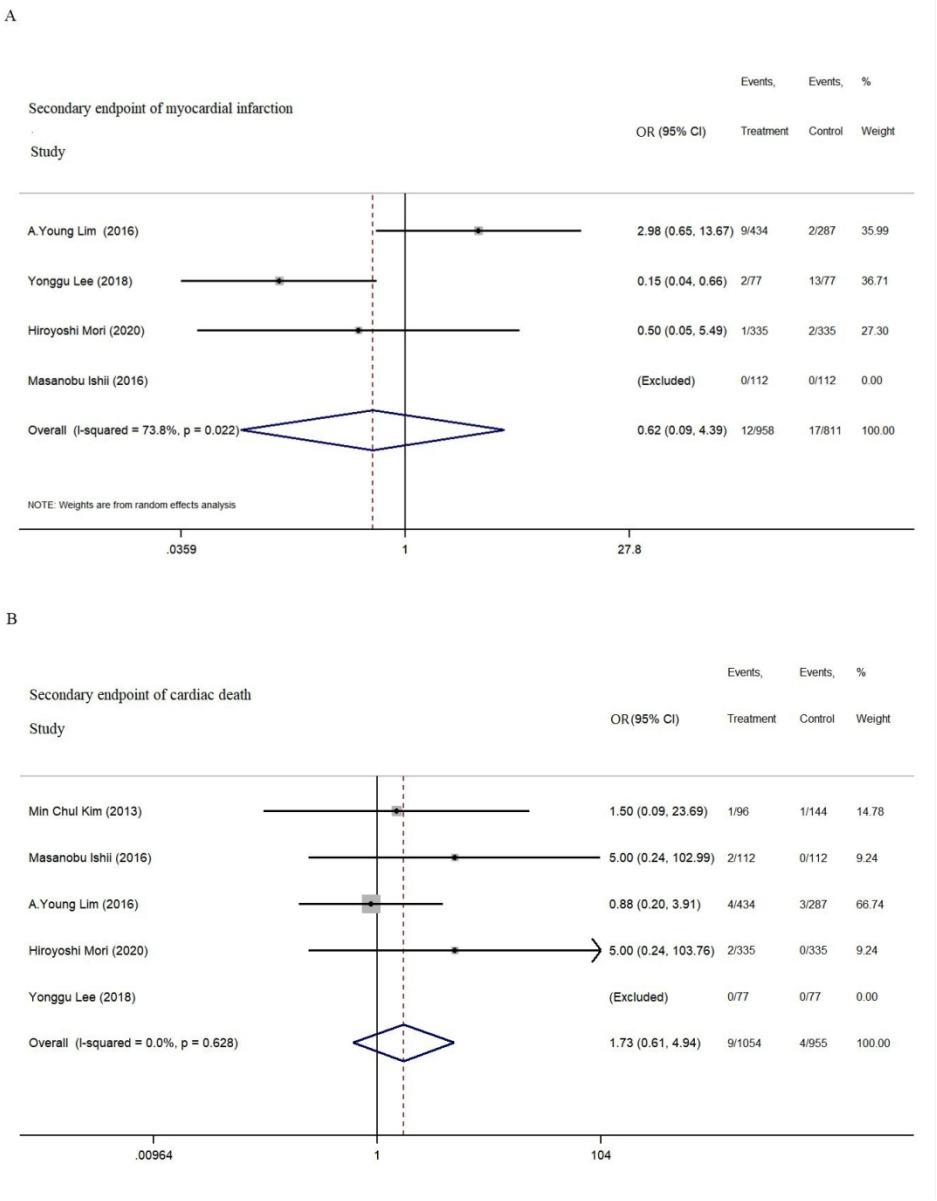

Figure 4. Secondary endpiont including myocardial infarction, cardiac death and all cause death during 1 to 5 years of follow-up.

240x305mm (144 x 144 DPI)

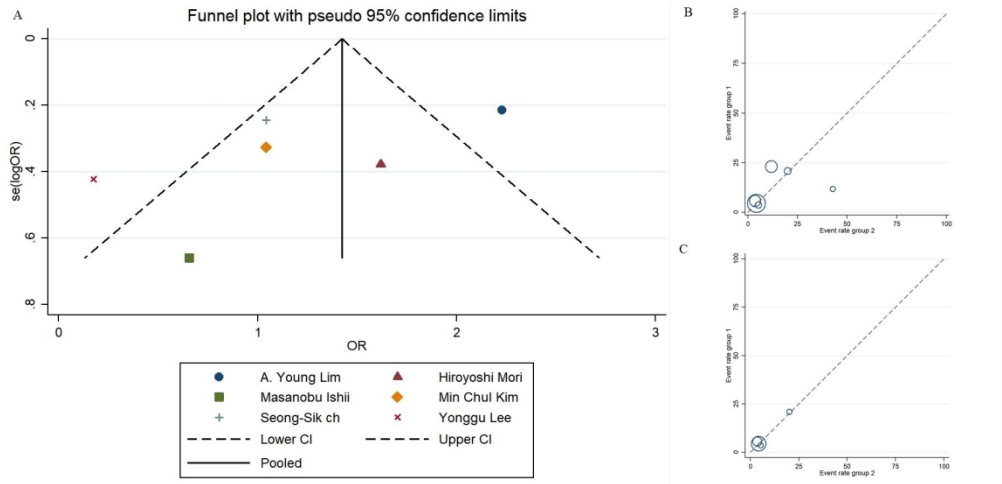

Figure 5. Assess of bias risk of the studies.

477x231mm (96 x 96 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 4-5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 4-5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 4-5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 4-5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 4-5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 4-5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 6-7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 6-7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 6-7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 6-7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 6-7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 6-7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 6-7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 7-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

BMJ Open

Impact of Aspirin Use on Clinical Outcomes in Patients With Vasospastic Angina: A Systematic Review and Meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-048719.R1
Article Type:	Original research
Date Submitted by the Author:	01-Jun-2021
Complete List of Authors:	lin, yaowang; Shenzhen People's Hospital, Department of Cardiology chen, qiuling; Shenzhen People's Hospital, Department of Pharmacy yuan, jie; Shenzhen People's Hospital, Department of Cardiology dong, shaohong; Shenzhen People's Hospital, Department of Cardiology Qin, Haiyan; Shenzhen People's Hospital, Department of Emergency chen, yang; Guangdong Medical University, School of Pharmacy
Primary Subject Heading:	Medical management
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Coronary heart disease < CARDIOLOGY, Myocardial infarction < CARDIOLOGY, Vascular medicine < INTERNAL MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Impact of Aspirin Use on Clinical Outcomes in Patients with Vasospastic Angina: A Systematic Review and Meta-analysis

Yaowang Lin[1,4], MD; Qiuling Chen[3,4], MD; Jie Yuan[1,4], MD; Shaohong Dong[1,4], MD; Haiyan Qin[2,4], MD; Yang Chen[5], MD

Author's Affiliation:

[1]Department of Cardiology; [2]Department of Health Management; [3]Department of Pharmacy; [4]Shenzhen People's Hospital, Second Clinical Medical College of Jinan University, first affiliated Hospital of South University of Science and Technology, Shenzhen, Guangdong. No. 1017, Dongmen Northern Road, 518020, Shenzhen, Guangdong, PR China. [5]School of Pharmacy, Guangdong Medical University, Dongguan 523808, Guangdong, China

Correspondence should be addressed to Haiyan Qin and Yang Chen

Haiyan Qin, MD, e-mail: lgqinhaiyan@yeah.net and Yang Chen, MD, e-mail: ychan227@163.com.

ABSTRACT

Objectives: The use of aspirin to prevent cardiovascular disease in vasospastic angina (VSA) patients without significant stenosis is yet to be investigated. The efficacy of aspirin use among VSA patients has been investigated in this study.

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 against no aspirin (placebo or no treatment) among VSA patients in the absence of significant stenosis.

Data extraction and synthesis: Two investigators extracted the study data. Odds ratios (ORs) and the 95% confidence intervals (CI) were calculated and graphed as forest plots. The Newcastle-Ottawa Quality Assessment Scale (NOS) tool and Begg's funnel plot were used to assess risk of bias.

Results: Four propensity-matched cohorts, one retrospective analysis, and one prospective multicenter cohort, totally comprising 3661 patients (aspirin use group, n = 1,695; no aspirin use group, n = 1,966) were included in this meta-analysis. Aspirin use and the incidence of MACE with follow-up of 1–5 years were not found to be significantly correlated (combined odds ratio [OR] = 0.90, 95% confidence interval [CI]: 0.55–1.68, p = 0.829, I^2 = 82.2%; subgroup analysis: OR = 1.09, 95% CI: 0.81–1.47, I^2 = 0%). Aspirin use was tended to be linked with lower incidence of myocardial infarction (OR = 0.62, 95% CI: 0.09–4.36, p = 0.615, I^2 = 73.8%) and

higher incidence of cardiac death (OR = 1.73, 95% CI: 0.61–4.94, p = 0.444, I^2 = 0%) during follow-up, but with no significant difference between-group.

Conclusion: Aspirin use may be not likely to reduce future cardiovascular events in VSA patients without significant stenosis.

Trial registration number: PROSPERO (CRD42020214891)

Keywords: aspirin, vasospastic angina, MACE, cardiac death, myocardial infarction, longtime follow-up

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 VSA.

► The therapeutic drug in one of the studies by Mori (2020) is an antiplatelet drug comprising aspirin and P2Y12 inhibitors.

► The limitations inherent to multicenter observational studies performed in both retrospective and prospective manners could not be avoided in this analysis.

► The conclusions should be confirmed by further randomized controlled trials with larger sample size.

INTRODUCTION

Coronary spasm characterized by vasospastic angina (VSA) is one of the causes of ischemia with non-obstructive coronary artery (INOCA) [1, 2]. VSA patients who parallelly suffer from endothelial dysfunction or coronary atherosclerosis commonly use aspirin [3, 4], as per the guidelines of the European Society of Cardiology (ESC) for the management of chronic stable angina and acute coronary syndromes [5, 6].

The ASCEND study has showed the use of low-dose aspirin lead to a lower risk of serious vascular events (8.5% vs. 9.6%; p=0.01) than placebo among persons with diabetes in primary treatment, but the absolute benefits are largely counterbalanced by the bleeding hazard (4.1% vs. 3.2%; p=0.003) [7]. Additionally, the ARRIVE study has suggested that aspirin use may result in a higher incidence of gastrointestinal bleeding events (0.97% vs. 0.46%; p=0.0007) or overall incidence of treatment-related adverse events (16.75% vs. 13.54%; p<0.0001) than that with control [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 explained [11-16]. Therefore, this meta-analysis was planned 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 related research articles conducted before October 2020 in search engines such as PubMed, web of science, and Cochrane Central Register of

Controlled Trials was carried out for gathering 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, antiplatelet therapy". Certain additional related publications, such as review articles and editorials, were also assessed. This study was registered with PROSPERO (CRD42020214891).

Patient and public involvement

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

Study selection and data extraction

Following are the inclusion criteria: (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 no aspirin or placebo, and (iv) articles published in English. The exclusion criteria included significant stenosis (≥ 50%), intravenous aspirin, case report, and case series. The study data was independently extracted by two investigators, namely, Lin and Chen, using pre-defined extraction forms and conflict was resolved by a third reviewer.

Data analysis and risk of bias assessment

Major cardiovascular adverse event (MACE) was the primary endpoint, while myocardial infarction and cardiac death during follow-up were the secondary endpoints. MACE has been described as cardiac death, acute coronary syndrome, and

hospitalization due to unstable angina, percutaneous coronary intervention, symptomatic arrhythmia, appropriate implantable cardioverter defibrillator (ICD), and shock. The Newcastle-Ottawa Quality Assessment Scale (NOS) tool was utilized to assess the risk of bias and Begg's funnel plot was used to evaluated publication bias.

Statistical analysis

STATA software (version 14.0; StataCorp, College Station, TX, USA) was utilized to perform the meta-analysis. MACE, the primary endpoint, and myocardial infarction and cardiac death, the secondary endpoints, were evaluated as combined odds ratios with 95% confidence intervals (CIs). Heterogeneity between studies was derived with the help of I^2 statistic. If $I^2 > 50\%$, the random effect model was used to assess heterogeneity, whereas if $I^2 < 50\%$, the fixed effect model was utilized to evaluate heterogeneity. Subgroups were studied to reduce the heterogeneity if $I^2 > 50\%$. *P* values < 0.05 were considered to be statistically significant.

RESULTS

Characteristics of included studies

Search engines mentioned herein before were scanned to identify about 3,645 related studies, among which 1,303 articles were duplicated, whereas 2,414 articles did not fulfill the inclusion criteria and were thus expelled from the study. Therefore, four propensity-matched cohorts, one retrospective analysis, and one prospective multicenter cohort (Figure 1), including a total of 3,661 patients (aspirin group, n = 1,695; no aspirin group, n = 1,966, Table 1) eventually formed part of the study. 4 studies underwent coronary provocation test, except for 1 study (Seong-Sik Cho, 2019)

receiving ECG provocation test. All studies provided the 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 with follow-up of 1–5 years (combined odds ratio [OR] = 0.90, 95% confidence interval [CI]: 0.55–1.68, p = 0.829, I^2 = 82.2% [Figure 2]; subgroup analysis: OR = 1.09, 95% CI: 0.81–1.47, I^2 = 0%, [Figure 3]).

Myocardial infarction was reported in four studies, and cardiac death was reported in five studies for the secondary endpoint. Moreover, aspirin use was tended to be linked to a lower incidence of myocardial infarction (OR = 0.62, 95% CI: 0.09–4.36, p = 0.615, I^2 = 73.8%) and a higher incidence of cardiac death (OR = 1.73, 95% CI: 0.61–4.94, p = 0.444, I^2 = 0%) during follow-up, but statistical difference was lacking between the two groups (Figure 4).

Risk of bias assessment and heterogeneity analysis

The scores of NOS for study quality assessment of included studies ranged from 7 to 9 scores (Table 3). Publication bias with the studies of Lee and Lim was presented by an asymmetry in the funnel plot (Figure 5). Between-study heterogeneity in MACE-related research was 82.2%. Therefore, the outcome of subgroup analyses of I^2 was 0%, indicating low publication bias (Figure 3). The between-study heterogeneities in myocardial infarction and cardiac death-related studies were found to be 73.8% and 0%, respectively, indicating the occurrence of high publication bias regarding studies on myocardial infarction (Figure 4).

DISCUSSION

Aspirin use was found to have no significant effect on reducing MACE, myocardial infarction, and cardiac death in VSA patients without significant stenosis, as per the outcomes of this meta-analysis. A tendency of higher risk of MACE and cardiac death was recognized, but not that of myocardial infarction.

Coronary artery spasm (CAS) appears to play a significant role in the pathogenesis of ischemic heart disease including acute coronary syndrome (ACS) and chronic coronary syndrome (CCS) [17]. A common mechanism by which myocardial infarction (MI) or MINOCA manifests by 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], yet being controversial in VSA patients. Earlier studies have evidenced aspirin use to aggravate CAS due to the lowered production of thromboxane A2 and increased MACE incidence in VSA patients [20, 21].

MACE incidence exhibited by patients administered low-dose aspirin was significantly higher than that among patients not administered aspirin (hazard ratio [HR] = 1.54; CI: 1.04-2.28; p = 0.037) during a 52-months median follow-up period [13]. On the contrary, MI (HR = 0.13; CI: 0.03–0.61; p = 0.014) and chest pain recurrence (HR = 0.29; CI: 0.12–0.71; p = 0.006) were observed by Lee et al. to have

been significantly reduced by aspirin use among VSA patients during follow-up [11]. Acute intimal tears and erosion identified by optical coherence tomography (OCT) are susceptible to thrombosis leading to MI as per Lee's findings. Therefore, aspirin was thus 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 nonsignificant stenosis during a 49-months mean follow-up period (p = 0.541) Ishi et al. [14]. Moreover, the aspirin-treated group exhibited a similar MACE compared with the no-antiplatelet agent group (HR 0.96, CI: 0.59–1.55, p = 0.872) as reported by Cho. S.S et al. [15]. Antiplatelet therapy was recently shown by Mori et al. to exert no beneficial effects on MACE (5.7% vs. 3.6%, p = 0.20) among VSA patients during a 32-months median follow-up period [16].

A systematic analysis of the available studies investigating the effects of aspirin use among VSA patients was conducted. Aspirin use may not be linked to a lower risk of MACE and cardiac death as per this meta-analysis. The subgroup analysis for MACE indicated that the study by Lee [11] and Lim [13] is quite heterogeneous. The origin of heterogeneity in these studies may be attributable to chest pain recurrence in the MACE, which gives an entirely different outcome due to the inclusion of other literature. The following may be the possible reasons for the lack of beneficial effects of aspirin use: (i) aspirin use is known to damage the gastric mucosal barrier and increase the risk of erosions, ulcers, and bleeding by way of inhibiting cyclooxygenase-1 enzyme activity [22]. Several meta-analyses have indicated that

aspirin's efficacy in primary prevention of cardiovascular disease needs to be weighed against any increase in major bleeding [23-25]; (ii) attributable to adverse effects of causing asthma and dyspnea, aspirin is likely to cause CAS and increase the occurrence of MACE or cardiogenic death [26, 27]; (iii) the synthesis of prostacyclin, a well-known vasodilator released by endothelial cells is inhibited by aspirin [28] and CAS induced by aspirin, which could, in turn, cause recurrent angina leading to rehospitalization, myocardial infarction, and cardiac death.

In addition, aspirin use has been found in this analysis to have a possible protective effect on MI. The pharmacological mechanism easily explains the aspirin's beneficial effects on MI. However there is great heterogeneity, which may be attributed to the lack of related studies and a different definition of MI by Mori in his study [16]. Aspirin use in CAS patients is both advantageous as well as disadvantageous. Further investigations are necessary for the analysis of beneficial effects to determine whether to recommend.

Several potential limitations should also be considered in the case of this meta-analysis. First, MACE and MI have been defined differently in the included articles. Ascribe to lack of original data, no standard definition of MACE is accessible in this meta-analysis. Second, in one of the studies by Mori (2020), not aspirin but an antiplatelet drug comprising aspirin and P2Y12 inhibitors have been used as the therapeutic drug. Third, the sample size in the included studies is too small; only a few studies have conducted propensity matching analysis to balance baseline characteristics. The limitations inherent to multicenter observational studies

performed in both retrospective and prospective manners could not be avoided in this analysis. Fourth, patients with 40% stenosis are deemed to be VSA patients without coronary stenosis but might be benefit from aspirin. A subgroup analysis should be performed next study. Finally, the major bleeding outcome was excluded from this study, which is essential for understanding the advantages of antiplatelet therapy. Considering that this study evaluated the prognosis of VSA patients using low-dose aspirin as the first of its kind, it has its merits.

CONCLUSIONS

Aspirin use may not lessen cardiovascular events among 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.

Acknowledgments

None

Contributors

YWL, YC and HYQ conceived, designed and led the study. YWL, QLC, YJ and SHD investigated, conducted the study and collected data. YWL, HYQ and YC wrote, revised and edited the manuscript. All authors supervised the study and approved of the final version submitted.

Funding

This study was supported by a grant from the Shenzhen Key Medical Discipline Construction Fund (No. SZXK003 and No. SZXK059) and Sanming Project of Medicine in Shenzhen (No. SZSM201412012).

Conflict of interest

No conflict of interest

Patient consent for publication

Not required

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.

ORCID iD

Yaowang Lin: https://orcid.org/0000-0002-4075-4259

Ethics Statement

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

REFERENCES

1. Montone RA, Niccoli G, Fracassi F, *et al*. Patients with acute myocardial infarction and non-obstructive coronary arteries: safety and prognostic relevance of invasive coronary provocative tests. *Eur Heart J* 2018, 39(2):91-98.
2. Kunadian V, Chieffo A, Camici PG, *et al*. An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaborati on with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. *Eur Heart J* 2020, 41(37):3504-3520.
3. Lee BK, Lim HS, Fearon WF, *et al*. Invasive evaluation of patients with angina in the absence of obstructive coronary artery disease. *Circulation* 2015, 131(12):1054-1060.
4. Khuddus MA, Pepine CJ, Handberg EM, *et al*. An intravascular ultrasound analysis in women experiencing chest pain in the absence of obstructive coronary artery disease: a substudy from the National Heart, Lung and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *J Interv Cardiol* 2010, 23(6):511-519.
5. Knuuti J, Wijns W, Saraste A, *et al*. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020, 41(3):407-477.

6. Collet JP, Thiele H, Barbato E, *et al*. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2020.

7. Group ASC, Bowman L, Mafham M, *et al*. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. *N Engl J Med* 2018, 379(16):1529-1539.

8. Gaziano JM, Brotons C, Coppolecchia R, *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):1036-1046.

9. Guirguis-Blake JM, Evans CV, Senger CA, *et al*. Aspirin for the Primary Prevention of Cardiovascular Events: A Systematic Evidence Review for the U.S . Preventive Services Task Force. *Ann Intern Med* 2016, 164(12):804-813.

10. Zheng SL, Roddick AJ. Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events: A S ystematic Review and Meta-analysis. *Jama* 2019, 321(3):277-287.

11. Lee Y, Park HC, Shin J. Clinical efficacy of aspirin with identification of intimal morphology by optical coherence tomography in preventing event recurrence in patients with vasospasm-induced acute coronary syndrome. *Int J Cardiovasc Imaging* 2018, 34(11):1697-1706.

12. Kim MC, Ahn Y, Park KH, *et al*. Clinical outcomes of low-dose aspirin administration in patients with variant angina pectoris. *Int J Cardiol* 2013,

167(5):2333-2334.

13. Lim AY, Park TK, Cho SW, *et al*. Clinical implications of low-dose aspirin on vasospastic angina patients without significant coronary artery stenosis; a propensity score-matched analysis. *Int J Cardiol* 2016, 221:161-166.

14. Ishii M, Kaikita K, Sato K, *et al*. Impact of aspirin on the prognosis in patients with coronary spasm without significant atherosclerotic stenosis. *Int J Cardiol* 2016, 220:328-332.

15. Cho SS, Jo SH, Han SH, *et al*. Clopidogrel plus Aspirin Use is Associated with Worse Long-Term Outcomes, but Aspirin Use Alone is Safe in Patients with Vasospastic Angina: Results from the VA-Korea Registry, A Prospective Multi-Center Cohort. *Sci Rep* 2019, 9(1):17783.

16. Mori H, Takahashi J, Sato K, *et al*. The impact of antiplatelet therapy on patients with vasospastic angina: A multicenter registry study of the Japanese Coronary Spasm Association. *Int J Cardiol Heart Vasc* 2020, 29:100561.

17. Yasue H, Mizuno Y, Harada E. Coronary artery spasm - Clinical features, pathogenesis and treatment. *Proc Jpn Acad Ser B Phys Biol Sci* 2019, 95(2):53-66.

18. Capodanno D, Alfonso F, Levine GN, *et al*. ACC/AHA Versus ESC Guidelines on Dual Antiplatelet Therapy: JACC Guideline Comparison. *J Am Coll Cardiol* 2018, 72(23 Pt A):2915-2931.

19. Valgimigli M, Bueno H, Byrne RA, *et al*. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with

EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the Eur opean Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018, 39(3):213-260.

20. Picard F, Sayah N, Spagnoli V, *et al*. Vasospastic angina: A literature review of current evidence. *Arch Cardiovasc Dis* 2019, 112(1):44-55.

21. Miwa K, Kambara H, Kawai C. Effect of aspirin in large doses on attacks of variant angina. *Am Heart J* 1983, 105(2):351-355.

22. Iwamoto J, Saito Y, Honda A, *et al*. Clinical features of gastroduodenal injury associated with long-term low-dose aspirin therapy. *World J Gastroenterol* 2013, 19(11):1673-1682.

23. Antithrombotic Trialists C, Baigent C, Blackwell L, *et al*. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009, 373(9678):1849-1860.

24. Xie W, Luo Y, Liang X, *et al*. The Efficacy And Safety Of Aspirin As The Primary Prevention Of Cardiovascular Disease: An Updated Me ta-Analysis. *Ther Clin Risk Manag* 2019, 15:1129-1140.

25. Whitlock EP, Burda BU, Williams SB, *et al*. Bleeding Risks With Aspirin Use for Primary Prevention in Adults: A Systematic Review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2016, 164(12):826-835.

26. Hangouche AJE, Lamliki O, Oukerraj L, *et al*. Kounis syndrome induced by

oral intake of aspirin: case report and literature review. *Pan Afr Med J* 2018, 30:301.

27. Shah NH, Schneider TR, DeFaria Yeh D, *et al*. Eosinophilia-Associated Coronary Artery Vasospasm in Patients with Aspirin-Exacerbated Respiratory Di sease. *J Allergy Clin Immunol Pract* 2016, 4(6):1215-1219.

28. Bates ER, Lau WC. Controversies in antiplatelet therapy for patients with cardiovascular disease. *Circulation* 2005, 111(17):e267-271.

Table 1. Clinical characteristics of patients in included studies.

Characteristics Aspirin vs. no	Min Chul Kim 2013	Masanobu Ishii 2016	A. Young Lim 2016	Yonggu Lee 2018	Seong-Sik Cho 2019	Hiroyoshi Mori 2020
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
Dyslipidemia, n (%)	/	62 (55.4) vs. 60 (53.6) , p = 0.788	91 (21.0) vs. 62 (21.6), p = 0.84	/	98 (15.4) vs.160(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

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
Min Chul Kim	2013	Retrospective analysis	Vasospastic angina (stenosis≤50%)	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
Masanobu Ishii	2016	Retrospective analysis, propensity score matched analysis	Vasospastic angina (stenosis≤50%)	224	112	112	81–100	Cardiac death, nonfatal acute myocardial infarction, and unstable angina	4 (3.6) vs. 6 (5.4)	0 vs. 0	2 (1.8) vs. 0 (0)	/	1-year
A.Young Lim	2016	Retrospective analysis, propensity score matched analysis	Coronary artery spasm (stenosis≤50%)	721	434	287	100	Cardiac death, acute myocardial infarction, revascularization, or rehospitalization 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
Yonggu Lee	2018	Retrospective study, propensity score-matched analysis	Coronary artery spasm (stenosis≤50%)	154	77	77	100	Chest pain recurrence, myocardial infarction, cardiac death	9 (11.7) vs. 33 (42.9)	2 (3) vs.13 (17)	0 vs. 0	0 vs. 0	4-year
Seong-Sik Cho	2019	Prospective multicenter 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

Hiroyoshi Mori	2020	Retrospective study, propensity score-matched analysis	Coronary artery spasm (stenosis≤50%)	670	335	335	Aspirin 100 and P2Y12 inhibitors.	cardiac death, nonfatal myocardial infarction, hospitalization 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

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

	Selection				Comparability	Outcome			
Study	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
Min Chul Kim	★	★	★	★	☆★	★	★	★	8
Masanobu Ishii	★	☆	★	★	★★	★	★	★	8
A.Young Lim	★	★	★	★	☆★	★	★	★	8
Yonggu Lee	★	★	★	★	★★	★	★	★	9
Seong-Sik Cho	★	★	★	★	☆★	★	★	★	8
Hiroyoshi Mori	☆	★	★	★	☆★	★	★	★	7

Figure legend.

Figure 1. Flow diagram for identification processes.

Figure 2. Aspirin use is not associated with a low incidence of MACE in patients with VSA.

Figure 3. Subgroup analysis of MACE of aspirin use in patients with VSA.

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

Figure 5. Assessment of bias risk of the studies.

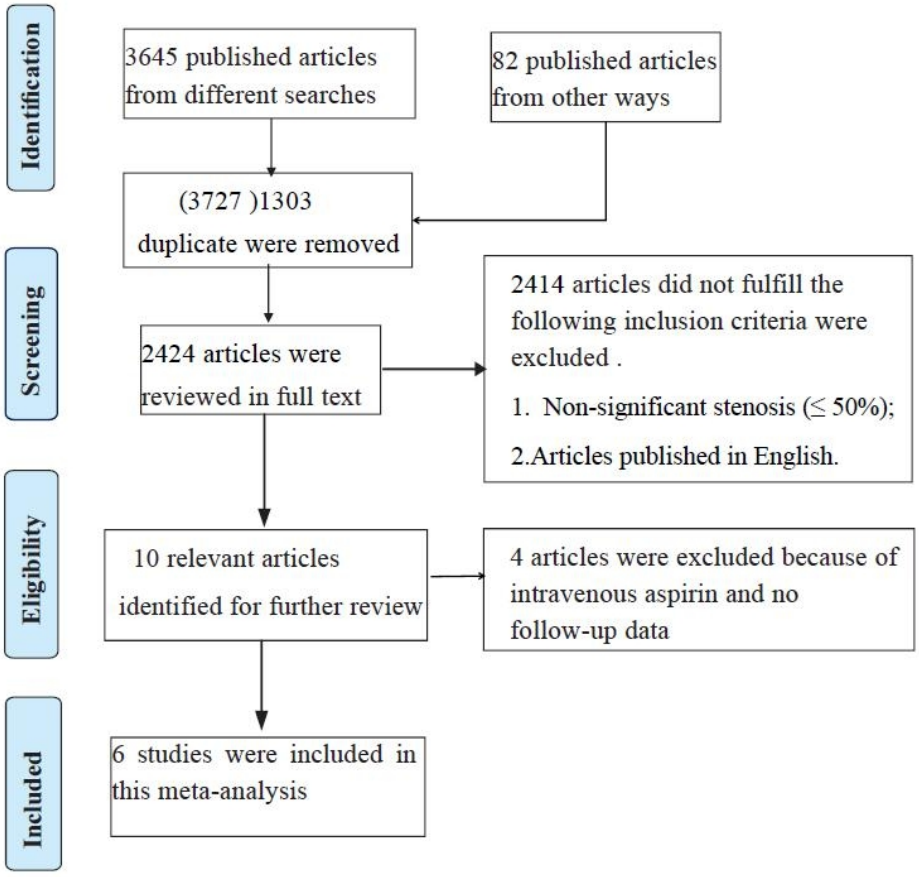

Figure 1. Flow diagram for identification processes.

Figure 1. Flow diagram for identification processes.

139x148mm (144 x 144 DPI)

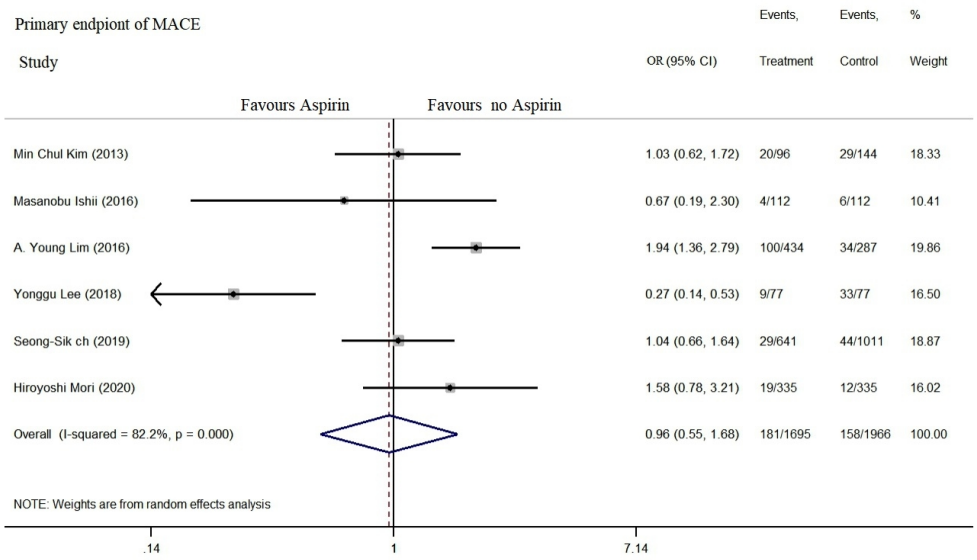

Figure 2. Aspirin use is not associated with a low incidence of MACE in patients with VSA.

231x135mm (144 x 144 DPI)

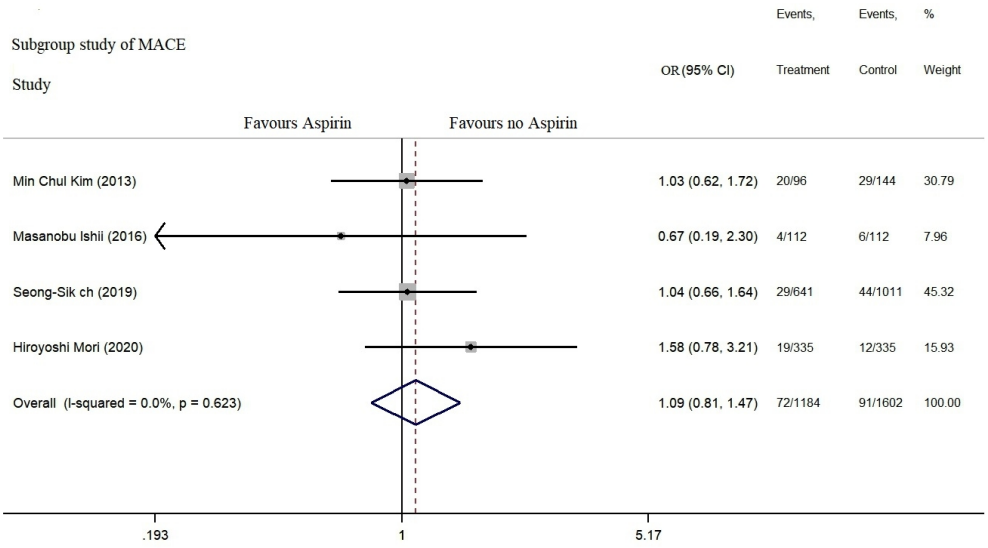

Figure 3. Subgroup analysis of MACE of aspirin use in patients with VSA.

233x136mm (144 x 144 DPI)

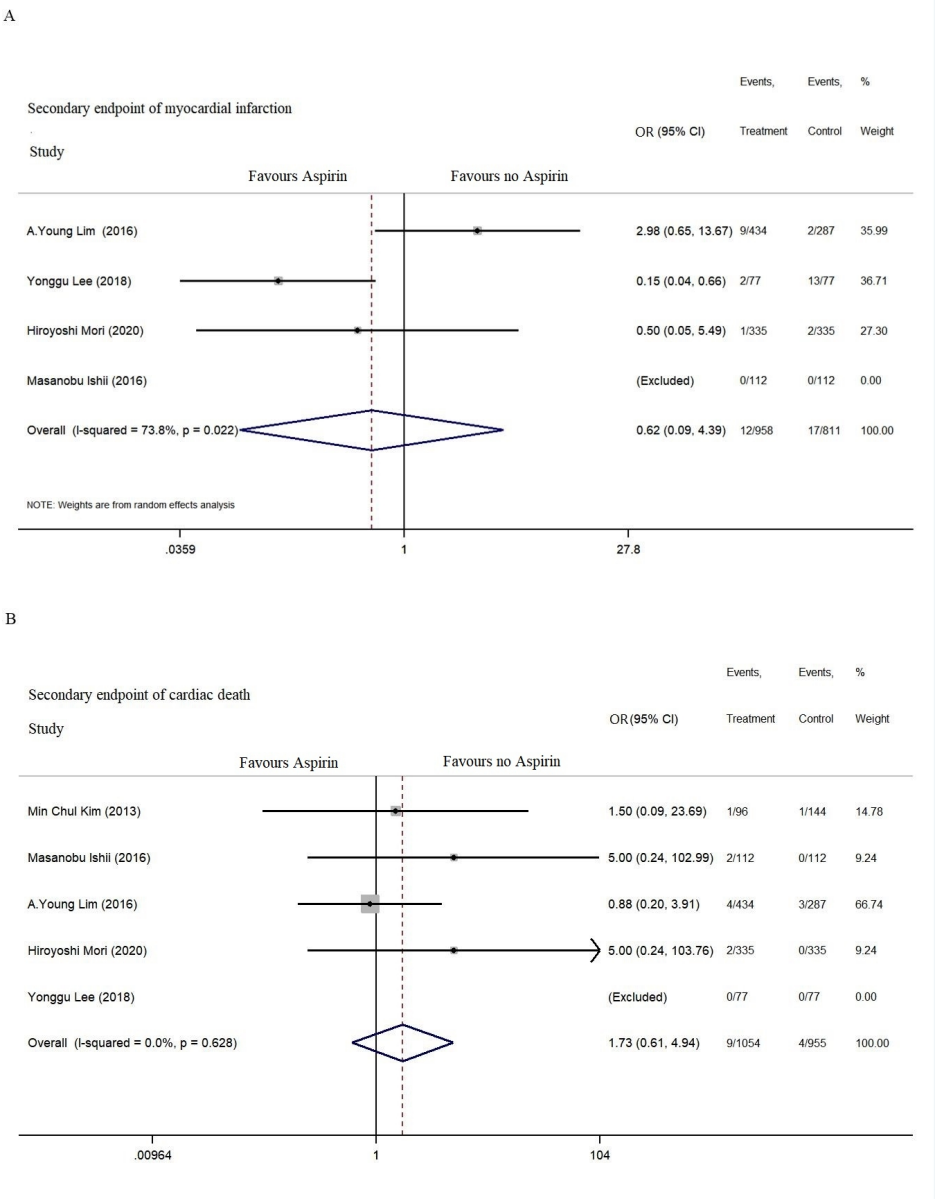

Figure 4. Secondary endpoints including myocardial infarction, cardiac death, and all-cause death during 1–5 years of follow-up.

240x305mm (144 x 144 DPI)

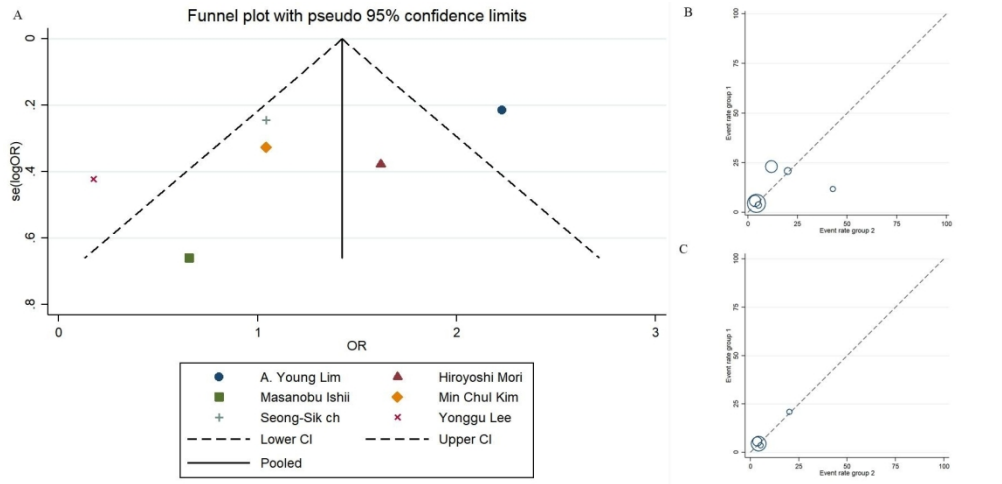

Figure 5. Assess of bias risk of the studies.

477x231mm (96 x 96 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 4-5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 4-5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 4-5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 4-5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 4-5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 4-5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 6-7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 6-7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 6-7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 6-7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 6-7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 6-7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 6-7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 7-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

BMJ Open

Impact of Aspirin Use on Clinical Outcomes in Patients With Vasospastic Angina: A Systematic Review and Meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-048719.R2
Article Type:	Original research
Date Submitted by the Author:	28-Jun-2021
Complete List of Authors:	lin, yaowang; Shenzhen People's Hospital, Department of Cardiology chen, yang; Guangdong Medical University, School of Pharmacy yuan, jie; Shenzhen People's Hospital, Department of Cardiology dong, shaohong; Shenzhen People's Hospital, Department of Cardiology Qin, Haiyan; Shenzhen People's Hospital, Department of Emergency chen, qiuling; Shenzhen People's Hospital, Department of Pharmacy
Primary Subject Heading:	Medical management
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Coronary heart disease < CARDIOLOGY, Myocardial infarction < CARDIOLOGY, Vascular medicine < INTERNAL MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Impact of Aspirin Use on Clinical Outcomes in Patients with Vasospastic Angina: A Systematic Review and Meta-analysis

Yaowang Lin, MD [1,4]; Yang Chen, MD [5]; Jie Yuan, MD [1,4]; Shaohong Dong, MD [1,4]; Haiyan Qin, MD [2,4#]; Qiuling Chen, MD [3,4#]

Author Affiliations:

[1]Department of Cardiology; [2]Department of Health Management; [3]Department of Pharmacy; [4]Shenzhen People's Hospital, Second Clinical Medical College of Jinan University, First affiliated Hospital of South University of Science and Technology, Shenzhen, Guangdong. No. 1017, Dongmen Northern Road, 518020, Shenzhen, Guangdong, PR China. [5]School of Pharmacy, Guangdong Medical University, Dongguan 523808, Guangdong, China

Correspondence should be addressed to Haiyan Qin and Qiuling Chen

Haiyan Qin, MD, e-mail: lgqinhaiyan@yeah.net

Qiuling Chen, MD, e-mail: szchenqiuling@yeah.net

ABSTRACT

Objectives: The use of aspirin to prevent cardiovascular disease in vasospastic angina (VSA) patients without significant stenosis has yet to be investigated. In this study we investigated 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 in the absence of significant stenosis.

Data extraction and synthesis: Two investigators extracted the study data. Odds ratios (ORs) and 95% confidence intervals (CI) were calculated and graphed as forest plots. The Newcastle-Ottawa Quality Assessment Scale (NOS) tool and Begg's funnel plot were used to assess risk of bias.

Results: Four propensity-matched cohorts, one retrospective analysis, and one prospective multicenter cohort, in total comprising 3,661 patients (aspirin use group, *n* = 1,695; no aspirin use group, *n* = 1,966) were included in this meta-analysis. Aspirin use and the incidence of major cardiovascular adverse events (MACE) with follow-up of 1–5 years were not significantly correlated (combined OR = 0.90, 95% CI: 0.55–1.68, $p = 0.829$, $I^2 = 82.2\%$; subgroup analysis: OR = 1.09, 95% CI: 0.81–1.47, $I^2 = 0\%$). No significant difference was found between aspirin use and the incidence of myocardial infarction (OR = 0.62, 95% CI: 0.09–4.36, $p = 0.615$, $I^2 = 73.8\%$) or cardiac death (OR = 1.73, 95% CI: 0.61–4.94, 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.

Trial registration number: PROSPERO (CRD42020214891)

Keywords: Aspirin, Vasospastic angina, MACE, Cardiac death, Myocardial infarction, Long-term follow-up

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 VSA.

► The therapeutic drug in used in the study by Mori (2020) is an antiplatelet drug that includes aspirin and P2Y12 inhibitors.

► The limitations inherent to multicenter observational studies performed in both retrospective and prospective manners may have affected data analysis.

► The conclusions of this study should be verified with randomized controlled trials with larger sample size.

INTRODUCTION

Coronary spasm characterized by vasospastic angina (VSA) is one cause of ischemia with a non-obstructive coronary artery (INOCA) [1, 2]. VSA patients who also suffer from endothelial dysfunction or coronary atherosclerosis commonly use aspirin [3, 4], per the guidelines of the European Society of Cardiology (ESC), 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 to 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 has 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 to 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 related research articles conducted before October 2020 in search engines such as PubMed, Web of Science, and Cochrane Central Register of Controlled Trials was used 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. This study was registered with PROSPERO (CRD42020214891).

Patient and public involvement

Study participants met the eligibility criteria as outlined above. All included patients were diagnosed with epicardial coronary vasospams 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 pre-defined 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 and cardiac death during follow-up were the secondary endpoints. MACE have been described as cardiac death, acute coronary syndrome, and hospitalization due to unstable angina, percutaneous coronary intervention, symptomatic arrhythmia, appropriate implantable cardioverter defibrillator (ICD), and shock. The Newcastle-Ottawa Quality Assessment Scale (NOS) tool was utilized to assess the risk of bias, and Begg's funnel plot was used to evaluated publication bias.

Statistical analysis

STATA software (version 14.0; StataCorp, College Station, TX, USA) was used for the meta-analysis. MACE (primary endpoints) and myocardial infarction and cardiac death (secondary endpoints) were evaluated as combined odds ratios (ORs) with 95% confidence intervals (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 utilized to evaluate heterogeneity. Subgroups were

studied to reduce the heterogeneity if $I^2 > 50\%$. P values < 0.05 were considered statistically significant.

RESULTS

Characteristics of included studies

The search engines were reviewed to identify 3,645 related studies, among which 1,303 articles were duplicates and 2,414 articles did not fulfill the inclusion criteria and were exclused from the study. After removing these studies, 4 propensity-matched cohorts [11,13,14,16], 1 retrospective analysis [12], and 1 prospective multicenter cohort [15] (Figure 1), including a total of 3,661 patients (aspirin group, $n = 1,695$; no aspirin group, $n = 1,966$, Table 1) were included in the study. Four studies underwent coronary provocation test, except for 1 study (Seong-Sik Cho, 2019) that used the ECG provocation test. All studies provided the 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: 0.55–1.68, $p = 0.829$, $I^2 = 82.2\%$ [Figure 2]; subgroup analysis: OR = 0.89, 95% CI: 0.40–2.02, $I^2 = 86.9\%$ and OR = 1.09, 95% CI: 0.81–1.47, $I^2 = 0\%$, [Figure 3 A and B]).

Myocardial infarction was reported in 4 studies, and cardiac death was reported in 5 studies for the secondary endpoint. No significant difference was found between aspirin use and the incidence of myocardial infarction (OR = 0.62, 95% CI: 0.09–4.36, $p = 0.615$, $I^2 = 73.8\%$) or cardiac death (OR = 1.73, 95% CI: 0.61–4.94, $p = 0.444$, $I^2 = 0\%$) 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 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 myocardial infarction and cardiac death-related studies were 73.8% and 0%, respectively, indicating the occurrence of high publication bias for the myocardial infarction endpoint (Figure 4).

DISCUSSION

Our meta-analysis showed that aspirin had no significant effect on reducing MACE, myocardial infarction, 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 ischemic heart disease, including acute coronary syndrome (ACS) and

chronic coronary syndrome (CCS) [17]. A common mechanism by which myocardial infarction (MI) or MINOCA manifests is by 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 not administered aspirin (hazard ratio [HR] = 1.54; CI: 1.04-2.28; $p = 0.037$) during a 52-month median follow-up period [13]. In contrast, MI (HR = 0.13; CI: 0.03–0.61; $p = 0.014$) and chest pain recurrence (HR = 0.29; CI: 0.12–0.71; $p = 0.006$) 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 (OCT) 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 nonsignificant stenosis during a 49-month mean follow-up period ($p = 0.541$) Ishi *et al*. [14]. Moreover, the aspirin-treated group exhibited a

similar MACE incidence compared with the non-antiplatelet agent group (HR 0.96, CI: 0.59–1.55, $p = 0.872$) 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 gives 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 dyspnea 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 by aspirin. This could, in turn, cause recurrent angina leading to rehospitalization, 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 [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 have been 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 (2020) showed that an antiplatelet drug containing both aspirin and P2Y12 inhibitors was used as the therapeutic drug. 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 multicenter 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. A 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.

Acknowledgments

None

Contributors

YWL, QLC, and HYQ conceived, designed, and led the study. YWL, YC, YJ, and SHD investigated, conducted the study, and collected data. YWL, HYQ, and QLC wrote, revised, and edited the manuscript. All authors supervised the study and approved the final version of the manuscript.

Funding

This study was supported by a grant from the Shenzhen Key Medical Discipline Construction Fund (No. SZXK003 and No. SZXK059) and Sanming Project of Medicine in Shenzhen (No. SZSM201412012).

Conflict of interest

No conflict of interest

Patient consent for publication

Not required

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.

ORCID iD

Yaowang Lin: https://orcid.org/0000-0002-4075-4259

Ethics Statement

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

REFERENCES

1. Montone RA, Niccoli G, Fracassi F, *et al*. Patients with acute myocardial infarction and non-obstructive coronary arteries: safety and prognostic relevance of invasive coronary provocative tests. *Eur Heart J* 2018, 39(2):91-98.

2. Kunadian V, Chieffo A, Camici PG, *et al*. An EAPCI Expert Consensus

Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaborati on with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. *Eur Heart J* 2020, 41(37):3504-3520.

3. Lee BK, Lim HS, Fearon WF, *et al*. Invasive evaluation of patients with angina in the absence of obstructive coronary artery disease. *Circulation* 2015, 131(12):1054-1060.

4. Khuddus MA, Pepine CJ, Handberg EM, *et al*. An intravascular ultrasound analysis in women experiencing chest pain in the absence of obstructive coronary artery disease: a substudy from the National Heart, Lung and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *J Interv Cardiol* 2010, 23(6):511-519.

5. Knuuti J, Wijns W, Saraste A, *et al*. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020, 41(3):407-477.

6. Collet JP, Thiele H, Barbato E, *et al*. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2020.

7. Group ASC, Bowman L, Mafham M, *et al*. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. *N Engl J Med* 2018, 379(16):1529-1539.

8. Gaziano JM, Brotons C, Coppolecchia R, *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):1036-1046.

9. Guirguis-Blake JM, Evans CV, Senger CA, *et al*. Aspirin for the Primary Prevention of Cardiovascular Events: A Systematic Evidence Review for the U.S . Preventive Services Task Force. *Ann Intern Med* 2016, 164(12):804-813.

10. Zheng SL, Roddick AJ. Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events: A S ystematic Review and Meta-analysis. *Jama* 2019, 321(3):277-287.

11. Lee Y, Park HC, Shin J. Clinical efficacy of aspirin with identification of intimal morphology by optical coherence tomography in preventing event recurrence in patients with vasospasm-induced acute coronary syndrome. *Int J Cardiovasc Imaging* 2018, 34(11):1697-1706.

12. Kim MC, Ahn Y, Park KH, *et al*. Clinical outcomes of low-dose aspirin administration in patients with variant angina pectoris. *Int J Cardiol* 2013, 167(5):2333-2334.

13. Lim AY, Park TK, Cho SW, *et al*. Clinical implications of low-dose aspirin on vasospastic angina patients without significant coronary artery stenosis; a propensity score-matched analysis. *Int J Cardiol* 2016, 221:161-166.

14. Ishii M, Kaikita K, Sato K, *et al*. Impact of aspirin on the prognosis in patients with coronary spasm without significant atherosclerotic stenosis. *Int J Cardiol* 2016, 220:328-332.

15. Cho SS, Jo SH, Han SH, *et al*. Clopidogrel plus Aspirin Use is Associated with Worse Long-Term Outcomes, but Aspirin Use Alone is Safe in Patients with Vasospastic Angina: Results from the VA-Korea Registry, A Prospective Multi-Center Cohort. *Sci Rep* 2019, 9(1):17783.

16. Mori H, Takahashi J, Sato K, *et al*. The impact of antiplatelet therapy on patients with vasospastic angina: A multicenter registry study of the Japanese Coronary Spasm Association. *Int J Cardiol Heart Vasc* 2020, 29:100561.

17. Yasue H, Mizuno Y, Harada E. Coronary artery spasm - Clinical features, pathogenesis and treatment. *Proc Jpn Acad Ser B Phys Biol Sci* 2019, 95(2):53-66.

18. Capodanno D, Alfonso F, Levine GN, *et al*. ACC/AHA Versus ESC Guidelines on Dual Antiplatelet Therapy: JACC Guideline Comparison. *J Am Coll Cardiol* 2018, 72(23 Pt A):2915-2931.

19. Valgimigli M, Bueno H, Byrne RA, *et al*. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018, 39(3):213-260.

20. Picard F, Sayah N, Spagnoli V, *et al*. Vasospastic angina: A literature review of current evidence. *Arch Cardiovasc Dis* 2019, 112(1):44-55.

21. Miwa K, Kambara H, Kawai C. Effect of aspirin in large doses on attacks of variant angina. *Am Heart J* 1983, 105(2):351-355.

22. Iwamoto J, Saito Y, Honda A, *et al*. Clinical features of gastroduodenal injury associated with long-term low-dose aspirin therapy. *World J Gastroenterol* 2013, 19(11):1673-1682.

23. Antithrombotic Trialists C, Baigent C, Blackwell L, *et al*. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009, 373(9678):1849-1860.

24. Xie W, Luo Y, Liang X, *et al*. The Efficacy And Safety Of Aspirin As The Primary Prevention Of Cardiovascular Disease: An Updated Meta-Analysis. *Ther Clin Risk Manag* 2019, 15:1129-1140.

25. Whitlock EP, Burda BU, Williams SB, *et al*. Bleeding Risks With Aspirin Use for Primary Prevention in Adults: A Systematic Review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2016, 164(12):826-835.

26. Hangouche AJE, Lamliki O, Oukerraj L, *et al*. Kounis syndrome induced by oral intake of aspirin: case report and literature review. *Pan Afr Med J* 2018, 30:301.

27. Shah NH, Schneider TR, DeFaria Yeh D, *et al*. Eosinophilia-Associated Coronary Artery Vasospasm in Patients with Aspirin-Exacerbated Respiratory Disease. *J Allergy Clin Immunol Pract* 2016, 4(6):1215-1219.

28. Bates ER, Lau WC. Controversies in antiplatelet therapy for patients with cardiovascular disease. *Circulation* 2005, 111(17):e267-271.

Table 1. Clinical characteristics of patients in included studies.

Characteristics Aspirin vs. no	Min Chul Kim 2013	Masanobu Ishii 2016	A. Young Lim 2016	Yonggu Lee 2018	Seong-Sik Cho 2019	Hiroyoshi Mori 2020
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

Dyslipidemia, n (%)	/	62 (55.4) vs. 60 (53.6)，p = 0.788	91 (21.0) vs. 62 (21.6), p = 0.84	/	98 (15.4) vs.160(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

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
Min Chul Kim	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
Masanobu Ishii	2016	Retrospective analysis, propensity score matched analysis	Vasospastic angina (stenosis ≤ 50%)	224	112	112	81–100	Cardiac death, nonfatal acute myocardial infarction, and unstable angina	4 (3.6) vs. 6 (5.4)	0 vs. 0	2 (1.8) vs. 0 (0)	/	1-year
A.Young Lim	2016	Retrospective analysis, propensity score matched analysis	Coronary artery spasm (stenosis ≤ 50%)	721	434	287	100	Cardiac death, acute myocardial infarction, revascularization, or rehospitalization 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
Yonggu Lee	2018	Retrospective study, propensity score-matched analysis	Coronary artery spasm (stenosis ≤ 50%)	154	77	77	100	Chest pain recurrence, myocardial infarction, cardiac death	9 (11.7) vs. 33 (42.9)	2 (3) vs.13 (17)	0 vs. 0	0 vs. 0	4-year

Seong-Sik Cho	2019	Prospective multicenter 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
Hiroyoshi Mori	2020	Retrospective study, propensity score-matched analysis	Coronary artery spasm (stenosis ≤ 50%)	670	335	335	Aspirin 100 and P2Y12 inhibitors.	cardiac death, nonfatal myocardial infarction, hospitalization 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

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

	Selection	Comparability	Outcome

Study	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
Min Chul Kim	★	★	★	★	☆★	★	★	★	8
Masanobu Ishii	★	☆	★	★	★★	★	★	★	8
A.Young Lim	★	★	★	★	☆★	★	★	★	8
Yonggu Lee	★	★	★	★	★★	★	★	★	9
Seong-Sik Cho	★	★	★	★	☆★	★	★	★	8
Hiroyoshi Mori	☆	★	★	★	☆★	★	★	★	7

Figure legends.

Figure 1. Flow diagram for identification processes.

Figure 2. Aspirin use is not associated with a low incidence of MACE in patients with VSA.

Figure 3. Subgroup analysis of MACE with aspirin use in patients with VSA.

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

Figure 5. Assessment of bias risk of the studies.

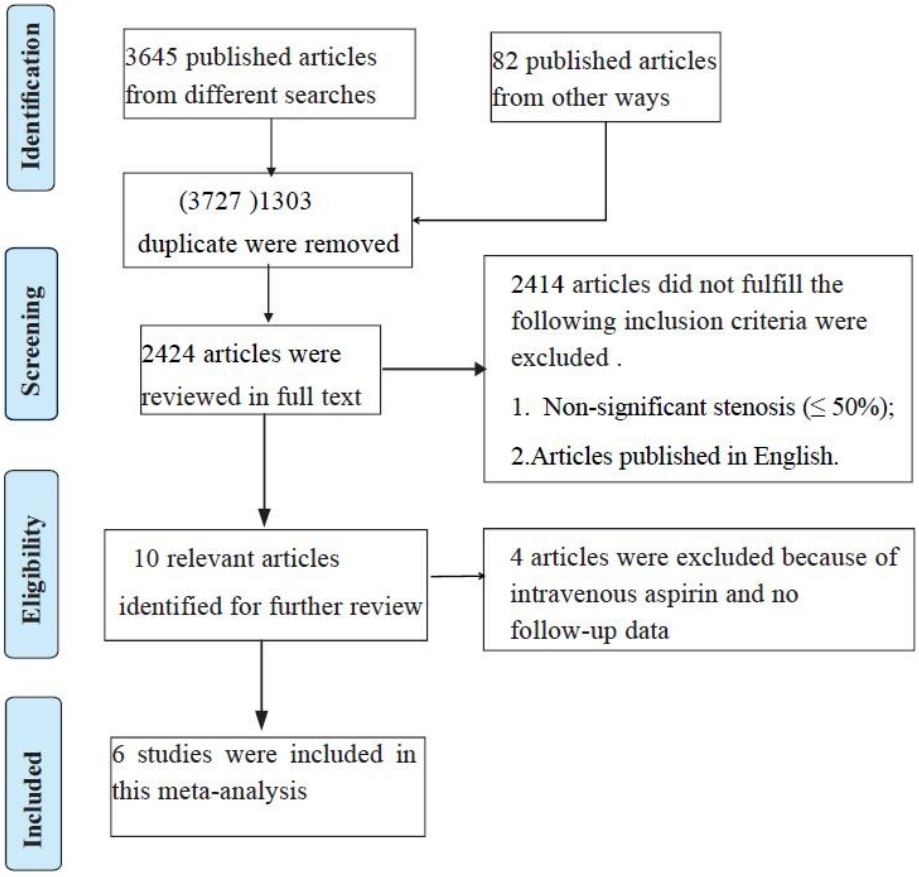

Figure 1. Flow diagram for identification processes.

Figure 1. Flow diagram for identification processes.

139x148mm (144 x 144 DPI)

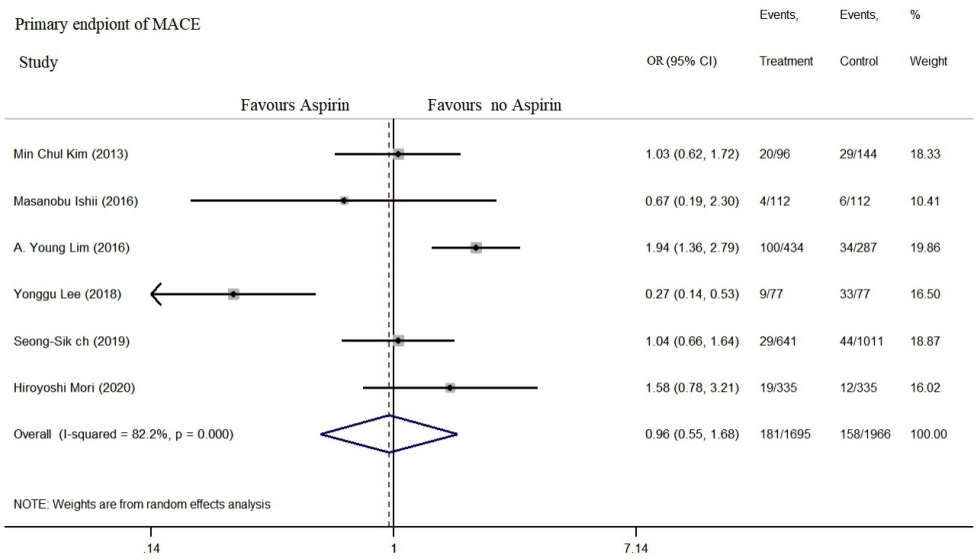

Figure 2. Aspirin use is not associated with a low incidence of MACE in patients with VSA.

231x135mm (144 x 144 DPI)

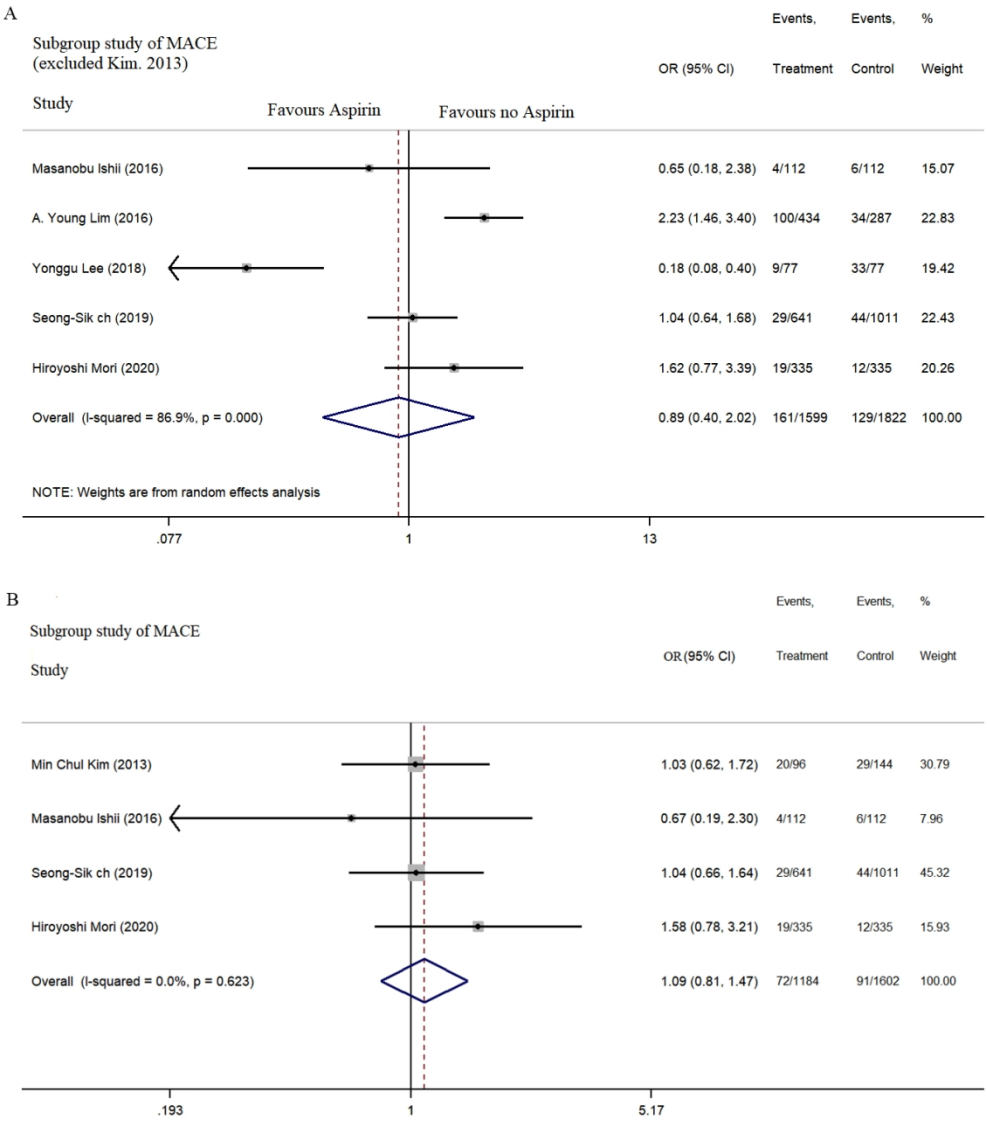

Figure 3. Subgroup analysis of MACE with aspirin use in patients with VSA.

358x411mm (96 x 96 DPI)

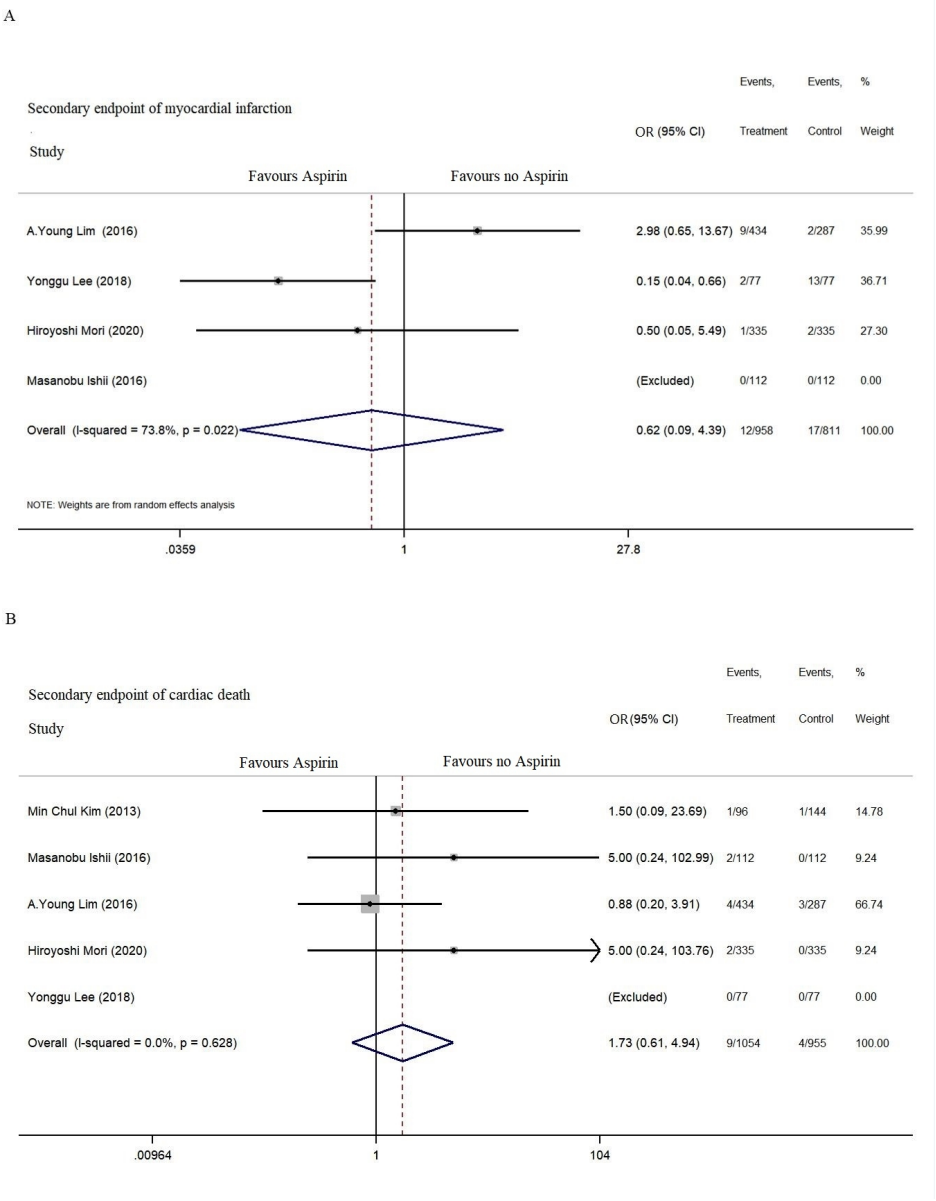

Figure 4. Secondary endpoints including myocardial infarction, cardiac death, and all-cause death during 1–5 years of follow-up.

240x305mm (144 x 144 DPI)

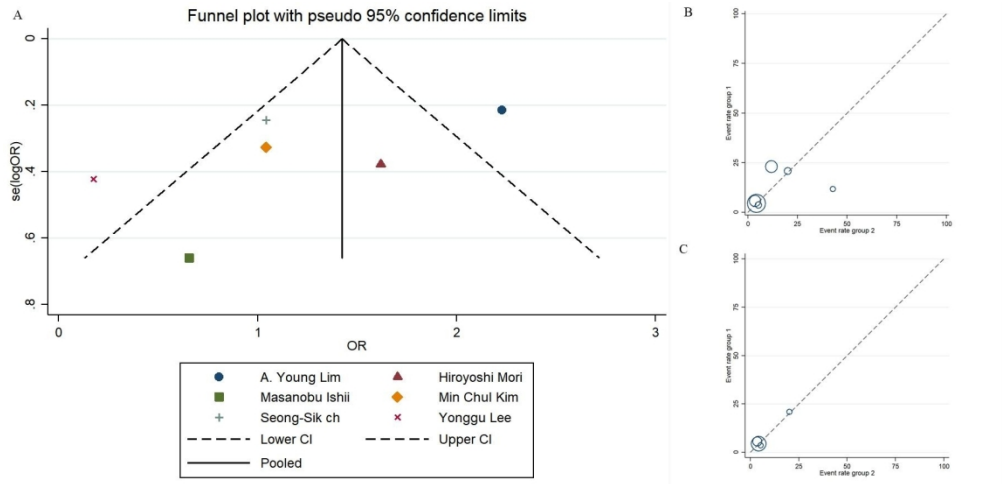

Figure 5. Assess of bias risk of the studies.

477x231mm (96 x 96 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 4-5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 4-5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 4-5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 4-5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 4-5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 4-5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 6-7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 6-7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 6-7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 6-7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 6-7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 6-7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 6-7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 7-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

BMJ Open

Impact of Aspirin Use on Clinical Outcomes in Patients With Vasospastic Angina: A Systematic Review and Meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-048719.R3
Article Type:	Original research
Date Submitted by the Author:	03-Jul-2021
Complete List of Authors:	lin, yaowang; Shenzhen People's Hospital, Department of Cardiology chen, yang; Guangdong Medical University, School of Pharmacy yuan, jie; Shenzhen People's Hospital, Department of Cardiology Qin, Haiyan; Shenzhen People's Hospital, Department of Emergency dong, shaohong; Shenzhen People's Hospital, Department of Cardiology chen, qiuling; Shenzhen People's Hospital, Department of Pharmacy
Primary Subject Heading:	Medical management
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Coronary heart disease < CARDIOLOGY, Myocardial infarction < CARDIOLOGY, Vascular medicine < INTERNAL MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Impact of Aspirin Use on Clinical Outcomes in Patients with Vasospastic Angina: A Systematic Review and Meta-analysis

Yaowang Lin, MD [1,4]; Yang Chen, MD [5]; Jie Yuan, MD [1,4]; Haiyan Qin, MD [2,4]; Shaohong Dong, MD [1,4#]; Qiuling Chen, MD [3,4#]

Author Affiliations:

[1]Department of Cardiology; [2]Department of Health Management; [3]Department of Pharmacy; [4]Shenzhen People's Hospital, Second Clinical Medical College of Jinan University, First affiliated Hospital of South University of Science and Technology, Shenzhen, Guangdong. No. 1017, Dongmen Northern Road, 518020, Shenzhen, Guangdong, PR China. [5]School of Pharmacy, Guangdong Medical University, Dongguan 523808, Guangdong, China

Correspondence should be addressed to Shaohong Dong and Qiuling Chen

Shaohong Dong, MD, e-mail:xnkdsh@yeah.net

Qiuling Chen, MD, e-mail: szchenqiuling@yeah.net

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. Odds ratios (ORs) and 95% confidence intervals (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 multicenter cohort, in total comprising 3,661 patients (aspirin use group, *n*

= 1,695; no aspirin use group, n = 1,966) 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: 0.55–1.68, p = 0.829, I^2 = 82.2%; subgroup analysis: OR = 1.09, 95% CI: 0.81–1.47, I^2 = 0%). No significant difference was found between aspirin use and the incidence of myocardial infarction (OR = 0.62, 95% CI: 0.09–4.36, p = 0.615, I^2 = 73.8%) or cardiac death (OR = 1.73, 95% CI: 0.61–4.94, 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.

Trial registration number: PROSPERO (CRD42020214891)

Keywords: Aspirin, Vasospastic angina, MACE, Cardiac death, Myocardial infarction, Long-term follow-up

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 VSA.

► The therapeutic drug used in the study by Mori (2020) is an antiplatelet drug that includes aspirin and P2Y12 inhibitors.

► The limitations inherent to multi-center observational studies performed in both retrospective and prospective manners may have affected data analysis.

► The conclusions of this study should be verified with randomized controlled trials

with a larger sample size.

INTRODUCTION

Coronary spasm characterized by vasospastic angina (VSA) is one cause of ischemia in a non-obstructive coronary artery (INOCA) [1, 2]. VSA patients who also suffer from

endothelial dysfunction or coronary atherosclerosis commonly use aspirin [3, 4], per the guidelines of the European Society of Cardiology (ESC), 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 to 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 to 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. This study was registered with PROSPERO (CRD42020214891).

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 pre-defined 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 hospitalization due to unstable angina, percutaneous coronary intervention, symptomatic arrhythmia, appropriate implantable cardioverter defibrillator (ICD), and shock. The Newcastle-Ottawa Quality Assessment Scale (NOS) tool was utilized to assess the risk of bias, and Begg's funnel plot was used to evaluated publication bias.

Statistical analysis

STATA software (version 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 odds ratios (ORs) with 95% confidence intervals (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 utilized to evaluate heterogeneity. Subgroups were studied to reduce the heterogeneity if $I^2 > 50\%$. P values < 0.05 were considered statistically significant.

RESULTS

Characteristics of included studies

The search engines were reviewed to identify 3,645 related studies, among which 1,303 articles were duplicates and 2,414 articles did not fulfill the inclusion criteria and were excluded from the study. After removing these studies, 4 propensity-matched cohorts [11,13,14,16], 1 retrospective analysis [12], and 1 prospective multicenter cohort [15] (Figure 1), including a total of 3,661 patients (aspirin group, $n = 1,695$; no aspirin group, $n = 1,966$, Table 1) were included in the study. Four studies underwent coronary provocation test, except for 1 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: 0.55–1.68, $p = 0.829$, $I^2 = 82.2\%$ [Figure 2]; subgroup analysis: OR = 0.89, 95% CI: 0.40–2.02, $I^2 = 86.9\%$ and OR = 1.09, 95% CI: 0.81–1.47, $I^2 = 0\%$, [Figure 3A and B]).

MI was reported in 4 studies, and cardiac death was reported in 5 studies for the secondary endpoint. No significant difference was found between aspirin use and the incidence of MI (OR = 0.62, 95% CI: 0.09–4.36, $p = 0.615$, $I^2 = 73.8\%$) or cardiac death (OR = 1.73, 95% CI: 0.61–4.94, $p = 0.444$, $I^2 = 0\%$) 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 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 ischemic 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 not administered aspirin (hazard ratio [HR] = 1.54; CI: 1.04-2.28; $p = 0.037$) during a 52-month median follow-up period [13]. In contrast, MI (HR = 0.13; CI: 0.03–0.61; $p = 0.014$) and chest pain recurrence (HR = 0.29; CI: 0.12–0.71; $p = 0.006$) 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 nonsignificant stenosis during a 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: 0.59–1.55, $p = 0.872$) 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 dyspnea 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 by aspirin. This could, in turn, cause recurrent angina leading to rehospitalization, 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*. (2020) 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 multi-center 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.

Acknowledgments

None

Contributors

YWL, QLC, and HYQ conceived, designed, and led the study. YWL, YC, YJ, and SHD investigated, conducted the study, and collected data. YWL, SHD, and QLC wrote,

revised, and edited the manuscript. All authors supervised the study and approved the final version of the manuscript.

Funding

This study was supported by a grant from the Shenzhen Key Medical Discipline Construction Fund (No. SZXK003 and No. SZXK059) and Sanming Project of Medicine in Shenzhen (No. SZSM201412012).

Conflict of interest

No conflict of interest

Patient consent for publication

Not required

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.

ORCID iD

Yaowang Lin: https://orcid.org/0000-0002-4075-4259

Ethics Statement

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

REFERENCES

1. Montone RA, Niccoli G, Fracassi F, *et al*. Patients with acute myocardial infarction and non-obstructive coronary arteries: safety and prognostic relevance of invasive coronary provocative tests. *Eur Heart J* 2018, 39(2):91-98.

2. Kunadian V, Chieffo A, Camici PG, *et al*. An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaborati on with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. *Eur Heart J* 2020, 41(37):3504-3520.

3. Lee BK, Lim HS, Fearon WF, *et al*. Invasive evaluation of patients with angina in the absence of obstructive coronary artery disease. *Circulation* 2015, 131(12):1054-1060.

4. Khuddus MA, Pepine CJ, Handberg EM, *et al*. An intravascular ultrasound analysis in women experiencing chest pain in the absence of obstructive coronary artery disease: a substudy from the National Heart, Lung and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *J Interv Cardiol* 2010, 23(6):511-519.

5. Knuuti J, Wijns W, Saraste A, *et al*. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020, 41(3):407-477.

6. Collet JP, Thiele H, Barbato E, *et al*. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2020.

7. Group ASC, Bowman L, Mafham M, *et al*. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. *N Engl J Med* 2018, 379(16):1529-1539.

8. Gaziano JM, Brotons C, Coppolecchia R, *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):1036-1046.

9. Guirguis-Blake JM, Evans CV, Senger CA, *et al*. Aspirin for the Primary Prevention of Cardiovascular Events: A Systematic Evidence Review for the U.S . Preventive Services Task Force. *Ann Intern Med* 2016, 164(12):804-813.

10. Zheng SL, Roddick AJ. Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events: A S ystematic Review and Meta-analysis. *Jama* 2019, 321(3):277-287.

11. Lee Y, Park HC, Shin J. Clinical efficacy of aspirin with identification of intimal morphology by optical coherence tomography in preventing event recurrence in patients with vasospasm-induced acute coronary syndrome. *Int J Cardiovasc Imaging* 2018, 34(11):1697-1706.

12. Kim MC, Ahn Y, Park KH, *et al*. Clinical outcomes of low-dose aspirin administration in patients with variant angina pectoris. *Int J Cardiol* 2013, 167(5):2333-2334.

13. Lim AY, Park TK, Cho SW, *et al*. Clinical implications of low-dose aspirin on vasospastic angina patients without significant coronary artery stenosis; a propensity score-matched analysis. *Int J Cardiol* 2016, 221:161-166.

14. Ishii M, Kaikita K, Sato K, *et al*. Impact of aspirin on the prognosis in patients with coronary spasm without significant atherosclerotic stenosis. *Int J Cardiol* 2016, 220:328-332.

15. Cho SS, Jo SH, Han SH, *et al*. Clopidogrel plus Aspirin Use is Associated with Worse Long-Term Outcomes, but Aspirin Use Alone is Safe in Patients with Vasospastic Angina: Results from the VA-Korea Registry, A Prospective Multi-Center Cohort. *Sci Rep* 2019, 9(1):17783.

16. Mori H, Takahashi J, Sato K, *et al*. The impact of antiplatelet therapy on patients with vasospastic angina: A multicenter registry study of the Japanese Coronary Spasm Association. *Int J Cardiol Heart Vasc* 2020, 29:100561.

17. Yasue H, Mizuno Y, Harada E. Coronary artery spasm - Clinical features, pathogenesis and treatment. *Proc Jpn Acad Ser B Phys Biol Sci* 2019, 95(2):53-66.

18. Capodanno D, Alfonso F, Levine GN, *et al*. ACC/AHA Versus ESC Guidelines on Dual Antiplatelet Therapy: JACC Guideline Comparison. *J Am Coll Cardiol* 2018, 72(23 Pt A):2915-2931.

19. Valgimigli M, Bueno H, Byrne RA, *et al*. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collabor ation with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the Eur opean Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018, 39(3):213-260.

20. Picard F, Sayah N, Spagnoli V, *et al*. Vasospastic angina: A literature review of current evidence. *Arch Cardiovasc Dis* 2019, 112(1):44-55.

21. Miwa K, Kambara H, Kawai C. Effect of aspirin in large doses on attacks of variant angina. *Am Heart J* 1983, 105(2):351-355.

22. Iwamoto J, Saito Y, Honda A, *et al*. Clinical features of gastroduodenal injury associated with long-term low-dose aspirin therapy. *World J Gastroenterol*

2013, 19(11):1673-1682.

23. Antithrombotic Trialists C, Baigent C, Blackwell L, *et al*. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009, 373(9678):1849-1860.

24. Xie W, Luo Y, Liang X, *et al*. The Efficacy And Safety Of Aspirin As The Primary Prevention Of Cardiovascular Disease: An Updated Meta-Analysis. *Ther Clin Risk Manag* 2019, 15:1129-1140.

25. Whitlock EP, Burda BU, Williams SB, *et al*. Bleeding Risks With Aspirin Use for Primary Prevention in Adults: A Systematic Review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2016, 164(12):826-835.

26. Hangouche AJE, Lamliki O, Oukerraj L, *et al*. Kounis syndrome induced by oral intake of aspirin: case report and literature review. *Pan Afr Med J* 2018, 30:301.

27. Shah NH, Schneider TR, DeFaria Yeh D, *et al*. Eosinophilia-Associated Coronary Artery Vasospasm in Patients with Aspirin-Exacerbated Respiratory Disease. *J Allergy Clin Immunol Pract* 2016, 4(6):1215-1219.

28. Bates ER, Lau WC. Controversies in antiplatelet therapy for patients with cardiovascular disease. *Circulation* 2005, 111(17):e267-271.

Table 1. Clinical characteristics of patients in included studies.

Characteristics	Min Chul Kim	Masanobu Ishii	A. Young Lim	Yonggu Lee	Seong-Sik Cho	Hiroyoshi Mori
Aspirin vs. no	2013	2016	2016	2018	2019	2020
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

Dyslipidemia, n (%)	/	62 (55.4) vs. 60 (53.6)，p = 0.788	91 (21.0) vs. 62 (21.6), p = 0.84	/	98 (15.4) vs.160(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

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
Min Chul Kim	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
Masanobu Ishii	2016	Retrospective analysis, propensity score matched analysis	Vasospastic angina (stenosis ≤ 50%)	224	112	112	81–100	Cardiac death, nonfatal acute myocardial infarction, and unstable angina	4 (3.6) vs. 6 (5.4)	0 vs. 0	2 (1.8) vs. 0 (0)	/	1-year
A.Young Lim	2016	Retrospective analysis, propensity score matched analysis	Coronary artery spasm (stenosis ≤ 50%)	721	434	287	100	Cardiac death, acute myocardial infarction, revascularization, or rehospitalization 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

Yonggu Lee	2018	Retrospective study, propensity score-matched analysis	Coronary artery spasm (stenosis ≤ 50%)	154	77	77	100	Chest pain recurrence, myocardial infarction, cardiac death	9 (11.7) vs. 33 (42.9)	2 (3) vs.13 (17)	0 vs. 0	0 vs. 0	4-year
Seong-Sik Cho	2019	Prospective multicenter 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
Hiroyoshi Mori	2020	Retrospective study, propensity score-matched analysis	Coronary artery spasm (stenosis ≤ 50%)	670	335	335	Aspirin 100 and P2Y12 inhibitors.	cardiac death, nonfatal myocardial infarction, hospitalization 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

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

	Selection				Comparability		Outcome		
Study	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
Min Chul Kim	★	★	★	★	☆★	★	★	★	8
Masanobu Ishii	★	☆	★	★	★★	★	★	★	8
A.Young Lim	★	★	★	★	☆★	★	★	★	8
Yonggu Lee	★	★	★	★	★★	★	★	★	9
Seong-Sik Cho	★	★	★	★	☆★	★	★	★	8
Hiroyoshi Mori	☆	★	★	★	☆★	★	★	★	7

Figure legends.

Figure 1. Flow diagram for identification processes.

Figure 2. Aspirin use is not associated with a low incidence of MACE in patients with VSA.

Figure 3. Subgroup analysis of MACE with aspirin use in patients with VSA.

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

Figure 5. Assessment of bias risk of the studies.

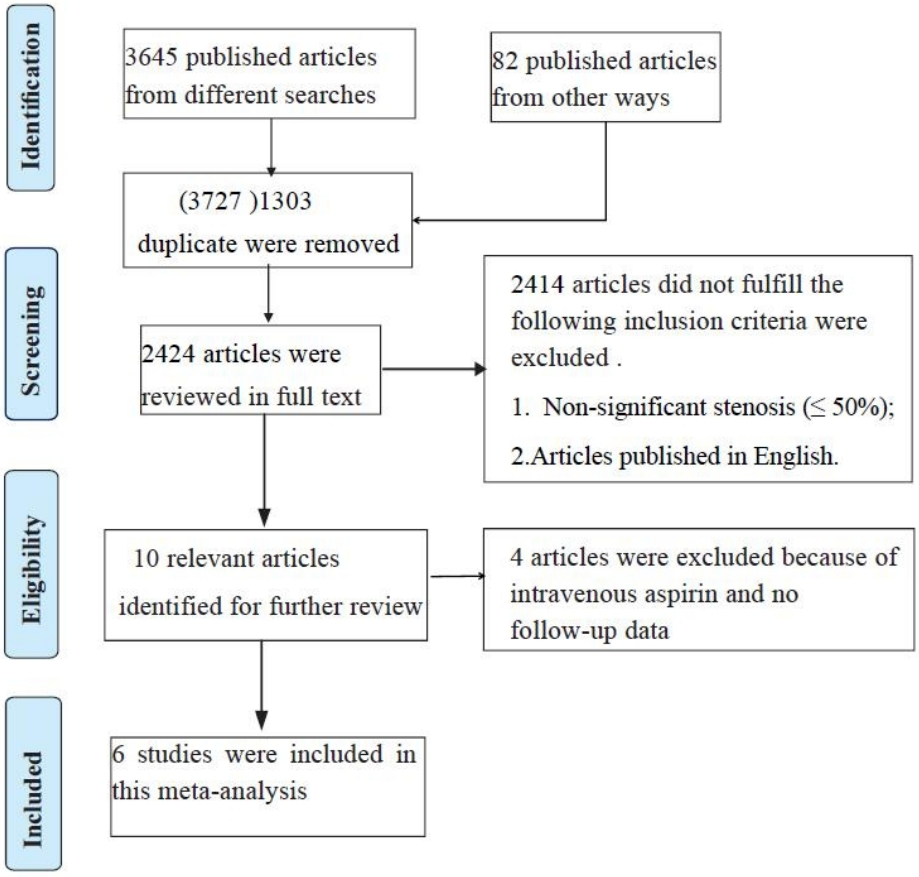

Figure 1. Flow diagram for identification processes.

Figure 1. Flow diagram for identification processes.

139x148mm (144 x 144 DPI)

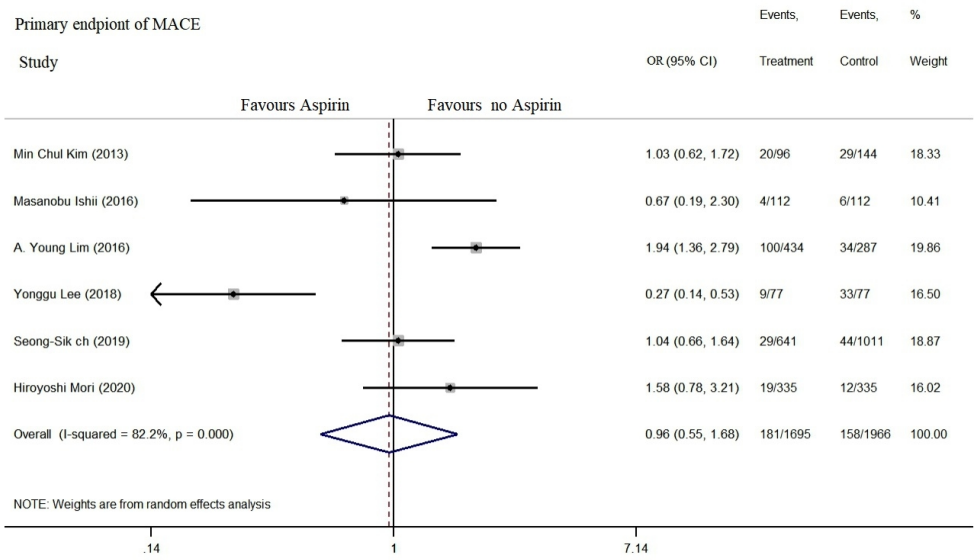

Figure 2. Aspirin use is not associated with a low incidence of MACE in patients with VSA.

231x135mm (144 x 144 DPI)

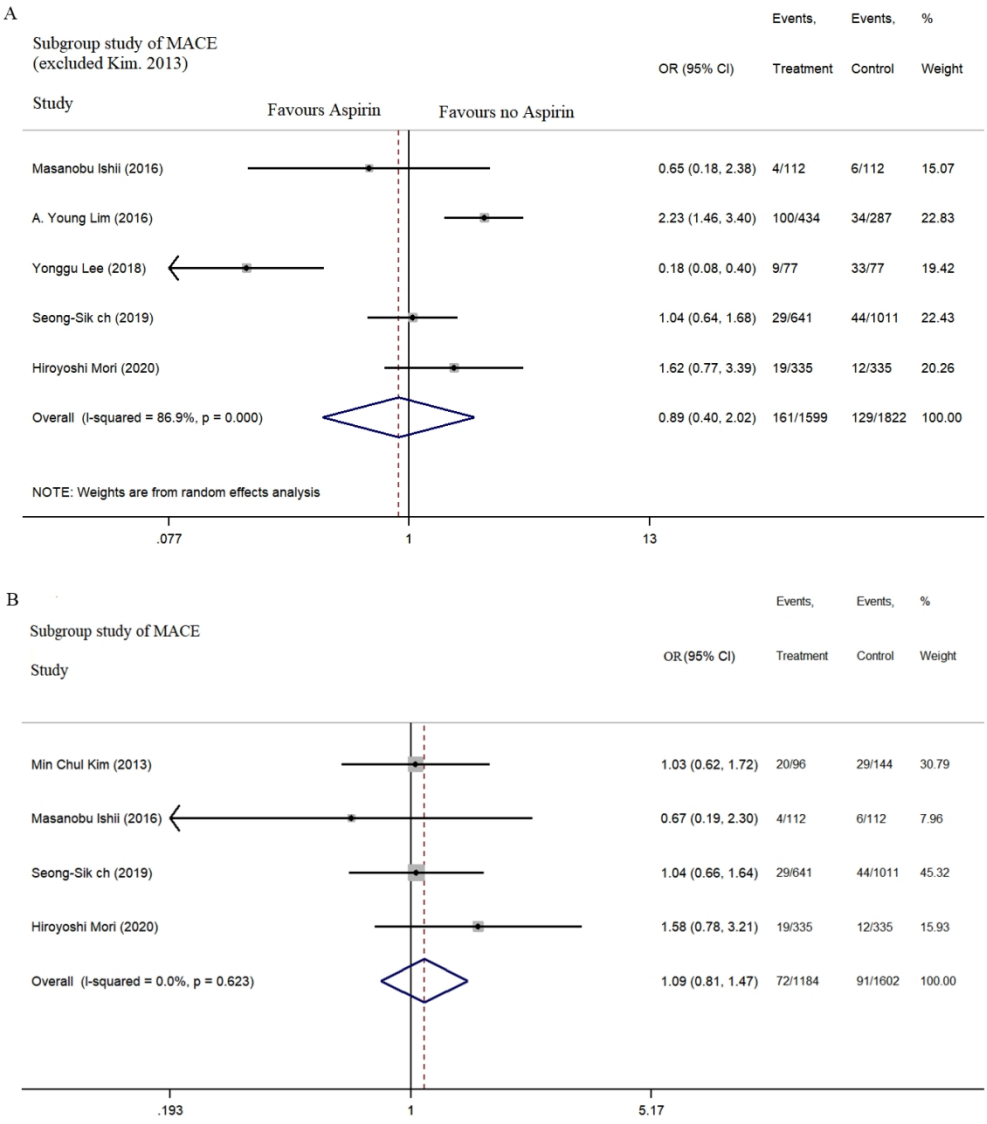

Figure 3. Subgroup analysis of MACE with aspirin use in patients with VSA.

358x411mm (96 x 96 DPI)

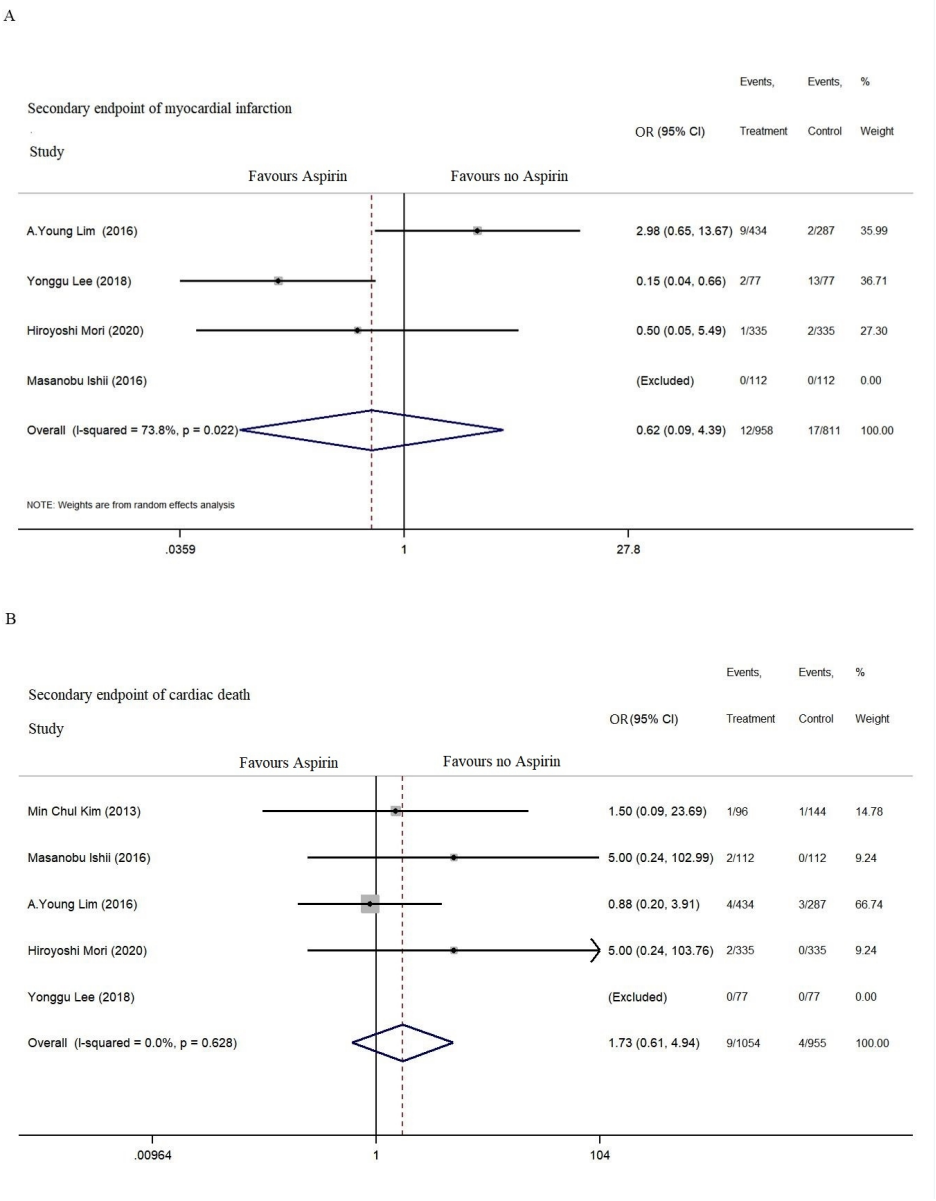

Figure 4. Secondary endpoints including myocardial infarction, cardiac death, and all-cause death during 1–5 years of follow-up.

240x305mm (144 x 144 DPI)

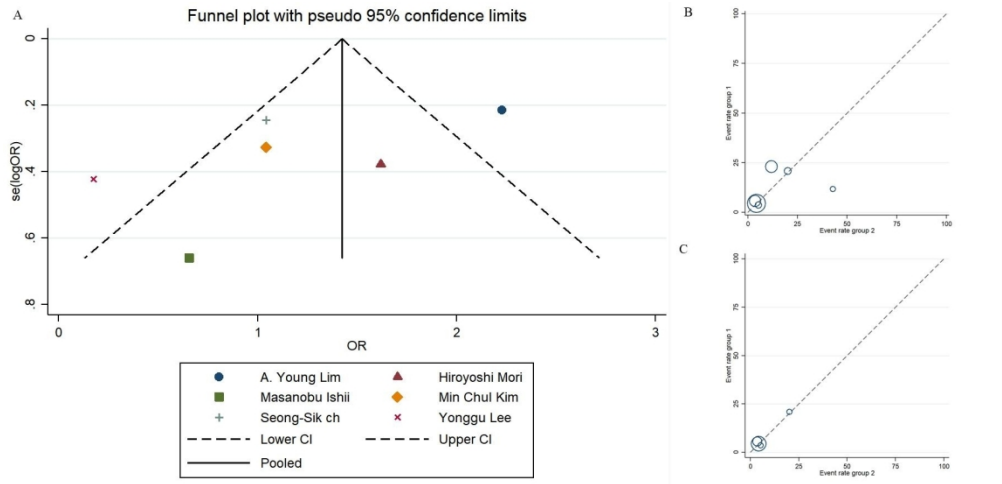

Figure 5. Assess of bias risk of the studies.

477x231mm (96 x 96 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 4-5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 4-5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 4-5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 4-5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 4-5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 4-5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 6-7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 6-7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 6-7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 6-7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 6-7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 6-7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 6-7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 7-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist