

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
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

SCHOLARONE™
Manuscripts



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 Chen⁵, MD

Author's Affiliation:

¹Department of Cardiology; ²Department of Emergency; ³Department of Pharmacy;

⁴Shenzhen 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.

⁵School 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

1
2
3
4 significantly correlated (combined odds ratio [OR] = 0.90, 95% confidence interval
5 [CI]: 0.55–1.68, $p = 0.829$, $I^2 = 82.2\%$; subgroup analysis: OR = 1.09, 95% CI: 0.81–
6
7 1.47, $I^2 = 0\%$). Aspirin use was found to be linked with a lower of incidence of
8
9 myocardial infarction (OR = 0.62, 95% CI: 0.09–4.36, $p = 0.615$, $I^2 = 73.8\%$) and
10
11 higher tendency of incidence of cardiac death during follow-up, but no significant
12
13 difference (OR = 1.73, 95% CI: 0.61–4.94, $p = 0.444$, $I^2 = 0\%$).
14
15
16
17
18
19

20 **Conclusion:** Aspirin use is not likely to reduce future cardiovascular events in VSA
21
22 patients without significant stenosis.
23
24

25
26 **Keywords:** aspirin, vasospastic angina, MACE, cardiac death, myocardial infarction,
27
28 longtime follow-up
29
30
31
32
33
34
35
36
37
38
39
40
41
42

43 **Strengths and limitations of this study**

44
45
46 ► This is the first meta-analysis to evaluate the impact of aspirin use on clinical
47
48 outcomes in patients with VSA.
49
50

51
52 ► Aspirin use was found to have no significant effect on reducing MACE,
53
54 myocardial infarction, and cardiac death in VSA patients without significant stenosis,
55
56 as per the outcomes of this meta-analysis. A tendency of higher risk of MACE and
57
58 cardiac death was recognized, but not that of myocardial infarction.
59
60

1
2
3
4 ▶ Owing to the increased MACE, routine use of aspirin use in VSA patients without
5
6 significant stenosis should be avoided.
7
8

9
10 ▶ The conclusions should be confirmed by further randomized controlled trials with
11
12 larger sample size.
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35

36 **INTRODUCTION**

37
38
39
40 Coronary spasm characterized by vasospastic angina (VSA) is one of the causes of
41
42 myocardial infarction with non-obstructive coronary arteries (MINOCA) and
43
44 ischemia and non-obstructive coronary arteries (INOCA) [1-2]. VSA patients who
45
46 parallelly suffer from endothelial dysfunction or coronary atherosclerosis commonly
47
48 use aspirin [3-4] as per the guidelines of the European Society of Cardiology (ESC)
49
50 for the management of chronic stable angina and acute coronary syndromes [5-6]
51
52
53
54

55
56 Owing to the latest controversy and reduced key usage of aspirin in preventing
57
58 cardiovascular events [7-8], the aspirin's efficiency in VSA patients without
59
60

1
2
3
4 significant stenosis has not yet been explained [9-14]. Therefore, this meta-analysis
5
6 was planned to assess the correlation between aspirin use and cardiovascular events,
7
8 and cardiac death among VSA patients during long-term follow-up.
9
10

11 12 **MATERIALS AND METHODS**

13 14 15 16 *Search strategy*

17
18
19 A comprehensive search of related research articles conducted before October 2020 in
20
21 various search engines such as PubMed, web of science, and Cochrane Central
22
23 Register of Controlled Trials was carried out for gathering data. The keywords were
24
25 “vasospastic angina, coronary vasospasms, vasospasm, variant angina, Prinzmetal's
26
27 variant angina, spastic coronary angina, coronary artery spasm,” as well as “aspirin,
28
29 antiplatelet therapy.” Certain additional related publications, such as review articles
30
31 and editorials, were also assessed. This study was registered with PROSPERO
32
33 (CRD42020214891).
34
35
36
37
38
39
40

41 42 *Patient and public involvement*

43
44 Study participants who met the eligibility criteria as outlined above. Participants and
45
46 other members of public were not involved in the recruitment, design, conduct,
47
48 reporting or dissemination plans.
49
50
51

52 53 *Study selection and data extraction*

54
55
56 Following are the inclusion criteria: (i) diagnosed with VSA on provocation test, (ii)
57
58 absence of significant stenosis ($\leq 50\%$), (iii) the treatment group was administered
59
60

1
2
3
4 oral aspirin and the control group no aspirin or placebo, and (iv) articles published in
5
6 English. The exclusion criteria included significant stenosis ($\geq 50\%$), intravenous
7
8 aspirin, case report, and case series. Two investigators, namely, Lin and Chen,
9
10 extracted the study data, which have been presented in Table 1
11
12
13
14

15 ***Data analysis and subgroup study***

16
17
18 Major cardiovascular adverse event (MACE) was the primary endpoint, while
19
20 myocardial infarction and cardiac death during follow-up were the secondary
21
22 endpoints. MACE has been described as cardiac death, acute coronary syndrome, and
23
24 hospitalization due to unstable angina, percutaneous coronary intervention,
25
26 symptomatic arrhythmia in heart failure, appropriate implantable
27
28 cardioverter-defibrillator (ICD), and shock. The Cochrane Collaboration tool was
29
30 utilized to assess the risk of bias in the included studies. If $I^2 > 50\%$, the random
31
32 effect model was used to assess heterogeneity, whereas if $I^2 < 50\%$, the fixed effect
33
34 model was used to assess heterogeneity. In the case of high heterogeneity ($I^2 >$
35
36 50%), subgroup analysis was carried out.
37
38
39
40
41
42
43
44

45 ***Statistical analysis***

46
47
48 STATA software (version 14.0; StataCorp, College Station, TX, USA) was utilized to
49
50 perform the meta-analysis. MACE, the primary endpoint, and myocardial infarction
51
52 and cardiac death, the secondary endpoints, were evaluated as combined odds ratios
53
54 with 95% confidence intervals (CIs). Heterogeneity between studies was derived with
55
56 the help of I^2 statistic. Subgroups were studied to reduce the heterogeneity if $I^2 >$
57
58 50% .
59
60

1
2
3
4 Publication bias was evaluated with the help of Begg's funnel plots. P values < 0.05
5
6 were considered to be statistically significant.
7
8

9 10 **RESULTS**

11 12 *Characteristics of included studies*

13
14 Various search engines mentioned hereinbefore were scanned to identify about 3,645
15
16 related studies, among which 1,303 articles were duplicated whereas 2,414 articles did
17
18 not fulfill the inclusion criteria and were thus expelled from the study. Therefore, four
19
20 propensity-matched cohorts, one retrospective analysis, and one prospective
21
22 multicenter cohort (Figure 1), including a total of 3,661 patients (aspirin group, $n =$
23
24 1,695; no aspirin group, $n = 1,966$, Table 2) eventually formed part of the study. All
25
26 studies except five studies provided the secondary endpoint, with follow-up durations
27
28 ranging from 1 to 5 years (Table 1).
29
30
31
32
33
34
35

36 37 *Primary and secondary endpoints*

38
39 No significant correlation was recorded between aspirin use and MACE incidence
40
41 with follow-up of 1–5 years (combined odds ratio [OR] = 0.90, 95% confidence
42
43 interval [CI]: 0.55–1.68, $p = 0.829$, $I^2 = 82.2\%$ [Figure 2]; subgroup analysis: OR =
44
45 1.09, 95% CI: 0.81–1.47, $I^2 = 0\%$, [Figure 3]).
46
47
48
49
50

51 Myocardial infarction was reported in four studies, and cardiac death was reported
52
53 in five studies for the secondary endpoint. Moreover, aspirin use was tended to be
54
55 linked to a lower incidence of myocardial infarction (OR = 0.62, 95% CI: 0.09–4.36,
56
57 $p = 0.615$, $I^2 = 73.8\%$) and a higher incidence of cardiac death during follow-up (OR
58
59
60

1
2
3
4 = 1.73, 95% CI: 0.61–4.94, $p = 0.444$, $I^2 = 0\%$), but statistical difference was lacking
5
6
7 between the two groups (Figure 4).

8 9 10 ***Risk of bias assessment and publication bias***

11
12
13 A high risk of bias was exhibited in selective outcome reporting and assessment by all
14 included studies. Publication bias with the studies of Lee and Lim was presented by
15 an asymmetry in the funnel plot (Figure 5). Between-studies heterogeneity on MACE
16 related research was 82.2%. Therefore, the outcome of subgroup analyses of I^2 was
17 0%, indicating low publication bias (Figure 3). The between-studies heterogeneities
18 on myocardial infarction and cardiac death related studies were found to be 73.8%
19 and 0%, respectively, indicating the occurrence of high publication bias regarding
20 studies on myocardial infarction (Figure 4).
21
22
23
24
25
26
27
28
29
30
31
32
33

34 35 **DISCUSSION**

36
37
38 Aspirin use was found to have no significant effect on reducing MACE, myocardial
39 infarction, and cardiac death in VSA patients without significant stenosis, as per the
40 outcomes of this meta-analysis. A tendency of higher risk of MACE and cardiac death
41 was recognized, but not that of myocardial infarction.
42
43
44
45
46
47
48

49
50 Coronary artery spasm (CAS) appeared to play a significant role in the
51 pathogenesis of ischemic heart disease, besides acute coronary syndromes (ACS) or
52 chronic coronary syndromes (CCS) [15]. A common mechanism by which myocardial
53 infarction (MI) or MINOCA manifests by thrombus formation. Aspirin inhibits
54 cyclooxygenase-1 by reducing the production of thromboxane A2 and therefore has
55
56
57
58
59
60

1
2
3
4 been extensively used in primary or secondary prevention of thrombosis among
5
6 patients with atherosclerosis or coronary artery disease [16-17], yet being
7
8 controversial in VSA patients. Earlier studies have evidenced aspirin use to aggravate
9
10 CAS due to the lowered production of thromboxane A₂ and increase MACE
11
12 incidence in VSA patients [18-19].
13
14
15

16
17
18 MACE incidence exhibited by patients administered low-dose aspirin was
19
20 reported to be significantly higher than that among patients not administered aspirin
21
22 (hazard ratio [HR] = 1.54; CI: 1.04-2.28; $p = 0.037$) with a 52-months median
23
24 follow-up period [11]. On the contrary, MI (HR = 0.13; CI: 0.03–0.61; $p = 0.014$) and
25
26 chest pain recurrence (HR = 0.29; CI: 0.12–0.71; $p = 0.006$) were observed by Lee et
27
28 al. to have been significantly reduced by aspirin use among VSA patients during
29
30 follow-up [9]. Acute intimal tears and erosion identified by Optical coherence
31
32 tomography (OCT) are susceptible to thrombosis leading to MI as per Lee's findings.
33
34 Therefore, aspirin was thus evidenced to reduce adverse events in VSA patients with a
35
36 greater number of thrombotic intracoronary lesions. Nevertheless, aspirin use was not
37
38 significantly correlated with the occurrence of cardiovascular events among VSA
39
40 patients with nonsignificant stenosis during a 49-months mean follow-up period ($p =$
41
42 0.541) Ishi et al. [12]. Moreover, the aspirin-treated group exhibited a similar MACE
43
44 compared with the no-antiplatelet agent group (HR 0.96, CI: 0.59–1.55, $p = 0.872$) as
45
46 reported by Cho. S.S et al. [13]. Antiplatelet therapy was recently shown by Mori et al.
47
48 to exert no beneficial effects on MACE (5.7% vs. 3.6%, $p = 0.20$) among VSA
49
50 patients during a 32-months median follow-up period [14].
51
52
53
54
55
56
57
58
59
60

1
2
3
4 A systematic analysis of the available studies investigating the effects of aspirin
5
6 use among VSA patients was conducted. Aspirin use was not linked to a lower risk of
7
8 MACE and cardiac death as per this meta-analysis. The subgroup analysis for MACE
9
10 indicated that the study by Lee[9] and Lim [11] is quite heterogeneous. The origin of
11
12 heterogeneity in these studies may be attributable to chest pain recurrence in the
13
14 MACE, which gives an entirely different outcome due to the inclusion of other
15
16 literature. Following may be the possible reasons for no beneficial effects of aspirin
17
18 use: (i) aspirin use is known to damage the gastric mucosal barrier and increase the
19
20 risk of erosions, ulcers, and bleeding by way of inhibiting cyclooxygenase-1 enzyme
21
22 activity [20]. Several meta-analyses have indicated that aspirin's efficacy in primary
23
24 prevention of cardiovascular disease needs to be weighed against any increase in major
25
26 bleeding [21-23]; (ii) attributable to adverse effects of causing asthma and dyspnea,
27
28 aspirin is likely to cause CAS and increase the occurrence of MACE or cardiogenic
29
30 death [24-25]; (iii) the synthesis of prostacyclin, a well-known vasodilator released by
31
32 endothelial cells is inhibited by aspirin [26] and CAS induced by aspirin, which could,
33
34 in turn, cause recurrent angina leading to rehospitalization, myocardial infarction, and
35
36 cardiac death.
37
38
39
40
41
42
43
44
45
46
47
48

49 In addition, aspirin use has been found in this analysis to have a possible
50
51 protective effect on MI. The pharmacological mechanism easily explains the aspirin's
52
53 beneficial effects on MI. But there is great heterogeneity, which may be attributable to
54
55 the lack of related studies and a different definition of myocardial infarction by Mori
56
57 in his study[14]. Aspirin use in CAS patients is both advantageous as well as
58
59
60

1
2
3
4 disadvantageous. Further investigations are necessary for the analysis of beneficial
5
6 effects to determine whether to recommend.
7
8
9

10 Several potential limitations should also be considered in the case of this
11
12 meta-analysis. First, MACE and MI have been defined differently in the included
13
14 articles. Second, in one of the studies by Mori (2020), not aspirin but an antiplatelet
15
16 drug comprising aspirin and P2Y12 inhibitors have been used as the therapeutic drug.
17
18 Third, the sample size in the included studies is too small; only a few studies have
19
20 conducted propensity matching analysis to balance baseline characteristics. The
21
22 limitations inherent to multicenter observational studies performed in both
23
24 retrospective and prospective manners could not be avoided in this analysis. Finally,
25
26 the major bleeding outcome was excluded from this study, which is essential for
27
28 understanding the advantages of antiplatelet therapy. Considering that this study
29
30 evaluated the prognosis of VSA patients using low-dose aspirin is the first of its kind,
31
32 it has its merits.
33
34
35
36
37
38
39
40
41

42 **CONCLUSIONS**

43
44
45 Aspirin use may not lessen cardiovascular events among VSA patients without
46
47 significant stenosis. Owing to its potential adverse effects, regular use of aspirin in
48
49 VSA patients without significant stenosis is best avoided.
50
51

52 **Acknowledgments**

53
54
55
56 None
57
58

59 **Contributors**

1
2
3 YW, YC and YJ conceived, designed and led the study. YW, YJ, SH, XL and QL
4
5 investigated, conducted the study and collected data. YW, YJ and YC wrote, revised
6
7 and edited the manuscript. All authors supervised the study and approved of the final
8
9 version submitted.
10
11
12

13 **Funding**

14
15
16 This study was supported by a grant from the Shenzhen Key Medical Discipline
17
18 Construction Fund (no. SZXK059) and Shenzhen Foundation (SZLY2017025 and
19
20 JCYJ20170307100512856).
21
22

23 **Conflict of interest**

24
25 No conflict of interest
26
27
28
29

30 **Patient consent for publication**

31
32 Not required
33
34
35

36 **Provenance and peer review**

37
38 Not commissioned; externally peer reviewed.
39
40
41
42

43 **Data availability statement**

44
45 Data are available upon reasonable request. Data are available upon request.
46
47
48

49 **ORCID iD**

50
51 Yaowang Lin: <https://orcid.org/0000-0002-4075-4259>
52
53
54
55
56
57
58
59
60

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.

- 1
2
3
4 6. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management
5
6 of acute coronary syndromes in patients presenting without persistent ST-segment
7
8 elevation. *Eur Heart J*. 2020.
- 9
10
11
12 7. Guirguis-Blake JM, Evans CV, Senger CA, O'Connor EA, Whitlock EP. Aspirin
13
14 for the Primary Prevention of Cardiovascular Events: A Systematic Evidence Review
15
16 for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2016; 164(12): 804-13.
- 17
18
19
20 8. Zheng SL, Roddick AJ. Association of Aspirin Use for Primary Prevention With
21
22 Cardiovascular Events and Bleeding Events: A Systematic Review and
23
24 Meta-analysis. *Jama*. 2019; 321(3): 277-87.
- 25
26
27
28 9. Lee Y, Park HC, Shin J. Clinical efficacy of aspirin with identification of intimal
29
30 morphology by optical coherence tomography in preventing event recurrence in
31
32 patients with vasospasm-induced acute coronary syndrome. *Int J Cardiovasc Imaging*.
33
34 2018; 34(11): 1697-706.
- 35
36
37
38 10. Kim MC, Ahn Y, Park KH, et al. Clinical outcomes of low-dose aspirin
39
40 administration in patients with variant angina pectoris. *Int J Cardiol*. 2013; 167(5):
41
42 2333-4.
- 43
44
45
46 11. Lim AY, Park TK, Cho SW, et al. Clinical implications of low-dose aspirin on
47
48 vasospastic angina patients without significant coronary artery stenosis; a propensity
49
50 score-matched analysis. *Int J Cardiol*. 2016; 221: 161-6.
- 51
52
53
54
55
56
57
58 12. Ishii M, Kaikita K, Sato K, et al. Impact of aspirin on the prognosis in patients
59
60

1
2
3
4 with coronary spasm without significant atherosclerotic stenosis. *Int J Cardiol.* 2016;
5
6 220: 328-32.
7

8
9
10 13. Cho SS, Jo SH, Han SH, et al. Clopidogrel plus Aspirin Use is Associated with
11
12 Worse Long-Term Outcomes, but Aspirin Use Alone is Safe in Patients with
13
14 Vasospastic Angina: Results from the VA-Korea Registry, A Prospective
15
16 Multi-Center Cohort. *Sci Rep.* 2019; 9(1): 17783.
17

18
19
20 14. Mori H, Takahashi J, Sato K, et al. The impact of antiplatelet therapy on patients
21
22 with vasospastic angina: A multicenter registry study of the Japanese Coronary Spasm
23
24 Association. *Int J Cardiol Heart Vasc.* 2020; 29: 100561.
25
26

27
28
29 15. Yasue H, Mizuno Y, Harada E. Coronary artery spasm - Clinical features,
30
31 pathogenesis and treatment. *Proc Jpn Acad Ser B Phys Biol Sci.* 2019; 95(2): 53-66.
32
33

34
35
36 16. Capodanno D, Alfonso F, Levine GN, Valgimigli M, Angiolillo DJ. ACC/AHA
37
38 Versus ESC Guidelines on Dual Antiplatelet Therapy: JACC Guideline Comparison.
39
40 *J Am Coll Cardiol.* 2018; 72(23 Pt A): 2915-31.
41
42

43
44
45 17. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual
46
47 antiplatelet therapy in coronary artery disease developed in collaboration with
48
49 EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the
50
51 European Society of Cardiology (ESC) and of the European Association for
52
53 Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2018; 39(3): 213-60.
54
55
56

57
58 18. Picard F, Sayah N, Spagnoli V, Adjedj J, Varenne O. Vasospastic angina: A
59
60

- 1
2
3
4 literature review of current evidence. *Arch Cardiovasc Dis.* 2019; 112(1): 44-55.
5
6
7
8 19. Miwa K, Kambara H, Kawai C. Effect of aspirin in large doses on attacks of
9
10 variant angina. *Am Heart J.* 1983; 105(2): 351-5.
11
12
13 20. Iwamoto J, Saito Y, Honda A, Matsuzaki Y. Clinical features of gastroduodenal
14
15 injury associated with long-term low-dose aspirin therapy. *World J Gastroenterol.*
16
17 2013; 19(11): 1673-82.
18
19
20 21. Antithrombotic Trialists C, Baigent C, Blackwell L, et al. Aspirin in the primary
22
23 and secondary prevention of vascular disease: collaborative meta-analysis of
24
25 individual participant data from randomised trials. *Lancet.* 2009; 373(9678): 1849-60.
26
27
28
29 22. Xie W, Luo Y, Liang X, Lin Z, Wang Z, Liu M. The Efficacy And Safety Of
30
31 Aspirin As The Primary Prevention Of Cardiovascular Disease: An Updated
32
33 Meta-Analysis. *Ther Clin Risk Manag.* 2019; 15: 1129-40.
34
35
36
37 23. Whitlock EP, Burda BU, Williams SB, Guirguis-Blake JM, Evans CV. Bleeding
38
39 Risks With Aspirin Use for Primary Prevention in Adults: A Systematic Review for
40
41 the U.S. Preventive Services Task Force. *Ann Intern Med.* 2016; 164(12): 826-35.
42
43
44
45 24. Hangouche AJE, Lamliki O, Oukerraj L, et al. Kounis syndrome induced by oral
46
47 intake of aspirin: case report and literature review. *Pan Afr Med J.* 2018; 30: 301.
48
49
50
51 25. Shah NH, Schneider TR, DeFaria Yeh D, Cahill KN, Laidlaw TM.
52
53 Eosinophilia-Associated Coronary Artery Vasospasm in Patients with
54
55 Aspirin-Exacerbated Respiratory Disease. *J Allergy Clin Immunol Pract.* 2016; 4(6):
56
57
58
59
60

1
2
3
4 1215-9.
5
6

7 26. Bates ER, Lau WC. Controversies in antiplatelet therapy for patients with
8 cardiovascular disease. *Circulation*. 2005; 111(17): e267-71.
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33

34 Figure 1. Flow diagram fo identification process
35
36

37 Figure 2. Aspirin use is not associated with low incidence of MACE in patients with
38 VSA.
39
40
41
42

43 Figure 3. Subgroub analysis of MACE of aspirin use in patients with VSA.
44
45

46 Figure 4. Secondary endpiont including myocardial infarction, cardiac death and all
47 cause death during 1 to 5 years of follow-up.
48
49
50

51 Figure 5. Assess of bias risk of the studies.
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

	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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

For peer review only

Table 2. Clinical characteristics of patients in included studies.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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
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,	/	104 (92.9) vs. 101 (90.2) ,	420 (96.9) vs. 275 (95.8),	50 (65) vs. 48 (62),	152 (24.2) vs. 162(16.12),	316 (94.3%) vs. 313 (93.4%),
n (%)		p = 0.472	p = 0.46	p = 0.738	p = 0.001	p = 0.75
Statin,	/	38 (33.9) vs. 40 (35.7),	182 (42.0) vs. 113 (39.4) ,	/	123 (19.7) vs. 119(11.9),	103 (30.7%) vs. 95 (28.4%),
n (%)		p = 0.779	p = 0.49		p = 0.001	p = 0.55
ACEI / ARB,	/	33(29.5) vs. 25 (22.3),	69 (15.9) vs. 43 (15.0) ,	/	152 (24.3) vs.126(12.6),	73 (21.8%) vs. 71 (21.2%) ,
n (%)		p = 0.288	p = 0.74		p = 0.001	p = 0.93
Beta-blocker,	/	6 (5.4) vs. 7 (6.3),	1 (0.2) vs. 0 (0.0),	17 (22) vs. 23 (30),	54 (8.65) vs. 59(5.88),	/
n (%)		p = 0.775	p = 0.48	p = 0.270	p = 0.065	

ACEI / ARB = angiotensin-converting enzyme inhibitor / angiotensin receptor blocker

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

For peer review only

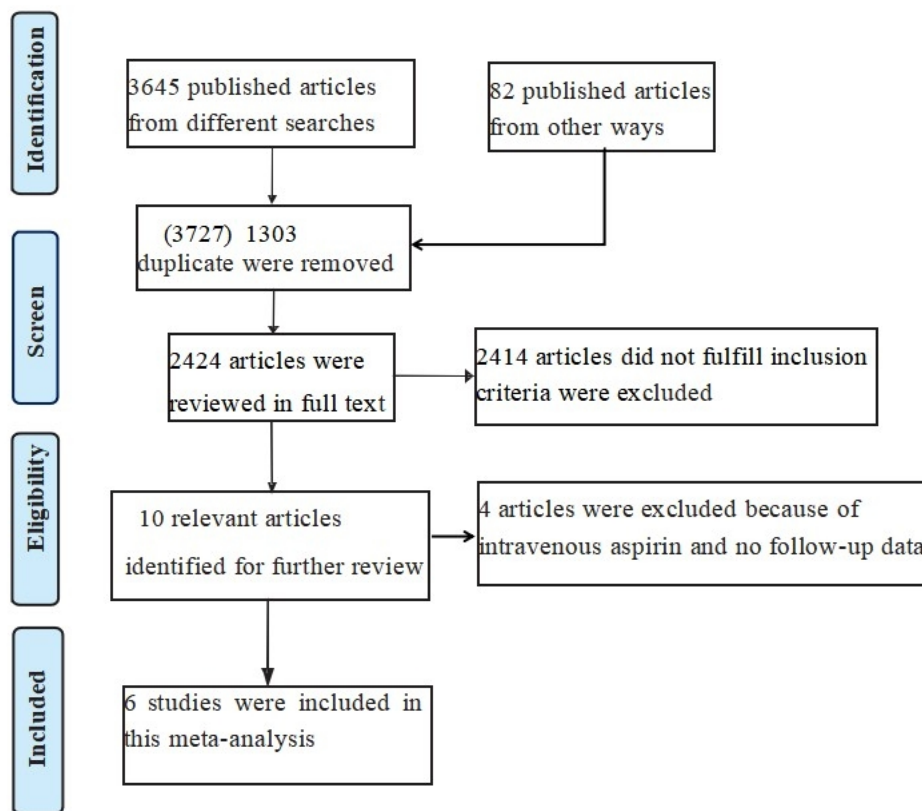


Figure 1. Flow diagram for identification process

132x119mm (144 x 144 DPI)

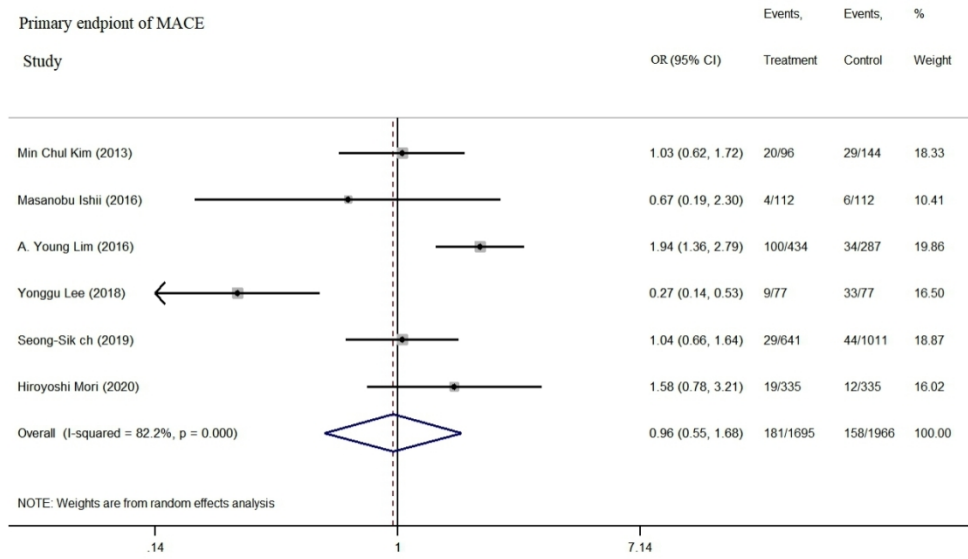


Figure 2. Aspirin use is not associated with low incidence of MACE in patients with VSA.

231x135mm (144 x 144 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

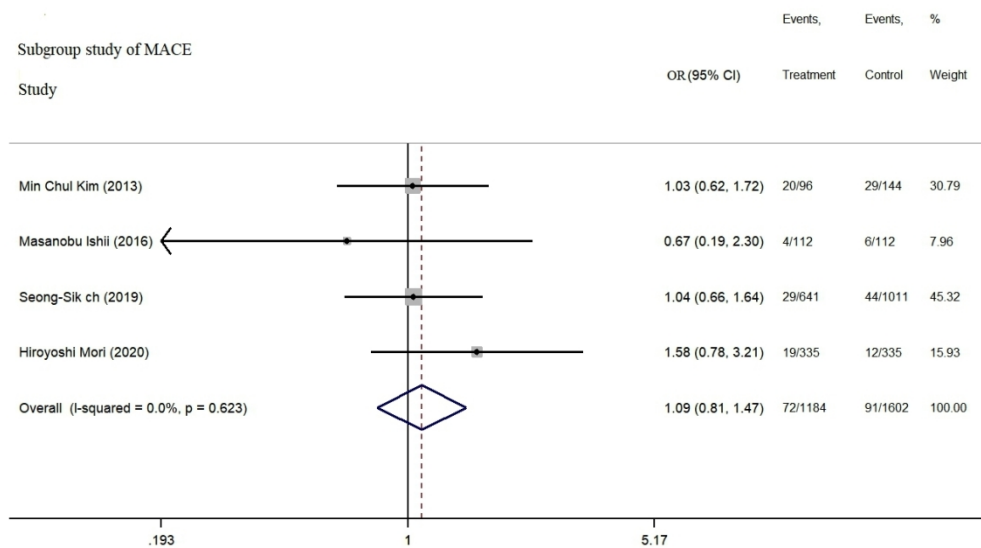


Figure 3. Subgroup analysis of MACE of aspirin use in patients with VSA.

233x136mm (144 x 144 DPI)

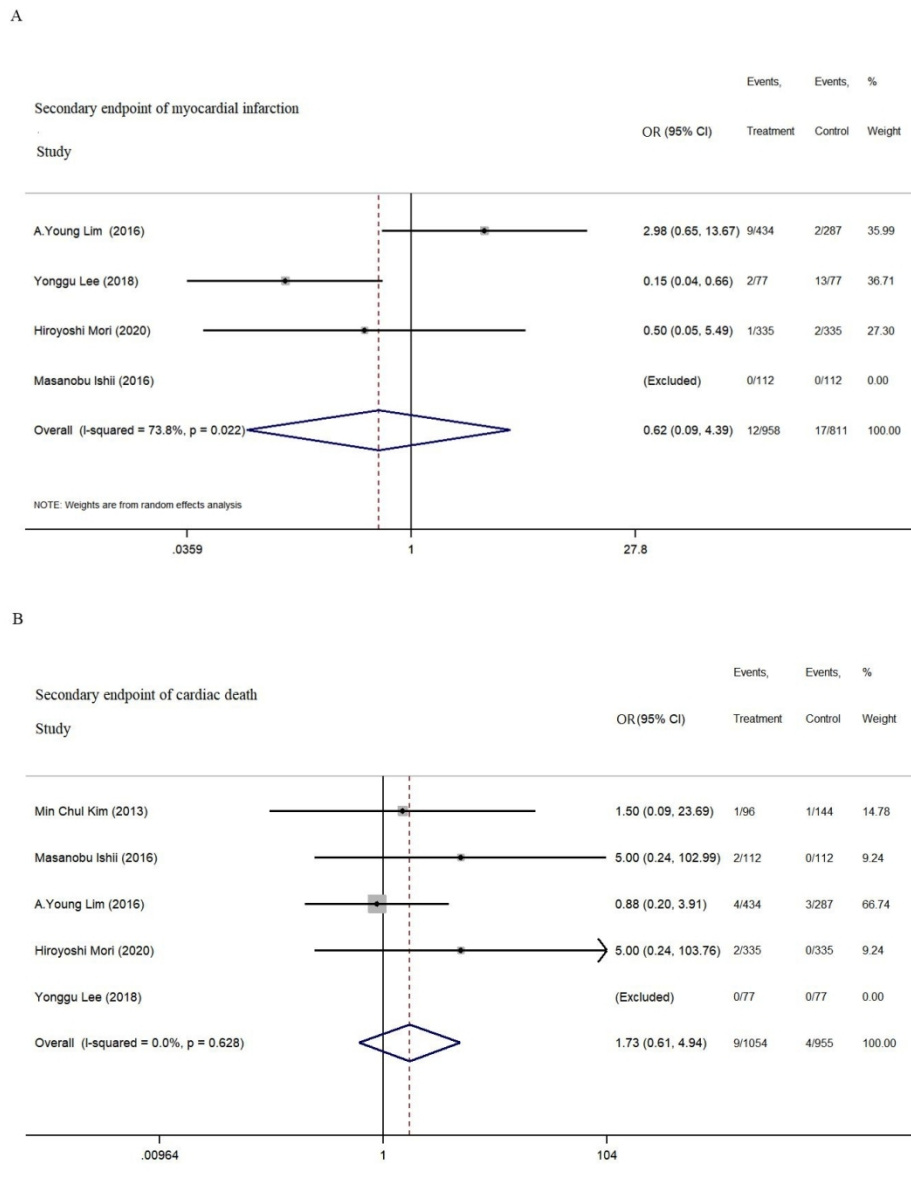


Figure 4. Secondary endpoint including myocardial infarction, cardiac death and all cause death during 1 to 5 years of follow-up.

240x305mm (144 x 144 DPI)

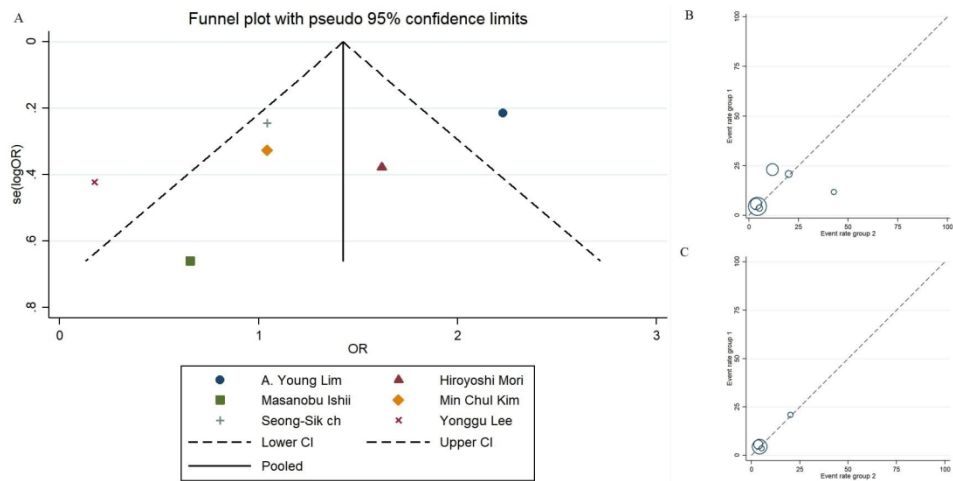


Figure 5. Assess of bias risk of the studies.

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

Page 1 of 2

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

For peer review only, <http://bmjopen.bmj.com/site/about/guidelines.xhtml>
For more information, visit: www.prisma-statement.org



PRISMA 2009 Checklist

For peer review only

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- 11
- 12
- 13
- 14
- 15
- 16
- 17
- 18
- 19
- 20
- 21
- 22
- 23
- 24
- 25
- 26
- 27
- 28
- 29
- 30
- 31
- 32
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47

BMJ Open

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

Journal:	<i>BMJ Open</i>
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

SCHOLARONE™
Manuscripts



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 Chen⁵, MD

Author's Affiliation:

¹Department of Cardiology; ²Department of Health Management; ³Department of Pharmacy; ⁴Shenzhen 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. ⁵School 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

1
2
3
4 higher incidence of cardiac death (OR = 1.73, 95% CI: 0.61–4.94, p = 0.444, $I^2 = 0\%$)
5
6 during follow-up, but with no significant difference between-group.
7
8

9 **Conclusion:** Aspirin use may be not likely to reduce future cardiovascular events in
10
11 VSA patients without significant stenosis.
12
13
14
15
16

17 **Trial registration number:** PROSPERO (CRD42020214891)
18
19
20
21

22 **Keywords:** aspirin, vasospastic angina, MACE, cardiac death, myocardial infarction,
23
24 longtime follow-up
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3
4 Controlled Trials was carried out for gathering data. The keywords were “vasospastic
5
6 angina, coronary vasospasms, vasospasm, variant angina, Prinzmetal's variant angina,
7
8 spastic coronary angina, coronary artery spasm,” as well as “aspirin, antiplatelet
9
10 therapy”. Certain additional related publications, such as review articles and editorials,
11
12 were also assessed. This study was registered with PROSPERO (CRD42020214891).
13
14
15

16 ***Patient and public involvement***

17
18 Study participants who met the eligibility criteria as outlined above. All the included
19
20 patients were diagnosed with epicardial coronary vasospasms by provocation test.
21
22 Participants and other members of public were not involved in the recruitment, design,
23
24 conduct, reporting or dissemination plans.
25
26
27
28

29 ***Study selection and data extraction***

30
31 Following are the inclusion criteria: (i) diagnosed with VSA on provocation test, (ii)
32
33 absence of significant stenosis ($\leq 50\%$), (iii) the treatment group was administered
34
35 oral aspirin and the control group no aspirin or placebo, and (iv) articles published in
36
37 English. The exclusion criteria included significant stenosis ($\geq 50\%$), intravenous
38
39 aspirin, case report, and case series. The study data was independently extracted by
40
41 two investigators, namely, Lin and Chen, using pre-defined extraction forms and
42
43 conflict was resolved by a third reviewer.
44
45
46
47
48
49

50 ***Data analysis and risk of bias assessment***

51
52 Major cardiovascular adverse event (MACE) was the primary endpoint, while
53
54 myocardial infarction and cardiac death during follow-up were the secondary
55
56 endpoints. MACE has been described as cardiac death, acute coronary syndrome, and
57
58
59
60

1
2
3
4 hospitalization due to unstable angina, percutaneous coronary intervention,
5
6 symptomatic arrhythmia, appropriate implantable cardioverter defibrillator (ICD), and
7
8 shock. The Newcastle-Ottawa Quality Assessment Scale (NOS) tool was utilized to
9
10 assess the risk of bias and Begg's funnel plot was used to evaluate publication bias.
11
12

13 ***Statistical analysis***

14
15
16 STATA software (version 14.0; StataCorp, College Station, TX, USA) was utilized to
17
18 perform the meta-analysis. MACE, the primary endpoint, and myocardial infarction
19
20 and cardiac death, the secondary endpoints, were evaluated as combined odds ratios
21
22 with 95% confidence intervals (CIs). Heterogeneity between studies was derived with
23
24 the help of I^2 statistic. If $I^2 > 50\%$, the random effect model was used to assess
25
26 heterogeneity, whereas if $I^2 < 50\%$, the fixed effect model was utilized to evaluate
27
28 heterogeneity. Subgroups were studied to reduce the heterogeneity if $I^2 > 50\%$. P
29
30 values < 0.05 were considered to be statistically significant.
31
32
33
34
35
36

37 **RESULTS**

38 ***Characteristics of included studies***

39
40
41 Search engines mentioned herein before were scanned to identify about 3,645 related
42
43 studies, among which 1,303 articles were duplicated, whereas 2,414 articles did not
44
45 fulfill the inclusion criteria and were thus expelled from the study. Therefore, four
46
47 propensity-matched cohorts, one retrospective analysis, and one prospective
48
49 multicenter cohort (Figure 1), including a total of 3,661 patients (aspirin group, $n =$
50
51 1,695; no aspirin group, $n = 1,966$, Table 1) eventually formed part of the study. 4
52
53 studies underwent coronary provocation test, except for 1 study (Seong-Sik Cho, 2019)
54
55
56
57
58
59
60

1
2
3
4 receiving ECG provocation test. All studies provided the primary endpoint, with
5
6 follow-up durations ranging from 1 to 5 years (Table 2).
7

8 9 ***Primary and secondary endpoints***

10
11 No significant correlation was recorded between aspirin use and MACE incidence
12
13 with follow-up of 1–5 years (combined odds ratio [OR] = 0.90, 95% confidence
14
15 interval [CI]: 0.55–1.68, $p = 0.829$, $I^2 = 82.2\%$ [Figure 2]; subgroup analysis: OR =
16
17 1.09, 95% CI: 0.81–1.47, $I^2 = 0\%$, [Figure 3]).
18
19

20
21
22 Myocardial infarction was reported in four studies, and cardiac death was
23
24 reported in five studies for the secondary endpoint. Moreover, aspirin use was tended
25
26 to be linked to a lower incidence of myocardial infarction (OR = 0.62, 95% CI: 0.09–
27
28 4.36, $p = 0.615$, $I^2 = 73.8\%$) and a higher incidence of cardiac death (OR = 1.73, 95%
29
30 CI: 0.61–4.94, $p = 0.444$, $I^2 = 0\%$) during follow-up, but statistical difference was
31
32 lacking between the two groups (Figure 4).
33
34
35

36 37 ***Risk of bias assessment and heterogeneity analysis***

38
39
40 The scores of NOS for study quality assessment of included studies ranged from 7 to
41
42 9 scores (Table 3). Publication bias with the studies of Lee and Lim was presented by
43
44 an asymmetry in the funnel plot (Figure 5). Between-study heterogeneity in
45
46 MACE-related research was 82.2%. Therefore, the outcome of subgroup analyses of
47
48 I^2 was 0%, indicating low publication bias (Figure 3). The between-study
49
50 heterogeneities in myocardial infarction and cardiac death-related studies were found
51
52 to be 73.8% and 0%, respectively, indicating the occurrence of high publication bias
53
54 regarding studies on myocardial infarction (Figure 4).
55
56
57
58
59
60

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

1
2
3
4 been significantly reduced by aspirin use among VSA patients during follow-up [11].
5
6 Acute intimal tears and erosion identified by optical coherence tomography (OCT) are
7
8 susceptible to thrombosis leading to MI as per Lee's findings. Therefore, aspirin was
9
10 thus evidenced to reduce adverse events in VSA patients with a greater number of
11
12 thrombotic intracoronary lesions. Nevertheless, aspirin use was not significantly
13
14 correlated with the occurrence of cardiovascular events among VSA patients with
15
16 nonsignificant stenosis during a 49-months mean follow-up period ($p = 0.541$) Ishi et
17
18 al. [14]. Moreover, the aspirin-treated group exhibited a similar MACE compared
19
20 with the no-antiplatelet agent group (HR 0.96, CI: 0.59–1.55, $p = 0.872$) as reported
21
22 by Cho. S.S et al. [15]. Antiplatelet therapy was recently shown by Mori et al. to exert
23
24 no beneficial effects on MACE (5.7% vs. 3.6%, $p = 0.20$) among VSA patients during
25
26 a 32-months median follow-up period [16].
27
28
29
30
31
32
33
34

35 A systematic analysis of the available studies investigating the effects of aspirin
36
37 use among VSA patients was conducted. Aspirin use may not be linked to a lower risk
38
39 of MACE and cardiac death as per this meta-analysis. The subgroup analysis for
40
41 MACE indicated that the study by Lee [11] and Lim [13] is quite heterogeneous. The
42
43 origin of heterogeneity in these studies may be attributable to chest pain recurrence in
44
45 the MACE, which gives an entirely different outcome due to the inclusion of other
46
47 literature. The following may be the possible reasons for the lack of beneficial effects
48
49 of aspirin use: (i) aspirin use is known to damage the gastric mucosal barrier and
50
51 increase the risk of erosions, ulcers, and bleeding by way of inhibiting
52
53 cyclooxygenase-1 enzyme activity [22]. Several meta-analyses have indicated that
54
55
56
57
58
59
60

1
2
3
4 aspirin's efficacy in primary prevention of cardiovascular disease needs to be weighed
5
6 against any increase in major bleeding [23-25]; (ii) attributable to adverse effects of
7
8 causing asthma and dyspnea, aspirin is likely to cause CAS and increase the
9
10 occurrence of MACE or cardiogenic death [26, 27]; (iii) the synthesis of prostacyclin,
11
12 a well-known vasodilator released by endothelial cells is inhibited by aspirin [28] and
13
14 CAS induced by aspirin, which could, in turn, cause recurrent angina leading to
15
16 rehospitalization, myocardial infarction, and cardiac death.
17
18
19
20
21

22 In addition, aspirin use has been found in this analysis to have a possible
23
24 protective effect on MI. The pharmacological mechanism easily explains the aspirin's
25
26 beneficial effects on MI. However there is great heterogeneity, which may be
27
28 attributed to the lack of related studies and a different definition of MI by Mori in his
29
30 study [16]. Aspirin use in CAS patients is both advantageous as well as
31
32 disadvantageous. Further investigations are necessary for the analysis of beneficial
33
34 effects to determine whether to recommend.
35
36
37
38
39

40 Several potential limitations should also be considered in the case of this
41
42 meta-analysis. First, MACE and MI have been defined differently in the included
43
44 articles. Ascribe to lack of original data, no standard definition of MACE is accessible
45
46 in this meta-analysis. Second, in one of the studies by Mori (2020), not aspirin but an
47
48 antiplatelet drug comprising aspirin and P2Y12 inhibitors have been used as the
49
50 therapeutic drug. Third, the sample size in the included studies is too small; only a
51
52 few studies have conducted propensity matching analysis to balance baseline
53
54 characteristics. The limitations inherent to multicenter observational studies
55
56
57
58
59
60

1
2
3
4 performed in both retrospective and prospective manners could not be avoided in this
5
6 analysis. Fourth, patients with 40% stenosis are deemed to be VSA patients without
7
8 coronary stenosis but might be benefit from aspirin. A subgroup analysis should be
9
10 performed next study. Finally, the major bleeding outcome was excluded from this
11
12 study, which is essential for understanding the advantages of antiplatelet therapy.
13
14
15 Considering that this study evaluated the prognosis of VSA patients using low-dose
16
17 aspirin as the first of its kind, it has its merits.
18
19
20
21

22 **CONCLUSIONS**

23
24 Aspirin use may not lessen cardiovascular events among VSA patients without
25
26 significant stenosis. Owing to its potential adverse effects, regular use of aspirin in
27
28 VSA patients without significant stenosis should involve a thoughtful discussion.
29
30
31

32 **Acknowledgments**

33
34 None
35

36 **Contributors**

37
38 YWL, YC and HYQ conceived, designed and led the study. YWL, QLC, YJ and SHD
39
40 investigated, conducted the study and collected data. YWL, HYQ and YC wrote,
41
42 revised and edited the manuscript. All authors supervised the study and approved of
43
44 the final version submitted.
45
46
47

48 **Funding**

49
50 This study was supported by a grant from the Shenzhen Key Medical Discipline
51
52 Construction Fund (No. SZXK003 and No. SZXK059) and Sanming Project of
53
54 Medicine in Shenzhen (No. SZSM201412012).
55
56

57 **Conflict of interest**

58
59 No conflict of interest
60

1
2
3 **Patient consent for publication**
4

5 Not required
6

7
8 **Provenance and peer review**
9

10 Not commissioned; externally peer reviewed.
11

12 **Data availability statement**
13

14 All data relevant to the study are included in the article or uploaded as supplementary
15 information.
16
17

18
19 **ORCID iD**
20

21 Yaowang Lin: <https://orcid.org/0000-0002-4075-4259>
22

23
24 **Ethics Statement**
25

26 The institutional review board at the Shenzhen People's Hospital approved the study
27 protocol
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 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):3504-3520.
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.

- 1
2
3
4 6. Collet JP, Thiele H, Barbato E, *et al.* 2020 ESC Guidelines for the
5
6 management of acute coronary syndromes in patients presenting without
7
8 persistent ST-segment elevation. *Eur Heart J* 2020.
- 9
10
11 7. Group ASC, Bowman L, Mafham M, *et al.* Effects of Aspirin for Primary
12
13 Prevention in Persons with Diabetes Mellitus. *N Engl J Med* 2018,
14
15 379(16):1529-1539.
- 16
17 8. Gaziano JM, Brotons C, Coppolecchia R, *et al.* Use of aspirin to reduce risk of
18
19 initial vascular events in patients at moderate risk of cardiovascular disease
20
21 (ARRIVE): a randomised, double-blind, placebo-controlled trial. *Lancet* 2018,
22
23 392(10152):1036-1046.
- 24
25 9. Guirguis-Blake JM, Evans CV, Senger CA, *et al.* Aspirin for the Primary
26
27 Prevention of Cardiovascular Events: A Systematic Evidence Review for the
28
29 U.S . Preventive Services Task Force. *Ann Intern Med* 2016, 164(12):804-813.
- 30
31 10. Zheng SL, Roddick AJ. Association of Aspirin Use for Primary Prevention
32
33 With Cardiovascular Events and Bleeding Events: A Systematic Review and
34
35 Meta-analysis. *Jama* 2019, 321(3):277-287.
- 36
37 11. Lee Y, Park HC, Shin J. Clinical efficacy of aspirin with identification of
38
39 intimal morphology by optical coherence tomography in preventing event
40
41 recurrence in patients with vasospasm-induced acute coronary syndrome. *Int J*
42
43 *Cardiovasc Imaging* 2018, 34(11):1697-1706.
- 44
45 12. Kim MC, Ahn Y, Park KH, *et al.* Clinical outcomes of low-dose aspirin
46
47 administration in patients with variant angina pectoris. *Int J Cardiol* 2013,
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4 167(5):2333-2334.
5
6
7 13. Lim AY, Park TK, Cho SW, *et al.* Clinical implications of low-dose aspirin on
8
9 vasospastic angina patients without significant coronary artery stenosis; a
10
11 propensity score-matched analysis. *Int J Cardiol* 2016, 221:161-166.
12
13
14 14. Ishii M, Kaikita K, Sato K, *et al.* Impact of aspirin on the prognosis in patients
15
16 with coronary spasm without significant atherosclerotic stenosis. *Int J Cardiol*
17
18 2016, 220:328-332.
19
20
21 15. Cho SS, Jo SH, Han SH, *et al.* Clopidogrel plus Aspirin Use is Associated
22
23 with Worse Long-Term Outcomes, but Aspirin Use Alone is Safe in Patients
24
25 with Vasospastic Angina: Results from the VA-Korea Registry, A Prospective
26
27 Multi-Center Cohort. *Sci Rep* 2019, 9(1):17783.
28
29
30
31 16. Mori H, Takahashi J, Sato K, *et al.* The impact of antiplatelet therapy on
32
33 patients with vasospastic angina: A multicenter registry study of the Japanese
34
35 Coronary Spasm Association. *Int J Cardiol Heart Vasc* 2020, 29:100561.
36
37
38
39 17. Yasue H, Mizuno Y, Harada E. Coronary artery spasm - Clinical features,
40
41 pathogenesis and treatment. *Proc Jpn Acad Ser B Phys Biol Sci* 2019,
42
43 95(2):53-66.
44
45
46
47 18. Capodanno D, Alfonso F, Levine GN, *et al.* ACC/AHA Versus ESC
48
49 Guidelines on Dual Antiplatelet Therapy: JACC Guideline Comparison. *J Am*
50
51 *Coll Cardiol* 2018, 72(23 Pt A):2915-2931.
52
53
54
55 19. Valgimigli M, Bueno H, Byrne RA, *et al.* 2017 ESC focused update on dual
56
57 antiplatelet therapy in coronary artery disease developed in collaboration with
58
59
60

- 1
2
3
4 EACTS: The Task Force for dual antiplatelet therapy in coronary artery
5
6 disease of the European Society of Cardiology (ESC) and of the European
7
8 Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018,
9
10 39(3):213-260.
11
12
13
14 20. Picard F, Sayah N, Spagnoli V, *et al.* Vasospastic angina: A literature review
15
16 of current evidence. *Arch Cardiovasc Dis* 2019, 112(1):44-55.
17
18
19 21. Miwa K, Kambara H, Kawai C. Effect of aspirin in large doses on attacks of
20
21 variant angina. *Am Heart J* 1983, 105(2):351-355.
22
23
24 22. Iwamoto J, Saito Y, Honda A, *et al.* Clinical features of gastroduodenal injury
25
26 associated with long-term low-dose aspirin therapy. *World J Gastroenterol*
27
28 2013, 19(11):1673-1682.
29
30
31 23. Antithrombotic Trialists C, Baigent C, Blackwell L, *et al.* Aspirin in the
32
33 primary and secondary prevention of vascular disease: collaborative
34
35 meta-analysis of individual participant data from randomised trials. *Lancet*
36
37 2009, 373(9678):1849-1860.
38
39
40
41 24. Xie W, Luo Y, Liang X, *et al.* The Efficacy And Safety Of Aspirin As The
42
43 Primary Prevention Of Cardiovascular Disease: An Updated Meta-Analysis.
44
45 *Ther Clin Risk Manag* 2019, 15:1129-1140.
46
47
48
49 25. Whitlock EP, Burda BU, Williams SB, *et al.* Bleeding Risks With Aspirin Use
50
51 for Primary Prevention in Adults: A Systematic Review for the U.S.
52
53 Preventive Services Task Force. *Ann Intern Med* 2016, 164(12):826-835.
54
55
56
57 26. Hangouche AJE, Lamliki O, Oukerraj L, *et al.* Kounis syndrome induced by
58
59
60

1
2
3
4 oral intake of aspirin: case report and literature review. *Pan Afr Med J* 2018,
5
6 30:301.
7

- 8
9 27. Shah NH, Schneider TR, DeFaria Yeh D, *et al.* Eosinophilia-Associated
10
11 Coronary Artery Vasospasm in Patients with Aspirin-Exacerbated Respiratory
12
13 Di sease. *J Allergy Clin Immunol Pract* 2016, 4(6):1215-1219.
14
15
16
17 28. Bates ER, Lau WC. Controversies in antiplatelet therapy for patients with
18
19 cardiovascular disease. *Circulation* 2005, 111(17):e267-271.
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

Beta-blocker,	/	6 (5.4) vs. 7 (6.3),	1 (0.2) vs. 0 (0.0),	17 (22) vs. 23 (30),	54 (8.65) vs. 59(5.88),	/
n (%)		p = 0.775	p = 0.48	p = 0.270	p = 0.065	

ACEI / ARB = angiotensin-converting enzyme inhibitor / angiotensin receptor blocker

For peer review only

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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) (0.6)	vs. 2	2 (0.6) 0 (0.0)	vs. vs. 6 (1.8)	2 (0.6) vs. 6 (1.8)	32-months
-------------------	------	---	--	-----	-----	-----	---	---	--------------------------	------------------	-------	--------------------	--------------------	------------------------	-----------

For peer review only

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

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

1
2
3
4
5
6 **Figure legend.**
7

8 Figure 1. Flow diagram for identification processes.
9

10
11 Figure 2. Aspirin use is not associated with a low incidence of MACE in patients with
12
13 VSA.
14

15
16 Figure 3. Subgroup analysis of MACE of aspirin use in patients with VSA.
17

18
19 Figure 4. Secondary endpoints including myocardial infarction, cardiac death, and
20
21 all-cause death during 1–5 years of follow-up.
22

23
24 Figure 5. Assessment of bias risk of the studies.
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

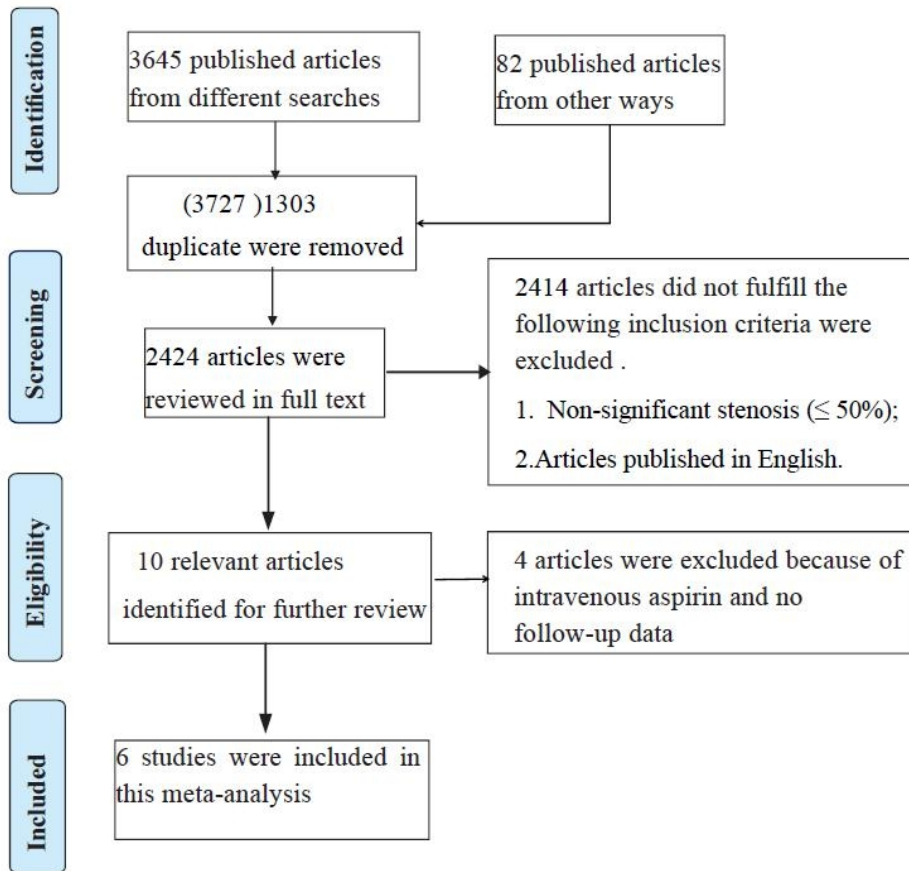


Figure 1. Flow diagram for identification processes.

Figure 1. Flow diagram for identification processes.

139x148mm (144 x 144 DPI)

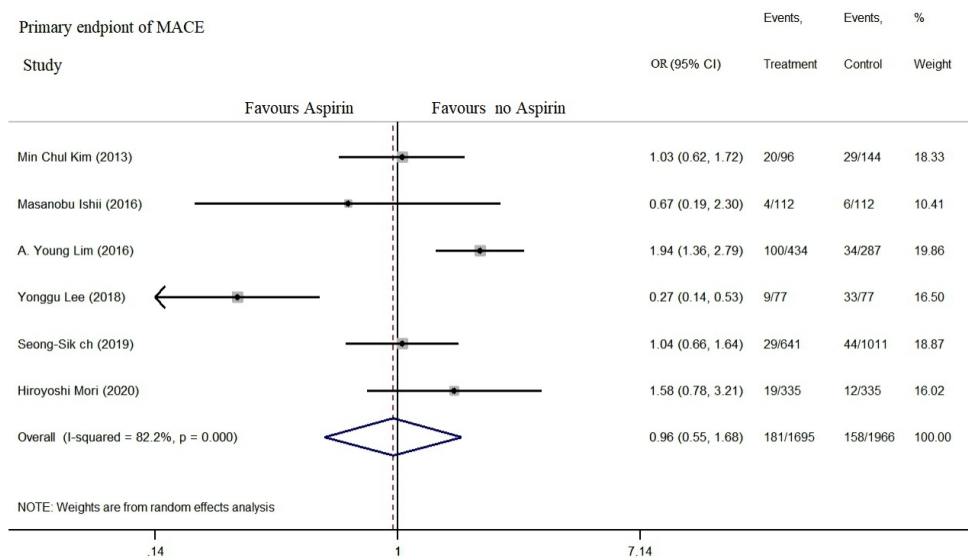


Figure 2. Aspirin use is not associated with a low incidence of MACE in patients with VSA.

231x135mm (144 x 144 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

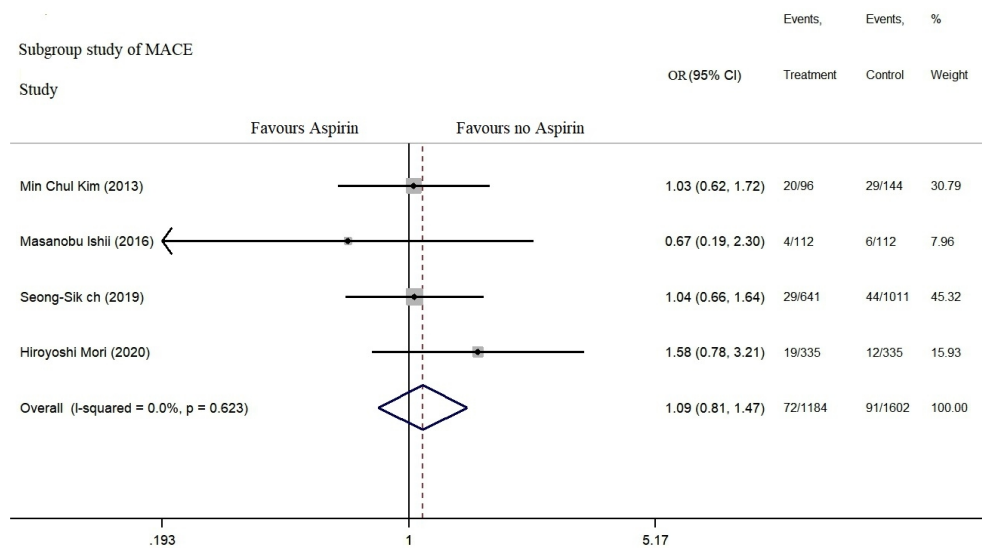


Figure 3. Subgroup analysis of MACE of aspirin use in patients with VSA.

233x136mm (144 x 144 DPI)

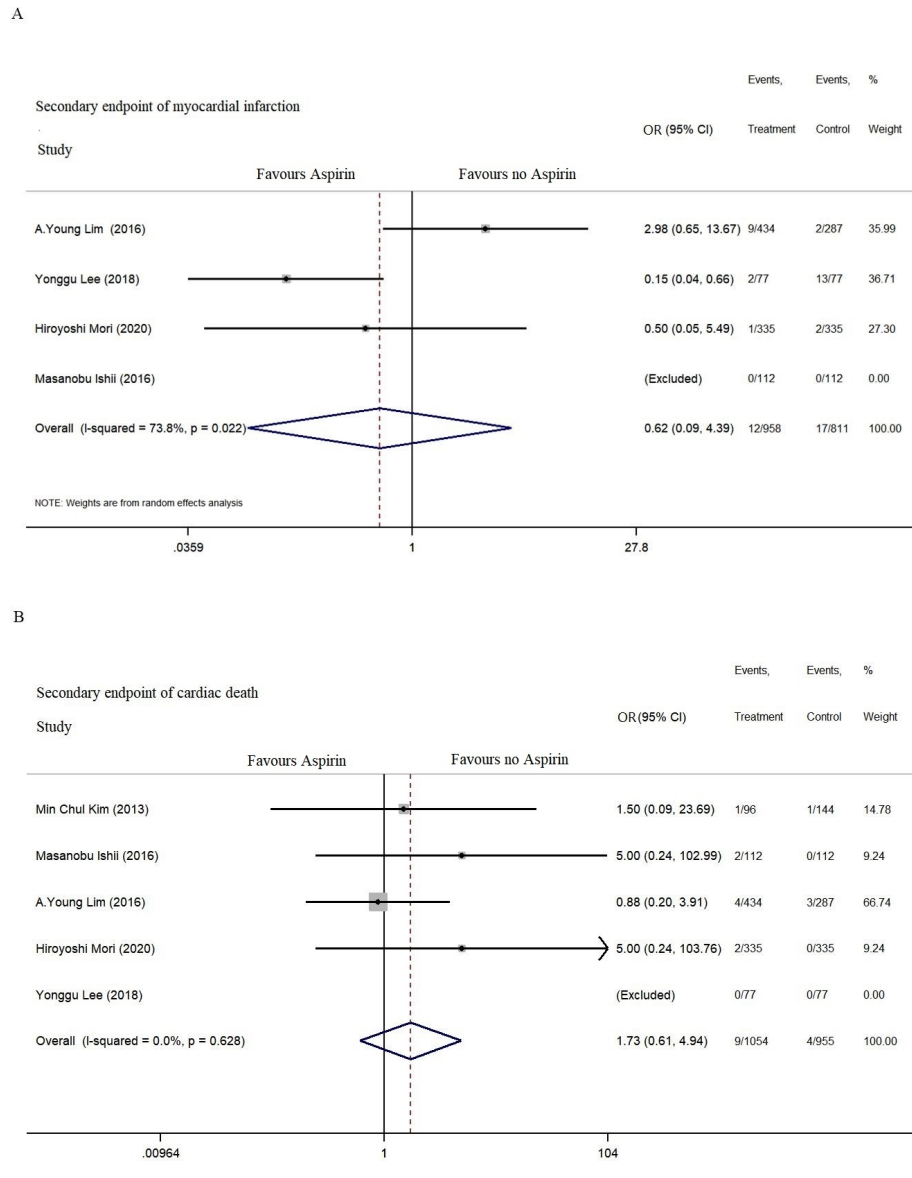


Figure 4. Secondary endpoints including myocardial infarction, cardiac death, and all-cause death during 1–5 years of follow-up.

240x305mm (144 x 144 DPI)

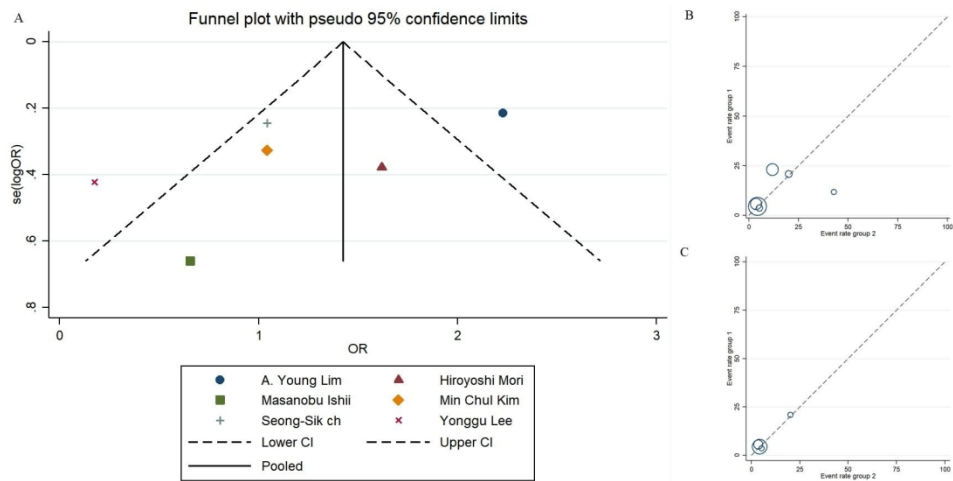


Figure 5. Assess of bias risk of the studies.

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

Page 1 of 2

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

For peer review only, <http://bmjopen.bmj.com/site/about/guidelines.xhtml>
For more information, visit: www.prisma-statement.org



PRISMA 2009 Checklist

For peer review only

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- 11
- 12
- 13
- 14
- 15
- 16
- 17
- 18
- 19
- 20
- 21
- 22
- 23
- 24
- 25
- 26
- 27
- 28
- 29
- 30
- 31
- 32
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47

BMJ Open

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

Journal:	<i>BMJ Open</i>
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

SCHOLARONE™
Manuscripts



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.

1
2
3
4 **Impact of Aspirin Use on Clinical Outcomes in Patients with Vasospastic Angina:**
5
6 **A Systematic Review and Meta-analysis**
7
8

9 Yaowang Lin, MD ^{1,4}; Yang Chen, MD ⁵; Jie Yuan, MD ^{1,4}; Shaohong Dong, MD ^{1,4};
10
11 Haiyan Qin, MD ^{2,4#}; Qiuling Chen, MD ^{3,4#}
12
13

14
15 **Author Affiliations:**
16

17
18 ¹Department of Cardiology; ²Department of Health Management; ³Department of
19
20 Pharmacy; ⁴Shenzhen People's Hospital, Second Clinical Medical College of Jinan
21
22 University, First affiliated Hospital of South University of Science and Technology,
23
24 Shenzhen, Guangdong. No. 1017, Dongmen Northern Road, 518020, Shenzhen,
25
26 Guangdong, PR China. ⁵School of Pharmacy, Guangdong Medical University,
27
28 Dongguan 523808, Guangdong, China
29
30
31
32
33
34
35

36
37 **Correspondence should be addressed to Haiyan Qin and Qiuling Chen**
38

39
40 Haiyan Qin, MD, e-mail: lgqinhaiyan@yeah.net
41
42

43
44 Qiuling Chen, MD, e-mail: szchenqiuling@yeah.net
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

1
2
3
4 **Results:** Four propensity-matched cohorts, one retrospective analysis, and one
5
6 prospective multicenter cohort, in total comprising 3,661 patients (aspirin use group, n
7
8 = 1,695; no aspirin use group, $n = 1,966$) were included in this meta-analysis. Aspirin
9
10 use and the incidence of major cardiovascular adverse events (MACE) with follow-up
11
12 of 1–5 years were not significantly correlated (combined OR = 0.90, 95% CI: 0.55–
13
14 1.68, $p = 0.829$, $I^2 = 82.2\%$; subgroup analysis: OR = 1.09, 95% CI: 0.81–1.47, $I^2 =$
15
16 0%). No significant difference was found between aspirin use and the incidence of
17
18 myocardial infarction (OR = 0.62, 95% CI: 0.09–4.36, $p = 0.615$, $I^2 = 73.8\%$) or cardiac
19
20 death (OR = 1.73, 95% CI: 0.61–4.94, $p = 0.444$, $I^2 = 0\%$) during follow-up.
21
22
23
24
25
26
27

28 **Conclusion:** Aspirin use may not reduce the risk of future cardiovascular events in
29
30 VSA patients without significant stenosis.
31
32
33
34
35
36
37

38 **Trial registration number:** PROSPERO (CRD42020214891)
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

44 **Keywords:** Aspirin, Vasospastic angina, MACE, Cardiac death, Myocardial infarction,
45
46
47 Long-term follow-up
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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.

1
2
3
4 ▶ The limitations inherent to multicenter observational studies performed in both
5
6 retrospective and prospective manners may have affected data analysis.
7

8
9
10 ▶ The conclusions of this study should be verified with randomized controlled trials
11
12 with larger sample size.
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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

1
2
3
4 A comprehensive search of related research articles conducted before October 2020 in
5
6 search engines such as PubMed, Web of Science, and Cochrane Central Register of
7
8 Controlled Trials was used to gather data. The keywords were “vasospastic angina”,
9
10 “coronary vasospasms”, “vasospasm”, “variant angina”, “Prinzmetal's variant angina”,
11
12 “spastic coronary angina”, “coronary artery spasm,” as well as “aspirin” and
13
14 “antiplatelet therapy”. Certain additional related publications, such as review articles
15
16 and editorials, were also assessed. This study was registered with PROSPERO
17
18 (CRD42020214891).
19
20
21
22
23
24
25
26
27
28

29 ***Patient and public involvement***

30
31
32 Study participants met the eligibility criteria as outlined above. All included patients
33
34 were diagnosed with epicardial coronary vasospasms by provocation test. Participants
35
36 and other members of the public were not involved in the recruitment, design, conduct,
37
38 reporting, or dissemination of this study.
39
40
41
42
43
44
45
46

47 ***Study selection and data extraction***

48
49
50 The patient inclusion criteria were as follows: (i) diagnosed with VSA on provocation
51
52 test, (ii) absence of significant stenosis ($\leq 50\%$), (iii) the treatment group was
53
54 administered oral aspirin and the control group received no aspirin or placebo, and (iv)
55
56 articles published in English. The exclusion criteria were as follows: significant stenosis
57
58
59
60

1
2
3
4 ($\geq 50\%$), intravenous aspirin, case report, and case series. The study data were
5
6 independently extracted by two investigators, namely Lin and Chen, using pre-defined
7
8 extraction forms; any conflict was resolved by a third reviewer.
9
10

11 12 13 14 15 16 ***Data analysis and risk of bias assessment*** 17

18
19 Major cardiovascular adverse events (MACE) were the primary endpoints, while
20
21 myocardial infarction and cardiac death during follow-up were the secondary endpoints.
22
23 MACE have been described as cardiac death, acute coronary syndrome, and
24
25 hospitalization due to unstable angina, percutaneous coronary intervention,
26
27 symptomatic arrhythmia, appropriate implantable cardioverter defibrillator (ICD), and
28
29 shock. The Newcastle-Ottawa Quality Assessment Scale (NOS) tool was utilized to
30
31 assess the risk of bias, and Begg's funnel plot was used to evaluate publication bias.
32
33
34
35
36
37
38
39
40
41

42 ***Statistical analysis*** 43 44

45 STATA software (version 14.0; StataCorp, College Station, TX, USA) was used for the
46
47 meta-analysis. MACE (primary endpoints) and myocardial infarction and cardiac death
48
49 (secondary endpoints) were evaluated as combined odds ratios (ORs) with 95%
50
51 confidence intervals (CIs). Heterogeneity between studies was derived using the I^2
52
53 statistic. If $I^2 > 50\%$, the random effect model was used to assess heterogeneity; if $I^2 <$
54
55 50% , the fixed effect model was utilized to evaluate heterogeneity. Subgroups were
56
57
58
59
60

1
2
3
4 studied to reduce the heterogeneity if $I^2 > 50\%$. P values < 0.05 were considered
5
6 statistically significant.
7
8
9

10 11 12 **RESULTS**

13 *Characteristics of included studies*

14
15
16
17
18 The search engines were reviewed to identify 3,645 related studies, among which 1,303
19
20 articles were duplicates and 2,414 articles did not fulfill the inclusion criteria and were
21
22 excluded from the study. After removing these studies, 4 propensity-matched cohorts
23
24 [11,13,14,16], 1 retrospective analysis [12], and 1 prospective multicenter cohort [15]
25
26 (Figure 1), including a total of 3,661 patients (aspirin group, $n = 1,695$; no aspirin group,
27
28 $n = 1,966$, Table 1) were included in the study. Four studies underwent coronary
29
30 provocation test, except for 1 study (Seong-Sik Cho, 2019) that used the ECG
31
32 provocation test. All studies provided the primary endpoint, with follow-up durations
33
34 ranging from 1 to 5 years (Table 2).
35
36
37
38
39
40
41
42
43
44
45
46
47
48

49 *Primary and secondary endpoints*

50
51 No significant correlation was recorded between aspirin use and MACE incidence
52
53 within the follow-up of 1–5 years (combined OR = 0.90, 95% CI: 0.55–1.68, $p = 0.829$,
54
55 $I^2 = 82.2\%$ [Figure 2]; subgroup analysis: OR = 0.89, 95% CI: 0.40–2.02, $I^2 = 86.9\%$
56
57 and OR = 1.09, 95% CI: 0.81–1.47, $I^2 = 0\%$, [Figure 3 A and B]).
58
59
60

1
2
3
4 Myocardial infarction was reported in 4 studies, and cardiac death was reported in
5
6 5 studies for the secondary endpoint. No significant difference was found between
7
8 aspirin use and the incidence of myocardial infarction (OR = 0.62, 95% CI: 0.09–4.36,
9
10 $p = 0.615$, $I^2 = 73.8\%$) or cardiac death (OR = 1.73, 95% CI: 0.61–4.94, $p = 0.444$, $I^2 =$
11
12 0%) during the follow-up (Figure 4).
13
14
15
16
17
18
19
20

21 ***Risk of bias assessment and heterogeneity analysis***

22
23
24 The NOS scores for study quality assessment of the included studies ranged from 7 to
25
26 9 (Table 3). Publication bias is presented by asymmetry in the funnel plot (Figure 5).
27
28 Between-study heterogeneity in MACE-related research was 82.2% and 86.9%.
29
30 Therefore, the outcome of subgroup analyses of I^2 was 0%, indicating low publication
31
32 bias (Figure 3). The between-study heterogeneities in myocardial infarction and cardiac
33
34 death-related studies were 73.8% and 0%, respectively, indicating the occurrence of
35
36 high publication bias for the myocardial infarction endpoint (Figure 4).
37
38
39
40
41
42
43
44
45
46

47 **DISCUSSION**

48
49
50 Our meta-analysis showed that aspirin had no significant effect on reducing MACE,
51
52 myocardial infarction, and cardiac death in VSA patients without significant stenosis.
53
54
55

56
57 Coronary artery spasm (CAS) has been reported to play a significant role in the
58
59 pathogenesis of ischemic heart disease, including acute coronary syndrome (ACS) and
60

1
2
3
4 chronic coronary syndrome (CCS) [17]. A common mechanism by which myocardial
5
6 infarction (MI) or MINOCA manifests is by platelet aggregation, which leads to
7
8 coronary thrombus formation. Aspirin inhibits cyclooxygenase-1 by reducing the
9
10 production of thromboxane A2 and therefore has been extensively used in primary or
11
12 secondary prevention of thrombosis among patients with atherosclerosis or coronary
13
14 artery disease [18, 19]. However, the benefit of low dosage aspirin in primary
15
16 prevention was counterbalanced by higher rates of treatment-related adverse events [7,
17
18 8]. Earlier studies have shown that aspirin use can aggravate CAS due to the lowered
19
20 production of thromboxane A2 and increased MACE incidence in VSA patients [20,
21
22 21]. Thus, the use of aspirin in VSA patients remains controversial.

23
24
25
26
27
28
29
30
31 MACE incidence in patients administered low-dose aspirin was significantly higher
32
33 than that among patients not administered aspirin (hazard ratio [HR] = 1.54; CI: 1.04-
34
35 2.28; $p = 0.037$) during a 52-month median follow-up period [13]. In contrast, MI (HR
36
37 = 0.13; CI: 0.03–0.61; $p = 0.014$) and chest pain recurrence (HR = 0.29; CI: 0.12–0.71;
38
39 $p = 0.006$) were observed by Lee *et al.* to have been significantly reduced by aspirin
40
41 use among VSA patients during follow-up [11]. Lee *et al.* showed that acute intimal
42
43 tears and erosion identified by optical coherence tomography (OCT) are susceptible to
44
45 thrombosis leading to MI. Therefore, aspirin was evidenced to reduce adverse events in
46
47 VSA patients with a greater number of thrombotic intracoronary lesions. Nevertheless,
48
49 aspirin use was not significantly correlated with the occurrence of cardiovascular events
50
51 among VSA patients with nonsignificant stenosis during a 49-month mean follow-up
52
53 period ($p = 0.541$) Ishi *et al.* [14]. Moreover, the aspirin-treated group exhibited a
54
55
56
57
58
59
60

1
2
3
4 similar MACE incidence compared with the non-antiplatelet agent group (HR 0.96, CI:
5
6 0.59–1.55, $p = 0.872$) as reported by Cho *et al.* [15]. Antiplatelet therapy was recently
7
8 shown by Mori *et al.* to have no beneficial effects on MACE (5.7% vs. 3.6%, $p = 0.20$)
9
10 among VSA patients during a 32-month median follow-up period [16].
11
12
13
14

15 Our meta-analysis indicates that aspirin use may not be linked to a lower risk of
16
17 MACE and cardiac death. The subgroup analysis of MACE indicated that the studies
18
19 by Lee [11] and Lim [13] were heterogeneous. The origin of heterogeneity in these
20
21 studies may be attributable to chest pain recurrence in the MACE, which gives an
22
23 entirely different outcome due to the definition. The following may potentially explain
24
25 the lack of beneficial effects of aspirin use: (i) Aspirin use is known to damage the
26
27 gastric mucosal barrier and increase risk of erosions, ulcers, and bleeding by inhibiting
28
29 cyclooxygenase-1 enzyme activity [22]. Several meta-analyses have indicated that
30
31 aspirin's efficacy in primary prevention of cardiovascular disease should be weighed
32
33 against any increase in major bleeding [23-25]. (ii) The adverse effects of asthma and
34
35 dyspnea may lead to CAS and increase the occurrence of MACE or cardiogenic death
36
37 with aspirin use [26, 27]. (iii) The synthesis of prostacyclin, a well-known vasodilator
38
39 released by endothelial cells, is inhibited by aspirin [28] and CAS is induced by aspirin.
40
41 This could, in turn, cause recurrent angina leading to rehospitalization, MI, and cardiac
42
43 death.
44
45
46
47
48
49
50
51
52
53

54 We found that aspirin use may have a protective effect against MI, which may be
55
56 explained by aspirin's pharmacological mechanism. However, there was high
57
58 heterogeneity in the study, which may be attributed to the lack of related studies and a
59
60

1
2
3
4 different definition of MI used by Mori [16]. Aspirin use in CAS patients can be both
5
6 advantageous and disadvantageous. Further investigation is necessary to determine
7
8 when to recommend aspirin use.
9
10

11
12 Several potential limitations should be considered in this meta-analysis. First,
13
14 MACE and MI have been defined differently in the included articles. Due to the lack
15
16 of original data, no standard definition of MACE was accessible in this meta-analysis.
17
18 Second, one study by Mori (2020) showed that an antiplatelet drug containing both
19
20 aspirin and P2Y12 inhibitors was used as the therapeutic drug. Third, the sample size
21
22 in this analysis is too small; only a few studies conducted propensity matching analysis
23
24 to balance baseline characteristics. The limitations inherent to multicenter observational
25
26 studies performed in both retrospective and prospective manners could not be avoided
27
28 in this analysis. Fourth, patients with 40% stenosis are considered to have VSA without
29
30 coronary stenosis but might benefit from aspirin. A subgroup analysis should be
31
32 performed in the next study. Finally, the major bleeding outcome was excluded from
33
34 this study, which is essential for understanding the advantages of antiplatelet therapy.
35
36 Despite these limitations, the merit of this study is that it is the first to evaluate the
37
38 prognosis of VSA patients using low-dose aspirin.
39
40
41
42
43
44
45
46
47
48
49
50
51
52

53 **CONCLUSIONS**

54
55
56 Aspirin use may not reduce the risk of cardiovascular events in VSA patients without
57
58 significant stenosis. Owing to its potential adverse effects, regular use of aspirin in VSA
59
60

1
2
3
4 patients without significant stenosis should involve a thoughtful discussion.
5
6
7
8
9

10 **Acknowledgments**

11
12
13 None
14
15

16 **Contributors**

17
18
19 YWL, QLC, and HYQ conceived, designed, and led the study. YWL, YC, YJ, and SHD
20 investigated, conducted the study, and collected data. YWL, HYQ, and QLC wrote,
21 revised, and edited the manuscript. All authors supervised the study and approved the
22 final version of the manuscript.
23
24
25
26
27
28
29
30
31
32

33 **Funding**

34
35
36 This study was supported by a grant from the Shenzhen Key Medical Discipline
37 Construction Fund (No. SZXK003 and No. SZXK059) and Sanming Project of
38 Medicine in Shenzhen (No. SZSM201412012).
39
40
41
42
43

44 **Conflict of interest**

45
46
47 No conflict of interest
48
49

50 **Patient consent for publication**

51
52
53 Not required
54
55

56 **Provenance and peer review**

57
58
59 Not commissioned; externally peer reviewed.
60

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

- 1
2
3
4 Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaborati
5
6 on with European Society of Cardiology Working Group on Coronary
7
8 Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor
9
10 Disorders International Study Group. *Eur Heart J* 2020, 41(37):3504-3520.
11
12
13
14
15 3. Lee BK, Lim HS, Fearon WF, *et al.* Invasive evaluation of patients with angina
16
17 in the absence of obstructive coronary artery disease. *Circulation* 2015,
18
19 131(12):1054-1060.
20
21
22
23 4. Khuddus MA, Pepine CJ, Handberg EM, *et al.* An intravascular ultrasound
24
25 analysis in women experiencing chest pain in the absence of obstructive
26
27 coronary artery disease: a substudy from the National Heart, Lung and Blood
28
29 Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *J Interv*
30
31 *Cardiol* 2010, 23(6):511-519.
32
33
34
35
36
37 5. Knuuti J, Wijns W, Saraste A, *et al.* 2019 ESC Guidelines for the diagnosis and
38
39 management of chronic coronary syndromes. *Eur Heart J* 2020, 41(3):407-477.
40
41
42
43 6. Collet JP, Thiele H, Barbato E, *et al.* 2020 ESC Guidelines for the management
44
45 of acute coronary syndromes in patients presenting without persistent ST-
46
47 segment elevation. *Eur Heart J* 2020.
48
49
50
51
52 7. Group ASC, Bowman L, Mafham M, *et al.* Effects of Aspirin for Primary
53
54 Prevention in Persons with Diabetes Mellitus. *N Engl J Med* 2018,
55
56 379(16):1529-1539.
57
58
59
60

- 1
2
3
4 8. Gaziano JM, Brotons C, Coppolecchia R, *et al.* Use of aspirin to reduce risk of
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
10. Zheng SL, Roddick AJ. Association of Aspirin Use for Primary Prevention With
Cardiovascular Events and Bleeding Events: A Systematic 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.

- 1
2
3
4 14. Ishii M, Kaikita K, Sato K, *et al.* Impact of aspirin on the prognosis in patients
5
6 with coronary spasm without significant atherosclerotic stenosis. *Int J Cardiol*
7
8 2016, 220:328-332.
9
10
11
12 15. Cho SS, Jo SH, Han SH, *et al.* Clopidogrel plus Aspirin Use is Associated with
13
14 Worse Long-Term Outcomes, but Aspirin Use Alone is Safe in Patients with
15
16 Vasospastic Angina: Results from the VA-Korea Registry, A Prospective Multi-
17
18 Center Cohort. *Sci Rep* 2019, 9(1):17783.
19
20
21
22
23 16. Mori H, Takahashi J, Sato K, *et al.* The impact of antiplatelet therapy on patients
24
25 with vasospastic angina: A multicenter registry study of the Japanese Coronary
26
27 Spasm Association. *Int J Cardiol Heart Vasc* 2020, 29:100561.
28
29
30
31
32 17. Yasue H, Mizuno Y, Harada E. Coronary artery spasm - Clinical features,
33
34 pathogenesis and treatment. *Proc Jpn Acad Ser B Phys Biol Sci* 2019, 95(2):53-
35
36 66.
37
38
39
40
41 18. Capodanno D, Alfonso F, Levine GN, *et al.* ACC/AHA Versus ESC Guidelines
42
43 on Dual Antiplatelet Therapy: JACC Guideline Comparison. *J Am Coll Cardiol*
44
45 2018, 72(23 Pt A):2915-2931.
46
47
48
49 19. Valgimigli M, Bueno H, Byrne RA, *et al.* 2017 ESC focused update on dual
50
51 antiplatelet therapy in coronary artery disease developed in collaboration with
52
53 EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease
54
55 of the European Society of Cardiology (ESC) and of the European Association
56
57 for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018, 39(3):213-260.
58
59
60

- 1
2
3
4 20. Picard F, Sayah N, Spagnoli V, *et al.* Vasospastic angina: A literature review of
5
6 current evidence. *Arch Cardiovasc Dis* 2019, 112(1):44-55.
7
8
9
10 21. Miwa K, Kambara H, Kawai C. Effect of aspirin in large doses on attacks of
11
12 variant angina. *Am Heart J* 1983, 105(2):351-355.
13
14
15
16 22. Iwamoto J, Saito Y, Honda A, *et al.* Clinical features of gastroduodenal injury
17
18 associated with long-term low-dose aspirin therapy. *World J Gastroenterol*
19
20 2013, 19(11):1673-1682.
21
22
23
24 23. Antithrombotic Trialists C, Baigent C, Blackwell L, *et al.* Aspirin in the primary
25
26 and secondary prevention of vascular disease: collaborative meta-analysis of
27
28 individual participant data from randomised trials. *Lancet* 2009,
29
30 373(9678):1849-1860.
31
32
33
34
35 24. Xie W, Luo Y, Liang X, *et al.* The Efficacy And Safety Of Aspirin As The
36
37 Primary Prevention Of Cardiovascular Disease: An Updated Meta-Analysis.
38
39 *Theor Clin Risk Manag* 2019, 15:1129-1140.
40
41
42
43
44 25. Whitlock EP, Burda BU, Williams SB, *et al.* Bleeding Risks With Aspirin Use
45
46 for Primary Prevention in Adults: A Systematic Review for the U.S. Preventive
47
48 Services Task Force. *Ann Intern Med* 2016, 164(12):826-835.
49
50
51
52
53 26. Hangouche AJE, Lamliki O, Oukerraj L, *et al.* Kounis syndrome induced by
54
55 oral intake of aspirin: case report and literature review. *Pan Afr Med J* 2018,
56
57 30:301.
58
59
60

- 1
2
3
4 27. Shah NH, Schneider TR, DeFaria Yeh D, *et al.* Eosinophilia-Associated
5
6 Coronary Artery Vasospasm in Patients with Aspirin-Exacerbated Respiratory
7
8 Disease. *J Allergy Clin Immunol Pract* 2016, 4(6):1215-1219.
9
10
11
12 28. Bates ER, Lau WC. Controversies in antiplatelet therapy for patients with
13
14 cardiovascular disease. *Circulation* 2005, 111(17):e267-271.
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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,	/	62 (55.4) vs. 60 (53.6) ,	91 (21.0) vs. 62 (21.6),	/	98 (15.4) vs.160(15.8) ,	156 (46.6%) vs. 142 (42.4%) ,
n (%)		p = 0.788	p = 0.84		p = 0.800	p = 0.31
Ca channel blocker,	/	104 (92.9) vs. 101	420 (96.9) vs. 275 (95.8),	50 (65) vs. 48 (62),	152 (24.2) vs. 162(16.12),	316 (94.3%) vs. 313 (93.4%),
n (%)		(90.2) ,	p = 0.46	p = 0.738	p = 0.001	p = 0.75
		p = 0.472				
Statin,	/	38 (33.9) vs. 40 (35.7),	182 (42.0) vs. 113 (39.4) ,	/	123 (19.7) vs. 119(11.9),	103 (30.7%) vs. 95 (28.4%),
n (%)		p = 0.779	p = 0.49		p = 0.001	p = 0.55
ACEI / ARB,	/	33(29.5) vs. 25 (22.3),	69 (15.9) vs. 43 (15.0) ,	/	152 (24.3) vs.126(12.6),	73 (21.8%) vs. 71 (21.2%) ,
n (%)		p = 0.288	p = 0.74		p = 0.001	p = 0.93
Beta-blocker,	/	6 (5.4) vs. 7 (6.3),	1 (0.2) vs. 0 (0.0),	17 (22) vs. 23 (30),	54 (8.65) vs. 59(5.88),	/
n (%)		p = 0.775	p = 0.48	p = 0.270	p = 0.065	

ACEI / ARB = angiotensin-converting enzyme inhibitor / angiotensin receptor blocker

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

For peer review only

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

1															
2															
3															
4															
5			Coronary artery					all cause death, acute coronary							
6	Seong-Sik	2019	Prospective	spasm (stenosis ≤ 1652	641	1011	100	syndrome, and symptomatic	29 (4.5) vs.	/	/	3 (0.5) vs.	3-year		
7	Cho		multicenter cohort	50%)				arrhythmia	44(4.4)			7(0.7)			
8															
9															
10								cardiac death, nonfatal							
11								myocardial infarction,							
12	Hiroyoshi	2020	Retrospective study,	Coronary artery			Aspirin 100	hospitalization due to unstable	19 (5.7)	1 (0.3) vs. 2	2 (0.6) vs.	2 (0.6)	32-months		
13	Mori		propensity score-	spasm (stenosis ≤ 670	335	335	and P2Y12	angina pectoris,	vs. 12 (3.6)	(0.6)	0 (0.0)	vs. 6 (1.8)			
14			matched analysis	50%)			inhibitors.	and appropriate ICD shock							
15															
16															
17															
18															
19															
20															
21															
22															
23															
24															
25															
26															
27															
28															
29															
30															
31															
32															
33															
34															
35															
36															
37															
38															
39															
40															
41															
42															
43															
44															
45															
46															

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

For peer review only

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

1
2
3
4
5
6
7
8 **Figure legends.**
9

10
11 Figure 1. Flow diagram for identification processes.
12

13
14 Figure 2. Aspirin use is not associated with a low incidence of MACE in patients with
15
16
17 VSA.
18

19
20 Figure 3. Subgroup analysis of MACE with aspirin use in patients with VSA.
21

22
23 Figure 4. Secondary endpoints including myocardial infarction, cardiac death, and all-
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
cause death during 1–5 years of follow-up.

Figure 5. Assessment of bias risk of the studies.

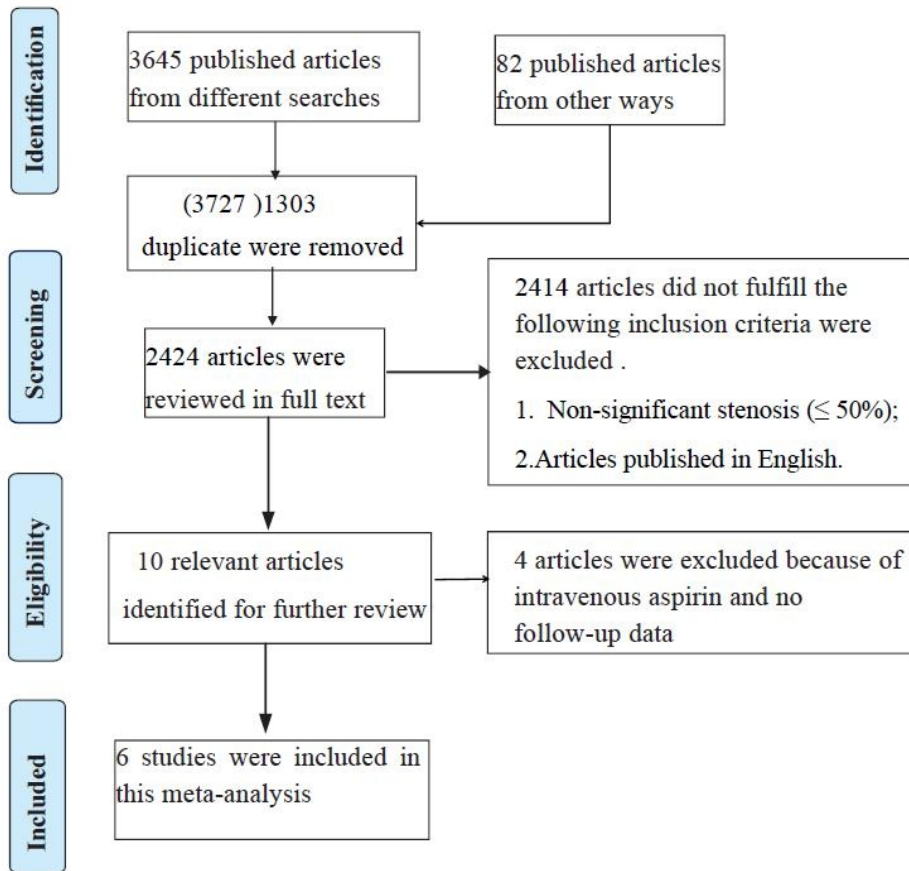


Figure 1. Flow diagram for identification processes.

Figure 1. Flow diagram for identification processes.

139x148mm (144 x 144 DPI)

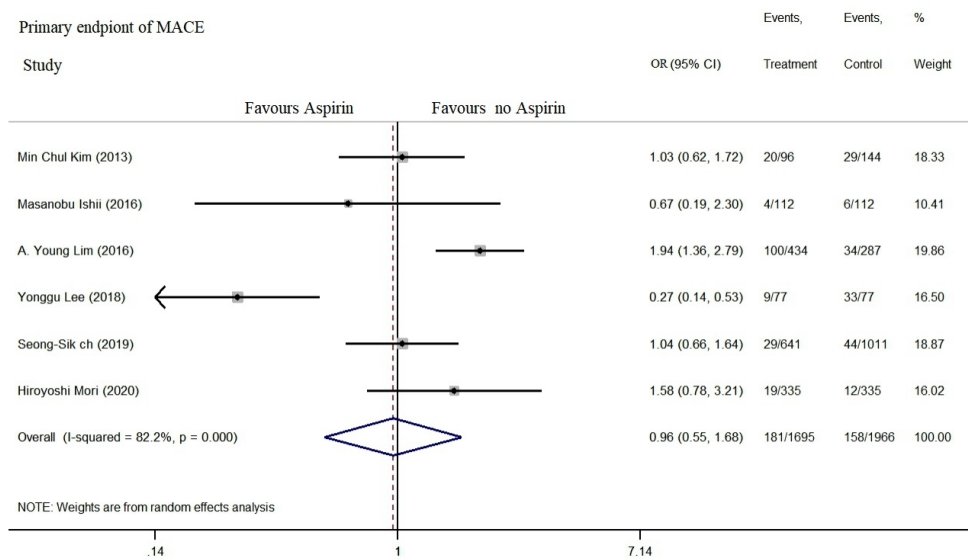


Figure 2. Aspirin use is not associated with a low incidence of MACE in patients with VSA.

231x135mm (144 x 144 DPI)

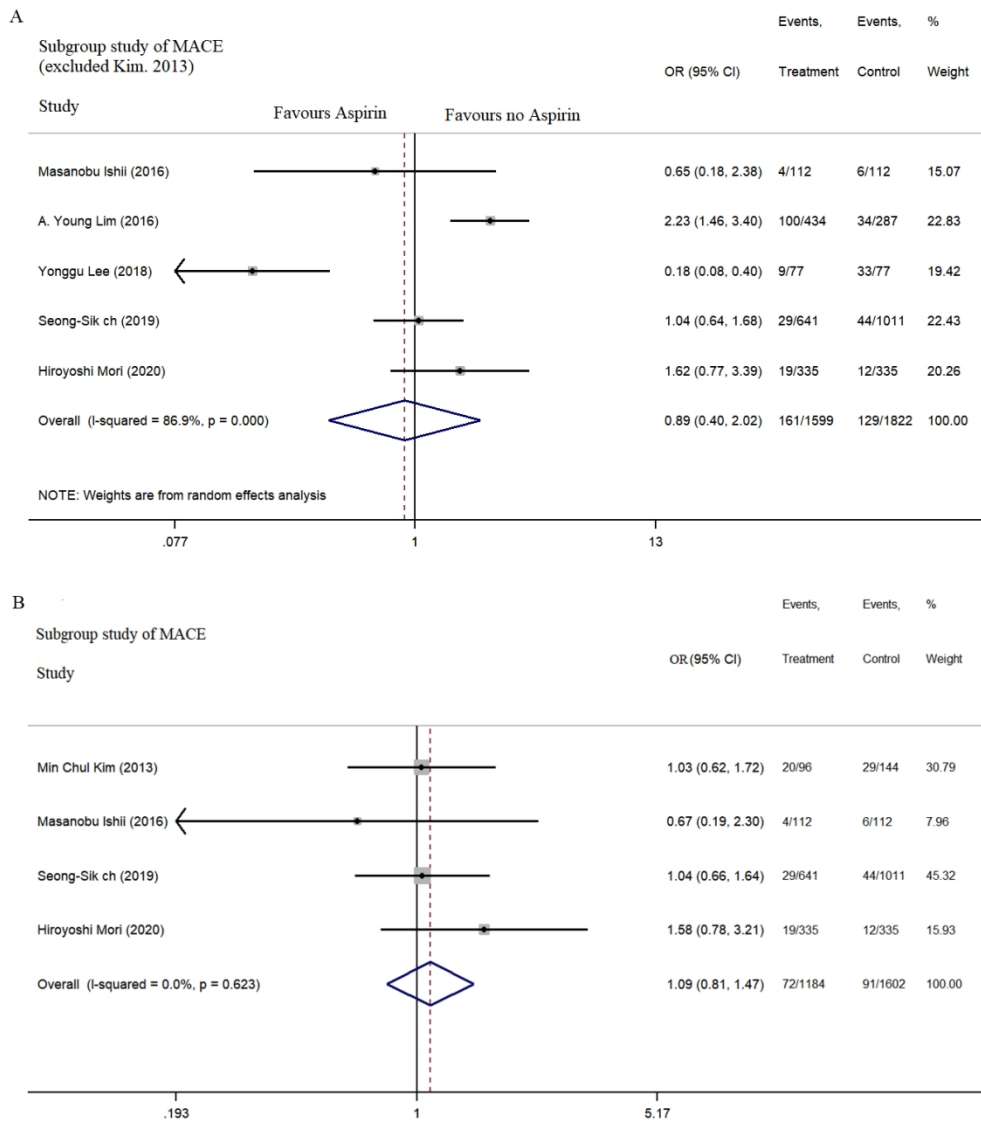


Figure 3. Subgroup analysis of MACE with aspirin use in patients with VSA.

358x411mm (96 x 96 DPI)

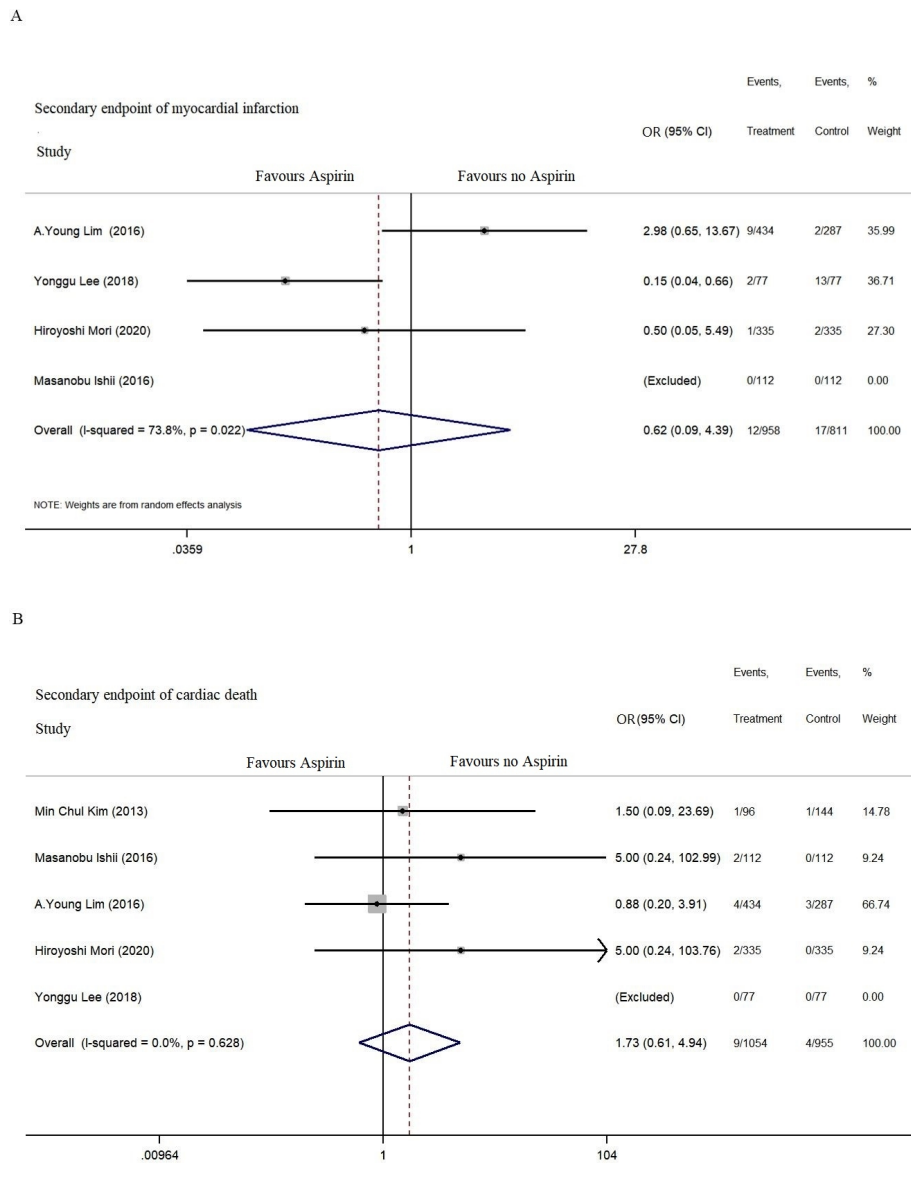


Figure 4. Secondary endpoints including myocardial infarction, cardiac death, and all-cause death during 1–5 years of follow-up.

240x305mm (144 x 144 DPI)

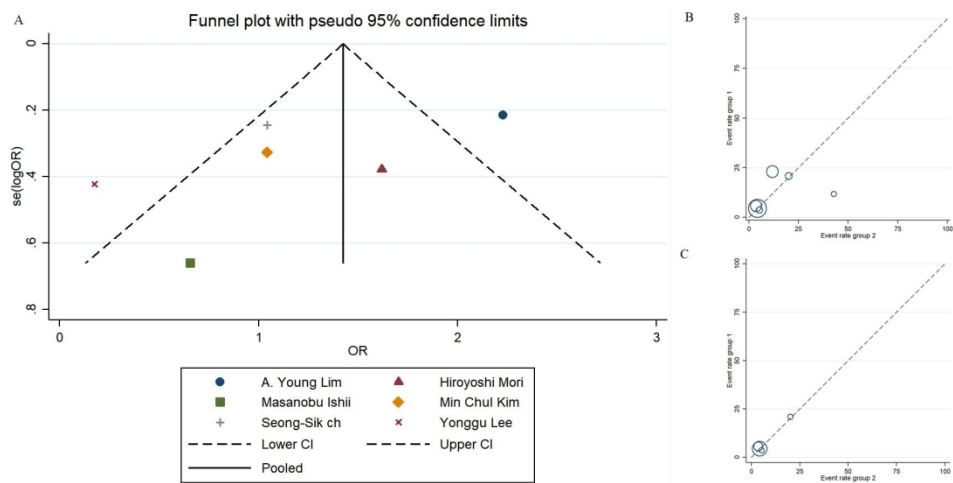


Figure 5. Assess of bias risk of the studies.

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

Page 1 of 2

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

For peer review only, <http://bmjopen.bmj.com/site/about/guidelines.xhtml>
For more information, visit: www.prisma-statement.org



PRISMA 2009 Checklist

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- 11
- 12
- 13
- 14
- 15
- 16
- 17
- 18
- 19
- 20
- 21
- 22
- 23
- 24
- 25
- 26
- 27
- 28
- 29
- 30
- 31
- 32
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47

For peer review only

BMJ Open

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

Journal:	<i>BMJ Open</i>
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

SCHOLARONE™
Manuscripts



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.

1
2
3
4 **Impact of Aspirin Use on Clinical Outcomes in Patients with Vasospastic Angina:**
5
6 **A Systematic Review and Meta-analysis**
7
8

9 Yaowang Lin, MD ^{1,4}; Yang Chen, MD ⁵; Jie Yuan, MD ^{1,4}; Haiyan Qin, MD ^{2,4};
10
11 Shaohong Dong, MD ^{1,4#}; Qiuling Chen, MD ^{3,4#}
12
13

14
15 **Author Affiliations:**
16

17
18 ¹Department of Cardiology; ²Department of Health Management; ³Department of
19
20 Pharmacy; ⁴Shenzhen People's Hospital, Second Clinical Medical College of Jinan
21
22 University, First affiliated Hospital of South University of Science and Technology,
23
24 Shenzhen, Guangdong. No. 1017, Dongmen Northern Road, 518020, Shenzhen,
25
26 Guangdong, PR China. ⁵School of Pharmacy, Guangdong Medical University,
27
28 Dongguan 523808, Guangdong, China
29
30
31
32

33 **Correspondence should be addressed to Shaohong Dong and Qiuling Chen**
34
35

36
37 Shaohong Dong, MD, e-mail: xnkds@yeah.net
38
39

40
41 Qiuling Chen, MD, e-mail: szchenqiuling@yeah.net
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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
2
3
4 = 1,695; no aspirin use group, $n = 1,966$) were included in this meta-analysis. Aspirin
5
6 use and the incidence of major cardiovascular adverse events with follow-up of 1–5
7
8 years were not significantly correlated (combined OR = 0.90, 95% CI: 0.55–1.68, $p =$
9
10 0.829, $I^2 = 82.2\%$; subgroup analysis: OR = 1.09, 95% CI: 0.81–1.47, $I^2 = 0\%$). No
11
12 significant difference was found between aspirin use and the incidence of myocardial
13
14 infarction (OR = 0.62, 95% CI: 0.09–4.36, $p = 0.615$, $I^2 = 73.8\%$) or cardiac death (OR
15
16 = 1.73, 95% CI: 0.61–4.94, $p = 0.444$, $I^2 = 0\%$) during follow-up.
17
18
19
20
21
22

23 **Conclusion:** Aspirin use may not reduce the risk of future cardiovascular events in
24
25 VSA patients without significant stenosis.
26
27
28
29
30
31
32

33 **Trial registration number:** PROSPERO (CRD42020214891)
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

39 **Keywords:** Aspirin, Vasospastic angina, MACE, Cardiac death, Myocardial infarction,
40
41
42 Long-term follow-up
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3
4 with a larger sample size.
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50

51 **INTRODUCTION**

52
53
54
55 Coronary spasm characterized by vasospastic angina (VSA) is one cause of ischemia in
56
57
58 a non-obstructive coronary artery (INOCA) [1, 2]. VSA patients who also suffer from
59
60

1
2
3
4 endothelial dysfunction or coronary atherosclerosis commonly use aspirin [3, 4], per
5
6 the guidelines of the European Society of Cardiology (ESC), for the management of
7
8 chronic stable angina and acute coronary syndromes [5, 6].
9
10

11
12 The ASCEND study showed that the use of low-dose aspirin leads to a lower risk
13
14 of serious vascular events (8.5% vs. 9.6%; $p = 0.01$) compared to placebo among
15
16 persons with diabetes in primary treatment, but the absolute benefits of aspirin are
17
18 largely counterbalanced by the bleeding hazard (4.1% vs. 3.2%; $p = 0.003$) [7]. The
19
20 ARRIVE study also suggested that aspirin use may result in a higher incidence of
21
22 gastrointestinal bleeding (0.97% vs. 0.46%; $p = 0.0007$) or overall incidence of
23
24 treatment-related adverse events (16.75% vs. 13.54%; $p < 0.0001$) compared to control
25
26 groups [8]. Owing to the latest controversy and reduced usage of aspirin in preventing
27
28 cardiovascular events [9, 10], aspirin's efficiency in VSA patients without significant
29
30 stenosis has not yet been reported [11-16]. Therefore, this meta-analysis was designed
31
32 to assess the correlation between aspirin use and cardiovascular events and cardiac
33
34 death among VSA patients during long-term follow-up.
35
36
37
38
39
40
41
42
43
44
45
46
47

48 **MATERIALS AND METHODS**

49 *Search strategy*

50
51
52 A comprehensive search of PubMed, Web of Science, and Cochrane Central Register
53
54 of Controlled Trials databases for related research articles conducted before October
55
56 2020 was conducted to gather data. The keywords were “vasospastic angina”,
57
58
59
60

1
2
3
4 “coronary vasospasms”, “vasospasm”, “variant angina”, “Prinzmetal's variant angina”,
5
6 “spastic coronary angina”, “coronary artery spasm,” as well as “aspirin” and
7
8 “antiplatelet therapy”. Certain additional related publications, such as review articles
9
10 and editorials, were also assessed. This study was registered with PROSPERO
11
12 (CRD42020214891).
13
14
15
16
17
18
19
20

21 ***Patient and public involvement***

22
23
24 Study participants met the eligibility criteria as outlined above. All included patients
25
26 were diagnosed with epicardial coronary vasospasms by provocation test. Participants
27
28 and other members of the public were not involved in the recruitment, design, conduct,
29
30 reporting, or dissemination of this study.
31
32
33
34
35
36
37
38

39 ***Study selection and data extraction***

40
41
42 The patient inclusion criteria were as follows: (i) diagnosed with VSA on provocation
43
44 test, (ii) absence of significant stenosis ($\leq 50\%$), (iii) the treatment group was
45
46 administered oral aspirin and the control group received no aspirin or placebo, and (iv)
47
48 articles published in English. The exclusion criteria were as follows: significant stenosis
49
50 ($\geq 50\%$), intravenous aspirin, case report, and case series. The study data were
51
52 independently extracted by two investigators, namely Lin and Chen, using pre-defined
53
54 extraction forms; any conflict was resolved by a third reviewer.
55
56
57
58
59
60

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 evaluate 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

1
2
3
4 CAS due to the lowered production of thromboxane A2 and increased MACE incidence
5
6 in VSA patients [20, 21]. Thus, the use of aspirin in VSA patients remains controversial.
7
8
9

10 MACE incidence in patients administered low-dose aspirin was significantly higher
11
12 than that among patients not administered aspirin (hazard ratio [HR] = 1.54; CI: 1.04-
13 2.28; $p = 0.037$) during a 52-month median follow-up period [13]. In contrast, MI (HR
14
15 = 0.13; CI: 0.03–0.61; $p = 0.014$) and chest pain recurrence (HR = 0.29; CI: 0.12–0.71;
16
17 $p = 0.006$) were observed by Lee *et al.* to have been significantly reduced by aspirin
18
19 use among VSA patients during follow-up [11]. Lee *et al.* showed that acute intimal
20
21 tears and erosion identified by optical coherence tomography are susceptible to
22
23 thrombosis leading to MI. Therefore, aspirin was evidenced to reduce adverse events in
24
25 VSA patients with a greater number of thrombotic intracoronary lesions. Nevertheless,
26
27 aspirin use was not significantly correlated with the occurrence of cardiovascular events
28
29 among VSA patients with nonsignificant stenosis during a 49-month mean follow-up
30
31 period ($p = 0.541$) [14]. Moreover, the aspirin-treated group exhibited a similar MACE
32
33 incidence compared with the non-antiplatelet agent group (HR = 0.96, CI: 0.59–1.55, p
34
35 = 0.872) as reported by Cho *et al.* [15]. Antiplatelet therapy was recently shown by
36
37 Mori *et al.* to have no beneficial effects on MACE (5.7% vs. 3.6%, $p = 0.20$) among
38
39 VSA patients during a 32-month median follow-up period [16].
40
41
42
43
44
45
46
47
48
49
50
51

52 Our meta-analysis indicates that aspirin use may not be linked to a lower risk of
53
54 MACE and cardiac death. The subgroup analysis of MACE indicated that the studies
55
56 by Lee [11] and Lim [13] were heterogeneous. The origin of heterogeneity in these
57
58 studies may be attributable to chest pain recurrence in the MACE, which results in an
59
60

1
2
3
4 entirely different outcome due to the definition. The following may potentially explain
5
6 the lack of beneficial effects of aspirin use: (i) Aspirin use is known to damage the
7
8 gastric mucosal barrier and increase risk of erosions, ulcers, and bleeding by inhibiting
9
10 cyclooxygenase-1 enzyme activity [22]. Several meta-analyses have indicated that
11
12 aspirin's efficacy in primary prevention of cardiovascular disease should be weighed
13
14 against any increase in major bleeding [23-25]. (ii) The adverse effects of asthma and
15
16 dyspnea may lead to CAS and increase the occurrence of MACE or cardiogenic death
17
18 with aspirin use [26, 27]. (iii) The synthesis of prostacyclin, a well-known vasodilator
19
20 released by endothelial cells, is inhibited by aspirin [28] and CAS is induced by aspirin.
21
22 This could, in turn, cause recurrent angina leading to rehospitalization, MI, and cardiac
23
24 death.
25
26
27
28
29
30
31
32

33 We found that aspirin use may have a protective effect against MI, which may be
34
35 explained by aspirin's pharmacological mechanism. However, there was high
36
37 heterogeneity in the study, which may be attributed to the lack of related studies and a
38
39 different definition of MI used by Mori *et al.* [16]. Aspirin use in CAS patients can be
40
41 both advantageous and disadvantageous. Further investigation is necessary to
42
43 determine when to recommend aspirin use.
44
45
46
47
48
49

50 Several potential limitations should be considered in this meta-analysis. First,
51
52 MACE and MI were defined differently in the included articles. Due to the lack of
53
54 original data, no standard definition of MACE was accessible in this meta-analysis.
55
56 Second, one study by Mori *et al.* (2020) showed that an antiplatelet drug containing
57
58 both aspirin and P2Y12 inhibitors was used as the treatment strategy. Third, the sample
59
60

1
2
3
4 size in this analysis is too small; only a few studies conducted propensity matching
5
6 analysis to balance baseline characteristics. The limitations inherent to multi-center
7
8 observational studies performed in both retrospective and prospective manners could
9
10 not be avoided in this analysis. Fourth, patients with 40% stenosis are considered to
11
12 have VSA without coronary stenosis but might benefit from aspirin. Subgroup analysis
13
14 should be performed in the next study. Finally, the major bleeding outcome was
15
16 excluded from this study, which is essential for understanding the advantages of
17
18 antiplatelet therapy. Despite these limitations, the merit of this study is that it is the first
19
20 to evaluate the prognosis of VSA patients using low-dose aspirin.
21
22
23
24
25
26
27
28
29
30

31 **CONCLUSIONS**

32
33
34 Aspirin use may not reduce the risk of cardiovascular events in VSA patients without
35
36 significant stenosis. Owing to its potential adverse effects, regular use of aspirin in VSA
37
38 patients without significant stenosis should involve a thoughtful discussion.
39
40
41
42
43
44
45
46

47 **Acknowledgments**

48
49 None
50
51

52 **Contributors**

53
54
55
56 YWL, QLC, and HYQ conceived, designed, and led the study. YWL, YC, YJ, and SHD
57
58 investigated, conducted the study, and collected data. YWL, SHD, and QLC wrote,
59
60

1
2
3 revised, and edited the manuscript. All authors supervised the study and approved the
4
5 final version of the manuscript.
6
7

8 **Funding**

9
10
11 This study was supported by a grant from the Shenzhen Key Medical Discipline
12
13 Construction Fund (No. SZXK003 and No. SZXK059) and Sanming Project of
14
15 Medicine in Shenzhen (No. SZSM201412012).
16
17

18 **Conflict of interest**

19
20
21 No conflict of interest
22
23

24 **Patient consent for publication**

25
26
27 Not required
28
29

30 **Provenance and peer review**

31
32
33 Not commissioned; externally peer reviewed.
34
35

36 **Data availability statement**

37
38
39 All data relevant to the study are included in the article or uploaded as supplementary
40
41 information.
42
43

44 **ORCID iD**

45
46
47 Yaowang Lin: <https://orcid.org/0000-0002-4075-4259>
48
49

50 **Ethics Statement**

51
52
53 The institutional review board at the Shenzhen People's Hospital approved the study
54
55 protocol.
56
57
58
59
60

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 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):3504-3520.
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.

- 1
2
3
4 4. Khuddus MA, Pepine CJ, Handberg EM, *et al.* An intravascular ultrasound
5
6 analysis in women experiencing chest pain in the absence of obstructive
7
8 coronary artery disease: a substudy from the National Heart, Lung and Blood
9
10 Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *J Interv*
11
12 *Cardiol* 2010, 23(6):511-519.
13
14
- 15
16
17
18 5. Knuuti J, Wijns W, Saraste A, *et al.* 2019 ESC Guidelines for the diagnosis and
19
20 management of chronic coronary syndromes. *Eur Heart J* 2020, 41(3):407-477.
21
22
- 23
24 6. Collet JP, Thiele H, Barbato E, *et al.* 2020 ESC Guidelines for the management
25
26 of acute coronary syndromes in patients presenting without persistent ST-
27
28 segment elevation. *Eur Heart J* 2020.
29
30
- 31
32 7. Group ASC, Bowman L, Mafham M, *et al.* Effects of Aspirin for Primary
33
34 Prevention in Persons with Diabetes Mellitus. *N Engl J Med* 2018,
35
36 379(16):1529-1539.
37
38
- 39
40
41 8. Gaziano JM, Brotons C, Coppolecchia R, *et al.* Use of aspirin to reduce risk of
42
43 initial vascular events in patients at moderate risk of cardiovascular disease
44
45 (ARRIVE): a randomised, double-blind, placebo-controlled trial. *Lancet* 2018,
46
47 392(10152):1036-1046.
48
49
- 50
51
52 9. Guirguis-Blake JM, Evans CV, Senger CA, *et al.* Aspirin for the Primary
53
54 Prevention of Cardiovascular Events: A Systematic Evidence Review for the
55
56 U.S . Preventive Services Task Force. *Ann Intern Med* 2016, 164(12):804-813.
57
58
59
60

- 1
2
3
4 10. Zheng SL, Roddick AJ. Association of Aspirin Use for Primary Prevention With
5
6 Cardiovascular Events and Bleeding Events: A Systematic Review and Meta-
7
8 analysis. *Jama* 2019, 321(3):277-287.
9
10
- 11
12 11. Lee Y, Park HC, Shin J. Clinical efficacy of aspirin with identification of intimal
13
14 morphology by optical coherence tomography in preventing event recurrence in
15
16 patients with vasospasm-induced acute coronary syndrome. *Int J Cardiovasc*
17
18 *Imaging* 2018, 34(11):1697-1706.
19
20
- 21
22 12. Kim MC, Ahn Y, Park KH, *et al.* Clinical outcomes of low-dose aspirin
23
24 administration in patients with variant angina pectoris. *Int J Cardiol* 2013,
25
26 167(5):2333-2334.
27
28
- 29
30 13. Lim AY, Park TK, Cho SW, *et al.* Clinical implications of low-dose aspirin on
31
32 vasospastic angina patients without significant coronary artery stenosis; a
33
34 propensity score-matched analysis. *Int J Cardiol* 2016, 221:161-166.
35
36
- 37
38 14. Ishii M, Kaikita K, Sato K, *et al.* Impact of aspirin on the prognosis in patients
39
40 with coronary spasm without significant atherosclerotic stenosis. *Int J Cardiol*
41
42 2016, 220:328-332.
43
44
- 45
46 15. Cho SS, Jo SH, Han SH, *et al.* Clopidogrel plus Aspirin Use is Associated with
47
48 Worse Long-Term Outcomes, but Aspirin Use Alone is Safe in Patients with
49
50 Vasospastic Angina: Results from the VA-Korea Registry, A Prospective Multi-
51
52 Center Cohort. *Sci Rep* 2019, 9(1):17783.
53
54
55
56
57
58
59
60

- 1
2
3
4 16. Mori H, Takahashi J, Sato K, *et al.* The impact of antiplatelet therapy on patients
5
6 with vasospastic angina: A multicenter registry study of the Japanese Coronary
7
8 Spasm Association. *Int J Cardiol Heart Vasc* 2020, 29:100561.
9
10
11
12 17. Yasue H, Mizuno Y, Harada E. Coronary artery spasm - Clinical features,
13
14 pathogenesis and treatment. *Proc Jpn Acad Ser B Phys Biol Sci* 2019, 95(2):53-
15
16 66.
17
18
19
20 18. Capodanno D, Alfonso F, Levine GN, *et al.* ACC/AHA Versus ESC Guidelines
21
22 on Dual Antiplatelet Therapy: JACC Guideline Comparison. *J Am Coll Cardiol*
23
24 2018, 72(23 Pt A):2915-2931.
25
26
27
28 19. Valgimigli M, Bueno H, Byrne RA, *et al.* 2017 ESC focused update on dual
29
30 antiplatelet therapy in coronary artery disease developed in collaboration with
31
32 EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease
33
34 of the European Society of Cardiology (ESC) and of the European Association
35
36 for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018, 39(3):213-260.
37
38
39
40 20. Picard F, Sayah N, Spagnoli V, *et al.* Vasospastic angina: A literature review of
41
42 current evidence. *Arch Cardiovasc Dis* 2019, 112(1):44-55.
43
44
45
46
47
48 21. Miwa K, Kambara H, Kawai C. Effect of aspirin in large doses on attacks of
49
50 variant angina. *Am Heart J* 1983, 105(2):351-355.
51
52
53
54
55 22. Iwamoto J, Saito Y, Honda A, *et al.* Clinical features of gastroduodenal injury
56
57 associated with long-term low-dose aspirin therapy. *World J Gastroenterol*
58
59
60

- 1
2
3
4 2013, 19(11):1673-1682.
5
6
7
8 23. Antithrombotic Trialists C, Baigent C, Blackwell L, *et al.* Aspirin in the primary
9
10 and secondary prevention of vascular disease: collaborative meta-analysis of
11
12 individual participant data from randomised trials. *Lancet* 2009,
13
14 373(9678):1849-1860.
15
16
17
18 24. Xie W, Luo Y, Liang X, *et al.* The Efficacy And Safety Of Aspirin As The
19
20 Primary Prevention Of Cardiovascular Disease: An Updated Meta-Analysis.
21
22 *Ther Clin Risk Manag* 2019, 15:1129-1140.
23
24
25
26
27 25. Whitlock EP, Burda BU, Williams SB, *et al.* Bleeding Risks With Aspirin Use
28
29 for Primary Prevention in Adults: A Systematic Review for the U.S. Preventive
30
31 Services Task Force. *Ann Intern Med* 2016, 164(12):826-835.
32
33
34
35
36 26. Hangouche AJE, Lamliki O, Oukerraj L, *et al.* Kounis syndrome induced by
37
38 oral intake of aspirin: case report and literature review. *Pan Afr Med J* 2018,
39
40 30:301.
41
42
43
44 27. Shah NH, Schneider TR, DeFaria Yeh D, *et al.* Eosinophilia-Associated
45
46 Coronary Artery Vasospasm in Patients with Aspirin-Exacerbated Respiratory
47
48 Disease. *J Allergy Clin Immunol Pract* 2016, 4(6):1215-1219.
49
50
51
52
53 28. Bates ER, Lau WC. Controversies in antiplatelet therapy for patients with
54
55 cardiovascular disease. *Circulation* 2005, 111(17):e267-271.
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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,	/	62 (55.4) vs. 60 (53.6) ,	91 (21.0) vs. 62 (21.6),	/	98 (15.4) vs.160(15.8) ,	156 (46.6%) vs. 142 (42.4%) ,
n (%)		p = 0.788	p = 0.84		p = 0.800	p = 0.31
Ca channel blocker,	/	104 (92.9) vs. 101	420 (96.9) vs. 275 (95.8),	50 (65) vs. 48 (62),	152 (24.2) vs. 162(16.12),	316 (94.3%) vs. 313 (93.4%),
n (%)		(90.2) ,	p = 0.46	p = 0.738	p = 0.001	p = 0.75
		p = 0.472				
Statin,	/	38 (33.9) vs. 40 (35.7),	182 (42.0) vs. 113 (39.4) ,	/	123 (19.7) vs. 119(11.9),	103 (30.7%) vs. 95 (28.4%),
n (%)		p = 0.779	p = 0.49		p = 0.001	p = 0.55
ACEI / ARB,	/	33(29.5) vs. 25 (22.3),	69 (15.9) vs. 43 (15.0) ,	/	152 (24.3) vs.126(12.6),	73 (21.8%) vs. 71 (21.2%) ,
n (%)		p = 0.288	p = 0.74		p = 0.001	p = 0.93
Beta-blocker,	/	6 (5.4) vs. 7 (6.3),	1 (0.2) vs. 0 (0.0),	17 (22) vs. 23 (30),	54 (8.65) vs. 59(5.88),	/
n (%)		p = 0.775	p = 0.48	p = 0.270	p = 0.065	

ACEI / ARB = angiotensin-converting enzyme inhibitor / angiotensin receptor blocker

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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

1													
2													
3													
4													
5		Retrospective study,	Coronary artery					Chest pain recurrence,					
6	Yonggu	2018 propensity score-	spasm (stenosis ≤ 154	77	77	100		myocardial infarction, cardiac	9 (11.7) vs. 2 (3) vs.13		0 vs. 0	0 vs. 0	4-year
7	Lee	matched analysis	50%)					death	33 (42.9)	(17)			
8													
9													
10													
11	Seong-Sik	2019 Prospective	Coronary artery					all cause death, acute coronary	29 (4.5) vs.			3 (0.5) vs.	3-year
12	Cho	multicenter cohort	spasm (stenosis ≤ 1652	641	1011	100		syndrome, and symptomatic	44(4.4)	/	/	7(0.7)	
13			50%)					arrhythmia					
14													
15													
16								cardiac death, nonfatal					
17	Hiroyoshi	2020 Retrospective study,	Coronary artery				Aspirin 100	myocardial infarction,	19 (5.7)	1 (0.3) vs. 2	2 (0.6) vs.	2 (0.6)	32-months
18	Mori	propensity score-	spasm (stenosis ≤ 670	335	335		and P2Y12	hospitalization due to unstable	vs. 12 (3.6)	(0.6)	0 (0.0)	vs. 6 (1.8)	
19		matched analysis	50%)				inhibitors.	angina pectoris,					
20								and appropriate ICD shock					
21													
22													
23													
24													
25													
26													
27													
28													
29													
30													
31													
32													
33													
34													
35													
36													
37													
38													
39													
40													
41													
42													
43													
44													
45													
46													

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

For peer review only

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

1
2
3
4
5
6
7
8 **Figure legends.**
9

10
11 Figure 1. Flow diagram for identification processes.
12

13
14 Figure 2. Aspirin use is not associated with a low incidence of MACE in patients with
15
16
17 VSA.
18

19
20 Figure 3. Subgroup analysis of MACE with aspirin use in patients with VSA.
21

22
23
24 Figure 4. Secondary endpoints including myocardial infarction, cardiac death, and all-
25
26
27 cause death during 1–5 years of follow-up.
28

29
30 Figure 5. Assessment of bias risk of the studies.
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

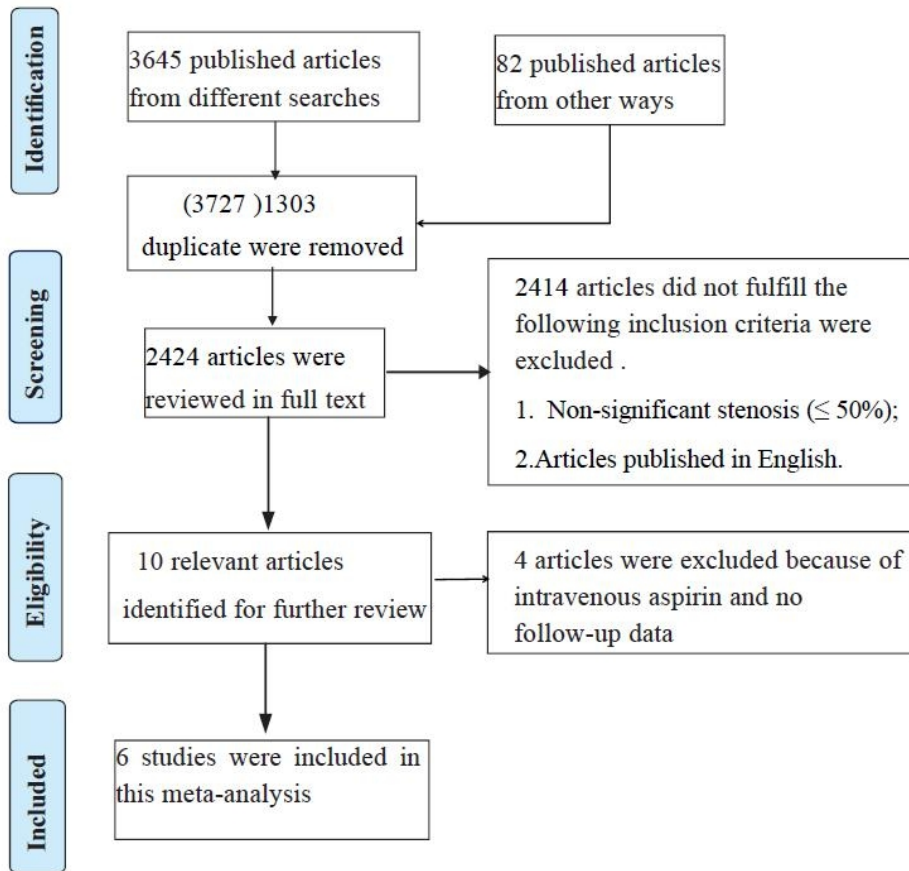


Figure 1. Flow diagram for identification processes.

Figure 1. Flow diagram for identification processes.

139x148mm (144 x 144 DPI)

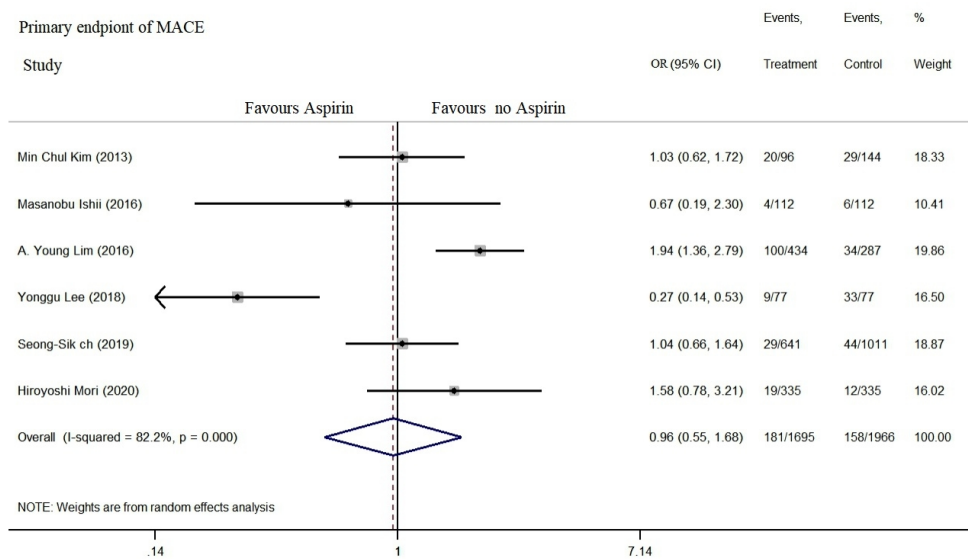


Figure 2. Aspirin use is not associated with a low incidence of MACE in patients with VSA.

231x135mm (144 x 144 DPI)

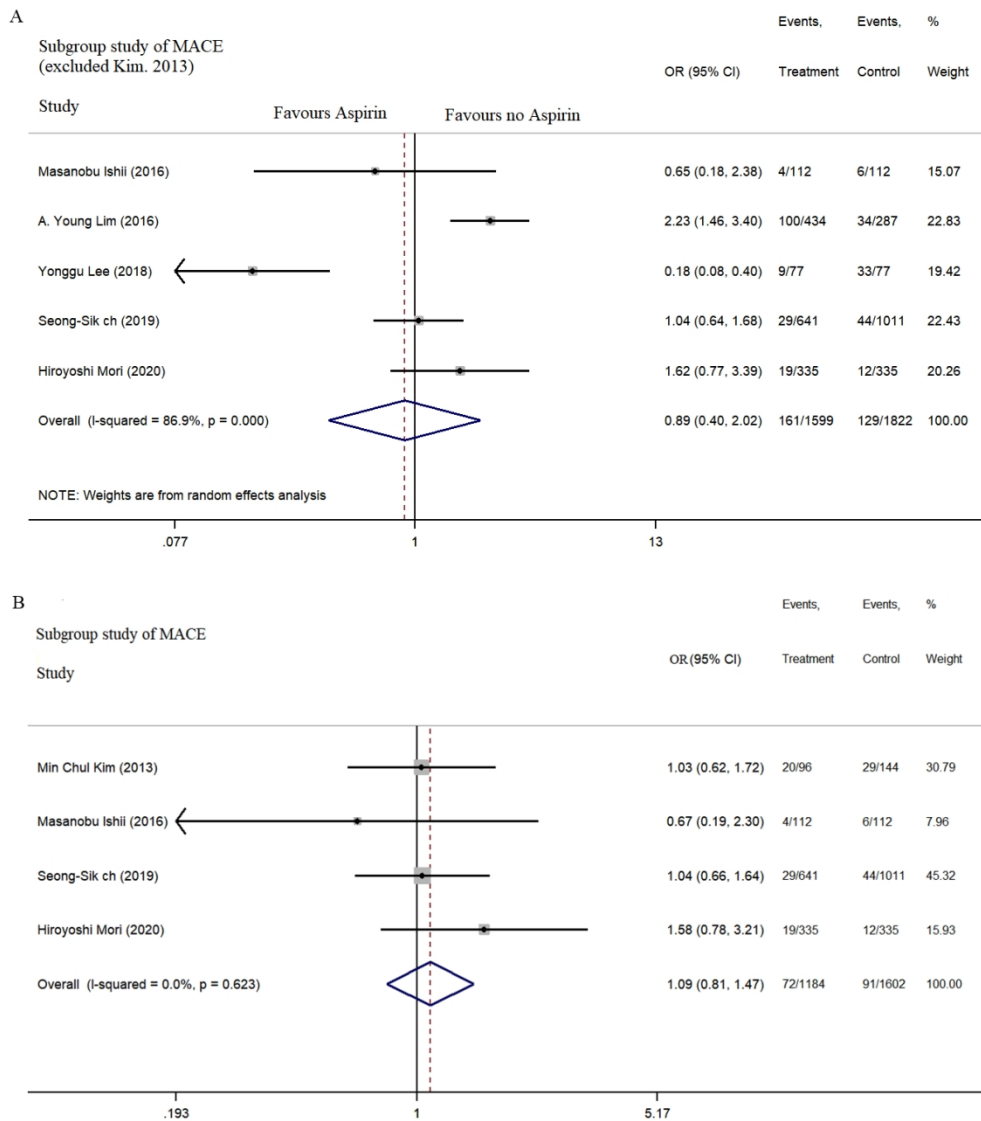


Figure 3. Subgroup analysis of MACE with aspirin use in patients with VSA.

358x411mm (96 x 96 DPI)

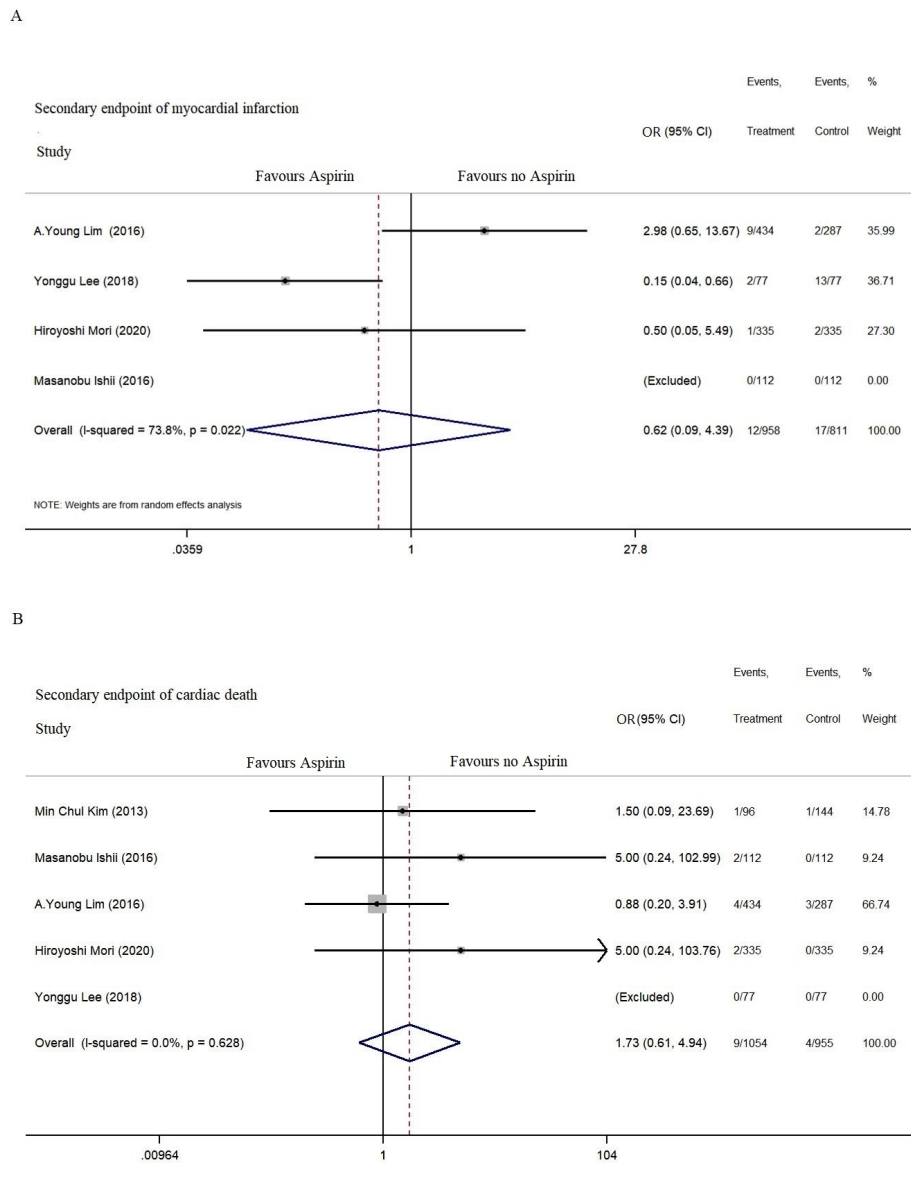


Figure 4. Secondary endpoints including myocardial infarction, cardiac death, and all-cause death during 1–5 years of follow-up.

240x305mm (144 x 144 DPI)

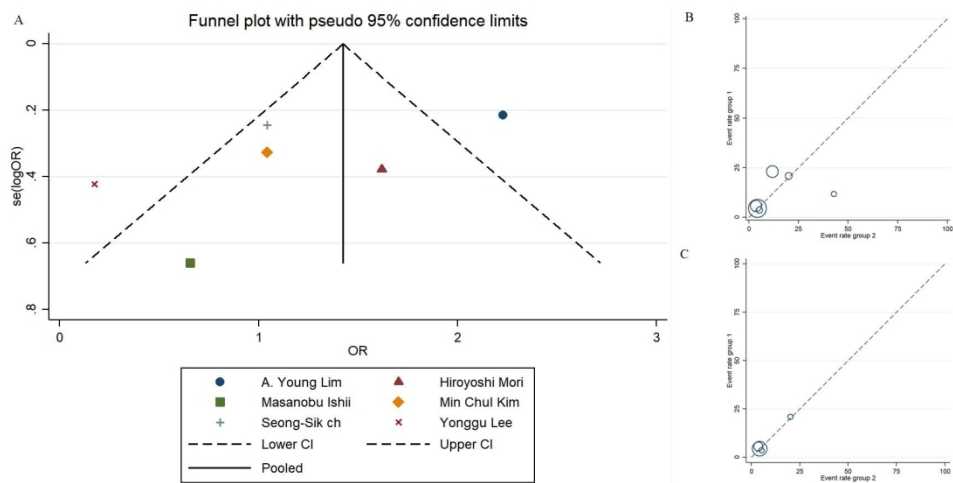


Figure 5. Assess of bias risk of the studies.

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

Page 1 of 2

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

For peer review only, <http://bmjopen.bmj.com/site/about/guidelines.xhtml>
For more information, visit: www.prisma-statement.org



PRISMA 2009 Checklist

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- 11
- 12
- 13
- 14
- 15
- 16
- 17
- 18
- 19
- 20
- 21
- 22
- 23
- 24
- 25
- 26
- 27
- 28
- 29
- 30
- 31
- 32
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47

For peer review only