

# 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](mailto:info.bmjopen@bmj.com)

# BMJ Open

## The Effect of Aspirin in Takotsubo Syndrome: Protocol of A Systematic Review and Meta-Analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-046727
Article Type:	Protocol
Date Submitted by the Author:	07-Nov-2020
Complete List of Authors:	Lin, Jinhai; Guangzhou University of Chinese Medicine, Wu, Bingxin; Guangzhou University of Traditional Chinese Medicine Lin, Luoqi; Guangzhou University of Traditional Chinese Medicine Ding, Yining; Guangzhou University of Traditional Chinese Medicine Zhong, Biying; Guangzhou University of Traditional Chinese Medicine, Guangzhou University of Traditional Chinese Medicine Huang, Zhiwei; Second Clinical Medical College of Guangzhou University of Chinese Medicine Lin, Miaoyang; Second Clinical Medical College of Guangzhou University of Chinese Medicine Xu, Dan-Ping; The Eighth Affiliated Hospital of Sun Yat-Sen University; Guangdong Hospital of Traditional Chinese Medicine
Keywords:	Cardiomyopathy < CARDIOLOGY, Thromboembolism < CARDIOLOGY, 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 1 **The Effect of Aspirin in Takotsubo Syndrome: Protocol of A Systematic Review and**  
5  
6 2 **Meta-Analysis**  
7  
8  
9 3

10 4 Jinhai Lin,<sup>A</sup> Bingxin Wu,<sup>A</sup> Luoqi Lin,<sup>A</sup> Yining Ding,<sup>A</sup> Biying Zhong,<sup>A</sup> Zhiwei Huang,<sup>A</sup>

11  
12  
13 5 Miaoyang Lin,<sup>A</sup> Danping Xu,<sup>B,A</sup>

14  
15  
16 6 A. The Second Clinical Medical College, Guangzhou University of Chinese Medicine, China

17  
18 7 B. The Eighth Affiliated Hospital, Sun Yat-sen University, China  
19  
20  
21 8

22  
23 9 **Correspondence:**

24  
25  
26 10 Danping Xu, Ph.D.

27  
28 11 Professor of Cardiology and Chinese Medicine

29  
30  
31 12 Department of Cardiology, The Eighth Affiliated Hospital, Sun Yat-sen University

32  
33  
34 13 No. 3025, Shennan Middle Road, Futian District, Shenzhen, Guangdong Province, China

35  
36 14 xudanping@hotmail.com  
37  
38  
39  
40 16

41  
42 17 **Abstract**

43  
44 18 [Introduction] Takotsubo syndrome (TTS) is a sudden reversible weakening of the left  
45  
46 19 ventricle function induced by severe stress and resembles many features as acute coronary  
47  
48 20 syndrome. Even though many guidelines had been published about TTS, there is no consensus  
49  
50 21 regarding the long-term treatment. Aspirin is one of the most common prescribed medicines at  
51  
52 22 discharge for patients with the intention to reduce thrombus events and improve the overall  
53  
54 23 prognosis. However, existing studies yielded conflicting results concerning its effects. This  
55  
56 24 study aims to evaluate the impact of long-term maintenance treatment of Aspirin in TTS and  
57  
58  
59  
60

1  
2  
3  
4 25 provides insights in clinic management.  
5

6 26 [Methods and analysis] After searching through electronic databases, gray literatures,  
7  
8  
9 27 conference abstract and trial registries for clinical studies investigating the impact of Aspirin  
10  
11 28 on patients with TTS, a systemic review and meta-analysis will be conducted. The outcomes  
12  
13  
14 29 including all-cause death, TTS recurrence, stroke, transient ischemic attack or myocardial  
15  
16  
17 30 infarction at 30-day and 5-year follow-up will be examined. Risk of bias will be assessed by  
18  
19  
20 31 Newcastle–Ottawa quality assessment scale for observational studies and Cochrane Effective  
21  
22 32 Practice Organization of Care evaluation tool for interventional studies. Grading of  
23  
24  
25 33 Recommendations, Assessment, Development and Evaluations (GRADE) method will be  
26  
27 34 applied to assess the quality of evidence. If available, the effects of Aspirin on the above  
28  
29  
30 35 outcomes for patients with TTS will be evaluated using random-effect modeling with relative  
31  
32 36 risk at 95% confidence intervals. Subgroup analysis and sensitivity analysis will also be  
33  
34  
35 37 performed when possible.  
36

37  
38 38 [Ethics and dissemination] Ethics approval was not required due to the retrospective nature  
39  
40 39 of the study. Results of the review will be published in a peer-reviewed journal.  
41

42  
43 40 [Systematic review registration number] INPLASY2020100030; CRD42020212729.  
44

#### 45 41 **Strengths and limitations of this study**

- 46  
47  
48 42 ● This study aims to identify the impact of Aspirin treatment on the prognosis of patients  
49  
50 43 with Takotsubo Syndrome.  
51  
52  
53 44 ● The systematic review will be performed according to the Meta-analysis of Observational  
54  
55 45 Studies in Epidemiology (MOOSE) guideline and will be reported according to the  
56  
57 46 Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA)  
58  
59  
60

1  
2  
3  
4 47 guidelines.

5  
6 48 ● As Takotsubo syndrome is easy to be misdiagnosed and omitted, there may be limited data  
7  
8  
9 49 available for the study.

## 10 50 **Introduction**

11  
12  
13  
14 51 Takotsubo syndrome (TTS) refers to a reversible form of acute heart failure induced by  
15  
16  
17 52 severe stress which shares many characteristics with acute coronary syndrome (ACS), including  
18  
19  
20 53 demographic features, onset symptoms, electrocardiogram abnormalities and elevation of  
21  
22  
23 54 cardiac biomarkers.<sup>1</sup> Due to a lack of non-invasive examinations method, the diagnosis and  
24  
25  
26 55 understanding of TTS remains poor. In clinical practice, TTS is mainly diagnosed by  
27  
28  
29 56 presentation of severe transient left ventricular (LV) dysfunction with typical apical ballooning  
30  
31  
32 57 or other regional wall motion abnormalities documented by coronary angiography with left  
33  
34  
35 58 ventriculography.<sup>2</sup>

36  
37  
38 59 Another characteristic feature of TTS is the reversible pathology change and self-limiting  
39  
40  
41 60 clinical course.<sup>3</sup> For a rather long time, TTS was generally considered as a benign disease with  
42  
43  
44 61 relatively low morbidity.<sup>4</sup> However, this view is challenged by recent studies.<sup>5,6</sup> Based on data  
45  
46  
47 62 obtained from the International Takotsubo Registry,<sup>7</sup> the rate of major adverse cardiac and  
48  
49  
50 63 cerebrovascular events (MACCE) for patients with TTS was 9.9% per patient-year and the  
51  
52  
53 64 mortality was 5.6% per patient-year in long-term follow-up.<sup>8</sup> In addition, the incidences of in-  
54  
55  
56 65 hospital complications including shock and death were also comparable to ACS.<sup>9,10</sup> But the  
57  
58  
59 66 understanding and management of TTS is behind compared to ACS. Even though many  
60  
61  
62 67 guidelines had been published about TTS, there is no consensus regarding the long-term  
63  
64  
65 68 treatment.<sup>11</sup>

1  
2  
3  
4 69 The LV thrombus and systematic embolism were reported to occur on approximately 2-8%  
5  
6 70 of all TTS patients with LV abnormalities.<sup>12</sup> In comparison, the incidence of thrombosis in TTS  
7  
8  
9 71 in 5 year follow up was 2-fold higher than ACS (21% vs 9%),<sup>13</sup> which indicated the necessity  
10  
11  
12 72 of applying antithrombotic therapy.<sup>14</sup>  
13

14 73 Recent studies suggested that the release of catecholamines during acute phase of TTS  
15  
16  
17 74 initiates platelet aggregation, secretion and activation of arachidonate pathway.<sup>2, 15, 16</sup> Therefore,  
18  
19  
20 75 Aspirin became one of the most commonly prescribed medicines at discharge for patients with  
21  
22 76 TTS.<sup>17</sup> However, it is important to acknowledge that existing studies yielded conflicting results  
23  
24  
25 77 concerning its effects.<sup>18-20</sup> Prior systematic review and meta-analysis demonstrated that Aspirin  
26  
27  
28 78 was unable to improve the prognosis of TTS.<sup>21</sup> However, its conclusion was challenged by  
29  
30 79 subsequent studies suggesting that more studies are needed to resolve this question.<sup>22</sup>  
31

32 80 To evaluate the effect as well as safety of Aspirin for patients with TTS, the protocol aims  
33  
34  
35 81 to systemically review existing literature and conduct a comprehensive meta-analysis to  
36  
37  
38 82 provide the most updated evidence for the treatment of TTS in clinical practice.  
39

## 40 83 **Methods and analysis**

### 41 42 43 84 **Study design**

44  
45 85 The design of this systematic review was carried out according to the recommendation of  
46  
47  
48 86 the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P)  
49  
50  
51 87 statement and was registered on INPLASY (INPLASY2020100030),<sup>23</sup> which is available on  
52  
53  
54 88 the inplasy.com. The protocol has also acquired approval automatically from the PROSPERO  
55  
56 89 (ID: CRD42020212729).  
57  
58  
59  
60

1  
2  
3  
4 90 The systematic review will be performed according to the Meta-analysis of  
5  
6 91 Observational Studies in Epidemiology (MOOSE) guidelines and will be reported according  
7  
8  
9 92 to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA)  
10  
11  
12 93 guidelines.<sup>24, 25</sup>

#### 14 94 **Search strategy**

16  
17 95 The information to be included in this study will cover electronic databases, gray  
18  
19  
20 96 literatures, conference abstract and trial registries.

21  
22 97 Databases including PubMed, Excerpta Medica Database (EMBASE), Cochrane Library,  
23  
24  
25 98 Web of Science, Clinicaltrials.gov, National Library of Medicine (NLM) Gateway, China  
26  
27  
28 99 National Knowledge Infrastructure (CNKI), Wanfang and Weipu (VIP) will be searched up to  
29  
30 100 August 1st, 2020. The search will follow the principle of PICOS (participants, intervention,  
31  
32  
33 101 comparison, outcome, and study design), employing subject words and free words for the term  
34  
35 102 “Takotsubo Cardiomyopathy” and “Aspirin” with adjustment as necessary per specific database.  
36  
37  
38 103 Reference list of included studies will also be scanned for additional relevant articles.

39  
40 104 The search is anticipated to be completed by November, 2020.

#### 42 105 **Eligibility criteria**

#### 44 106 **Study outcomes**

46  
47  
48 107 The co-primary outcome will be the incidence of MACCE, i.e., a composite of all-cause  
49  
50  
51 108 death, TTS recurrence, stroke, or transient ischemic attack (TIA) or myocardial infarction (MI)  
52  
53  
54 109 at 30-day and 5-year follow-up.

55  
56 110 The secondary outcome will be each component of MACCE. Included studies must  
57  
58  
59 111 contain at least one of the above outcome measurements.  
60



1  
2  
3  
4 112 **Types of studies**

5  
6 113 Both observational and interventional studies are eligible for the study. No limitations are  
7  
8  
9 114 set on the timing of taking Aspirin or the length of follow-up. Articles that published in  
10  
11  
12 115 languages other than English or Chinese will be translated into English when available.

13  
14 116 **Exclusion**

15  
16  
17 117 Studies including participants with malignancies or autoimmune diseases or taking  
18  
19  
20 118 antithrombotic therapy for other diseases will be excluded. Review articles, commentaries,  
21  
22  
23 119 laboratory science studies, case studies, case series, and other studies that do not meet the  
24  
25 120 requirements mentioned above will be excluded.

26  
27 121 **Study records**

28  
29  
30 122 **Data management**

31  
32  
33 123 Publication screening will be managed through Endnote software (version X9, Clarivate  
34  
35 124 Analytics), in which duplicates will be removed and further review will be performed.

36  
37  
38 125 **Selection process**

39  
40 126 Two investigators will independently screen each record by the title and abstract before  
41  
42  
43 127 categorizing all literatures into three groups: relevant, irrelevant and uncertain. After  
44  
45  
46 128 preliminary screening, irrelevant records agreed by both investigators will be eliminated, while  
47  
48  
49 129 the others will be retrieved by full text for further assessment. In the process, a list of eligible  
50  
51  
52 130 articles will be made separately by each reviewer. Discrepancies between the two lists will be  
53  
54  
55 131 resolved by discussion if possible. When an unsettled disagreement arises, a final decision will  
56  
57  
58 132 be made by consulting a third reviewer. Reference list of the included articles will also be  
59  
60 133 reviewed to check for additional studies that might be omitted previously.

1  
2  
3  
4 134 A flow diagram for the selection process will be drawn in accordance with the PRISMA  
5  
6 135 guidelines.

### 9 136 **Data collection process**

11 137 Data extraction will be completed by one reviewer using a pre-designed form.

13  
14 138 Data to be collected will include study characteristics such as author, publication year,  
15  
16  
17 139 time period of study, country and site; cohort characteristics such as sample size, demographics  
18  
19 140 (age, gender), diagnostic criteria, comorbid history and concomitant medication use; patient  
20  
21  
22 141 outcomes such as the incidence of all-cause death, TTS recurrence, stroke, or TIA or MI at 30-  
23  
24 142 day and 5-year follow-up.

25  
26  
27 143 Missing information will be estimated from the available data as appropriate. If the data  
28  
29 144 are incomplete or unclear, we will contact the corresponding author. The results of extraction  
30  
31 145 will be verified by two reviewers separately before data analysis and disagreements will be  
32  
33 146 resolved from consultation from a third reviewer.

34  
35  
36  
37 147 The process is expected to be completed by December 2020.

### 38 148 **Data synthesis**

39  
40  
41 149 The essential descriptions of all enrolled studies including type of publication, author,  
42  
43 150 publication year and country will be included in the systematic review. A brief summary of the  
44  
45  
46 151 study design, participant characteristics, diagnostic criteria, sample size, follow-up, and  
47  
48 152 outcome measurements will be included for all studies. Subgroups analyses based on age,  
49  
50  
51 153 gender, region, commodity diseases, medication, and each component of the outcomes will be  
52  
53  
54 154 measured if possible.

### 55 155 **Quality assessment and risk of bias**

1  
2  
3  
4 156 Risk of bias will be assessed by independent researchers following the Newcastle–Ottawa  
5  
6  
7 157 quality assessment scale (NOS) for observational studies and Cochrane Effective Practice  
8  
9 158 Organization of Care tool for interventional studies.<sup>26</sup> Discrepancies will be resolved through  
10  
11  
12 159 discussion. A third reviewer will arbitrate unsettled disagreements. The Grading of  
13  
14 160 Recommendations, Assessment, Development and Evaluations (GRADE) will be applied to  
15  
16  
17 161 assess the quality of evidence for disease outcomes.

### 162 **Meta-analysis**

163  
164 163 Meta-analysis will be performed using R software (version 4.0.2), in which package ‘meta’  
15  
16  
17 164 (version 4.14-0) and package ‘robvis’ (version 0.3.0) will be used in the study.

165  
166 165 Meta-analysis will be performed with different homogeneities among populations, which  
17  
18  
19 166 will be tested by the  $I^2$  statistics.  $I^2$  values of 0–30% will be considered as minimal heterogeneity,  
20  
21  
22 167 31–50% moderate heterogeneity, and > 50% substantial heterogeneity.

168  
169 168 If available, the effects of Aspirin on MACCE for patients with TTS will be evaluated  
20  
21  
22 169 using random-effect modeling. Relative risk (RR) with 95% confidence intervals (95%CI) will  
23  
24  
25 170 be calculated for dichotomous data and weighted mean difference (WMD) for continuous data.

171  
172 171 Begg’s funnel plot and Egger’s linear regression will be used to assess the publication bias  
25  
26  
27 172 and sample size bias. An asymmetrical funnel plot or p value of < 0.10 on Egger’s test will be  
28  
29  
30 173 considered as the presence of publication bias.

174  
175 174 Subgroup analysis will be performed based on gender, country, diagnostic criteria,  
31  
32  
33 175 comorbid history, concomitant medication use and each component of MACCE if possible.  
34  
35  
36 176 Meta regression analysis will be used to explore potential source of heterogeneity if more than  
37  
38  
39 177 10 studies were included in each measurement.

1  
2  
3  
4 178 Sensitivity will be analyzed by dropping one study at a time and measure stability of the  
5  
6 179 analysis. Graphics of pooled data (forest plots, L'Abbé plot, radial plot and meta regression)  
7  
8  
9 180 will be plotted and added into the manuscript.  
10

11 181 If pooled data remain heterogeneous within these pooled groups, a narrative description  
12  
13  
14 182 will be provided.  
15

### 16 183 **Authors' contributions**

17  
18  
19 184 Jinhai Lin and Danping Xu were involved in conception and generation of the study  
20  
21  
22 185 protocol. Jinhai Lin, Danping Xu, Bingxin Wu, Yining Ding and Biying Zhong were involved  
23  
24  
25 186 in study design. Luoqi Lin and Zhiwei Huang will review the literatures for inclusion. Bingxin  
26  
27  
28 187 Wu will be responsible for resolving disagreements in data selection, synthesis, and assessment.  
29  
30 188 Miaoyang Lin will verify the data. The manuscript is approved by all authors for publication.  
31

32 189

### 33 190 **Funding statement**

34  
35  
36  
37 191 This research received no specific grant from any funding agency in the public,  
38  
39  
40 192 commercial or not-for-profit sectors.  
41

42 193

### 43 194 **Competing interests**

44  
45  
46  
47 195 None declared.  
48  
49

50 196

### 51 197 **Reference**

52  
53  
54  
55 198 1. Ghadri JR, Wittstein IS, Prasad A, et al. International Expert Consensus Document on  
56  
57 199 Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and  
58  
59 200 Pathophysiology. *Eur Heart J* 2018; 39: 2032-2046. 2018/06/01. DOI:  
60 201 10.1093/eurheartj/ehy076.

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

- 202 2. Pelliccia F, Kaski JC, Crea F, et al. Pathophysiology of Takotsubo Syndrome. *Circulation*
- 203 2017; 135: 2426-2441. 2017/06/14. DOI: 10.1161/circulationaha.116.027121.
- 204 3. Akashi YJ, Goldstein DS, Barbaro G, et al. Takotsubo cardiomyopathy: a new form of
- 205 acute, reversible heart failure. *Circulation* 2008; 118: 2754-2762. 2008/12/25. DOI:
- 206 10.1161/circulationaha.108.767012.
- 207 4. Templin C, Napp LC and Ghadri JR. Takotsubo Syndrome: Underdiagnosed,
- 208 Underestimated, but Understood? *J Am Coll Cardiol* 2016; 67: 1937-1940. 2016/04/23. DOI:
- 209 10.1016/j.jacc.2016.03.006.
- 210 5. Dastidar AG, Frontera A, Palazzuoli A, et al. TakoTsubo cardiomyopathy: unravelling the
- 211 malignant consequences of a benign disease with cardiac magnetic resonance. *Heart Fail Rev*
- 212 2015; 20: 415-421. 2015/04/22. DOI: 10.1007/s10741-015-9489-4.
- 213 6. Deshmukh A, Kumar G, Pant S, et al. Prevalence of Takotsubo cardiomyopathy in the
- 214 United States. *Am Heart J* 2012; 164: 66-71.e61. 2012/07/17. DOI: 10.1016/j.ahj.2012.03.020.
- 215 7. Templin C, Ghadri JR, Diekmann J, et al. Clinical Features and Outcomes of Takotsubo
- 216 (Stress) Cardiomyopathy. *N Engl J Med* 2015; 373: 929-938. 2015/09/04. DOI:
- 217 10.1056/NEJMoal406761.
- 218 8. Boland TA, Lee VH and Bleck TP. Stress-induced cardiomyopathy. *Crit Care Med* 2015;
- 219 43: 686-693. 2015/01/08. DOI: 10.1097/ccm.0000000000000851.
- 220 9. Tornvall P, Collste O, Ehrenborg E, et al. A Case-Control Study of Risk Markers and
- 221 Mortality in Takotsubo Stress Cardiomyopathy. *J Am Coll Cardiol* 2016; 67: 1931-1936.
- 222 2016/04/23. DOI: 10.1016/j.jacc.2016.02.029.
- 223 10. Redfors B, Vedad R, Angerås O, et al. Mortality in takotsubo syndrome is similar to
- 224 mortality in myocardial infarction - A report from the SWEDEHEART registry. *Int J Cardiol*
- 225 2015; 185: 282-289. 2015/03/31. DOI: 10.1016/j.ijcard.2015.03.162.
- 226 11. Medina de Chazal H, Del Buono MG, Keyser-Marcus L, et al. Stress Cardiomyopathy
- 227 Diagnosis and Treatment: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2018; 72: 1955-
- 228 1971. 2018/10/13. DOI: 10.1016/j.jacc.2018.07.072.
- 229 12. Ghadri JR, Wittstein IS, Prasad A, et al. International Expert Consensus Document on
- 230 Takotsubo Syndrome (Part II): Diagnostic Workup, Outcome, and Management. *Eur Heart J*
- 231 2018; 39: 2047-2062. 2018/06/01. DOI: 10.1093/eurheartj/ehy077.
- 232 13. El-Battrawy I, Gietzen T, Lang S, et al. Short- and Long-Term Incidence of
- 233 Thromboembolic Events in Takotsubo Syndrome as Compared With Acute Coronary
- 234 Syndrome. *Angiology* 2019; 70: 838-843. 2019/04/17. DOI: 10.1177/0003319719842682.
- 235 14. Dias A, Franco E, Koshkelashvili N, et al. Antiplatelet therapy in Takotsubo
- 236 cardiomyopathy: does it improve cardiovascular outcomes during index event? *Heart Vessels*
- 237 2016; 31: 1285-1290. 2015/08/13. DOI: 10.1007/s00380-015-0729-2.
- 238 15. Pirzer R, Elmas E, Haghi D, et al. Platelet and monocyte activity markers and mediators
- 239 of inflammation in Takotsubo cardiomyopathy. *Heart Vessels* 2012; 27: 186-192. 2011/03/19.
- 240 DOI: 10.1007/s00380-011-0132-6.
- 241 16. Anfossi G and Trovati M. Role of catecholamines in platelet function: pathophysiological
- 242 and clinical significance. *Eur J Clin Invest* 1996; 26: 353-370. 1996/05/01. DOI:
- 243 10.1046/j.1365-2362.1996.150293.x.
- 244 17. Carmen Collado Moreno C, Garcia-Gonzalez RF, Valiente-Aleman I, et al. Management
- 245 of patients diagnosed with tako-tsubo syndrome. *European Journal of Heart Failure* 2018; 20:

- 1  
2  
3 246 487. Conference Abstract. DOI: 10.1002/ejhf.1197.
- 4 247 18. Bertaina M, D'Ascenzo F, Iannaccone M, et al. Is aspirin needed after Takotsubo  
5 248 syndrome?: A propensity score sub-analysis of inter-tak registry. *European Heart Journal* 2017;  
6 249 38: 647. Conference Abstract. DOI: 10.1093/eurheartj/ehx502.3113.
- 7 250 19. Fazio G, Pizzuto C, Barbaro G, et al. Chronic pharmacological treatment in takotsubo  
8 251 cardiomyopathy. *Int J Cardiol* 2008; 127: 121-123. 2007/06/05. DOI:  
9 252 10.1016/j.ijcard.2007.04.013.
- 10 253 20. Dias AM, Ross T, De Guevara EFL, et al. DOES GUIDELINE DIRECTED MEDICAL  
11 254 THERAPY FOR SYSTOLIC HEART FAILURE HELP PREVENT TAKOTSUBO  
12 255 RECURRENCE AND/OR READMISSION? *Journal of the American College of Cardiology*  
13 256 2020; 75: 879. Conference Abstract. DOI: 10.1016/S0735-1097(20)31506-0.
- 14 257 21. Santoro F, Ieva R, Musaico F, et al. Lack of efficacy of drug therapy in preventing  
15 258 takotsubo cardiomyopathy recurrence: a meta-analysis. *Clin Cardiol* 2014; 37: 434-439.  
16 259 2014/04/05. DOI: 10.1002/clc.22280.
- 17 260 22. Abanador-Kamper N, Kamper L, Wolfertz J, et al. Evaluation of therapy management and  
18 261 outcome in Takotsubo syndrome. *BMC Cardiovasc Disord* 2017; 17: 225. 2017/08/19. DOI:  
19 262 10.1186/s12872-017-0661-8.
- 20 263 23. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P)  
21 264 2015: elaboration and explanation. *Bmj* 2016; 354: i4086. 2016/07/23. DOI: 10.1136/bmj.i4086.
- 22 265 24. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic  
23 266 reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and  
24 267 elaboration. *Bmj* 2009; 339: b2700. 2009/07/23. DOI: 10.1136/bmj.b2700.
- 25 268 25. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in  
26 269 epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in  
27 270 Epidemiology (MOOSE) group. *Jama* 2000; 283: 2008-2012. 2000/05/02. DOI:  
28 271 10.1001/jama.283.15.2008.
- 29 272 26. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the  
30 273 quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010; 25: 603-605.  
31 274 2010/07/24. DOI: 10.1007/s10654-010-9491-z.
- 32 275  
33 276  
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

## PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
<b>ADMINISTRATIVE INFORMATION</b>					
<b>Title</b>					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not for update
<b>Registration</b>	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	40
<b>Authors</b>					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	4
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	183
<b>Amendments</b>	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input checked="" type="checkbox"/>	<input type="checkbox"/>	121
<b>Support</b>					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	190
Sponsor	5b	Provide name for the review funder and/or sponsor	<input type="checkbox"/>	<input checked="" type="checkbox"/>	None
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	<input checked="" type="checkbox"/>	None
<b>INTRODUCTION</b>					
<b>Rationale</b>	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	50
<b>Objectives</b>	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	80
<b>METHODS</b>					
<b>Eligibility criteria</b>	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for	<input checked="" type="checkbox"/>	<input type="checkbox"/>	105

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		eligibility for the review			
<b>Information sources</b>	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	94
<b>Search strategy</b>	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input checked="" type="checkbox"/>	<input type="checkbox"/>	94
<b>STUDY RECORDS</b>					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	121
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	125
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	136
<b>Data items</b>	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	136
<b>Outcomes and prioritization</b>	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	106
<b>Risk of bias in individual studies</b>	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input checked="" type="checkbox"/>	<input type="checkbox"/>	162
<b>DATA</b>					
<b>Synthesis</b>	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	148
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., $I^2$ , Kendall's tau)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	162
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	174
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	181
<b>Meta-bias(es)</b>	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	171
<b>Confidence in cumulative evidence</b>	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	155



# BMJ Open

## The Effect of Aspirin in Takotsubo Syndrome: Protocol of A Systematic Review and Meta-Analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-046727.R1
Article Type:	Protocol
Date Submitted by the Author:	19-Apr-2021
Complete List of Authors:	Lin, Jinhai; Guangzhou University of Chinese Medicine, The Second Clinical Medical College Wu, Bingxin; Guangzhou University of Chinese Medicine, The Second Clinical Medical College Lin, Luoqi; Guangzhou University of Chinese Medicine, The Second Clinical Medical College Ding, Yining; Guangzhou University of Chinese Medicine, The Second Clinical Medical College Zhong, Biying; Guangzhou University of Chinese Medicine, The Second Clinical Medical College Huang, Zhiwei; Second Clinical Medical College of Guangzhou University of Chinese Medicine Lin, Miaoyang; Guangzhou University of Chinese Medicine, The Second Clinical Medical College Xu, Dan-Ping; The Eighth Affiliated Hospital of Sun Yat-Sen University; Guangzhou University of Chinese Medicine, The Second Clinical Medical College
<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine, Evidence based practice
Keywords:	Cardiomyopathy < CARDIOLOGY, Thromboembolism < CARDIOLOGY, 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 1 **The Effect of Aspirin in Takotsubo Syndrome: Protocol of A Systematic Review and**  
5  
6 2 **Meta-Analysis**  
7  
8  
9 3

10 4 Jinhai Lin,<sup>A</sup> Bingxin Wu,<sup>A</sup> Luoqi Lin,<sup>A</sup> Yining Ding,<sup>A</sup> Biying Zhong,<sup>A</sup> Zhiwei Huang,<sup>A</sup>

11  
12  
13 5 Miaoyang Lin,<sup>A</sup> Danping Xu,<sup>B,A</sup>

14  
15  
16 6 A. The Second Clinical Medical College, Guangzhou University of Chinese Medicine, China

17  
18 7 B. The Eighth Affiliated Hospital, Sun Yat-sen University, China  
19  
20  
21  
22

23 9 **Correspondence:**

24  
25  
26 10 Danping Xu, Ph.D.

27  
28 11 Professor of Cardiology and Chinese Medicine

29  
30  
31 12 Department of Cardiology, The Eighth Affiliated Hospital, Sun Yat-sen University

32  
33  
34 13 No. 3025, Shennan Middle Road, Futian District, Shenzhen, Guangdong Province, China

35  
36 14 xudanping@hotmail.com  
37  
38  
39  
40  
41  
42

43 17 **Abstract**

44 18 [Introduction] Takotsubo syndrome (TTS) is a sudden reversible weakening of the left  
45  
46 19 ventricle function induced by severe stress and resembles many features as acute coronary  
47  
48 20 syndrome. Even though many guidelines had been published about TTS, there is no consensus  
49  
50 21 regarding the long-term treatment. Aspirin is one of the most common prescribed medicines at  
51  
52 22 discharge for patients with the intention to reduce thrombus events and improve the overall  
53  
54 23 prognosis. However, existing studies yielded conflicting results concerning its effects. This  
55  
56 24 study aims to evaluate the impact of long-term maintenance treatment of Aspirin in TTS and  
57  
58  
59  
60

25 provides insights in clinic management.

26 [Methods and analysis] After searching through electronic databases (PubMed, EMBASE,  
27 Cochrane Library, Web of Science, National Library of Medicine Gateway, CNKI, Wanfang  
28 and VIP), gray literatures, conference abstract and trial registries for clinical studies  
29 investigating the impact of Aspirin on patients with TTS, a systemic review and meta-analysis  
30 will be conducted. The search will be limited from inception of each database to 1st August,  
31 2020. The outcomes including all-cause death, TTS recurrence, stroke, transient ischemic  
32 attack or myocardial infarction at 30-day and 5-year follow-up will be examined. Risk of bias  
33 will be assessed by Newcastle–Ottawa quality assessment scale for observational studies and  
34 Cochrane Effective Practice Organization of Care evaluation tool for interventional studies.  
35 Grading of Recommendations, Assessment, Development and Evaluations (GRADE) method  
36 will be applied to assess the quality of evidence. If available, the effects of Aspirin on the above  
37 outcomes for patients with TTS will be evaluated using random-effect modeling with relative  
38 risk at 95% confidence intervals. Subgroup analysis and sensitivity analysis will also be  
39 performed when possible.

40 [Ethics and dissemination] Ethics approval was not required due to the retrospective nature  
41 of the study. Results of the review will be published in a peer-reviewed journal.

42 [Systematic review registration number] CRD42020212729.

### 43 **Strengths and limitations of this study**

- 44 ● Eligible literature from existing common databases will be included in this study.
- 45 ● The systematic review will be performed according to the Meta-analysis of Observational  
46 Studies in Epidemiology (MOOSE) guideline and will be reported according to the

1  
2  
3  
4 47 Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA)  
5  
6 48 guidelines.

7  
8  
9 ● 49 Subgroup analysis and sensitivity analysis will be performed to evaluate the bias and  
10  
11 stability in the study.  
12

## 13 14 51 **Introduction**

15  
16  
17 52 Takotsubo syndrome (TTS) refers to a reversible form of acute heart failure induced by  
18  
19 53 severe stress which shares many characteristics with acute coronary syndrome (ACS), including  
20  
21 54 demographic features, onset symptoms, electrocardiogram abnormalities and elevation of  
22  
23 55 cardiac biomarkers.<sup>1</sup> Due to a lack of non-invasive examinations method, the diagnosis and  
24  
25 56 understanding of TTS remains poor. In clinical practice, TTS is mainly diagnosed by  
26  
27 57 presentation of severe transient left ventricular (LV) dysfunction with typical apical ballooning  
28  
29 58 or other regional wall motion abnormalities documented by coronary angiography with left  
30  
31 59 ventriculography.<sup>2</sup>

32  
33  
34  
35  
36  
37 60 Another characteristic feature of TTS is the reversible pathology change and self-limiting  
38  
39 61 clinical course.<sup>3</sup> For a rather long time, TTS was generally considered as a benign disease with  
40  
41 62 relatively low morbidity.<sup>4</sup> However, this view is challenged by recent studies.<sup>5,6</sup> Based on data  
42  
43 63 obtained from the International Takotsubo Registry,<sup>7</sup> the rate of major adverse cardiac and  
44  
45 64 cerebrovascular events (MACCE) for patients with TTS was 9.9% per patient-year and the  
46  
47 65 mortality was 5.6% per patient-year in long-term follow-up.<sup>8</sup> In addition, the incidences of in-  
48  
49 66 hospital complications including shock and death were also comparable to ACS.<sup>9,10</sup> But the  
50  
51 67 understanding and management of TTS is behind compared to ACS. Even though many  
52  
53 68 guidelines had been published about TTS, there is no consensus regarding the long-term  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 69 treatment.<sup>11</sup>  
5

6 70 The LV thrombus and systematic embolism were reported to occur on approximately 2-8%  
7  
8  
9 71 of all TTS patients with LV abnormalities.<sup>12</sup> In comparison, the incidence of thrombosis in TTS  
10  
11 72 in 5 year follow up was 2-fold higher than ACS (21% vs 9%),<sup>13</sup> which indicated the necessity  
12  
13  
14 73 of applying antithrombotic therapy.<sup>14</sup>  
15

16  
17 74 Recent studies suggested that the release of catecholamines during acute phase of TTS  
18  
19 75 initiates platelet aggregation, secretion and activation of arachidonate pathway.<sup>2 15 16</sup> Therefore,  
20  
21  
22 76 Aspirin became one of the most commonly prescribed medicines at discharge for patients with  
23  
24  
25 77 TTS.<sup>17</sup> However, it is important to acknowledge that existing studies yielded conflicting results  
26  
27 78 concerning its effects.<sup>18-20</sup> Prior systematic review and meta-analysis demonstrated that Aspirin  
28  
29  
30 79 was unable to improve the prognosis of TTS.<sup>21</sup> However, its conclusion was challenged by  
31  
32  
33 80 subsequent studies suggesting that more studies are needed to resolve this question.<sup>22</sup>  
34

35 81 To evaluate the effect as well as safety of Aspirin for patients with TTS, the protocol aims  
36  
37  
38 82 to systemically review existing literature and conduct a comprehensive meta-analysis to  
39  
40  
41 83 provide the most updated evidence for the treatment of TTS in clinical practice.  
42

#### 43 84 **Methods and analysis**

#### 44 45 85 **Patient and public involvement**

46  
47  
48 86 There will be no patient or public involvement given the nature of the study.  
49

#### 50 51 87 **Study design**

52  
53 88 The design of this systematic review was carried out according to the recommendation of  
54  
55  
56 89 the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P)  
57  
58  
59  
60

1  
2  
3  
4 90 statement.<sup>23</sup> The protocol has also acquired approval automatically from the PROSPERO (ID:  
5  
6 91 CRD42020212729).

7  
8  
9 92 The systematic review will be performed according to the Meta-analysis of  
10  
11 93 Observational Studies in Epidemiology (MOOSE) guidelines and will be reported according  
12  
13  
14 94 to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA)  
15  
16  
17 95 guidelines.<sup>24 25</sup>

### 18 19 20 96 **Search strategy**

21  
22 97 The information to be included in this study will cover electronic databases, gray  
23  
24  
25 98 literatures, conference abstract and trial registries.

26  
27 99 Databases including PubMed, Excerpta Medica Database (EMBASE), Cochrane Library,  
28  
29  
30 100 Web of Science, Clinicaltrials.gov, National Library of Medicine (NLM) Gateway, China  
31  
32  
33 101 National Knowledge Infrastructure (CNKI), Wanfang and Weipu (VIP) will be searched from  
34  
35 102 inception of the library to August 1st, 2020. The search will follow the principle of PICOS  
36  
37  
38 103 (participants, intervention, comparison, outcome, and study design), employing subject words  
39  
40  
41 104 and free words for the term “Takotsubo Cardiomyopathy” and “Aspirin” with adjustment as  
42  
43  
44 105 necessary per specific database (see supplementary file). Reference list of included studies will  
45  
46  
47 106 also be scanned for additional relevant articles.

48 107 The search is anticipated to be completed by November, 2020.

### 49 50 51 108 **Eligibility criteria**

#### 52 53 109 **Participants and Intervention**

54  
55  
56 110 Patients with a diagnosis of TTS, regardless of the diagnostic criteria, will be included in  
57  
58  
59 111 the study. To estimate the long-term effect of Aspirin, only studies in which participants taking  
60

1  
2  
3  
4 112 Aspirin for no less than 90 days will be included.  
5

6 113 **Comparison**  
7

8  
9 114 The outcome measures for TTS patients taking and not taking Aspirin will be compared  
10  
11 115 in the study.  
12

13  
14 116 **Study outcomes**  
15

16  
17 117 The co-primary outcome will be the incidence of MACCE, i.e., a composite of all-cause  
18  
19 118 death, TTS recurrence, stroke, or transient ischemic attack (TIA) or myocardial infarction (MI)  
20  
21 119 at 30-day and 5-year follow-up.  
22

23  
24 120 The secondary outcome will be each component of MACCE. Included studies must  
25  
26 121 contain at least one of the above outcome measurements.  
27

28  
29 122 **Types of studies**  
30

31  
32 123 Both observational and interventional studies are eligible for the study. Articles that  
33  
34 124 published in languages other than English or Chinese will be translated into English when  
35  
36 125 available.  
37

38  
39 126 **Exclusion**  
40

41  
42 127 Studies including participants with malignancies or autoimmune diseases or taking  
43  
44 128 antithrombotic therapy for other diseases will be excluded. Review articles, commentaries,  
45  
46 129 laboratory science studies, case studies, case series, and other studies that do not meet the  
47  
48 130 requirements mentioned above will be excluded.  
49

50  
51 131 **Study records**  
52

53 132 **Data management**  
54

55  
56 133 Publication screening will be managed through Endnote software (version X9, Clarivate  
57  
58  
59  
60



1  
2  
3  
4 134 Analytics), in which duplicates will be removed and further review will be performed.  
5

6  
7 135 **Selection process**  
8

9 136 Two investigators will independently screen each record by the title and abstract before  
10  
11 137 categorizing all literatures into three groups: relevant, irrelevant and uncertain. After  
12  
13 138 preliminary screening, irrelevant records agreed by both investigators will be eliminated, while  
14  
15 139 the others will be retrieved by full text for further assessment. In the process, a list of eligible  
16  
17 140 articles will be made separately by each reviewer. Discrepancies between the two lists will be  
18  
19 141 resolved by discussion if possible. When an unsettled disagreement arises, a final decision will  
20  
21 142 be made by consulting a third reviewer. Reference list of the included articles will also be  
22  
23 143 reviewed to check for additional studies that might be omitted previously.  
24  
25  
26  
27  
28  
29

30 144 A flow diagram for the selection process will be drawn in accordance with the PRISMA  
31  
32 145 guidelines.  
33  
34

35 146 **Data collection process**  
36

37 147 Data extraction will be completed by one reviewer using a pre-designed form.  
38

39  
40 148 Data to be collected will include study characteristics such as author, publication year,  
41  
42 149 time period of study, country and site; cohort characteristics such as sample size, demographics  
43  
44 150 (age, gender), diagnostic criteria, comorbid history and concomitant medication use; patient  
45  
46 151 outcomes such as the incidence of all-cause death, TTS recurrence, stroke, or TIA or MI at 30-  
47  
48 152 day and 5-year follow-up.  
49  
50  
51  
52

53 153 Missing information will be estimated from the available data as appropriate. If the data  
54  
55 154 are incomplete or unclear, we will contact the corresponding author. The results of extraction  
56  
57 155 will be verified by two reviewers separately before data analysis and disagreements will be  
58  
59  
60

1  
2  
3  
4 156 resolved from consultation from a third reviewer.  
5

6 157 The process is expected to be completed by December 2020.  
7  
8

9 158 **Data synthesis**

10  
11 159 The essential descriptions of all enrolled studies including type of publication, author,  
12  
13  
14 160 publication year and country will be included in the systematic review. A brief summary of the  
15  
16  
17 161 study design, participant characteristics, diagnostic criteria, sample size, follow-up, and  
18  
19  
20 162 outcome measurements will be included for all studies. Subgroups analyses based on age,  
21  
22  
23 163 gender, region, commodity diseases, medication, and each component of the outcomes will be  
24  
25 164 measured if possible.  
26

27 165 **Quality assessment and risk of bias**

28  
29  
30 166 Risk of bias will be assessed by independent researchers following the Newcastle–Ottawa  
31  
32  
33 167 quality assessment scale (NOS) for observational studies and Cochrane Effective Practice  
34  
35 168 Organization of Care tool for interventional studies.<sup>26</sup> Discrepancies will be resolved through  
36  
37  
38 169 discussion. A third reviewer will arbitrate unsettled disagreements. The Grading of  
39  
40  
41 170 Recommendations, Assessment, Development and Evaluations (GRADE) will be applied to  
42  
43  
44 171 assess the quality of evidence for disease outcomes.  
45

46 172 **Meta-analysis**

47  
48 173 Meta-analysis will be performed using R software (version 4.0.2), in which package ‘meta’  
49  
50  
51 174 (version 4.14-0) and package ‘robvis’ (version 0.3.0) will be used in the study.  
52

53 175 Meta-analysis will be performed with different homogeneities among populations, which  
54  
55  
56 176 will be tested by the  $I^2$  statistics.  $I^2$  values of 0–30% will be considered as minimal heterogeneity,  
57  
58  
59 177 31–50% moderate heterogeneity, and > 50% substantial heterogeneity.  
60

1  
2  
3  
4 178 If available, the effects of Aspirin on MACCE for patients with TTS will be evaluated  
5  
6 179 using random-effect modeling. Relative risk (RR) with 95% confidence intervals (95%CI) will  
7  
8  
9 180 be calculated for dichotomous data and weighted mean difference (WMD) for continuous data.  
10

11 181 Begg's funnel plot and Egger's linear regression will be used to assess the publication bias  
12  
13  
14 182 and sample size bias. An asymmetrical funnel plot or p value of  $< 0.10$  on Egger's test will be  
15  
16  
17 183 considered as the presence of publication bias.  
18

19 184 Subgroup analysis will be performed based on gender, country, diagnostic criteria,  
20  
21  
22 185 comorbid history, concomitant medication use and each component of MACCE if possible.  
23  
24  
25 186 Meta regression analysis will be used to explore potential source of heterogeneity if more than  
26  
27 187 10 studies were included in each measurement.  
28

29  
30 188 Sensitivity will be analyzed by dropping one study at a time and measure stability of the  
31  
32 189 analysis. Graphics of pooled data (forest plots, L'Abbé plot, radial plot and meta regression)  
33  
34  
35 190 will be plotted and added into the manuscript.  
36

37  
38 191 If pooled data remain heterogeneous within these pooled groups, a narrative description  
39  
40 192 will be provided.  
41

#### 42 193 **Authors' contributions**

43  
44  
45 194 Jinhai Lin and Danping Xu were involved in conception and generation of the study  
46  
47  
48 195 protocol. Jinhai Lin, Danping Xu, Bingxin Wu, Yining Ding and Biying Zhong were involved  
49  
50 196 in study design. Luoqi Lin and Zhiwei Huang will review the literatures for inclusion. Bingxin  
51  
52  
53 197 Wu will be responsible for resolving disagreements in data selection, synthesis, and assessment.  
54  
55  
56 198 Miaoyang Lin will verify the data. The manuscript is approved by all authors for publication.  
57

#### 58 199 **Ethics and dissemination**

1  
2  
3  
4 200 All data will be acquired from existing publications available. Findings of the study will  
5  
6 201 be disseminated through peer-reviewed publications.  
7  
8

9 202 **Funding statement**

10  
11 203 This research received no specific grant from any funding agency in the public,  
12  
13  
14 204 commercial or not-for-profit sectors.  
15  
16  
17 205

18  
19 206 **Competing interests**

20  
21  
22 207 None declared.  
23  
24  
25 208

26  
27 209 **Reference**

- 28  
29 210 1. Ghadri JR, Wittstein IS, Prasad A, et al. International Expert Consensus Document on  
30 211 Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and  
31 212 Pathophysiology. *Eur Heart J* 2018;39(22):2032-46. doi: 10.1093/eurheartj/ehy076  
32 213 [published Online First: 2018/06/01]  
33 214 2. Pelliccia F, Kaski JC, Crea F, et al. Pathophysiology of Takotsubo Syndrome. *Circulation*  
34 215 2017;135(24):2426-41. doi: 10.1161/circulationaha.116.027121 [published Online  
35 216 First: 2017/06/14]  
36 217 3. Akashi YJ, Goldstein DS, Barbaro G, et al. Takotsubo cardiomyopathy: a new form of acute,  
37 218 reversible heart failure. *Circulation* 2008;118(25):2754-62. doi:  
38 219 10.1161/circulationaha.108.767012 [published Online First: 2008/12/25]  
39 220 4. Templin C, Napp LC, Ghadri JR. Takotsubo Syndrome: Underdiagnosed, Underestimated,  
40 221 but Understood? *J Am Coll Cardiol* 2016;67(16):1937-40. doi:  
41 222 10.1016/j.jacc.2016.03.006 [published Online First: 2016/04/23]  
42 223 5. Dastidar AG, Frontera A, Palazzuoli A, et al. TakoTsubo cardiomyopathy: unravelling the  
43 224 malignant consequences of a benign disease with cardiac magnetic resonance. *Heart*  
44 225 *Fail Rev* 2015;20(4):415-21. doi: 10.1007/s10741-015-9489-4 [published Online First:  
45 226 2015/04/22]  
46 227 6. Deshmukh A, Kumar G, Pant S, et al. Prevalence of Takotsubo cardiomyopathy in the United  
47 228 States. *Am Heart J* 2012;164(1):66-71.e1. doi: 10.1016/j.ahj.2012.03.020 [published  
48 229 Online First: 2012/07/17]  
49 230 7. Templin C, Ghadri JR, Diekmann J, et al. Clinical Features and Outcomes of Takotsubo  
50 231 (Stress) Cardiomyopathy. *N Engl J Med* 2015;373(10):929-38. doi:  
51 232 10.1056/NEJMoa1406761 [published Online First: 2015/09/04]  
52 233 8. Boland TA, Lee VH, Bleck TP. Stress-induced cardiomyopathy. *Crit Care Med*

- 234 2015;43(3):686-93. doi: 10.1097/ccm.0000000000000851 [published Online First:  
235 2015/01/08]
- 236 9. Tornvall P, Collste O, Ehrenborg E, et al. A Case-Control Study of Risk Markers and  
237 Mortality in Takotsubo Stress Cardiomyopathy. *J Am Coll Cardiol* 2016;67(16):1931-  
238 6. doi: 10.1016/j.jacc.2016.02.029 [published Online First: 2016/04/23]
- 239 10. Redfors B, Vedad R, Angerås O, et al. Mortality in takotsubo syndrome is similar to  
240 mortality in myocardial infarction - A report from the SWEDEHEART registry. *Int J*  
241 *Cardiol* 2015;185:282-9. doi: 10.1016/j.ijcard.2015.03.162 [published Online First:  
242 2015/03/31]
- 243 11. Medina de Chazal H, Del Buono MG, Keyser-Marcus L, et al. Stress Cardiomyopathy  
244 Diagnosis and Treatment: JACC State-of-the-Art Review. *J Am Coll Cardiol*  
245 2018;72(16):1955-71. doi: 10.1016/j.jacc.2018.07.072 [published Online First:  
246 2018/10/13]
- 247 12. Ghadri JR, Wittstein IS, Prasad A, et al. International Expert Consensus Document on  
248 Takotsubo Syndrome (Part II): Diagnostic Workup, Outcome, and Management. *Eur*  
249 *Heart J* 2018;39(22):2047-62. doi: 10.1093/eurheartj/ehy077 [published Online First:  
250 2018/06/01]
- 251 13. El-Battrawy I, Gietzen T, Lang S, et al. Short- and Long-Term Incidence of  
252 Thromboembolic Events in Takotsubo Syndrome as Compared With Acute Coronary  
253 Syndrome. *Angiology* 2019;70(9):838-43. doi: 10.1177/0003319719842682  
254 [published Online First: 2019/04/17]
- 255 14. Dias A, Franco E, Koshkelashvili N, et al. Antiplatelet therapy in Takotsubo  
256 cardiomyopathy: does it improve cardiovascular outcomes during index event? *Heart*  
257 *Vessels* 2016;31(8):1285-90. doi: 10.1007/s00380-015-0729-2 [published Online First:  
258 2015/08/13]
- 259 15. Pirzer R, Elmas E, Haghi D, et al. Platelet and monocyte activity markers and mediators of  
260 inflammation in Takotsubo cardiomyopathy. *Heart Vessels* 2012;27(2):186-92. doi:  
261 10.1007/s00380-011-0132-6 [published Online First: 2011/03/19]
- 262 16. Anfossi G, Trovati M. Role of catecholamines in platelet function: pathophysiological and  
263 clinical significance. *Eur J Clin Invest* 1996;26(5):353-70. doi: 10.1046/j.1365-  
264 2362.1996.150293.x [published Online First: 1996/05/01]
- 265 17. Carmen Collado Moreno C, Garcia-Gonzalez RF, Valiente-Aleman I, et al. Management of  
266 patients diagnosed with tako-tsubo syndrome. *European Journal of Heart Failure*  
267 2018;20:487. doi: 10.1002/ejhf.1197
- 268 18. Bertaina M, D'Ascenzo F, Iannaccone M, et al. Is aspirin needed after Takotsubo syndrome?:  
269 A propensity score sub-analysis of inter-tak registry. *European Heart Journal*  
270 2017;38:647. doi: 10.1093/eurheartj/ehx502.3113
- 271 19. Fazio G, Pizzuto C, Barbaro G, et al. Chronic pharmacological treatment in takotsubo  
272 cardiomyopathy. *Int J Cardiol* 2008;127(1):121-3. doi: 10.1016/j.ijcard.2007.04.013  
273 [published Online First: 2007/06/05]
- 274 20. Dias AM, Ross T, De Guevara EFL, et al. DOES GUIDELINE DIRECTED MEDICAL  
275 THERAPY FOR SYSTOLIC HEART FAILURE HELP PREVENT TAKOTSUBO  
276 RECURRENCE AND/OR READMISSION? *Journal of the American College of*  
277 *Cardiology* 2020;75(11):879. doi: 10.1016/S0735-1097(20)31506-0

- 1  
2  
3 278 21. Santoro F, Ieva R, Musaico F, et al. Lack of efficacy of drug therapy in preventing takotsubo  
4 279 cardiomyopathy recurrence: a meta-analysis. *Clin Cardiol* 2014;37(7):434-9. doi:  
5 280 10.1002/clc.22280 [published Online First: 2014/04/05]  
6  
7 281 22. Abanador-Kamper N, Kamper L, Wolfertz J, et al. Evaluation of therapy management and  
8 282 outcome in Takotsubo syndrome. *BMC Cardiovasc Disord* 2017;17(1):225. doi:  
9 283 10.1186/s12872-017-0661-8 [published Online First: 2017/08/19]  
10  
11 284 23. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P)  
12 285 2015: elaboration and explanation. *Bmj* 2016;354:i4086. doi: 10.1136/bmj.i4086  
13 286 [published Online First: 2016/07/23]  
14  
15 287 24. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic  
16 288 reviews and meta-analyses of studies that evaluate healthcare interventions:  
17 289 explanation and elaboration. *Bmj* 2009;339:b2700. doi: 10.1136/bmj.b2700 [published  
18 290 Online First: 2009/07/23]  
19  
20 291 25. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in  
21 292 epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in  
22 293 Epidemiology (MOOSE) group. *Jama* 2000;283(15):2008-12. doi:  
23 294 10.1001/jama.283.15.2008 [published Online First: 2000/05/02]  
24  
25 295 26. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality  
26 296 of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25(9):603-5. doi:  
27 297 10.1007/s10654-010-9491-z [published Online First: 2010/07/24]  
28  
29 298  
30 299

## Search Strategy for PubMed

(((((((((((((((((((Cardiomyopathy, Takotsubo[Title/Abstract]) OR (Stress  
 Cardiomyopathy[Title/Abstract])) OR (Cardiomyopathy, Stress[Title/Abstract])) OR (Tako-tsubo  
 Cardiomyopathy[Title/Abstract])) OR (Cardiomyopathy, Tako-tsubo[Title/Abstract])) OR (Tako  
 tsubo Cardiomyopathy[Title/Abstract])) OR (Broken Heart Syndrome[Title/Abstract])) OR  
 (Syndrome, Broken Heart[Title/Abstract])) OR (Syndromes, Broken Heart[Title/Abstract])) OR  
 (Takotsubo Syndrome[Title/Abstract])) OR (Transient Apical Ballooning  
 Syndrome[Title/Abstract])) OR (Apical Ballooning Syndrome[Title/Abstract])) OR (Syndrome,  
 Apical Ballooning[Title/Abstract])) OR (Left Ventricular Apical Ballooning  
 Syndrome[Title/Abstract])) OR (Tako-tsubo Syndrome[Title/Abstract])) OR (Syndrome,  
 Tako-tsubo[Title/Abstract])) OR (Syndromes, Tako-tsubo[Title/Abstract])) OR (Tako tsubo  
 Syndrome[Title/Abstract])) OR (Tako-tsubo Syndromes[Title/Abstract])) OR ("Takotsubo  
 Cardiomyopathy"[Mesh]) AND ("Aspirin"[Mesh]) OR (((((((((((((((((((Acetylsalicylic  
 Acid[Title/Abstract]) OR (Acid, Acetylsalicylic[Title/Abstract])) OR (2-(Acetyloxy)benzoic  
 Acid[Title/Abstract])) OR (Acylpyrin[Title/Abstract])) OR (Aloxiiprimum[Title/Abstract])) OR  
 (Colfarit[Title/Abstract])) OR (Dispril[Title/Abstract])) OR (Easprin[Title/Abstract])) OR  
 (Ecotrin[Title/Abstract])) OR (Endosprin[Title/Abstract])) OR (Magnecycl[Title/Abstract])) OR  
 (Micristin[Title/Abstract])) OR (Polopirin[Title/Abstract])) OR (Polopiryna[Title/Abstract])) OR  
 (Solprin[Title/Abstract])) OR (Solupsan[Title/Abstract])) OR (Zorprin[Title/Abstract])) OR  
 (Acetysal[Title/Abstract]))

Time Range: inception to 1<sup>st</sup> August 2020

## PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
<b>ADMINISTRATIVE INFORMATION</b>					
<b>Title</b>					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not for update
<b>Registration</b>	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	40
<b>Authors</b>					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	4
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	183
<b>Amendments</b>	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input checked="" type="checkbox"/>	<input type="checkbox"/>	121
<b>Support</b>					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	190
Sponsor	5b	Provide name for the review funder and/or sponsor	<input type="checkbox"/>	<input checked="" type="checkbox"/>	None
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	<input checked="" type="checkbox"/>	None
<b>INTRODUCTION</b>					
<b>Rationale</b>	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	50
<b>Objectives</b>	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	80
<b>METHODS</b>					
<b>Eligibility criteria</b>	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for	<input checked="" type="checkbox"/>	<input type="checkbox"/>	105



Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		eligibility for the review			
<b>Information sources</b>	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	94
<b>Search strategy</b>	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input checked="" type="checkbox"/>	<input type="checkbox"/>	94
<b>STUDY RECORDS</b>					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	121
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	125
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	136
<b>Data items</b>	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	136
<b>Outcomes and prioritization</b>	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	106
<b>Risk of bias in individual studies</b>	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input checked="" type="checkbox"/>	<input type="checkbox"/>	162
<b>DATA</b>					
<b>Synthesis</b>	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	148
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., $I^2$ , Kendall's tau)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	162
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	174
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	181
<b>Meta-bias(es)</b>	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	171
<b>Confidence in cumulative evidence</b>	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	155

# BMJ Open

## The Effect of Aspirin in Takotsubo Syndrome: Protocol of A Systematic Review and Meta-Analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-046727.R2
Article Type:	Protocol
Date Submitted by the Author:	24-Jun-2021
Complete List of Authors:	Lin, Jinhai; Guangzhou University of Chinese Medicine, The Second Clinical Medical College Wu, Bingxin; Guangzhou University of Chinese Medicine, The Second Clinical Medical College Lin, Luoqi; Guangzhou University of Chinese Medicine, The Second Clinical Medical College Ding, Yining; Guangzhou University of Chinese Medicine, The Second Clinical Medical College Zhong, Biying; Guangzhou University of Chinese Medicine, The Second Clinical Medical College Huang, Zhiwei; Second Clinical Medical College of Guangzhou University of Chinese Medicine Lin, Miaoyang; Guangzhou University of Chinese Medicine, The Second Clinical Medical College Xu, Dan-Ping; The Eighth Affiliated Hospital of Sun Yat-Sen University; Guangzhou University of Chinese Medicine, The Second Clinical Medical College
<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine, Evidence based practice
Keywords:	Cardiomyopathy < CARDIOLOGY, Thromboembolism < CARDIOLOGY, 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 1 **The Effect of Aspirin in Takotsubo Syndrome: Protocol of A Systematic Review and**  
5  
6 2 **Meta-Analysis**  
7  
8  
9 3

10 4 Jinhai Lin,<sup>A</sup> Bingxin Wu,<sup>A</sup> Luoqi Lin,<sup>A</sup> Yining Ding,<sup>A</sup> Biying Zhong,<sup>A</sup> Zhiwei Huang,<sup>A</sup>

11  
12  
13 5 Miaoyang Lin,<sup>A</sup> Danping Xu,<sup>B,A</sup>

14  
15  
16 6 A. The Second Clinical Medical College, Guangzhou University of Chinese Medicine, China

17  
18 7 B. The Eighth Affiliated Hospital, Sun Yat-sen University, China  
19  
20  
21 8

22  
23 9 **Correspondence:**

24  
25  
26 10 Danping Xu, Ph.D.

27  
28 11 Professor of Cardiology and Chinese Medicine

29  
30  
31 12 Department of Cardiology, The Eighth Affiliated Hospital, Sun Yat-sen University

32  
33  
34 13 No. 3025, Shennan Middle Road, Futian District, Shenzhen, Guangdong Province, China

35  
36 14 xudanping@hotmail.com  
37  
38  
39  
40 16

41  
42 17 **Abstract**

43  
44 18 [Introduction] Takotsubo syndrome (TTS) is a sudden reversible weakening of the left  
45  
46 19 ventricle function induced by severe stress and resembles many features as acute coronary  
47  
48 20 syndrome. Even though many guidelines had been published about TTS, there is no consensus  
49  
50 21 regarding the long-term treatment. Aspirin is one of the most common prescribed medicines at  
51  
52 22 discharge for patients with the intention to reduce thrombus events and improve the overall  
53  
54 23 prognosis. However, existing studies yielded conflicting results concerning its effects. This  
55  
56 24 study aims to evaluate the impact of long-term maintenance treatment of Aspirin in TTS and  
57  
58  
59  
60

25 provides insights in clinic management.

26 [Methods and analysis] After searching through electronic databases (PubMed, EMBASE,  
27 Cochrane Library, Web of Science, National Library of Medicine Gateway, CNKI, Wanfang  
28 and VIP), gray literatures, conference abstract and trial registries for clinical studies  
29 investigating the impact of Aspirin on patients with TTS, a systemic review and meta-analysis  
30 will be conducted. The search will be limited from inception of each database to 1st August,  
31 2020. The outcomes including all-cause death, TTS recurrence, stroke, transient ischemic  
32 attack or myocardial infarction at 30-day and 5-year follow-up will be examined. Risk of bias  
33 will be assessed by Newcastle–Ottawa quality assessment scale for observational studies and  
34 Cochrane Effective Practice Organization of Care evaluation tool for interventional studies.  
35 Grading of Recommendations, Assessment, Development and Evaluations (GRADE) method  
36 will be applied to assess the quality of evidence. If available, the effects of Aspirin on the above  
37 outcomes for patients with TTS will be evaluated using random-effect modeling with relative  
38 risk at 95% confidence intervals. Subgroup analysis and sensitivity analysis will also be  
39 performed when possible.

40 [Ethics and dissemination] Ethics approval was not required due to the retrospective nature  
41 of the study. Results of the review will be published in a peer-reviewed journal.

42 [Systematic review registration number] CRD42020212729.

#### 43 **Strengths and limitations of this study**

- 44 ● Eligible literature from existing common databases will be included in this study.
- 45 ● The systematic review will be performed according to the Meta-analysis of Observational  
46 Studies in Epidemiology (MOOSE) guideline and will be reported according to the

1  
2  
3  
4 47 Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA)

5  
6 48 guidelines.

7  
8  
9 49 ● Subgroup analysis and sensitivity analysis will be performed to evaluate the bias and  
10  
11 50 stability in the study.

12  
13  
14 51 ● Given the lack of understanding on Takotsubo syndrome, the number of finally included  
15  
16 52 studies might be limited.

17  
18  
19 53 **Introduction**

20  
21  
22 54 Takotsubo syndrome (TTS) refers to a reversible form of acute heart failure induced by  
23  
24 55 severe stress which shares many characteristics with acute coronary syndrome (ACS), including  
25  
26 56 demographic features, onset symptoms, electrocardiogram abnormalities and elevation of  
27  
28 57 cardiac biomarkers.<sup>1</sup> Due to a lack of non-invasive examinations method, the diagnosis and  
29  
30 58 understanding of TTS remains poor. In clinical practice, TTS is mainly diagnosed by  
31  
32 59 presentation of severe transient left ventricular (LV) dysfunction with typical apical ballooning  
33  
34 60 or other regional wall motion abnormalities documented by coronary angiography with left  
35  
36 61 ventriculography.<sup>2</sup>

37  
38  
39  
40  
41  
42  
43 62 Another characteristic feature of TTS is the reversible pathology change and self-limiting  
44  
45 63 clinical course.<sup>3</sup> For a rather long time, TTS was generally considered as a benign disease with  
46  
47 64 relatively low morbidity.<sup>4</sup> However, this view is challenged by recent studies.<sup>5 6</sup> Based on data  
48  
49 65 obtained from the International Takotsubo Registry,<sup>7</sup> the rate of major adverse cardiac and  
50  
51 66 cerebrovascular events (MACCE) for patients with TTS was 9.9% per patient-year and the  
52  
53 67 mortality was 5.6% per patient-year in long-term follow-up.<sup>8</sup> In addition, the incidences of in-  
54  
55 68 hospital complications including shock and death were also comparable to ACS.<sup>9 10</sup> But the  
56  
57  
58  
59  
60

69 understanding and management of TTS is behind compared to ACS. Even though many  
70 guidelines had been published about TTS, there is no consensus regarding the long-term  
71 treatment.<sup>11</sup>

72 The LV thrombus and systematic embolism were reported to occur on approximately 2-8%  
73 of all TTS patients with LV abnormalities.<sup>12</sup> In comparison, the incidence of thrombosis in TTS  
74 in 5 year follow up was 2-fold higher than ACS (21% vs 9%),<sup>13</sup> which indicated the necessity  
75 of applying antithrombotic therapy.<sup>14</sup>

76 Recent studies suggested that the release of catecholamines during acute phase of TTS  
77 initiates platelet aggregation, secretion and activation of arachidonate pathway.<sup>2,15,16</sup> Therefore,  
78 Aspirin became one of the most commonly prescribed medicines at discharge for patients with  
79 TTS.<sup>17</sup> However, it is important to acknowledge that existing studies yielded conflicting results  
80 concerning its effects.<sup>18-20</sup> Prior systematic review and meta-analysis demonstrated that Aspirin  
81 was unable to improve the prognosis of TTS.<sup>21</sup> However, its conclusion was challenged by  
82 subsequent studies suggesting that more studies are needed to resolve this question.<sup>22</sup>

83 To evaluate the effect as well as safety of Aspirin for patients with TTS, the protocol aims  
84 to systemically review existing literature and conduct a comprehensive meta-analysis to  
85 provide the most updated evidence for the treatment of TTS in clinical practice.

## 86 **Methods and analysis**

### 87 **Patient and public involvement**

88 There will be no patient or public involvement given the nature of the study.

### 89 **Study design**

1  
2  
3  
4 90 The design of this systematic review was carried out according to the recommendation of  
5  
6 91 the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P)  
7  
8  
9 92 statement.<sup>23</sup> The protocol has also acquired approval automatically from the PROSPERO (ID:  
10  
11 93 CRD42020212729).

14 94 The systematic review will be performed according to the Meta-analysis of  
15  
16  
17 95 Observational Studies in Epidemiology (MOOSE) guidelines and will be reported according  
18  
19  
20 96 to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA)  
21  
22 97 guidelines.<sup>24 25</sup>

#### 24 98 **Search strategy**

26  
27 99 The information to be included in this study will cover electronic databases, gray  
28  
29  
30 100 literatures, conference abstract and trial registries.

31  
32 101 Databases including PubMed, Excerpta Medica Database (EMBASE), Cochrane Library,  
33  
34  
35 102 Web of Science, Clinicaltrials.gov, National Library of Medicine (NLM) Gateway, China  
36  
37  
38 103 National Knowledge Infrastructure (CNKI), Wanfang and Weipu (VIP) will be searched from  
39  
40 104 inception of the library to August 1st, 2020. The search will follow the principle of PICOS  
41  
42  
43 105 (participants, intervention, comparison, outcome, and study design), employing subject words  
44  
45  
46 106 and free words for the term “Takotsubo Cardiomyopathy” and “Aspirin” with adjustment as  
47  
48 107 necessary per specific database (see supplementary file). Reference list of included studies will  
49  
50  
51 108 also be scanned for additional relevant articles.

52  
53 109 The search is anticipated to be completed by November, 2020.

#### 55 110 **Eligibility criteria**

#### 57 111 **Participants and Intervention**

58  
59  
60



1  
2  
3  
4 112 Patients with a diagnosis of TTS, regardless of the diagnostic criteria, will be included in  
5  
6 113 the study. To estimate the long-term effect of Aspirin, only studies in which participants taking  
7  
8  
9 114 Aspirin for no less than 90 days will be included.  
10

### 11 115 **Comparison**

12  
13  
14 116 The outcome measures for TTS patients taking and not taking Aspirin will be compared  
15  
16  
17 117 in the study.

### 18 118 **Study outcomes**

19  
20  
21  
22 119 The co-primary outcome will be the incidence of MACCE, i.e., a composite of all-cause  
23  
24 120 death, TTS recurrence, stroke, or transient ischemic attack (TIA) or myocardial infarction (MI)  
25  
26  
27 121 at 30-day and 5-year follow-up.

28  
29  
30 122 The secondary outcome will be each component of MACCE. Included studies must  
31  
32 123 contain at least one of the above outcome measurements.  
33

### 34 124 **Types of studies**

35  
36  
37 125 Both observational and interventional studies are eligible for the study. Articles that  
38  
39  
40 126 published in languages other than English or Chinese will be translated into English when  
41  
42  
43 127 available.  
44

### 45 128 **Exclusion**

46  
47  
48 129 Studies including participants with malignancies or autoimmune diseases or taking  
49  
50  
51 130 antithrombotic therapy for other diseases will be excluded. Review articles, commentaries,  
52  
53 131 laboratory science studies, case studies, case series, and other studies that do not meet the  
54  
55  
56 132 requirements mentioned above will be excluded.  
57

### 58 133 **Study records**

1  
2  
3  
4 134 **Data management**

5  
6 135 Publication screening will be managed through Endnote software (version X9, Clarivate  
7  
8  
9 136 Analytics), in which duplicates will be removed and further review will be performed.

10  
11  
12 137 **Selection process**

13  
14 138 Two investigators will independently screen each record by the title and abstract before  
15  
16  
17 139 categorizing all literatures into three groups: relevant, irrelevant and uncertain. After  
18  
19  
20 140 preliminary screening, irrelevant records agreed by both investigators will be eliminated, while  
21  
22 141 the others will be retrieved by full text for further assessment. In the process, a list of eligible  
23  
24  
25 142 articles will be made separately by each reviewer. Discrepancies between the two lists will be  
26  
27 143 resolved by discussion if possible. When an unsettled disagreement arises, a final decision will  
28  
29  
30 144 be made by consulting a third reviewer. Reference list of the included articles will also be  
31  
32  
33 145 reviewed to check for additional studies that might be omitted previously.

34  
35 146 A flow diagram for the selection process will be drawn in accordance with the PRISMA  
36  
37  
38 147 guidelines.

39  
40 148 **Data collection process**

41  
42  
43 149 Data extraction will be completed by one reviewer using a pre-designed form.

44  
45 150 Data to be collected will include study characteristics such as author, publication year,  
46  
47  
48 151 time period of study, country and site; cohort characteristics such as sample size, demographics  
49  
50  
51 152 (age, gender), diagnostic criteria, comorbid history and concomitant medication use; patient  
52  
53  
54 153 outcomes such as the incidence of all-cause death, TTS recurrence, stroke, or TIA or MI at 30-  
55  
56 154 day and 5-year follow-up.

57  
58 155 Missing information will be estimated from the available data as appropriate. If the data  
59  
60

1  
2  
3  
4 156 are incomplete or unclear, we will contact the corresponding author. The results of extraction  
5  
6 157 will be verified by two reviewers separately before data analysis and disagreements will be  
7  
8  
9 158 resolved from consultation from a third reviewer.  
10

11 159 The process is expected to be completed by December 2020.  
12  
13

#### 14 160 **Data synthesis**

15  
16  
17 161 The essential descriptions of all enrolled studies including type of publication, author,  
18  
19  
20 162 publication year and country will be included in the systematic review. A brief summary of the  
21  
22 163 study design, participant characteristics, diagnostic criteria, sample size, follow-up, and  
23  
24  
25 164 outcome measurements will be included for all studies. Subgroups analyses based on age,  
26  
27 165 gender, region, commodity diseases, medication, and each component of the outcomes will be  
28  
29  
30 166 measured if possible.  
31

#### 32 167 **Quality assessment and risk of bias**

33  
34  
35 168 Risk of bias will be assessed by independent researchers following the Newcastle–Ottawa  
36  
37  
38 169 quality assessment scale (NOS) for observational studies and Cochrane Effective Practice  
39  
40 170 Organization of Care tool for interventional studies.<sup>26</sup> Discrepancies will be resolved through  
41  
42  
43 171 discussion. A third reviewer will arbitrate unsettled disagreements. The Grading of  
44  
45 172 Recommendations, Assessment, Development and Evaluations (GRADE) will be applied to  
46  
47  
48 173 assess the quality of evidence for disease outcomes.  
49

#### 50 174 **Meta-analysis**

51  
52  
53 175 Meta-analysis will be performed using R software (version 4.0.2), in which package ‘meta’  
54  
55  
56 176 (version 4.14-0) and package ‘robvis’ (version 0.3.0) will be used in the study.  
57

58 177 Meta-analysis will be performed with different homogeneities among populations, which  
59  
60

1  
2  
3  
4 178 will be tested by the  $I^2$  statistics.  $I^2$  values of 0–30% will be considered as minimal heterogeneity,  
5  
6 179 31–50% moderate heterogeneity, and > 50% substantial heterogeneity.  
7  
8

9 180 If available, the effects of Aspirin on MACCE for patients with TTS will be evaluated  
10  
11 181 using random-effect modeling. Relative risk (RR) with 95% confidence intervals (95%CI) will  
12  
13 182 be calculated for dichotomous data and weighted mean difference (WMD) for continuous data.  
14  
15

16 183 Begg's funnel plot and Egger's linear regression will be used to assess the publication bias  
17  
18 184 and sample size bias. An asymmetrical funnel plot or p value of < 0.10 on Egger's test will be  
19  
20 185 considered as the presence of publication bias.  
21  
22

23 186 Subgroup analysis will be performed based on gender, country, diagnostic criteria,  
24  
25 187 comorbid history, concomitant medication use and each component of MACCE if possible.  
26  
27 188 Meta regression analysis will be used to explore potential source of heterogeneity if more than  
28  
29 189 10 studies were included in each measurement.  
30  
31

32 190 Sensitivity will be analyzed by dropping one study at a time and measure stability of the  
33  
34 191 analysis. Graphics of pooled data (forest plots, L'Abbé plot, radial plot and meta regression)  
35  
36 192 will be plotted and added into the manuscript.  
37  
38

39 193 If pooled data remain heterogeneous within these pooled groups, a narrative description  
40  
41 194 will be provided.  
42  
43

#### 44 195 **Authors' contributions**

45 196 Jinhai Lin and Danping Xu were involved in conception and generation of the study  
46  
47 197 protocol. Jinhai Lin, Danping Xu, Bingxin Wu, Yining Ding and Biying Zhong were involved  
48  
49 198 in study design. Luoqi Lin and Zhiwei Huang will review the literatures for inclusion. Bingxin  
50  
51 199 Wu will be responsible for resolving disagreements in data selection, synthesis, and assessment.  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 200 Miaoyang Lin will verify the data. The manuscript is approved by all authors for publication.  
5

6  
7 201 **Ethics and dissemination**  
8

9 202 All data will be acquired from existing publications available. Findings of the study will  
10  
11 203 be disseminated through peer-reviewed publications.  
12

13  
14 204 **Funding statement**  
15

16  
17 205 This research received no specific grant from any funding agency in the public,  
18  
19 206 commercial or not-for-profit sectors.  
20

21  
22 207  
23

24  
25 208 **Competing interests**  
26

27 209 None declared.  
28

29  
30 210  
31

32  
33 211 **Reference**  
34

- 35 212 1. Ghadri JR, Wittstein IS, Prasad A, et al. International Expert Consensus Document on  
36 213 Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and  
37 214 Pathophysiology. *Eur Heart J* 2018;39(22):2032-46. doi: 10.1093/eurheartj/ehy076  
38 215 [published Online First: 2018/06/01]  
39  
40 216 2. Pelliccia F, Kaski JC, Crea F, et al. Pathophysiology of Takotsubo Syndrome. *Circulation*  
41 217 2017;135(24):2426-41. doi: 10.1161/circulationaha.116.027121 [published Online  
42 218 First: 2017/06/14]  
43  
44 219 3. Akashi YJ, Goldstein DS, Barbaro G, et al. Takotsubo cardiomyopathy: a new form of acute,  
45 220 reversible heart failure. *Circulation* 2008;118(25):2754-62. doi:  
46 221 10.1161/circulationaha.108.767012 [published Online First: 2008/12/25]  
47  
48 222 4. Templin C, Napp LC, Ghadri JR. Takotsubo Syndrome: Underdiagnosed, Underestimated,  
49 223 but Understood? *J Am Coll Cardiol* 2016;67(16):1937-40. doi:  
50 224 10.1016/j.jacc.2016.03.006 [published Online First: 2016/04/23]  
51  
52 225 5. Dastidar AG, Frontera A, Palazzuoli A, et al. TakoTsubo cardiomyopathy: unravelling the  
53 226 malignant consequences of a benign disease with cardiac magnetic resonance. *Heart*  
54 227 *Fail Rev* 2015;20(4):415-21. doi: 10.1007/s10741-015-9489-4 [published Online First:  
55 228 2015/04/22]  
56  
57 229 6. Deshmukh A, Kumar G, Pant S, et al. Prevalence of Takotsubo cardiomyopathy in the United  
58 230 States. *Am Heart J* 2012;164(1):66-71.e1. doi: 10.1016/j.ahj.2012.03.020 [published  
59 231 Online First: 2012/07/17]  
60

- 1  
2  
3 232 7. Templin C, Ghadri JR, Diekmann J, et al. Clinical Features and Outcomes of Takotsubo  
4 233 (Stress) Cardiomyopathy. *N Engl J Med* 2015;373(10):929-38. doi:  
5 234 10.1056/NEJMoa1406761 [published Online First: 2015/09/04]  
6  
7 235 8. Boland TA, Lee VH, Bleck TP. Stress-induced cardiomyopathy. *Crit Care Med*  
8 236 2015;43(3):686-93. doi: 10.1097/ccm.0000000000000851 [published Online First:  
9 237 2015/01/08]  
10  
11 238 9. Tornvall P, Collste O, Ehrenborg E, et al. A Case-Control Study of Risk Markers and  
12 239 Mortality in Takotsubo Stress Cardiomyopathy. *J Am Coll Cardiol* 2016;67(16):1931-  
13 240 6. doi: 10.1016/j.jacc.2016.02.029 [published Online First: 2016/04/23]  
14  
15 241 10. Redfors B, Vedad R, Angerås O, et al. Mortality in takotsubo syndrome is similar to  
16 242 mortality in myocardial infarction - A report from the SWEDEHEART registry. *Int J*  
17 243 *Cardiol* 2015;185:282-9. doi: 10.1016/j.ijcard.2015.03.162 [published Online First:  
18 244 2015/03/31]  
19  
20 245 11. Medina de Chazal H, Del Buono MG, Keyser-Marcus L, et al. Stress Cardiomyopathy  
21 246 Diagnosis and Treatment: JACC State-of-the-Art Review. *J Am Coll Cardiol*  
22 247 2018;72(16):1955-71. doi: 10.1016/j.jacc.2018.07.072 [published Online First:  
23 248 2018/10/13]  
24  
25 249 12. Ghadri JR, Wittstein IS, Prasad A, et al. International Expert Consensus Document on  
26 250 Takotsubo Syndrome (Part II): Diagnostic Workup, Outcome, and Management. *Eur*  
27 251 *Heart J* 2018;39(22):2047-62. doi: 10.1093/eurheartj/ehy077 [published Online First:  
28 252 2018/06/01]  
29  
30 253 13. El-Battrawy I, Gietzen T, Lang S, et al. Short- and Long-Term Incidence of  
31 254 Thromboembolic Events in Takotsubo Syndrome as Compared With Acute Coronary  
32 255 Syndrome. *Angiology* 2019;70(9):838-43. doi: 10.1177/0003319719842682  
33 256 [published Online First: 2019/04/17]  
34  
35 257 14. Dias A, Franco E, Koshkelashvili N, et al. Antiplatelet therapy in Takotsubo  
36 258 cardiomyopathy: does it improve cardiovascular outcomes during index event? *Heart*  
37 259 *Vessels* 2016;31(8):1285-90. doi: 10.1007/s00380-015-0729-2 [published Online First:  
38 260 2015/08/13]  
39  
40 261 15. Pirzer R, Elmas E, Haghi D, et al. Platelet and monocyte activity markers and mediators of  
41 262 inflammation in Takotsubo cardiomyopathy. *Heart Vessels* 2012;27(2):186-92. doi:  
42 263 10.1007/s00380-011-0132-6 [published Online First: 2011/03/19]  
43  
44 264 16. Anfossi G, Trovati M. Role of catecholamines in platelet function: pathophysiological and  
45 265 clinical significance. *Eur J Clin Invest* 1996;26(5):353-70. doi: 10.1046/j.1365-  
46 266 2362.1996.150293.x [published Online First: 1996/05/01]  
47  
48 267 17. Carmen Collado Moreno C, Garcia-Gonzalez RF, Valiente-Aleman I, et al. Management of  
49 268 patients diagnosed with tako-tsubo syndrome. *European Journal of Heart Failure*  
50 269 2018;20:487. doi: 10.1002/ejhf.1197  
51  
52 270 18. Bertaina M, D'Ascenzo F, Iannaccone M, et al. Is aspirin needed after Takotsubo syndrome?:  
53 271 A propensity score sub-analysis of inter-tak registry. *European Heart Journal*  
54 272 2017;38:647. doi: 10.1093/eurheartj/ehx502.3113  
55  
56 273 19. Fazio G, Pizzuto C, Barbaro G, et al. Chronic pharmacological treatment in takotsubo  
57 274 cardiomyopathy. *Int J Cardiol* 2008;127(1):121-3. doi: 10.1016/j.ijcard.2007.04.013  
58 275 [published Online First: 2007/06/05]  
59

- 1  
2  
3 276 20. Dias AM, Ross T, De Guevara EFL, et al. DOES GUIDELINE DIRECTED MEDICAL  
4 277 THERAPY FOR SYSTOLIC HEART FAILURE HELP PREVENT TAKOTSUBO  
5 278 RECURRENCE AND/OR READMISSION? *Journal of the American College of*  
6 279 *Cardiology* 2020;75(11):879. doi: 10.1016/S0735-1097(20)31506-0  
7  
8 280 21. Santoro F, Ieva R, Musaico F, et al. Lack of efficacy of drug therapy in preventing takotsubo  
9 281 cardiomyopathy recurrence: a meta-analysis. *Clin Cardiol* 2014;37(7):434-9. doi:  
10 282 10.1002/clc.22280 [published Online First: 2014/04/05]  
11  
12 283 22. Abanador-Kamper N, Kamper L, Wolfertz J, et al. Evaluation of therapy management and  
13 284 outcome in Takotsubo syndrome. *BMC Cardiovasc Disord* 2017;17(1):225. doi:  
14 285 10.1186/s12872-017-0661-8 [published Online First: 2017/08/19]  
15  
16 286 23. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P)  
17 287 2015: elaboration and explanation. *Bmj* 2016;354:i4086. doi: 10.1136/bmj.i4086  
18 288 [published Online First: 2016/07/23]  
19  
20 289 24. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic  
21 290 reviews and meta-analyses of studies that evaluate healthcare interventions:  
22 291 explanation and elaboration. *Bmj* 2009;339:b2700. doi: 10.1136/bmj.b2700 [published  
23 292 Online First: 2009/07/23]  
24  
25 293 25. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in  
26 294 epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in  
27 295 Epidemiology (MOOSE) group. *Jama* 2000;283(15):2008-12. doi:  
28 296 10.1001/jama.283.15.2008 [published Online First: 2000/05/02]  
29  
30 297 26. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality  
31 298 of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25(9):603-5. doi:  
32 299 10.1007/s10654-010-9491-z [published Online First: 2010/07/24]  
33  
34 300  
35 301  
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

## Search Strategy for PubMed

(((((((((((((((((((Cardiomyopathy, Takotsubo[Title/Abstract]) OR (Stress  
 Cardiomyopathy[Title/Abstract])) OR (Cardiomyopathy, Stress[Title/Abstract])) OR (Tako-tsubo  
 Cardiomyopathy[Title/Abstract])) OR (Cardiomyopathy, Tako-tsubo[Title/Abstract])) OR (Tako  
 tsubo Cardiomyopathy[Title/Abstract])) OR (Broken Heart Syndrome[Title/Abstract])) OR  
 (Syndrome, Broken Heart[Title/Abstract])) OR (Syndromes, Broken Heart[Title/Abstract])) OR  
 (Takotsubo Syndrome[Title/Abstract])) OR (Transient Apical Ballooning  
 Syndrome[Title/Abstract])) OR (Apical Ballooning Syndrome[Title/Abstract])) OR (Syndrome,  
 Apical Ballooning[Title/Abstract])) OR (Left Ventricular Apical Ballooning  
 Syndrome[Title/Abstract])) OR (Tako-tsubo Syndrome[Title/Abstract])) OR (Syndrome,  
 Tako-tsubo[Title/Abstract])) OR (Syndromes, Tako-tsubo[Title/Abstract])) OR (Tako tsubo  
 Syndrome[Title/Abstract])) OR (Tako-tsubo Syndromes[Title/Abstract])) OR ("Takotsubo  
 Cardiomyopathy"[Mesh]) AND ("Aspirin"[Mesh]) OR (((((((((((((((((((Acetylsalicylic  
 Acid[Title/Abstract]) OR (Acid, Acetylsalicylic[Title/Abstract])) OR (2-(Acetyloxy)benzoic  
 Acid[Title/Abstract])) OR (Acylpyrin[Title/Abstract])) OR (Aloxiiprimum[Title/Abstract])) OR  
 (Colfarit[Title/Abstract])) OR (Dispril[Title/Abstract])) OR (Easprin[Title/Abstract])) OR  
 (Ecotrin[Title/Abstract])) OR (Endosprin[Title/Abstract])) OR (Magnecycl[Title/Abstract])) OR  
 (Micristin[Title/Abstract])) OR (Polopirin[Title/Abstract])) OR (Polopiryna[Title/Abstract])) OR  
 (Solprin[Title/Abstract])) OR (Solupsan[Title/Abstract])) OR (Zorprin[Title/Abstract])) OR  
 (Acetysal[Title/Abstract]))

Time Range: inception to 1<sup>st</sup> August 2020



## PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
<b>ADMINISTRATIVE INFORMATION</b>					
<b>Title</b>					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not for update
<b>Registration</b>	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	40
<b>Authors</b>					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	4
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	183
<b>Amendments</b>	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input checked="" type="checkbox"/>	<input type="checkbox"/>	121
<b>Support</b>					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	190
Sponsor	5b	Provide name for the review funder and/or sponsor	<input type="checkbox"/>	<input checked="" type="checkbox"/>	None
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	<input checked="" type="checkbox"/>	None
<b>INTRODUCTION</b>					
<b>Rationale</b>	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	50
<b>Objectives</b>	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	80
<b>METHODS</b>					
<b>Eligibility criteria</b>	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for	<input checked="" type="checkbox"/>	<input type="checkbox"/>	105

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		eligibility for the review			
<b>Information sources</b>	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	94
<b>Search strategy</b>	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input checked="" type="checkbox"/>	<input type="checkbox"/>	94
<b>STUDY RECORDS</b>					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	121
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	125
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	136
<b>Data items</b>	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	136
<b>Outcomes and prioritization</b>	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	106
<b>Risk of bias in individual studies</b>	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input checked="" type="checkbox"/>	<input type="checkbox"/>	162
<b>DATA</b>					
<b>Synthesis</b>	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	148
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., $I^2$ , Kendall's tau)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	162
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	174
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	181
<b>Meta-bias(es)</b>	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	171
<b>Confidence in cumulative evidence</b>	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	155