INPLASY PROTOCOL

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Support: **None.**

Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None.

Impact of Aspirin on Prognosis in patients with Takotsubo Syndrome: Protocol of A Systematic Review and Meta-Analysis

Lin, J[1]; Xu, D[2]; Wu, B[3]; Ding, Y[4]; Zhong, B[5]; Lin, L[6]; Huang, Z[7]; Lin, M[8].

Review question / Objective: **What is the impact of Aspirin on the incidence of major adverse cardiac and cerebrovascular events (including all-cause death, Takotsubo Syndrome recurrence, stroke or transient ischemic attack or myocardial infarction at 30-day and 5-year follow-up) for patients diagnosed with Takotsubo Syndrome?**
Condition being studied: **Takotsubo syndrome (TTS) refers to a reversible form of acute heart failure sharing many characteristics in common with acute coronary syndrome (ACS). It is reported to account for about 0.02% of all hospitalizations in the United States. In the International Takotsubo Registry, the rate of major adverse cardiac and cerebrovascular events (MACCE) for patients with TTS was 9.9% per patient-year and the mortality turned out to be 5.6% per patient-year in long-term follow-up. In addition, its incidences of in-hospital complications including shock and death are also comparable to ACS. To date there is no convincing evidence on the long-term management for TTS. As current researches have indicated that TTS results from an acute release of catecholamines which initiates platelet aggregation, secretion and arachidonate pathway activation, Aspirin remains one of the preferred treatments at discharge. However, existing studies have yielded conflicting results concerning its effects. The study aims to evaluate the impact of Aspirin on MACCE for patients with TTS and thereby provide available updated evidence for the treatment in clinical practice.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 09 October 2020 and was last updated on 09 October 2020 (registration number INPLASY2020100030).

INTRODUCTION

Review question / Objective: **What is the impact of Aspirin on the incidence of major adverse cardiac and cerebrovascular events (including all-cause death, Takotsubo Syndrome recurrence, stroke or transient ischemic attack or myocardial**

infarction at 30-day and 5-year follow-up) for patients diagnosed with Takotsubo Syndrome?

Condition being studied: Takotsubo syndrome (TTS) refers to a reversible form of acute heart failure sharing many characteristics in common with acute coronary syndrome (ACS). It is reported to account for about 0.02% of all hospitalizations in the United States. In the International Takotsubo Registry, the rate of major adverse cardiac and cerebrovascular events (MACCE) for patients with TTS was 9.9% per patient-year and the mortality turned out to be 5.6% per patient-year in long-term follow-up. In addition, its incidences of in-hospital complications including shock and death are also comparable to ACS. To date there is no convincing evidence on the long-term management for TTS. As current researches have indicated that TTS results from an acute release of catecholamines which initiates platelet aggregation, secretion and arachidonate pathway activation, Aspirin remains one of the preferred treatments at discharge. However, existing studies have yielded conflicting results concerning its effects. The study aims to evaluate the impact of Aspirin on MACCE for patients with TTS and thereby provide available updated evidence for the treatment in clinical practice.

METHODS

Search strategy: The source of information will include electronic databases, gray literatures, conference abstract, and trial registries. A search will be performed through PubMed, Excerpta Medica Database (EMBASE), Cochrane Library, Web of Science, Clinicaltrials.gov, National Library of Medicine (NLM) Gateway, China National Knowledge Infrastructure (CNKI), Wanfang and Weipu (VIP) databases from inception to August 1st ,2020. The search will follow the principle of PICOS (participants, intervention, comparison, outcome, and study design), employing subject words and free words for the term Takotsubo Cardiomyopathy and Aspirin with adjustment determined by multiple pre-searches and specific database. Reference list of included studies will also be scanned for additional relevant articles.

Participant or population: Eligible studies must pertain to patients with TTS and clear diagnostic criteria. When the participants of a study are divided into subgroups in which only one or several are eligible, data of the part will be extracted separately and included if possible.

Intervention: Included studies must contain information on the administration of Aspirin regardless of the length of period.

Comparator: The MACCE of patients with TTS taking or not taking Aspirin will be compared.

Study designs to be included: Both observational and interventional studies are eligible for the protocol. No limitations are set on the timing of taking Aspirin or the length of follow-up. Articles that published in languages other than English or Chinese will be translated into English when available.

Eligibility criteria: Eligible studies must pertain to patients with TTS and clear diagnostic criteria. When the participants of a study are divided into subgroups in which only one or several are eligible, data of the part will be extracted separately and included if possible. Included studies must contain information on the administration of Aspirin regardless of the length of period. The co-primary outcome will be the incidence of MACCE, i.e., a composite of all-cause death, TTS recurrence, stroke, or transient ischemic attack (TIA) or myocardial infarction (MI) at 30-day and 5-year follow-up. The secondary outcome measurement will be each component of MACCE. Therefore, included studies must contain data related to at least one of the above outcome measurements. Both observational and interventional studies are eligible for the protocol. No limitations are set on the timing of taking Aspirin or the length of follow-up. Articles that published in languages other than English

or Chinese will be translated into English when available.

Information sources: Reference list of included studies will also be scanned for additional relevant articles.

Main outcome(s): The co-primary outcome will be the incidence of MACCE, i.e., a composite of all-cause death, TTS recurrence, stroke, or transient ischemic attack (TIA) or myocardial infarction (MI) at 30-day and 5-year follow-up.

Additional outcome(s): The secondary outcome measurement will be each component of MACCE. Therefore, included studies must contain data related to at least one of the above outcome measurements.

Data management: Records of search will be managed through Endnote software (version X9, Clarivate Analytics), in which duplicates will be removed and further review will be performed.

Quality assessment / Risk of bias analysis: Risk of bias will be assessed by two independent reviewers specific to the study methodology. Tools will include the Newcastle–Ottawa quality assessment scale (NOS) for observational studies and Cochrane Effective Practice Organization of Care tool for interventional studies.26 Discrepancies will be resolved through discussion. A third reviewer will arbitrate in the case of any unsettled disagreement. The reviewers will also use the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) to assess the quality of evidence at the outcome level.

Strategy of data synthesis: Once the information has been extracted, we will present findings with essential descriptions of the study, including type of publication (author, year, country) in the systematic review, which will be presented in the systematic review. There will also be a narrative description of the study design, participant characteristics, diagnostic criteria, sample size, follow-up, and outcome measurements. If the condition allows, subgroups will be set up based on age, gender, region, commodity diseases, medication, and each component of the outcomes to identify the potential subgroups that benefit from taking Aspirin.

Subgroup analysis: If data are sufficient, subgroup analysis will be performed based on gender, country, diagnostic criteria, comorbid history, concomitant medication use and each component of MACCE. When more than 10 studies are included, Meta regression analysis will be used to explore potential source of heterogeneity.

Sensibility analysis: Sensitivity analysis will be performed by dropping one study at a time and thereby verify stability of the analysis. Graphics of pooled data (forest plots, L'Abbé plot, radial plot and meta regression) will be provided for the process.

Language: Articles that published in languages other than English or Chinese will be translated into English when available.

Country(ies) involved: China.

Keywords: Takotsubo Syndrome; Aspirin; Prognosis; Thrombus.

Dissemination plans: Results of the review will be published in a peer-reviewed journal.

Contributions of each author:
Author 1 - Jinhai Lin was involved in generation of the study protocol and drafted the manuscript.
Author 2 - Danping Xu was involved in generation of the idea and provided statistical expertise.
Author 3 - Bingxin Wu contributed to development of selection criteria and will be responsible for resolving disagreements.
Author 4 - Yining Ding was also involved in the study design and provided suggestions for the manuscript.
Author 5 - Biying Zhong also contributed to study design.

Author 6 - Luoqi Lin will be responsible for literatures review.
Author 7 - Zhiwei Huang will also be responsible for literatures review.