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

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

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Abstract

[Introduction] Takotsubo syndrome (TTS) is a sudden reversible weakening of the left ventricle function induced by severe stress and resembles many features as acute coronary syndrome. Even though many guidelines had been published about TTS, there is no consensus regarding the long-term treatment. Aspirin is one of the most common prescribed medicines at discharge for patients with the intention to reduce thrombus events and improve the overall prognosis. However, existing studies yielded conflicting results concerning its effects. This study aims to evaluate the impact of long-term maintenance treatment of Aspirin in TTS and

provides insights in clinic management.

[Methods and analysis] After searching through electronic databases, gray literatures, conference abstract and trial registries for clinical studies investigating the impact of Aspirin on patients with TTS, a systemic review and meta-analysis will be conducted. The outcomes including all-cause death, TTS recurrence, stroke, transient ischemic attack or myocardial infarction at 30-day and 5-year follow-up will be examined. Risk of bias will be assessed by Newcastle–Ottawa quality assessment scale for observational studies and Cochrane Effective Practice Organization of Care evaluation tool for interventional studies. Grading of Recommendations, Assessment, Development and Evaluations（GRADE）method will be applied to assess the quality of evidence. If available, the effects of Aspirin on the above outcomes for patients with TTS will be evaluated using random-effect modeling with relative risk at 95% confidence intervals. Subgroup analysis and sensitivity analysis will also be performed when possible.

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

[Systematic review registration number] INPLASY2020100030; CRD42020212729.

Strengths and limitations of this study

- This study aims to identify the impact of Aspirin treatment on the prognosis of patients with Takotsubo Syndrome.
- The systematic review will be performed according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guideline and will be reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA)

guidelines.

- As Takotsubo syndrome is easy to be misdiagnosed and omitted, there may be limited data available for the study.

Introduction

Takotsubo syndrome (TTS) refers to a reversible form of acute heart failure induced by severe stress which shares many characteristics with acute coronary syndrome (ACS), including demographic features, onset symptoms, electrocardiogram abnormalities and elevation of cardiac biomarkers.[1] Due to a lack of non-invasive examinations method, the diagnosis and understanding of TTS remains poor. In clinical practice, TTS is mainly diagnosed by presentation of severe transient left ventricular (LV) dysfunction with typical apical ballooning or other regional wall motion abnormalities documented by coronary angiography with left ventriculography.[2]

Another characteristic feature of TTS is the reversible pathology change and self-limiting clinical course.[3] For a rather long time, TTS was generally considered as a benign disease with relatively low morbidity.[4] However, this view is challenged by recent studies.[5, 6] Based on data obtained from the International Takotsubo Registry,[7] the rate of major adverse cardiac and cerebrovascular events (MACCE) for patients with TTS was 9.9% per patient-year and the mortality was 5.6% per patient-year in long-term follow-up.[8] In addition, the incidences of in-hospital complications including shock and death were also comparable to ACS.[9, 10] But the understanding and management of TTS is behind compared to ACS. Even though many guidelines had been published about TTS, there is no consensus regarding the long-term treatment.[11]

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

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

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

Methods and analysis

Study design

The design of this systematic review was carried out according to the recommendation of the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) statement and was registered on INPLASY (INPLASY2020100030),[23] which is available on the inplasy.com. The protocol has also acquired approval automatically from the PROSPERO (ID: CRD42020212729).

The systematic review will be performed according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines and will be reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines.[24, 25]

Search strategy

The information to be included in this study will cover electronic databases, gray literatures, conference abstract and trial registries.

Databases including 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) will be searched up 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 as necessary per specific database. Reference list of included studies will also be scanned for additional relevant articles.

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

Eligibility criteria

Study outcomes

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 will be each component of MACCE. Included studies must contain at least one of the above outcome measurements.

Types of studies

Both observational and interventional studies are eligible for the study. 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.

Exclusion

Studies including participants with malignancies or autoimmune diseases or taking antithrombotic therapy for other diseases will be excluded. Review articles, commentaries, laboratory science studies, case studies, case series, and other studies that do not meet the requirements mentioned above will be excluded.

Study records

Data management

Publication screening will be managed through Endnote software (version X9, Clarivate Analytics), in which duplicates will be removed and further review will be performed.

Selection process

Two investigators will independently screen each record by the title and abstract before categorizing all literatures into three groups: relevant, irrelevant and uncertain. After preliminary screening, irrelevant records agreed by both investigators will be eliminated, while the others will be retrieved by full text for further assessment. In the process, a list of eligible articles will be made separately by each reviewer. Discrepancies between the two lists will be resolved by discussion if possible. When an unsettled disagreement arises, a final decision will be made by consulting a third reviewer. Reference list of the included articles will also be reviewed to check for additional studies that might be omitted previously.

A flow diagram for the selection process will be drawn in accordance with the PRISMA guidelines.

Data collection process

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

Data to be collected will include study characteristics such as author, publication year, time period of study, country and site; cohort characteristics such as sample size, demographics (age, gender), diagnostic criteria, comorbid history and concomitant medication use; patient outcomes such as the incidence of all-cause death, TTS recurrence, stroke, or TIA or MI at 30-day and 5-year follow-up.

Missing information will be estimated from the available data as appropriate. If the data are incomplete or unclear, we will contact the corresponding author. The results of extraction will be verified by two reviewers separately before data analysis and disagreements will be resolved from consultation from a third reviewer.

The process is expected to be completed by December 2020.

Data synthesis

The essential descriptions of all enrolled studies including type of publication, author, publication year and country will be included in the systematic review. A brief summary of the study design, participant characteristics, diagnostic criteria, sample size, follow-up, and outcome measurements will be included for all studies. Subgroups analyses based on age, gender, region, commodity diseases, medication, and each component of the outcomes will be measured if possible.

Quality assessment and risk of bias

Risk of bias will be assessed by independent researchers following 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 unsettled disagreements. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) will be applied to assess the quality of evidence for disease outcomes.

Meta-analysis

Meta-analysis will be performed using R software (version 4.0.2), in which package 'meta' (version 4.14-0) and package 'robvis' (version 0.3.0) will be used in the study.

Meta-analysis will be performed with different homogeneities among populations, which will be tested by the I^2 statistics. I^2 values of 0–30% will be considered as minimal heterogeneity, 31–50% moderate heterogeneity, and > 50% substantial heterogeneity.

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

Begg's funnel plot and Egger's linear regression will be used to assess the publication bias and sample size bias. An asymmetrical funnel plot or p value of < 0.10 on Egger's test will be considered as the presence of publication bias.

Subgroup analysis will be performed based on gender, country, diagnostic criteria, comorbid history, concomitant medication use and each component of MACCE if possible. Meta regression analysis will be used to explore potential source of heterogeneity if more than 10 studies were included in each measurement.

Sensitivity will be analyzed by dropping one study at a time and measure stability of the analysis. Graphics of pooled data (forest plots, L'Abbé plot, radial plot and meta regression) will be plotted and added into the manuscript.

If pooled data remain heterogeneous within these pooled groups, a narrative description will be provided.

Authors' contributions

Jinhai Lin and Danping Xu were involved in conception and generation of the study protocol. Jinhai Lin, Danping Xu, Bingxin Wu, Yining Ding and Biying Zhong were involved in study design. Luoqi Lin and Zhiwei Huang will review the literatures for inclusion. Bingxin Wu will be responsible for resolving disagreements in data selection, synthesis, and assessment. Miaoyang Lin will verify the data. The manuscript is approved by all authors for publication.

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Competing interests

None declared.

Reference

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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	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	Not for update
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	40
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	4
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	183
Amendments	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	☒	☐	121
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	190
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☒	None
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	None
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	50
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	80
METHODS					
Eligibility criteria	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	☒	☐	105

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		eligibility for the review			
Information sources	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	☒	☐	94
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	94
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	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)	☒	☐	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	☒	☐	136
Data items	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	☒	☐	136
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	106
Risk of bias in individual studies	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	☒	☐	162
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	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)	☒	☐	162
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	174
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	181
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	171
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	155

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Secondary Subject Heading:	Cardiovascular medicine, Evidence based practice
Keywords:	Cardiomyopathy < CARDIOLOGY, Thromboembolism < CARDIOLOGY, INTERNAL MEDICINE

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Abstract

[Introduction] Takotsubo syndrome (TTS) is a sudden reversible weakening of the left ventricle function induced by severe stress and resembles many features as acute coronary syndrome. Even though many guidelines had been published about TTS, there is no consensus regarding the long-term treatment. Aspirin is one of the most common prescribed medicines at discharge for patients with the intention to reduce thrombus events and improve the overall prognosis. However, existing studies yielded conflicting results concerning its effects. This study aims to evaluate the impact of long-term maintenance treatment of Aspirin in TTS and

provides insights in clinic management.

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

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

[Systematic review registration number] CRD42020212729.

Strengths and limitations of this study

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

Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines.

- Subgroup analysis and sensitivity analysis will be performed to evaluate the bias and stability in the study.

Introduction

Takotsubo syndrome (TTS) refers to a reversible form of acute heart failure induced by severe stress which shares many characteristics with acute coronary syndrome (ACS), including demographic features, onset symptoms, electrocardiogram abnormalities and elevation of cardiac biomarkers.[1] Due to a lack of non-invasive examinations method, the diagnosis and understanding of TTS remains poor. In clinical practice, TTS is mainly diagnosed by presentation of severe transient left ventricular (LV) dysfunction with typical apical ballooning or other regional wall motion abnormalities documented by coronary angiography with left ventriculography.[2]

Another characteristic feature of TTS is the reversible pathology change and self-limiting clinical course.[3] For a rather long time, TTS was generally considered as a benign disease with relatively low morbidity.[4] However, this view is challenged by recent studies.[5 6] Based on data obtained from the International Takotsubo Registry,[7] the rate of major adverse cardiac and cerebrovascular events (MACCE) for patients with TTS was 9.9% per patient-year and the mortality was 5.6% per patient-year in long-term follow-up.[8] In addition, the incidences of in-hospital complications including shock and death were also comparable to ACS.[9 10] But the understanding and management of TTS is behind compared to ACS. Even though many guidelines had been published about TTS, there is no consensus regarding the long-term

treatment.[11]

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

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

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

Methods and analysis

Patient and public involvement

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

Study design

The design of this systematic review was carried out according to the recommendation of the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P)

statement.[23] The protocol has also acquired approval automatically from the PROSPERO (ID: CRD42020212729).

The systematic review will be performed according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines and will be reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines.[24 25]

Search strategy

The information to be included in this study will cover electronic databases, gray literatures, conference abstract and trial registries.

Databases including 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) will be searched from inception of the library 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 as necessary per specific database (see supplementary file). Reference list of included studies will also be scanned for additional relevant articles.

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

Eligibility criteria

Participants and Intervention

Patients with a diagnosis of TTS, regardless of the diagnostic criteria, will be included in the study. To estimate the long-term effect of Aspirin, only studies in which participants taking

Aspirin for no less than 90 days will be included.

Comparison

The outcome measures for TTS patients taking and not taking Aspirin will be compared in the study.

Study outcomes

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 will be each component of MACCE. Included studies must contain at least one of the above outcome measurements.

Types of studies

Both observational and interventional studies are eligible for the study. Articles that published in languages other than English or Chinese will be translated into English when available.

Exclusion

Studies including participants with malignancies or autoimmune diseases or taking antithrombotic therapy for other diseases will be excluded. Review articles, commentaries, laboratory science studies, case studies, case series, and other studies that do not meet the requirements mentioned above will be excluded.

Study records

Data management

Publication screening will be managed through Endnote software (version X9, Clarivate

Analytics), in which duplicates will be removed and further review will be performed.

Selection process

Two investigators will independently screen each record by the title and abstract before categorizing all literatures into three groups: relevant, irrelevant and uncertain. After preliminary screening, irrelevant records agreed by both investigators will be eliminated, while the others will be retrieved by full text for further assessment. In the process, a list of eligible articles will be made separately by each reviewer. Discrepancies between the two lists will be resolved by discussion if possible. When an unsettled disagreement arises, a final decision will be made by consulting a third reviewer. Reference list of the included articles will also be reviewed to check for additional studies that might be omitted previously.

A flow diagram for the selection process will be drawn in accordance with the PRISMA guidelines.

Data collection process

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

Data to be collected will include study characteristics such as author, publication year, time period of study, country and site; cohort characteristics such as sample size, demographics (age, gender), diagnostic criteria, comorbid history and concomitant medication use; patient outcomes such as the incidence of all-cause death, TTS recurrence, stroke, or TIA or MI at 30-day and 5-year follow-up.

Missing information will be estimated from the available data as appropriate. If the data are incomplete or unclear, we will contact the corresponding author. The results of extraction will be verified by two reviewers separately before data analysis and disagreements will be

resolved from consultation from a third reviewer.

The process is expected to be completed by December 2020.

Data synthesis

The essential descriptions of all enrolled studies including type of publication, author, publication year and country will be included in the systematic review. A brief summary of the study design, participant characteristics, diagnostic criteria, sample size, follow-up, and outcome measurements will be included for all studies. Subgroups analyses based on age, gender, region, commodity diseases, medication, and each component of the outcomes will be measured if possible.

Quality assessment and risk of bias

Risk of bias will be assessed by independent researchers following 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 unsettled disagreements. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) will be applied to assess the quality of evidence for disease outcomes.

Meta-analysis

Meta-analysis will be performed using R software (version 4.0.2), in which package 'meta' (version 4.14-0) and package 'robvis' (version 0.3.0) will be used in the study.

Meta-analysis will be performed with different homogeneities among populations, which will be tested by the I^2 statistics. I^2 values of 0–30% will be considered as minimal heterogeneity, 31–50% moderate heterogeneity, and > 50% substantial heterogeneity.

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

Begg's funnel plot and Egger's linear regression will be used to assess the publication bias and sample size bias. An asymmetrical funnel plot or p value of < 0.10 on Egger's test will be considered as the presence of publication bias.

Subgroup analysis will be performed based on gender, country, diagnostic criteria, comorbid history, concomitant medication use and each component of MACCE if possible. Meta regression analysis will be used to explore potential source of heterogeneity if more than 10 studies were included in each measurement.

Sensitivity will be analyzed by dropping one study at a time and measure stability of the analysis. Graphics of pooled data (forest plots, L'Abbé plot, radial plot and meta regression) will be plotted and added into the manuscript.

If pooled data remain heterogeneous within these pooled groups, a narrative description will be provided.

Authors' contributions

Jinhai Lin and Danping Xu were involved in conception and generation of the study protocol. Jinhai Lin, Danping Xu, Bingxin Wu, Yining Ding and Biying Zhong were involved in study design. Luoqi Lin and Zhiwei Huang will review the literatures for inclusion. Bingxin Wu will be responsible for resolving disagreements in data selection, synthesis, and assessment. Miaoyang Lin will verify the data. The manuscript is approved by all authors for publication.

Ethics and dissemination

All data will be acquired from existing publishments available. Findings of the study will be disseminated through peer-reviewed publications.

Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

None declared.

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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 (Aloxiprimum[Title/Abstract])) OR (Colfarit[Title/Abstract])) OR (Dispril[Title/Abstract])) OR (Easprin[Title/Abstract])) OR (Ecotrin[Title/Abstract])) OR (Endosprin[Title/Abstract])) OR (Magnecyl[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 1st 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	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	Not for update
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	40
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	4
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	183
Amendments	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	☒	☐	121
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	190
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☒	None
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	None
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	50
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	80
METHODS					
Eligibility criteria	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	☒	☐	105

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		eligibility for the review			
Information sources	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	☒	☐	94
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	94
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	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)	☒	☐	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	☒	☐	136
Data items	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	☒	☐	136
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	106
Risk of bias in individual studies	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	☒	☐	162
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	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)	☒	☐	162
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	174
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	181
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	171
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	155

BMJ Open

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

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine, Evidence based practice
Keywords:	Cardiomyopathy < CARDIOLOGY, Thromboembolism < CARDIOLOGY, INTERNAL MEDICINE

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

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Abstract

[Introduction] Takotsubo syndrome (TTS) is a sudden reversible weakening of the left ventricle function induced by severe stress and resembles many features as acute coronary syndrome. Even though many guidelines had been published about TTS, there is no consensus regarding the long-term treatment. Aspirin is one of the most common prescribed medicines at discharge for patients with the intention to reduce thrombus events and improve the overall prognosis. However, existing studies yielded conflicting results concerning its effects. This study aims to evaluate the impact of long-term maintenance treatment of Aspirin in TTS and

provides insights in clinic management.

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

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

[Systematic review registration number] CRD42020212729.

Strengths and limitations of this study

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

Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines.

- Subgroup analysis and sensitivity analysis will be performed to evaluate the bias and stability in the study.
- Given the lack of understanding on Takotsubo syndrome, the number of finally included studies might be limited.

Introduction

Takotsubo syndrome (TTS) refers to a reversible form of acute heart failure induced by severe stress which shares many characteristics with acute coronary syndrome (ACS), including demographic features, onset symptoms, electrocardiogram abnormalities and elevation of cardiac biomarkers.[1] Due to a lack of non-invasive examinations method, the diagnosis and understanding of TTS remains poor. In clinical practice, TTS is mainly diagnosed by presentation of severe transient left ventricular (LV) dysfunction with typical apical ballooning or other regional wall motion abnormalities documented by coronary angiography with left ventriculography.[2]

Another characteristic feature of TTS is the reversible pathology change and self-limiting clinical course.[3] For a rather long time, TTS was generally considered as a benign disease with relatively low morbidity.[4] However, this view is challenged by recent studies.[5 6] Based on data obtained from the International Takotsubo Registry,[7] the rate of major adverse cardiac and cerebrovascular events (MACCE) for patients with TTS was 9.9% per patient-year and the mortality was 5.6% per patient-year in long-term follow-up.[8] In addition, the incidences of in-hospital complications including shock and death were also comparable to ACS.[9 10] But the

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

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

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

Methods and analysis

Patient and public involvement

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

Study design

The design of this systematic review was carried out according to the recommendation of the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) statement.[23] The protocol has also acquired approval automatically from the PROSPERO (ID: CRD42020212729).

The systematic review will be performed according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines and will be reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines.[24 25]

Search strategy

The information to be included in this study will cover electronic databases, gray literatures, conference abstract and trial registries.

Databases including 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) will be searched from inception of the library 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 as necessary per specific database (see supplementary file). Reference list of included studies will also be scanned for additional relevant articles.

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

Eligibility criteria

Participants and Intervention

Patients with a diagnosis of TTS, regardless of the diagnostic criteria, will be included in the study. To estimate the long-term effect of Aspirin, only studies in which participants taking Aspirin for no less than 90 days will be included.

Comparison

The outcome measures for TTS patients taking and not taking Aspirin will be compared in the study.

Study outcomes

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 will be each component of MACCE. Included studies must contain at least one of the above outcome measurements.

Types of studies

Both observational and interventional studies are eligible for the study. Articles that published in languages other than English or Chinese will be translated into English when available.

Exclusion

Studies including participants with malignancies or autoimmune diseases or taking antithrombotic therapy for other diseases will be excluded. Review articles, commentaries, laboratory science studies, case studies, case series, and other studies that do not meet the requirements mentioned above will be excluded.

Study records

Data management

Publication screening will be managed through Endnote software (version X9, Clarivate Analytics), in which duplicates will be removed and further review will be performed.

Selection process

Two investigators will independently screen each record by the title and abstract before categorizing all literatures into three groups: relevant, irrelevant and uncertain. After preliminary screening, irrelevant records agreed by both investigators will be eliminated, while the others will be retrieved by full text for further assessment. In the process, a list of eligible articles will be made separately by each reviewer. Discrepancies between the two lists will be resolved by discussion if possible. When an unsettled disagreement arises, a final decision will be made by consulting a third reviewer. Reference list of the included articles will also be reviewed to check for additional studies that might be omitted previously.

A flow diagram for the selection process will be drawn in accordance with the PRISMA guidelines.

Data collection process

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

Data to be collected will include study characteristics such as author, publication year, time period of study, country and site; cohort characteristics such as sample size, demographics (age, gender), diagnostic criteria, comorbid history and concomitant medication use; patient outcomes such as the incidence of all-cause death, TTS recurrence, stroke, or TIA or MI at 30-day and 5-year follow-up.

Missing information will be estimated from the available data as appropriate. If the data

are incomplete or unclear, we will contact the corresponding author. The results of extraction will be verified by two reviewers separately before data analysis and disagreements will be resolved from consultation from a third reviewer.

The process is expected to be completed by December 2020.

Data synthesis

The essential descriptions of all enrolled studies including type of publication, author, publication year and country will be included in the systematic review. A brief summary of the study design, participant characteristics, diagnostic criteria, sample size, follow-up, and outcome measurements will be included for all studies. Subgroups analyses based on age, gender, region, commodity diseases, medication, and each component of the outcomes will be measured if possible.

Quality assessment and risk of bias

Risk of bias will be assessed by independent researchers following 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 unsettled disagreements. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) will be applied to assess the quality of evidence for disease outcomes.

Meta-analysis

Meta-analysis will be performed using R software (version 4.0.2), in which package 'meta' (version 4.14-0) and package 'robvis' (version 0.3.0) will be used in the study.

Meta-analysis will be performed with different homogeneities among populations, which

will be tested by the I^2 statistics. I^2 values of 0–30% will be considered as minimal heterogeneity, 31–50% moderate heterogeneity, and > 50% substantial heterogeneity.

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

Begg's funnel plot and Egger's linear regression will be used to assess the publication bias and sample size bias. An asymmetrical funnel plot or p value of < 0.10 on Egger's test will be considered as the presence of publication bias.

Subgroup analysis will be performed based on gender, country, diagnostic criteria, comorbid history, concomitant medication use and each component of MACCE if possible. Meta regression analysis will be used to explore potential source of heterogeneity if more than 10 studies were included in each measurement.

Sensitivity will be analyzed by dropping one study at a time and measure stability of the analysis. Graphics of pooled data (forest plots, L'Abbé plot, radial plot and meta regression) will be plotted and added into the manuscript.

If pooled data remain heterogeneous within these pooled groups, a narrative description will be provided.

Authors' contributions

Jinhai Lin and Danping Xu were involved in conception and generation of the study protocol. Jinhai Lin, Danping Xu, Bingxin Wu, Yining Ding and Biying Zhong were involved in study design. Luoqi Lin and Zhiwei Huang will review the literatures for inclusion. Bingxin Wu will be responsible for resolving disagreements in data selection, synthesis, and assessment.

Miaoyang Lin will verify the data. The manuscript is approved by all authors for publication.

Ethics and dissemination

All data will be acquired from existing publishments available. Findings of the study will be disseminated through peer-reviewed publications.

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Competing interests

None declared.

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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 (Aloxiprimum[Title/Abstract])) OR (Colfarit[Title/Abstract])) OR (Dispril[Title/Abstract])) OR (Easprin[Title/Abstract])) OR (Ecotrin[Title/Abstract])) OR (Endosprin[Title/Abstract])) OR (Magnecyl[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 1st 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	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	Not for update
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	40
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	4
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	183
Amendments	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	☒	☐	121
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	190
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☒	None
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	None
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	50
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	80
METHODS					
Eligibility criteria	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	☒	☐	105

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		eligibility for the review			
Information sources	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	☒	☐	94
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	94
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	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)	☒	☐	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	☒	☐	136
Data items	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	☒	☐	136
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	106
Risk of bias in individual studies	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	☒	☐	162
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	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)	☒	☐	162
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	174
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	181
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	171
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	155