INPLASY PROTOCOL

To cite: Zhang et al. Comparison of different transcatheter interventions for treatment of mitral regurgitation: a protocol for a network meta-analysis. Inplasy protocol 2020110034. doi: 10.37766/inplasy2020.11.0034

Received: 08 November 2020

Published: 09 November 2020

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Support: **There is no financial support.**

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

Conflicts of interest:
There is no conflicts of interest.

Comparison of different transcatheter interventions for treatment of mitral regurgitation: a protocol for a network meta-analysis

Zhang, BW[1]; Li, MY[2]; Kang, YY[3]; Xing, LN[4]; Zhang, Y[5].

Review question / Objective: **P: Patients with mitral regurgitation; I: Transcatheter mitral valve therapies; C: Traditional surgery or transcatheter mitral valve therapies; O: Efficacy and safety of different transcatheter mitral valve therapies; S: Randomized controlled trials and non-randomized controlled trials.**

Condition being studied: **There was lacking of head-to-head comparisons between different transcatheter techniques and paired meta-analysis has the disadvantage of not being able to simultaneously integrate all types of transcatheter methods from different original studies. Network meta-analysis has become gradually popular to estimate healthcare interventions since it allows to assess the relative effectiveness among all interventions and rank ordering of the interventions in the absence of direct evidence, which will play an increasingly supreme role in clinical decision-making because many indications have multiple therapeutic options that were lacking of comparisons with each other. Even when the results of the direct comparisons are conclusive, combining them with indirect evaluations in a mixed treatment comparison may yield more refined evaluations. This is the first study to estimate the relative efficacy and safety of different transcatheter MV therapies for MR patients through network meta-analysis in a Bayesian mixed-treatment framework.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 09 November 2020 and was last updated on 09 November 2020 (registration number INPLASY2020110034).

INTRODUCTION

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therapies; S: Randomized controlled trials and non-randomized controlled trials.

Rationale: Mitral regurgitation (MR) is one of the most common valvular heart diseases and characterized as primary or secondary according to the cause of disease. Untreated, severe MR results in high mortality and frequent hospitalization for treatment of heart failure. Surgery is still the first-line treatment to improve symptoms and prevent heart failure; however, a high percentage of patients with MR are not suitable for open-heart surgery due to high operative risk, mainly related to advanced age, impaired left ventricular function and complications, which posed an important therapeutic challenge. In recent years, the arrival of transcatheter MV therapies have provided feasible and safe alternatives to medical and surgical treatments, which take advantage of the less invasive approaches to maximize the outcomes and minimize the complications. And there were several corresponding devices which combines the respective advantages of cardiac surgery have aroused great interest. There was lacking of head-to-head comparisons between different transcatheter techniques and paired meta-analysis has the disadvantage of not being able to simultaneously integrate all types of transcatheter methods from different original studies. Network meta-analysis has become gradually popular to estimate healthcare interventions since it allows to assess the relative effectiveness among all interventions and rank ordering of the interventions in the absence of direct evidence, which will play an increasingly supreme role in clinical decision-making because many indications have multiple therapeutic options that were lacking of comparisons with each other. Even when the results of the direct comparisons are conclusive, combining them with indirect evaluations in a mixed treatment comparison may yield more refined evaluations. The aim of this study is to estimate the relative efficacy and safety of different transcatheter MV therapies for MR patients through network meta-analysis in a Bayesian mixed-treatment framework.

Condition being studied: There was lacking of head-to-head comparisons between different transcatheter techniques and paired meta-analysis has the disadvantage of not being able to simultaneously integrate all types of transcatheter methods from different original studies. Network meta-analysis has become gradually popular to estimate healthcare interventions since it allows to assess the relative effectiveness among all interventions and rank ordering of the interventions in the absence of direct evidence, which will play an increasingly supreme role in clinical decision-making because many indications have multiple therapeutic options that were lacking of comparisons with each other. Even when the results of the direct comparisons are conclusive, combining them with indirect evaluations in a mixed treatment comparison may yield more refined evaluations. This is the first study to estimate the relative efficacy and safety of different transcatheter MV therapies for MR patients through network meta-analysis in a Bayesian mixed-treatment framework.

METHODS

Search strategy: Full details of the search strategy with respect to PubMed was as follows: #1 "Mitral Valve Insufficiency"[Mesh]; #2 Mitral Valve Regurgitation[Title/Abstract] OR Regurgitation, Mitral Valve[Title/Abstract] OR Valve Regurgitation, Mitral[Title/Abstract] OR Mitral Valve Insufficiency [Title/Abstract] OR Insufficiency, Mitral Valve[Title/Abstract] OR Valve Insufficiency, Mitral[Title/Abstract] OR Mitral Regurgitation[Title/Abstract] OR Regurgitation, Mitral[Title/Abstract] OR Mitral Valve Incompetence[Title/Abstract] OR Incompetence, Mitral Valve[Title/Abstract] OR Valve Incompetence, Mitral [Title/Abstract] OR Mitral Incompetence [Title/Abstract] OR Incompetence, Mitral [Title/Abstract] OR Mitral Insufficiency [Title/Abstract] OR Insufficiency, Mitral [Title/Abstract]; #3 #1 OR #2; #4 Percutaneous edge-to-edge mitral valve repair[Title/Abstract] OR MitraClip[Title/Abstract] OR Pascal[Title/Abstract] OR

ValveClamp[Title/Abstract]; #5 Transcatheter chordae tendineae implantation[Title/Abstract] OR NeoChord*[Title/Abstract] OR Harppon [Title/Abstract]; #6 Transcatheter mitral annuloplasty[Title/Abstract] OR Carillon [Title/Abstract] OR Mitralign[Title/Abstract] OR Cardioband[Title/Abstract] OR ARTO system[Title/Abstract]; #7 Transcatheter mitral valve replacement [Title/Abstract] OR Transcatheter valve in valve[Title/Abstract] OR Transcatheter valve in ring[Title/Abstract] OR Tendyne[Title/Abstract] OR Intrepid[Title/Abstract]; #8 #4 OR #5 OR #6 OR #7; #9 #3 AND #8.

Participant or population: Patients with MR confirmed by clinical or transesophageal echocardiography.

Intervention: We will include studies that used at least one of the interventions about transcatheter MV technologies, as follows: (1) Percutaneous edge-to-edge mitral valve repair, which may use device names to represent this procedure including Mitraclip, Pascal or ValveClamp; (2) Transcatheter chordae tendineae implantation, the device including NeoChord, Neochordae or Harppon; (3) Transcatheter mitral annuloplasty, which may use device names to indicate this procedure including Carillon, Mitralign, Cardioband or ARTO system. (4) Transcatheter Mitral Valve Replacement, transcatheter valve in valve, transcatheter valve in ring, the device including Tendyne or Intrepid.

Comparator: Traditional surgery or transcatheter mitral valve therapies

Study designs to be included: Randomized and non-randomized controlled studies will be both included, and related systematic reviews or meta-analysis will be also included for retrieving their applicable reference.

Eligibility criteria: Type of studies: Randomized and non-randomized controlled studies will be both included, and related systematic reviews or meta-analysis will be also included for retrieving their applicable reference; Type of participants: Patients with MR confirmed by clinical and transesophageal echocardiography; Type of interventions: We will include studies that used at least one of the interventions about transcatheter MV technologies, as follows: (1) Percutaneous edge-to-edge mitral valve repair, which may use device names to represent this procedure including Mitraclip, Pascal or ValveClamp; (2) Transcatheter chordae tendineae implantation, the device including NeoChord, Neochordae or Harppon; (3) Transcatheter mitral annuloplasty, which may use device names to indicate this procedure including Carillon, Mitralign, Cardioband or ARTO system. (4) Transcatheter Mitral Valve Replacement, transcatheter valve in valve, transcatheter valve in ring, the device including Tendyne or Intrepid. Type of outcomes: The primary outcomes include all-cause mortality, unplanned rehospitalisation for cardiovascular reasons and mitral valve reintervention. The secondary outcomes include rate of periprocedural adverse events and serious adverse device effects, change in NYHA class, quality of life, biological parameters like B-type natriuretic peptide (BNP), and additional secondary outcomes include the situation of left and right cardiac chamber remodelling and restoration of function, and change in six-minute walk test. All of the follow-up time are comparable; Other criteria: we will include studies with language of English or Chinese and there will be no restrictions on the year of publication and publication status.

Information sources: PubMed, EMBASE, the Cochrane Library, Web of Science, Chinese Biomedical Literature Database, and China National Knowledge Infrastructure. Besides, the reference lists of included studies and other relevant articles will be retrieved for supplement.

Main outcome(s): The primary outcomes include all-cause mortality, unplanned rehospitalisation for cardiovascular reasons and mitral valve reintervention. The secondary outcomes include rate of

periprocedural adverse events and serious adverse device effects, change in NYHA class, quality of life, biological parameters like B-type natriuretic peptide (BNP).

Additional outcome(s): Additional secondary outcomes include the situation of left and right cardiac chamber remodelling and restoration of function, and change in six-minute walk test.

Data management: The identified records will be imported into EndNote X9 (Thomson Reuters (Scientific) LLC Philadelphia, PA, US) software for management.

Quality assessment / Risk of bias analysis: The risk of bias of included randomized studies will be evaluated using the tool from Cochrane Handbook version 5.1.0; and the risk of bias of included non-randomized studies will be assessed according to the tool named Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I). The quality of the evidence will be evaluated using the grading of recommendations assessment, development, and evaluation (GRADE) approach.

Strategy of data synthesis: 1. Pairwise meta-analysis: We calculated the average odds ratio (OR) with the 95% confidence interval (CI) for dichotomous outcomes and calculated the average standard mean difference (or the weighted mean difference which all studies used the same scale) with 95% CI for continuous outcomes. The heterogeneity within each pairwise comparison will be evaluated by I2 statistics. If I2 ≤50%, it suggests that there is negligible statistical heterogeneity and the fixed effects model will be used for meta-analysis. If I2 >50%, it indicates that there is possible statistical heterogeneity existed and we will explore the sources of heterogeneity by subgroup analysis and meta-regression using effect modifiers. If there is no clinical heterogeneity, the random effects model will be used to perform meta-analysis. 2. Network meta-analysis: We will perform a Bayesian network meta-analysis using package 'gemtc' version 0.8-7 of R-4.0.3 software. Four Markov chains will be run concurrently. Brooks-Gelman-Rubin plots method will be used to evaluate the model convergence. And the inconsistency between direct and indirect comparisons will be assessed by a node splitting method if there is a loop connecting three arms. Rank probabilities will be calculated to present the probability for each treatment to be the best, second best and so on. The recommendation of clinical decisions with respect to the choice of treatments can be based on the results of rank probabilities when different treatments have small differences in effect size. A matrix of the treatment rank probabilities and a plot of the rank probabilities can be provided by the 'gemtc' package. 3. Funnel plot analysis: Begg's and Egger's funnel plot method will be performed to help distinguish asymmetry caused by publication bias. And whether there will be a small effect between intervention networks will be identified by the comparison-adjusted funnel plot.

Subgroup analysis: Year of publication, country of corresponding author, type of study design, mean age and length of follow-up time will be designed for subgroup analysis to find the possible sources on account of a possibility of significant heterogeneity or inconsistency.

Sensibility analysis: Stata 15.0 software is used to analyze the sensitivity if the results of network meta-analysis are positive, and more than 3 studies are included. The sensitivity analysis is carried out by excluding study one by one. If no significant change exists in the results before and after the exclusion, it indicates that the sensitivity is low and the results are of stability and reliability; otherwise, it means a high sensitivity, and unstable results.

Language: English or Chinese.

Country(ies) involved: China.

Keywords: Mitral regurgitation, transcatheter mitral valve therapy, efficacy, safety, network meta-analysis.

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