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Keywords:	pregnancy, mechanical heart valves, anticoagulation regimens, network meta-analysis

Anticoagulation regimens during pregnancy in patients with mechanical heart valves: a protocol for a systematic review and network meta-analysis

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ABSTRACT

Introduction Pregnancy in patients with mechanical heart valves (MHVs) is associated with high maternal complications and fetal complications. Anticoagulation treatments serve to decrease their venous clotting risk. Although some anticoagulation regimens have been used for patients during pregnancy with MHVs, no one is definitively superior among different regimens in recently studies. For a better understanding of the clinical treatment which anticoagulation regimen is more effective and safer during pregnancy in patients with MHVs, a network meta-analysis is necessary.

Methods and analysis This protocol has been reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols. Related studies until April 2019 will be searched in the following databases: PubMed, Embase, SinoMed, and the using the OVID interface to search for evidence-based medicine reviews. A clinical trial registry (www.ClinicalTrials.gov) was also searched for unpublished trials. Both experimental studies (randomized clinical trials (RCTs)) and observational studies (cohort studies, case control studies, and case series studies) will be included in this study. Quality assessment will be conducted using Cochrane Collaboration's tool or Newcastle-Ottawa Scale based on their study designs. The primary outcomes of interest will be the frequencies of serious maternal and fetal events. The additional outcomes of interest will be adverse maternal events, mode of delivery and adverse fetal events. Pairwise and network meta-analysis will be conducted using R (version 3.4.4, R Foundation for Statistical Computing, Vienna, Austria) and Stata (version 14, StataCorp, College Station, Texas, USA).The ranking probabilities will be estimated at each possible rank for each anticoagulation regimen using the surface under the cumulative ranking curve. Statistical inconsistency assessment, subgroup analysis, sensitivity analysis and publication bias assessment will be performed.

Ethics and dissemination Either ethics approval or patient consent is not necessary, because this study will be based on literature. The results of this study will be published in a peer-reviewed journal.

PROSPERO registration number CRD42019130659

Strengths and limitations of this study

This review is anticipated to be the first network meta-analysis to evaluate the comparative effects of multiple anticoagulation regimens in patients during pregnancy with mechanical heart valves.

The strengths of the study are as follows: (1) We will include both experimental studies and observational studies in this study to strengthen the statistical power, because the number of related experimental studies, such as RCTs, is still small. (2) We will use GRADE to assess the quality of included studies.

The limitations of the study are as follows: (1) Most of the observational studies will be retrospective studies in our study. However, inclusion of those studies will increase the risk of inferior quality of the results. (2) If the number of included studies is small, the ability to explore heterogeneity, conduct meta regression and even perform NMA could also be limited. (3) Different types of study will generate potentially heterogeneity that may influence the results of this study.

INTRODUCTION

Although mechanical heart valves (MHVs) have excellent durability and hemodynamic profile, they are thrombogenic and require lifelong anticoagulation to prevent thromboembolic complications.[1] [2]Moreover,normal pregnancy is accompanied by changes in hemostasis that produce a hypercoagulable state.[3] As a result, pregnancy in a woman with a MHV is associated with high maternal complications (e.g.thromboembolic complications, heart failure, arrhythmias and bleeding, etc) and fetal complications (e.g.fetal wastage, preterm birth, low birth weight and teratogenicity, etc).[4] [5]Furthermore,the incidence and prevalence of cardiothoracic disease continue to increase globally.[6]It means that a large number of MHVs have been developed and are implanted worldwide, many in women of childbearing age.[7]Cardiac disease, for example, previous valve replacement because of rheumatic heart disease, is emerging as the most important indirect cause if maternal death globally.[8] [9]

Although women cannot alter the physiologic changes that occur naturally during pregnancy, anticoagulation treatments serve to decrease their venous clotting risk.[10]In recently guidelines, vitamin K antagonists (VKA), heparin (including Low molecular weight heparin(LMWH) and unfractionated heparin(UFH)) and sequential treatments are recommended to take into the anticoagulation regimens during pregnancy in patients with MHVs.[11] [12] However, the use of VKA such as warfarin during pregnancy carries the potential for serious risks of fetal embryopathy.[13] [14]Neither UFH nor LMWH crosses the placenta, and therefore are considered safe for mother and fetus, but in the previous literature,[15]some circumstances include the presence of heparin resistance and heparin allergy manifesting limited their use, moreover, heparin(specifically UFH) was associated with an increased thrombotic risk. Sequential treatments refers to

the use of VKAs in the second and third trimesters and heparin (most commonly LMWH but UFH in some centers) in the first trimester and also in the peripartum period, to mitigate the VKA-related risks previously alluded to.[16]Although the use of this regimen could avoid the risk of warfarin embryopathy and would minimize the time off VKA and perhaps be associated with a more favorable maternal risk profile, it would not prevent the fetal bleeding complications.[16]Evidence on the safety of new oral anticoagulant (NOACs) in pregnant women and in those planning pregnancy is scarce, therefore, NOACs currently have no place during pregnancy.[17 18]

Several regimens have been recommended and advised by different guidelines, however, recently study do not suggest that one regimen is definitively superior.[19]Thus,the evidence for the anticoagulation regimens comparisons during pregnancy in patients with MHVs consists of direct head-to-head comparison of treatments (including placebo) in randomised controlled trials (RCTs) and observational studies. This poses a practical challenge to clinicians for choosing a suitable anticoagulation regimen because a direct comparison is rarely seen or not available for many anticoagulation regimens. In addition, synthesising evidence using the traditional pairwise meta-analyses would not allow for the inclusion of data from treatments that have not been compared head-to-head and thus, the results from indirect combined with direct evidence can improve precision for treatments that have been directly evaluated.[20]Therefore,to address the challenge of to determine which anticoagulation regimen is more effective and safer during pregnancy in patients with MHVs, a network meta-analysis (NMA) is necessary.

OBJECTIVE

The objectives of this study are to synthesise the available evidence on anticoagulation regimens during pregnancy in patients with MHVs, estimate the treatment effects among direct and indirect treatment comparisons, and to determine which anticoagulation regimen is more effective and safer using a NMA.

METHODS AND DESIGN

Design

This protocol has been reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.[21 22] (see online supplementary 1)The study will be conducted and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for NMAs of healthcare interventions guidelines.[23] The Bayesian network meta-analysis will be used in this study.

Registration information

This systematic review and NMA protocol has been registered with the International Prospective Register for Systematic Reviews(PROSPERO). The PROSPERO registration number is CRD42019130659.

Patient and public involvement

No patients or the public were involved in this study. However, the results will be disseminated to during patients during pregnancy with MHVs receiving anticoagulation treatment.

Information source and search strategy

PubMed< to April 3 ,2019>, Embase< to April 3 ,2019 >,SinoMed<to April,2019>, and the using the OVID interface, to search for evidence-based medicine reviews: Cochrane Database of Systematic Reviews <2005 to March 27, 2019>, ACP Journal Club <1991 to March 2019>, Database of Abstracts of Reviews of Effects <1st Quarter 2016>, Cochrane Clinical Answers <March 2019>, Cochrane Central Register of Controlled Trials <March 2019>, Cochrane Methodology Register <3rd Quarter 2012>, Health Technology Assessment <4th Quarter 2016>, and NHS Economic Evaluation Database <1st Quarter 2016> .Clinical trial registries (such as www.ClinicalTrials.gov) were also searched for unpublished trials.

In addition, references of included studies and narrative reviews were considered for additional potential studies. No limitations will be imposed on publication status, language of dissemination, duration of study follow-up or period of study conduct. The search strategy is shown in online supplementary 2.

Eligibility criteria

Types of participants

This study will include pregnant patients (conception to six months post-pregnancy regardless of the outcome of pregnancy) who require long-term anticoagulation with MHVs. Non-pregnant patients and pregnant patients with bio-prosthetic valves not requiring anticoagulation will not included.

Types of interventions

This study will include studies comparing at least two different interventions among the following interventions:(1) Dose-adjusted VKA throughout pregnancy,(2)Dose-adjusted LMWH throughout pregnancy,(3) Dose-adjusted UFH throughout pregnancy,(4)Dose- adjusted LMWH for the first trimester, followed by a VKA for the remainder (LMWH and VKA),(5)Dose- adjusted UFH for the first trimester, followed by a VKA for the remainder (UFH and VKA).And other antagonists or placebo, including acetylsalicylic acid, NOACs, fondaparinux and argatroban, etc.

Type of outcomes

The primary outcomes of interest will be the frequencies of serious maternal and fetal events. Maternal events of interest will include all thromboembolic complications including valve thrombosis, major bleeding and maternal death. Fetal outcomes will include livebirths, anticoagulant-related fetal adverse events (including warfarin embryopathy, neurological sequelae related to VKA, other congenital abnormalities) and fetal wastage (including spontaneous abortions (fetal loss < 20 weeks), therapeutic abortions, stillbirths

(fetal loss > 20 weeks), fetal loss (where definitions of miscarriage/ stillbirth are uncertain) and neonatal death (death within the first 28 days of life)).The additional outcomes of interest will be adverse maternal events, mode of delivery and adverse fetal events. Maternal adverse events will include cardiac events including new maternal arrhythmia, infective endocarditis, valve deterioration, myocardial infarction, pregnancy hypertension, heart failure, and other adverse drug effects from anticoagulation. Mode of delivery will be either caesarean section or vaginal birth. Adverse fetal events will include prematurity, small for gestational age infants, preterm births under 37 weeks and infant admission to Neonatal Intensive Care Unit (NICU).The types of outcomes were chosen referred to previous investigation.[13 24-26]

Types of studies

We will include experimental studies (randomized clinical trials (RCTs)), and observational studies (cohort studies, case control studies, and case series studies).

Study selection

To assess study eligibility, all title/abstracts and full-text articles will be independently screened by two reviewers (SWH, and YZ) and disagreements will be resolved by a third reviewer (JL). If necessary, methodological experts will be consulted to reach consensus. Eligible articles will be selected according to inclusion criteria. If studies have duplicate data, only the study with larger sample size and longer follow-up time will be included.

Data extraction

Data will be extracted by three reviewers (SWH, JL, and YZ) based on a extraction form, independently and in duplicate, using Excel software regarding: (1) study information (author, publication year, sample size, duration of study, etc.),(2) participant characteristics (age; type, location and number of MHVs; time since valve repair; The New York Heart Association(NYHA) class and cardiac status at the onset of pregnancy; medical and obstetric co-morbidities; details of labour and delivery, etc.),(3)intervention characteristics(details of the anticoagulation regimens including the name of anticoagulants, duration of treatment, rate of compliance with treatment, details on adjustment of anticoagulation, and route of administration, etc.),(4) reported outcomes (outcome data for the main outcomes and additional outcomes of interest).The types of data were chosen referred to previous investigation.[13 24-26]Missing data will be requested from study authors. Discrepancies will be resolved by consensus and when necessary, consultation with an expert on the investigative team.

Risk of bias (quality) assessment

The risk of bias of the included studies will be assessed using the Cochrane risk of bias tool and Newcastle-Ottawa scale for randomised controlled trials and observational studies, respectively.[27 28]Two

reviewers (SWH and YZ) will conduct quality assessment independently and any disagreement will be solved by discussion with another author (JL).

Data synthesis

When quantitative analysis cannot be conducted, we will narratively describe the results. If quantitative analysis is feasible, all of the following statistical analyses will be conducted using R (version 3.4.4, R Foundation for Statistical Computing, Vienna, Austria) and Stata (version 14, StataCorp, College Station, Texas, USA). And the binary outcomes will be presented as ORs with 95% CIs.

Direct comparisons of interventions

All the direct comparisons will be performed using the DerSimonian-Laird method and random effects model.[29]Q-test and I-squared statistic will be used to assess heterogeneity levels, as a measure of the proportion of the overall variation that is attributable to between study heterogeneity.[30]

Indirect and mixed comparisons of interventions

A random-effects network meta-analysis within a Bayesian framework will then be applied.[31] [32]Interactions among all included studies will be shown in the network geometry, and the contribution plot for the network will show the contributions of direct comparisons.[33] We will estimate the ranking probabilities at each possible rank for each anticoagulation regimen using the surface under the cumulative ranking curve (SUCRA).[34]

Assessment of inconsistency

To check the assumption of consistency in the entire analytical network, a design-by-treatment approach will be used.[35]A loop-specific approach will be applied to evaluate the presence of inconsistency locally in each closed loop.[36]And the node-splitting method will be used to assess the inconsistency of the model by separating evidence on particular comparisons into direct and indirect evidence.[37]

Subgroup analysis and sensitivity analysis

If there are sufficient data, we will assess whether the results have been impacted by study characteristics, subgroup analyses may be conducted according to age group, sample size, quality of study, duration of treatment, and timing of medication usage in pregnancy. And a sensitivity analysis will also be conducted to validate the robustness of the results by excluding each study.

Publication bias

Publication bias will be assessed by visually examining the comparison-adjusted funnel plot asymmetry and Egger's regression test in the results between small and large studies.[38]

Quality of evidence

We will use the Grade of Recommendation Assessment, Development and Evaluation (GRADE) approach to appraise the quality of direct and indirect evidence.[39]

DISCUSSION

This study will first determine which anticoagulation regimen during pregnancy in patients with MHVs is more effective and safer using a NMA. We expect that our findings will inform clinicians, patients and guideline developers the best available evidence on the efficacy and safety of different anticoagulation regimen during pregnancy in patients with MHVs, which will help both clinical practice and study design in the future.

The strengths of the study are as follows:(1) We will include both experimental studies and observational studies in this study to strengthen the statistical power, because the number of related experimental studies, such as RCTs, is still small.(2)We will use GRADE to assess the quality of included studies.

The limitations of the study are as follows:(1) Most of the observational studies will be retrospective studies in our study. However, inclusion of those studies will increase the risk of inferior quality of the results. (2) If the number of included studies is small, the ability to explore heterogeneity, conduct meta regression and even perform NMA could also be limited. (3) Different types of study will generate potentially heterogeneity which may influence the results of this study.

ETHICS AND DISSEMINATION

Ethical issues

Either ethics approval or patient consent is not necessary, because this study will be based on literature.

Publication plan

This protocol has been successfully registered on PROSPERO. The final results of this study will be published in a peer-reviewed journal.

Contributors

SH and HY are responsible for the conception of the protocol. SW, YZ, Juan Li, Jumei Liu and HY were involved in the design of this protocol. SW, YZ, Juan Li, and Jumei Liu tested the feasibility of this protocol. SW, YZ and Juan Li wrote the original draft. HY,ZS and HY reviewed the draft and approved the final manuscript as submitted. All authors contributed to the development of the selection criteria. All authors read, provided feedback and approved the final manuscript as submitted.

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Competing interests None declared.

Patient consent for publication Not required.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Check results
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 3-4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 8
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	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 8-9
Sponsor	5b	Provide name for the review funder and/or sponsor	Page 8-9
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Page 8-9
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 5-6
Information	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial	Page 5

sources		registers or other grey literature sources) with planned dates of coverage	
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	Page 5
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 5-6
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	Page 6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 7
	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 (such as I^2, Kendall's τ)	Page 7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

PUBMED< to April 3 ,2019>

Search ((Pregnant Woman[Title/Abstract]) OR Pregnant Women[Title/Abstract]) OR Woman, Pregnant[Title/Abstract]) OR Women, Pregnant[Title/Abstract]) OR Pregnant patient[Title/Abstract]) OR Pregnancy[Title/Abstract]) OR Pregnant[Title/Abstract]) OR Pregnancies[Title/Abstract]) OR Gestation[Title/Abstract]) OR Gravidity) OR Gravidities) OR Maternity) OR Fetation) OR Conception)) OR Pregnan[Title/Abstract]) OR Obstetric[Title/Abstract]) OR Childbirth[Title/Abstract]) OR Parturition[Title/Abstract]) OR Birth[Title/Abstract]) OR Childbirth[Title/Abstract]) OR Fetus[Title/Abstract]) OR Fetuses[Title/Abstract]) OR Fetal[Title/Abstract]) OR Maternal-Fetal[Title/Abstract]) OR Perinatal[Title/Abstract]) OR Newborn[Title/Abstract]) OR Infant[Title/Abstract]) OR Newborns[Title/Abstract]) OR Newborn[Title/Abstract]) OR Neonate[Title/Abstract]) OR Neonates[Title/Abstract]) OR Placenta[Title/Abstract]) OR Placentas[Title/Abstract]) OR Placentome[Title/Abstract]) OR Placentoma[Title/Abstract])) AND ((Heart Valve[Title/Abstract]) OR Heart Valves[Title/Abstract]) OR Valve, Heart[Title/Abstract]) OR Valves, Heart[Title/Abstract]) OR Cardiac Valves[Title/Abstract]) OR Cardiac Valve[Title/Abstract]) OR Valve, Cardiac[Title/Abstract]) OR Valves, Cardiac[Title/Abstract]) OR Mechanical Valve[Title/Abstract]) OR Valve Replacement[Title/Abstract]) OR Heart Valve Prosthesis[Title/Abstract]) OR Heart Valve Prostheses[Title/Abstract]) OR Prostheses, Heart Valve[Title/Abstract]) OR Cardiac Valve Prosthesis[Title/Abstract]) OR Cardiac Valve Prostheses[Title/Abstract]) OR Prostheses, Cardiac Valve[Title/Abstract]) OR Prosthesis, Cardiac Valve[Title/Abstract]) OR Valve Prostheses, Cardiac[Title/Abstract]) OR Valve Prosthesis, Cardiac[Title/Abstract]) OR Mechanical Heart Valves[Title/Abstract]) OR Heart Valve Replacement[Title/Abstract]) OR Artificial Valve[Title/Abstract]) OR Artificial Heart Valve[Title/Abstract])) OR Valve[Title/Abstract]) OR Artificial[Title/Abstract]) OR Mechanical[Title/Abstract]) OR Prostheses[Title/Abstract]) OR Prosthesis[Title/Abstract]) OR Replacement[Title/Abstract])) OR Heart[Title/Abstract])) OR Cardiac[Title/Abstract])) AND

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Embase< to April 3 ,2019>

(('pregnant woman'/exp OR 'pregnant women':ab,ti OR 'woman, pregnant':ab,ti OR 'women, pregnant':ab,ti OR 'pregnant patient':ab,ti OR 'pregnant':ab,ti OR 'pregnancy':ab,ti OR 'pregnancies':ab,ti OR 'gestation':ab,ti OR 'gravidity':ab,ti OR 'gravidities':ab,ti OR 'maternity':ab,ti OR 'fetation':ab,ti OR 'conception':ab,ti OR 'pregnan':ab,ti OR 'obstetric':ab,ti OR 'childbirth':ab,ti OR 'parturition':ab,ti OR 'birth':ab,ti OR 'childbirth':ab,ti) OR ('fetus':ab,ti OR 'fetuses':ab,ti OR 'fetal':ab,ti OR 'maternal-fetal':ab,ti OR 'perinatal':ab,ti OR 'newborn':ab,ti OR 'infant':ab,ti OR 'newborns':ab,ti OR 'neonate':ab,ti OR 'neonates':ab,ti OR 'placenta':ab,ti OR 'placentas':ab,ti OR 'placentome':ab,ti OR 'placentoma':ab,ti)) AND (('anticoagulant agent':ab,ti OR 'anticoagulants':ab,ti OR 'agents, anticoagulation':ab,ti OR 'anticoagulation agents':ab,ti OR 'agents, anticoagulant':ab,ti OR 'anticoagulant drugs':ab,ti OR 'drugs, anticoagulant':ab,ti OR 'anticoagulant':ab,ti OR 'indirect thrombin inhibitors':ab,ti OR 'inhibitors, indirect thrombin':ab,ti OR 'thrombin inhibitors, indirect':ab,ti) OR ('vitamin k antagonists':ab,ti OR 'vka':ab,ti OR 'warfarin':ab,ti OR '4-hydroxy-3-(3-oxo-1-phenylbutyl)-2h-1-benzopyran-2-one':ab,ti OR 'apo-warfarin':ab,ti OR 'aldocumar':ab,ti OR 'gen-warfarin':ab,ti OR 'warfant':ab,ti OR 'coumadin':ab,ti OR 'marevan':ab,ti OR 'warfarin potassium':ab,ti OR 'potassium, warfarin':ab,ti OR 'warfarin sodium':ab,ti OR 'sodium, warfarin':ab,ti OR 'coumadine':ab,ti OR 'tedicumar':ab,ti OR 'acenocoumarol':ab,ti OR 'nicoumalone':ab,ti OR 'acenocoumarin':ab,ti OR 'phenprocoumon':ab,ti OR 'phenprocoumalol':ab,ti) OR ('heparin':ab,ti OR 'heparins':ab,ti OR 'unfractionated heparin':ab,ti OR 'ufh':ab,ti OR 'heparin, unfractionated':ab,ti OR 'heparinic acid':ab,ti OR 'liquaemin':ab,ti OR 'sodium heparin':ab,ti OR 'heparin, sodium':ab,ti OR 'heparin

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OVID:

EBM Reviews - Cochrane Database of Systematic Reviews<2005 to March 27, 2019>, EBM Reviews - ACP Journal Club <1991 to March 2019>, EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>, EBM Reviews - Cochrane Clinical Answers <March 2019>, EBM Reviews - Cochrane Central Register of Controlled Trials <March 2019>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>

Search Strategy:

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1 Valve.af,ab,kw,ti. (8402)

2 Artificial.ab,kw,ti. (11951)

3 Mechanical.ab,kw,ti. (18547)

4 Prostheses.ab,kw,ti. (1641)

5 Prosthesis.ab,kw,ti. (5645)

6 Replacement.ab,kw,ti. (24066)

7 Heart.ab,kw,ti. (116322)

8 Cardiac.ab,kw,ti. (55124)

9 Heart Valve.ab,kw,ti. (1100)

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11 Valve, Heart.ab,kw,ti. (29)

12 Valves, Heart.ab,kw,ti. (1)

13 Cardiac Valves.ab,kw,ti. (35)

14 Cardiac Valve.ab,kw,ti. (215)

15 Valve, Cardiac.ab,kw,ti. (12)

16 Valves, Cardiac.ab,kw,ti. (1)

17 mechanical valve.ab,kw,ti. (79)

18 valve replacement.ab,kw,ti. (2302)

19 heart valve prosthesis.ab,kw,ti. (233)

20 Heart Valve Prostheses.ab,kw,ti. (33)

21 Prostheses, Heart Valve.ab,kw,ti. (0)

22 Valve Prostheses, Heart.ab,kw,ti. (0)

23 Valve Prosthesis, Heart.ab,kw,ti. (20)

24 Prosthesis, Heart Valve.ab,kw,ti. (17)

25 Cardiac Valve Prosthesis.ab,kw,ti. (1)

26 Cardiac Valve Prostheses.ab,kw,ti. (0)

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28 Prosthesis, Cardiac Valve.ab,kw,ti. (1)

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30 Valve Prosthesis, Cardiac.ab,kw,ti. (1)

31 mechanical heart valves.ab,kw,ti. (71)

32 heart valve replacement.ab,kw,ti. (337)

33 artificial valve.ab,kw,ti. (19)

34 artificial heart valve.ab,kw,ti. (12)

35 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (190001)

36 Pregnant Women.ab,kw,ti. (11301)

37 Pregnant Woman.ab,kw,ti. (3078)

38 Woman, Pregnant.ab,kw,ti. (14)

39 Women, Pregnant.ab,kw,ti. (151)

40 Pregnant patient.ab,kw,ti. (49)

41 Pregnant.ab,kw,ti. (17827)

42 Pregnancy.ab,kw,ti. (42184)

43 Pregnancies.ab,kw,ti. (5993)

44 Gestation.ab,kw,ti. (10292)

45 Gravidity.ab,kw,ti. (245)

46 Gravidities.ab,kw,ti. (6)

47 Maternity.ab,kw,ti. (1721)

48 Fetation.ab,kw,ti. (0)

49 Conception.ab,kw,ti. (1602)

50 Pregnan.ab,kw,ti. (30)

51 Obstetric.ab,kw,ti. (5169)

52 Childbirth.ab,kw,ti. (3642)

53 Parturition.ab,kw,ti. (224)

54 Birth.ab,kw,ti. (24389)

55 Childbirth.ab,kw,ti. (3642)

56 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 (70390)

57 Fetus.ab,kw,ti. (5027)

58 Fetuses.ab,kw,ti. (888)

59 Fetal.ab,kw,ti. (9129)

60 Maternal-Fetal.ab,kw,ti. (1622)

61 Perinatal.ab,kw,ti. (5214)

62 Newborn.ab,kw,ti. (11850)
63 Infant.ab,kw,ti. (21930)
64 Newborns.ab,kw,ti. (4279)
65 Newborn.ab,kw,ti. (11850)
66 Neonate.ab,kw,ti. (1381)
67 Neonates.ab,kw,ti. (6955)
68 Placenta.ab,kw,ti. (1980)
69 Placentas.ab,kw,ti. (147)
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71 Placentoma.ab,kw,ti. (0)
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74 Warfarin.ab,kw,ti. (4486)
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76 Apo-Warfarin.ab,kw,ti. (1)
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80 Coumadin.ab,kw,ti. (170)
81 Marevan.ab,kw,ti. (9)
82 Warfarin Potassium.ab,kw,ti. (2)
83 Potassium, Warfarin.ab,kw,ti. (1)
84 Warfarin Sodium.ab,kw,ti. (153)
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86 Coumadine.ab,kw,ti. (9)
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95 heparins.ab,kw,ti. (653)
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97 UFH.ab,kw,ti. (744)
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107 nadroparin.ab,kw,ti. (244)
108 fraxiparin.ab,kw,ti. (32)
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110 LMWH.ab,kw,ti. (1427)
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118 Aspirin.ab,kw,ti. (12027)
119 Acetylsalicylic Acid.ab,kw,ti. (3218)
120 Acid, Acetylsalicylic.ab,kw,ti. (54)
121 "2-(Acetyloxy)benzoic Acid".ab,kw,ti. (2)
122 Acylpyrin.ab,kw,ti. (129)
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124 new oral anticoagulants.ab,kw,ti. (142)

125 NOACs.ab,kw,ti. (254)
126 Direct oral anticoagulants.ab,kw,ti. (236)
127 DOACs.ab,kw,ti. (179)
128 dabigatran.ab,kw,ti. (950)
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135 118 or 119 or 120 or 121 or 122 or 123 (29601)
136 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 (11674)
137 Fondaparinux.ab,kw,ti. (405)
138 Fondaparinux Sodium.ab,kw,ti. (42)
139 137 or 138 (405)
140 Argatroban.ab,kw,ti. (151)
141 hirudin.ab,kw,ti. (195)
142 Hirudins.ab,kw,ti. (15)
143 bivalirudin.ab,kw,ti. (530)
144 lepirudin.ab,kw,ti. (28)
145 140 or 141 or 142 or 143 or 144 (877)
146 93 or 134 or 135 or 136 or 139 or 145 (44462)
147 35 and 73 and 146 (676)

SinoMed<to April,2019>

(妊娠[全字段] or 怀孕[全字段] or 孕期[全字段] or 孕妇[全字段]) and (抗凝[全字段] or 凝血[全字段] or 华法林[全字段] or 肝素 or[全字段] AND 抗凝药[全字段]) and (心脏瓣膜手术[全字段] or 心脏瓣膜[全字段] or 机械心脏瓣膜[全字段] or 人工心脏瓣膜[全字段] or 瓣膜[全字段] or 置换[全字段])

Clinical trial registry (www.ClinicalTrials.gov) < to April 3 ,2019>

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BMJ Open

Anticoagulation regimens during pregnancy in patients with mechanical heart valves: a protocol for a systematic review and network meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033917.R1
Article Type:	Protocol
Date Submitted by the Author:	21-Dec-2019
Complete List of Authors:	He, Shiwei; School of Public Health, Xiamen University Zou, Yue; School of Public Health, Xiamen University Li, Juan; Women and Chilidren's Hospital, School of Medicine, Xiamen University, Department of Clinical Laboratory Liu, Jumei; Women and Chilidren's Hospital, School of Medicine, Xiamen University, Department of Clinical Laboratory Zhao, Li; School of Medicine, Xiamen University Yang, Hua; Women and Chilidren's Hospital, School of Medicine, Xiamen University, Department of Obstetrics Su, Zhiying; Women and Chilidren's Hospital, School of Medicine, Xiamen University Ye, Huiming; Women and Chilidren's Hospital, School of Medicine, Xiamen University, Department of Clinical Laboratory
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Obstetrics and gynaecology, Cardiovascular medicine
Keywords:	pregnancy, mechanical heart valves, anticoagulation regimens, network meta-analysis

Anticoagulation regimens during pregnancy in patients with mechanical heart valves: a protocol for a systematic review and network meta-analysis

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WORD COUNT:2252

KEYWORDS pregnancy,mechanical heart valves,anticoagulation regimens,network meta-analysis

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ABSTRACT

Introduction Pregnancy in patients with mechanical heart valves(MHVs) is associated with high maternal complications and fetal complications.Anticoagulation treatments serve to decrease their venous clotting risk.Although some anticoagulation regimens has been used for patients during pregnancy with MHVs,no one is definitively superior among different regimens in recently studies.For a better understanding of the clinical treatment which anticoagulation regimen is more effective and safer during pregnancy in patients with MHVs, a Bayesian network meta-analysis is necessary.

Methods and analysis This protocol has been reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols. Related studies until April 2019 will be searched in the following databases: PubMed, Embase,SinoMed, and the using the OVID interface to search for evidence-based medicine reviews.A clinical trial registry (www.ClinicalTrials.gov) were also searched for unpublished trials.Both experimental studies (randomized clinical trials (RCTs)) and observational studies (cohort studies, case control studies, and case series studies) will be included in this study.Quality assessment will be conducted using Cochrane Collaboration's tool or Newcastle-Ottawa Scale based on their study designs. The primary outcomes of interest will be the frequencies of serious maternal and fetal events. The additional outcomes of interest will be adverse maternal events, mode of delivery and adverse fetal events.Pairwise and network meta-analysis will be conducted using R (version 3.4.4, R Foundation for Statistical Computing, Vienna, Austria) and Stata (version 14, StataCorp, College Station, Texas, USA).The ranking probabilities will be estimated at each possible rank for each anticoagulation regimen using the

surface under the cumulative ranking curve.Statistical inconsistency assessment, subgroup analysis, sensitivity analysis and publication bias assessment will be performed.

Ethics and dissemination Either ethics approval or patient consent is not necessary,because this study will be based on literature.The results of this study will be published in a peer-reviewed journal.

PROSPERO registration number CRD42019130659

Strengths and limitations of this study

This study will be the first Bayesian network meta-analysis that evaluate the comparative effects of multiple anticoagulation regimen in patients during pregnancy with mechanical heart valves.

This study will include both experimental studies and observational studies in this study to strengthen the statistical power.

This study will use Grade of Recommendations Assessment, Development and Evaluation system to assess the quality of included studies.

Most of the observational studies in this study will be retrospective studies which will increase the risk of inferior quality of the results.

The number of included studies may be relatively small which will reduce the ability to explore heterogeneity, conduct meta regression and even perform NMA.

INTRODUCTION

Although mechanical heart valves(MHVs) have excellent durability and hemodynamic profiles,they are thrombogenic and require lifelong anticoagulation to prevent thromboembolic complications.[1] [2]Moreover,normal pregnancy is accompanied by changes in hemostasis that produce a hypercoagulable state.[3] As a result,pregnancy in a woman with a MHV is associated with high maternal complications(e.g. thromboembolic complications,heart failure,arrhythmias and bleeding,etc.) and fetal complications(e.g. fetal wastage,preterm birth,low birth weight and teratogenicity,etc.).[4] [5]Furthermore,the incidence and prevalence of cardiothoracic disease continue to increase globally.[6]It means that a large number of MHVs have been developed and are implanted world-wide, many in women of child-bearing age.[7]Cardiac disease, for example, previous valve replacement because of rheumatic heart disease, is emerging as the most important indirect cause of maternal death globally.[8] [9]

Although women cannot alter the physiologic changes that occur naturally during pregnancy, anticoagulation treatments serve to decrease their venous clotting risk.[10]In recently guidelines, vitamin K antagonists (VKA),heparin(including Low molecular weight heparin(LMWH) and unfractionated heparin(UFH)) and sequential treatments are recommended to take into the anticoagulation regimens during pregnancy in patients with MHVs.[11] [12]However,the use of VKA such as warfarin during pregnancy carries the potential for serious risks of fetal embryopathy.[13] [14]Neither UFH nor LMWH crosses the placenta, and therefore are considered safe for mother and fetus, but in the previous literature,[15]some circumstances included the presence of heparin resistance and heparin allergy manifesting limited their use,moreover,

heparin(specifically UFH) was associated with an increased thrombotic risk.Sequential treatments refer to the use of VKAs in the second and third trimesters and heparin in the first trimester and also in the peripartum period, to mitigate the VKA-related risks previously alluded to.[16]Although the use of this regimen could avoid the risk of warfarin embryopathy and would minimize the time off VKAs and perhaps be associated with a more favorable maternal risk profile,it would not prevent the fetal bleeding complications.[16]The evidence related to the safety of new oral anticoagulant(NOACs) in pregnant women and in those planning pregnancy is scarce,therefore,NOACs currently have no place during pregnancy.[17 18]

Several regimens have been recommended and advised by different guidelines, however,recently study do not suggest that one regimen is definitively superior.[19]Thus,the evidence for the anticoagulation regimens comparisons during pregnancy in patients with MHVs consists of direct head-to-head comparison of treatments in randomized controlled trials (RCTs) and observational studies. Although,several meta-analysis related to this research topic have been published previously,all of them are traditional pairwise meta-analyses which included some obvious limitations that need to be urgently improved.[13 20-22]Firstly,synthesising evidence using the traditional pairwise meta-analyses would not allow for the inclusion of data from treatments(e.g. the comparations of different sequential treatments) that have not been compared head-to-head in Xu et al.'s,D'Souza et al.'s,Steinberg et al.'s,and Chan et al.'s studies. [13 20-23] The results from indirect combined with direct evidence using network meta-analysis (NMA) allows for simultaneous consideration of the relative effectiveness and safety of all available anticoagulation treatments .[23] Furthermore, a network meta-analysis can estimate the rank of these treatments[23 24].Secondly,some high-quality and latest studies(one RCT[25] and nine observational studies[26-34]) in recent years were not included in these studies,which reduced trustworthiness and statistical power of these studies.Finally,some subgroups of anticoagulation treatments (e.g. different VKAs and heparin doses,different combinations of sequential treatments,and type,location and number of MHVs,etc.) were not considered in these studies,which led to the lack of results of effectiveness and safety by comparing these subgroups.These research gaps pose a urgently practical challenge to clinicians for choosing a suitable anticoagulation regimen because a direct comparison is rarely seen or not available for many anticoagulation regimens.Therefore,to address the challenge of clinicians to determine which anticoagulation regimen is more effective and safer during pregnancy in patients with MHVs, a Bayesian network meta-analysis is necessary.

OBJECTIVE

The objectives of this study are to synthesise the available evidence on anticoagulation regimens during pregnancy in patients with MHVs,to estimate the treatment effects among direct and indirect treatment comparisons,and to determine which anticoagulation regimen is more effective and safer using a Bayesian NMA.

METHODS AND DESIGN

Design

This protocol has been reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.[35 36] (see online supplementary 1)The study will be conducted and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for NMAs of healthcare interventions guidelines.[37] The Bayesian network meta-analysis will be used in this study.

Registration information

This systematic review and NMA protocol has been registered with the International Prospective Register for Systematic Reviews(PROSPERO). The PROSPERO registration number is CRD42019130659.

Patient and public involvement

No patients or the public were involved in this study. However, the results will be disseminated to during patients during pregnancy with MHVs receiving anticoagulation treatment.

Information source and search strategy

PubMed< to April 3 ,2019>, Embase< to April 3 ,2019 >,SinoMed<to April,2019>, and the using the OVID interface, to search for evidence-based medicine reviews: Cochrane Database of Systematic Reviews <2005 to March 27, 2019>, ACP Journal Club <1991 to March 2019>, Database of Abstracts of Reviews of Effects <1st Quarter 2016>, Cochrane Clinical Answers <March 2019>, Cochrane Central Register of Controlled Trials <March 2019>, Cochrane Methodology Register <3rd Quarter 2012>, Health Technology Assessment <4th Quarter 2016>, and NHS Economic Evaluation Database <1st Quarter 2016> .Clinical trial registries (such as www.ClinicalTrials.gov) were also searched for unpublished trials.

In addition, references of included studies and narrative reviews were considered for additional potential studies. No limitations will be imposed on publication status, language of dissemination, duration of study follow-up or period of study conduct.The search strategy is shown in online supplementary 2.

Eligibility criteria

Types of participants

This study will include pregnant patients (conception to six months post-pregnancy regardless of the outcome of pregnancy) who require long-term anticoagulation with MHVs.Non-pregnant patients and pregnant patients with bio-prosthetic valves not requiring anticoagulation will not included.

Types of interventions

This study will include studies comparing at least two different interventions among the following

interventions:(1) Dose-adjusted VKA throughout pregnancy,(2)Dose-adjusted LMWH throughout pregnancy,(3) Dose-adjusted UFH throughout pregnancy,(4)Dose- adjusted LMWH for the first trimester, followed by a VKA for the remainder (LMWH and VKA),(5)Dose- adjusted UFH for the first trimester, followed by a VKA for the remainder (UFH and VKA).And other antagonists or placebo, including acetylsalicylic acid, NOACs, fondaparinux and argatroban, etc.

Type of outcomes

The primary outcomes of interest will be the frequencies of serious maternal and fetal events. Maternal events of interest will include all thromboembolic complications including valve thrombosis, major bleeding and maternal death. Fetal outcomes will include livebirths, anticoagulant-related fetal adverse events (including warfarin embryopathy, neurological sequelae related to VKA,other congenital abnormalities) and fetal wastage (including spontaneous abortions (fetal loss < 20 weeks), therapeutic abortions, stillbirths(fetal loss > 20 weeks), fetal loss (where definitions of miscarriage/ stillbirth are uncertain) and neonatal death (death within the first 28 days of life)).The additional outcomes of interest will be adverse maternal events, mode of delivery and adverse fetal events. Maternal adverse events will include cardiac events including new maternal arrhythmia, infective endocarditis, valve deterioration, myocardial infarction, pregnancy hypertension, heart failure, and other adverse drug effects from anticoagulation. Mode of delivery will be either caesarean section or vaginal birth. Adverse fetal events will include prematurity,small for gestational age infants, preterm births under 37 weeks and infant admission to Neonatal Intensive Care Unit (NICU).The types of outcomes were chosen referred to previous investigation.[13 20-22]

Types of studies

We will include experimental studies (randomized clinical trials (RCTs)), and observational studies (cohort studies, case control studies, and case series studies).

Study selection

To assess study eligibility, all title/abstracts and full-text articles will be independently screened by two reviewers (SWH, and YZ) and disagreements will be resolved by a third reviewer (JL). If necessary, methodological experts will be consulted to reach consensus. Eligible articles will be selected according to inclusion criteria. If studies have duplicate data, only the study with larger sample size and longer follow-up time will be included..

Data extraction

Data will be extracted by three reviewers (SWH, JL, and YZ) based on a extraction form, independently and in duplicate, using Excel software regarding: (1) study information (author, publication year, sample size, duration of study, etc.),(2) participant characteristics (age;type,location and number of MHVs;time

since valve repair;The New York Heart Association(NYHA) class and cardiac status at the onset of pregnancy;medical and obstetric co-morbidities;details of labour and delivery,etc.),(3)intervention characteristics(details of the anticoagulation regimens including the name of anticoagulants,duration of treatment, rate of compliance with treatment, details on adjustment of anticoagulation,and route of administration, etc.),(4) reported outcomes (outcome data for the main outcomes and additional outcomes of interest).The types of data were chosen referred to previous investigation.[13 20-22]Missing data will be requested from study authors. Discrepancies will be resolved by consensus and when necessary, consultation with an expert on the investigative team.

Risk of bias (quality) assessment

The risk of bias of the included studies will be assessed using the Cochrane risk of bias tool and Newcastle-Ottawa scale for randomised controlled trials and observational studies, respectively.[38 39]Two reviewers(SWH and YZ) will conduct quality assessment independently and any disagreement will be solved by discussion with another author (JL).

Data synthesis

When quantitative analysis cannot be conducted, we will narratively describe the results. If quantitative analysis is feasible, all of the following statistical analyses will be conducted using R (version 3.4.4, R Foundation for Statistical Computing, Vienna, Austria) and Stata (version 14, StataCorp, College Station, Texas, USA).And the binary outcomes will be presented as ORs with 95% CIs.

Direct comparisons of interventions

All the direct comparisons will be performed using the DerSimonian-Laird method and random effects model.[40]Q-test and I-squared statistic will be used to assess heterogeneity levels, as a measure of the proportion of the overall variation that is attributable to between study heterogeneity.[41]

Indirect and mixed comparisons of interventions

A random-effects network meta-analysis within a Bayesian framework will then be applied.[42 43]Interactions among all included studies will be shown in the network geometry, and the contribution plot for the network will show the contributions of direct comparisons.[44] We will estimate the ranking probabilities at each possible rank for each anticoagulation regimen using the surface under the cumulative ranking curve (SUCRA).[45]

Assessment of inconsistency

To check the assumption of consistency in the entire analytical network, a design-by-treatment approach will be used.[46]A loop-specific approach will be applied to evaluate the presence of inconsistency locally in

each closed loop.[47]And the node-splitting method will be used to assess the inconsistency of the model by separating evidence on particular comparisons into direct and indirect evidence.[48]

Subgroup analysis and sensitivity analysis

If there are sufficient data, we will assess whether the results have been impacted by study characteristics, subgroup analyses may be conducted according to age group, sample size, quality of study, duration of treatment, and timing of medication usage in pregnancy.And a sensitivity analysis will also be conducted to validate the robustness of the results by excluding each study.

Publication bias

Publication bias will be assessed by visually examining the comparison-adjusted funnel plot asymmetry and Egger's regression test in the results between small and large studies.[49]

Quality of evidence

We will use the Grade of Recommendation Assessment, Development and Evaluation (GRADE) approach to appraise the quality of direct and indirect evidence.[50]

DISCUSSION

This study will first determine which anticoagulation regimen during pregnancy in patients with MHVs is more effective and safer using a Bayesian NMA.We expect that our findings will inform clinicians, patients and guideline developers the best available evidence on the efficacy and safety of different anticoagulation regimen during pregnancy in patients with MHVs, which will help both clinical practice and study design in the future.We will include both experimental studies and observational studies in this study to strengthen the statistical power,because the number of related experimental studies,such as RCTs,is still small.Moreover,we will use GRADE to assess the quality of included studies. However,most of the observational studies will be retrospective studies in our study, inclusion of those studies will increase the risk of inferior quality of the results.Futhermore,different types of study will generate potentially heterogeneity which may influence the results of this study.

ETHICS AND DISSEMINATION

Ethical issues

Either ethics approval or patient consent is not necessary,because this study will be based on literature.

Publication plan

This protocol has been successfully registered on PROSPERO. The final results of this study will be published in a peer-reviewed journal.

Contributors

SH and HY are responsible for the conception of the protocol. SH,YZ,Juan Li,Jumei Liu, LZ and HY were involved in the design of this protocol. SH,YZ,Juan Li, and Jumei Liu tested the feasibility of this protocol. SH, YZ and Juan Li wrote the original draft. HY,ZS and HuaYang reviewed the draft and approved the final manuscript as submitted. All authors contributed to the development of the selection criteria. All authors read, provided feedback and approved the final manuscript as submitted.

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Competing interests None declared.

Patient consent for publication Not required.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Check results
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 3-4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 8
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	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 8-9
Sponsor	5b	Provide name for the review funder and/or sponsor	Page 8-9
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Page 8-9
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 5-6
Information	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial	Page 5

sources		registers or other grey literature sources) with planned dates of coverage	
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	Page 5
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 5-6
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	Page 6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 7
	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 (such as I^2, Kendall's τ)	Page 7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

PUBMED< to April 3 ,2019>

Search ((Pregnant Woman[Title/Abstract]) OR Pregnant Women[Title/Abstract]) OR Woman, Pregnant[Title/Abstract]) OR Women, Pregnant[Title/Abstract]) OR Pregnant patient[Title/Abstract]) OR Pregnancy[Title/Abstract]) OR Pregnant[Title/Abstract]) OR Pregnancies[Title/Abstract]) OR Gestation[Title/Abstract]) OR Gravidity) OR Gravidities) OR Maternity) OR Fetation) OR Conception)) OR Pregnan[Title/Abstract]) OR Obstetric[Title/Abstract]) OR Childbirth[Title/Abstract]) OR Parturition[Title/Abstract]) OR Birth[Title/Abstract]) OR Childbirth[Title/Abstract]) OR Fetus[Title/Abstract]) OR Fetuses[Title/Abstract]) OR Fetal[Title/Abstract]) OR Maternal-Fetal[Title/Abstract]) OR Perinatal[Title/Abstract]) OR Newborn[Title/Abstract]) OR Infant[Title/Abstract]) OR Newborns[Title/Abstract]) OR Newborn[Title/Abstract]) OR Neonate[Title/Abstract]) OR Neonates[Title/Abstract]) OR Placenta[Title/Abstract]) OR Placentas[Title/Abstract]) OR Placentome[Title/Abstract]) OR Placentoma[Title/Abstract])) AND ((((((((((((((((((((((((((((((((Heart Valve[Title/Abstract]) OR Heart Valves[Title/Abstract]) OR Valve, Heart[Title/Abstract]) OR Valves, Heart[Title/Abstract]) OR Cardiac Valves[Title/Abstract]) OR Cardiac Valve[Title/Abstract]) OR Valve, Cardiac[Title/Abstract]) OR Valves, Cardiac[Title/Abstract]) OR Mechanical Valve[Title/Abstract]) OR Valve Replacement[Title/Abstract]) OR Heart Valve Prosthesis[Title/Abstract]) OR Heart Valve Prostheses[Title/Abstract]) OR Prostheses, Heart Valve[Title/Abstract]) OR Cardiac Valve Prosthesis[Title/Abstract]) OR Cardiac Valve Prostheses[Title/Abstract]) OR Prostheses, Cardiac Valve[Title/Abstract]) OR Prosthesis, Cardiac Valve[Title/Abstract]) OR Valve Prostheses, Cardiac[Title/Abstract]) OR Valve Prosthesis, Cardiac[Title/Abstract]) OR Mechanical Heart Valves[Title/Abstract]) OR Heart Valve Replacement[Title/Abstract]) OR Artificial Valve[Title/Abstract]) OR Artificial Heart Valve[Title/Abstract])) OR Valve[Title/Abstract]) OR Artificial[Title/Abstract]) OR Mechanical[Title/Abstract]) OR Prostheses[Title/Abstract]) OR Prosthesis[Title/Abstract]) OR Replacement[Title/Abstract])) OR Heart[Title/Abstract])) OR Cardiac[Title/Abstract])) AND

((Anticoagulants[Title/Abstract]) OR Anticoagulation Agents[Title/Abstract]) OR Agents, Anticoagulation[Title/Abstract]) OR Anticoagulant Agents[Title/Abstract]) OR Agents, Anticoagulant[Title/Abstract]) OR Anticoagulant Drugs[Title/Abstract]) OR Drugs, Anticoagulant[Title/Abstract]) OR Anticoagulant[Title/Abstract]) OR Indirect Thrombin Inhibitors[Title/Abstract]) OR Inhibitors, Indirect Thrombin[Title/Abstract]) OR Thrombin Inhibitors, Indirect[Title/Abstract]) OR Vitamin K antagonists[Title/Abstract]) OR VKA[Title/Abstract]) OR Warfarin[Title/Abstract]) OR 4-Hydroxy-3-(3-oxo-1-phenylbutyl)-2H-1-benzopyran-2-one[Title/Abstract]) OR Apo-Warfarin[Title/Abstract]) OR Aldocumar[Title/Abstract]) OR Gen-Warfarin[Title/Abstract]) OR Coumadin[Title/Abstract]) OR Marevan[Title/Abstract]) OR Warfarin Potassium[Title/Abstract]) OR Potassium, Warfarin[Title/Abstract]) OR Warfarin Sodium[Title/Abstract]) OR Sodium, Warfarin[Title/Abstract]) OR Coumadine[Title/Abstract]) OR Tedicumar[Title/Abstract]) OR Acenocoumarol[Title/Abstract]) OR Nicoumalone[Title/Abstract]) OR Acenocoumarin[Title/Abstract]) OR phenprocoumon[Title/Abstract]) OR Phenprocoumalol[Title/Abstract]) OR Heparins[Title/Abstract]) OR Heparin[Title/Abstract]) OR Unfractionated Heparin[Title/Abstract]) OR UFH[Title/Abstract]) OR Heparin, Unfractionated[Title/Abstract]) OR Heparinic Acid[Title/Abstract]) OR Liquaemin[Title/Abstract]) OR Sodium Heparin[Title/Abstract]) OR Heparin, Sodium[Title/Abstract]) OR Heparin Sodium[Title/Abstract]) OR Alpha-Heparin[Title/Abstract]) OR Alpha Heparin[Title/Abstract]) OR LMWH[Title/Abstract]) OR Heparin, Low Molecular Weight[Title/Abstract]) OR Low Molecular Weight Heparin[Title/Abstract]) OR Low-Molecular-Weight Heparin[Title/Abstract]) OR Danaparoid[Title/Abstract]) OR Danaproid[Title/Abstract]) OR Danaparoid Sodium[Title/Abstract]) OR Danaproid Sodium[Title/Abstract]) OR Aspirin[Title/Abstract]) OR Acetylsalicylic Acid[Title/Abstract]) OR Acid, Acetylsalicylic[Title/Abstract]) OR 2-(Acetyloxy)benzoic Acid[Title/Abstract]) OR Acylpyrin[Title/Abstract]) OR ASA[Title/Abstract]) OR New Oral Anticoagulants[Title/Abstract]) OR NOACs[Title/Abstract]) OR Direct Oral Anticoagulants[Title/Abstract]) OR DOACs[Title/Abstract]) OR Dabigatran[Title/Abstract]) OR

Rivaroxaban[Title/Abstract]) OR Apixaban[Title/Abstract]) OR Edoxaban[Title/Abstract]) OR Fondaparinux[Title/Abstract]) OR Fondaparinux Sodium[Title/Abstract]) OR Argatroban[Title/Abstract]) OR Hirudin[Title/Abstract]) OR Hirudins[Title/Abstract]) OR Bivalirudin[Title/Abstract]) OR Lepirudin[Title/Abstract])) OR Enoxaparin[Title/Abstract]) OR Nadroparin[Title/Abstract]) OR Fraxiparin[Title/Abstract]) OR Xarelto[Title/Abstract]) OR Ximelagatran[

Embase< to April 3 ,2019>

(('pregnant woman'/exp OR 'pregnant women':ab,ti OR 'woman, pregnant':ab,ti OR 'women, pregnant':ab,ti OR 'pregnant patient':ab,ti OR 'pregnant':ab,ti OR 'pregnancy':ab,ti OR 'pregnancies':ab,ti OR 'gestation':ab,ti OR 'gravidity':ab,ti OR 'gravidities':ab,ti OR 'maternity':ab,ti OR 'fetation':ab,ti OR 'conception':ab,ti OR 'pregnan':ab,ti OR 'obstetric':ab,ti OR 'childbirth':ab,ti OR 'parturition':ab,ti OR 'birth':ab,ti OR 'childbirth':ab,ti) OR ('fetus':ab,ti OR 'fetuses':ab,ti OR 'fetal':ab,ti OR 'maternal-fetal':ab,ti OR 'perinatal':ab,ti OR 'newborn':ab,ti OR 'infant':ab,ti OR 'newborns':ab,ti OR 'neonate':ab,ti OR 'neonates':ab,ti OR 'placenta':ab,ti OR 'placentas':ab,ti OR 'placentome':ab,ti OR 'placentoma':ab,ti)) AND (('anticoagulant agent':ab,ti OR 'anticoagulants':ab,ti OR 'agents, anticoagulation':ab,ti OR 'anticoagulation agents':ab,ti OR 'agents, anticoagulant':ab,ti OR 'anticoagulant drugs':ab,ti OR 'drugs, anticoagulant':ab,ti OR 'anticoagulant':ab,ti OR 'indirect thrombin inhibitors':ab,ti OR 'inhibitors, indirect thrombin':ab,ti OR 'thrombin inhibitors, indirect':ab,ti) OR ('vitamin k antagonists':ab,ti OR 'vka':ab,ti OR 'warfarin':ab,ti OR '4-hydroxy-3-(3-oxo-1-phenylbutyl)-2h-1-benzopyran-2-one':ab,ti OR 'apo-warfarin':ab,ti OR 'aldocumar':ab,ti OR 'gen-warfarin':ab,ti OR 'warfant':ab,ti OR 'coumadin':ab,ti OR 'marevan':ab,ti OR 'warfarin potassium':ab,ti OR 'potassium, warfarin':ab,ti OR 'warfarin sodium':ab,ti OR 'sodium, warfarin':ab,ti OR 'coumadine':ab,ti OR 'tedicumar':ab,ti OR 'acenocoumarol':ab,ti OR 'nicoumalone':ab,ti OR 'acenocoumarin':ab,ti OR 'phenprocoumon':ab,ti OR 'phenprocoumalol':ab,ti) OR ('heparin':ab,ti OR 'heparins':ab,ti OR 'unfractionated heparin':ab,ti OR 'ufh':ab,ti OR 'heparin, unfractionated':ab,ti OR 'heparinic acid':ab,ti OR 'liquaemin':ab,ti OR 'sodium heparin':ab,ti OR 'heparin, sodium':ab,ti OR 'heparin

sodium':ab,ti OR 'alpha-heparin':ab,ti OR 'alpha heparin':ab,ti OR 'enoxaparin':ab,ti OR 'nadroparin':ab,ti OR 'fraxiparin':ab,ti OR 'low molecular weight heparin':ab,ti OR 'lmwh':ab,ti OR 'heparin, low molecular weight':ab,ti OR 'low-molecular-weight heparin':ab,ti OR 'danaparoid':ab,ti OR 'danaproid':ab,ti OR 'danaparoid sodium':ab,ti OR 'danaproid sodium':ab,ti) OR ('acetylsalicylic acid':ab,ti OR 'aspirin':ab,ti OR 'acid, acetylsalicylic':ab,ti OR '2-(acetyloxy)benzoic acid':ab,ti OR 'acylpyrin':ab,ti OR 'asa':ab,ti) OR ('new oral anticoagulants':ab,ti OR 'noacs':ab,ti OR 'direct oral anticoagulants':ab,ti OR 'doacs':ab,ti OR 'dabigatran':ab,ti OR 'rivaroxaban':ab,ti OR 'apixaban':ab,ti OR 'edoxaban':ab,ti OR 'xarelto':ab,ti OR 'ximelagatran':ab,ti) OR ('fondaparinux'/exp OR 'fondaparinux sodium':ab,ti) OR ('argatroban'/exp OR 'hirudin'/exp OR 'hirudins':ab,ti OR 'bivalirudin':ab,ti OR 'lepirudin':ab,ti)) AND ('heart valve replacement'/exp OR 'valve':ab,ti OR 'heart valve':ab,ti OR 'heart valves':ab,ti OR 'valve, heart':ab,ti OR 'valves, heart':ab,ti OR 'cardiac valves':ab,ti OR 'cardiac valve':ab,ti OR 'valve, cardiac':ab,ti OR 'valves, cardiac':ab,ti OR 'mechanical valve':ab,ti OR 'valve replacement':ab,ti OR 'heart valve prosthesis':ab,ti OR 'heart valve prostheses':ab,ti OR 'prostheses, heart valve':ab,ti OR 'valve prostheses, heart':ab,ti OR 'valve prosthesis, heart':ab,ti OR 'prosthesis, heart valve':ab,ti OR 'cardiac valve prosthesis':ab,ti OR 'cardiac valve prostheses':ab,ti OR 'prostheses, cardiac valve':ab,ti OR 'prosthesis, cardiac valve':ab,ti OR 'valve prostheses, cardiac':ab,ti OR 'valve prosthesis, cardiac':ab,ti OR 'mechanical heart valves':ab,ti OR 'heart valve replacement':ab,ti OR 'artificial valve':ab,ti OR 'artificial heart valve':ab,ti)

OVID:

EBM Reviews - Cochrane Database of Systematic Reviews<2005 to March 27, 2019>, EBM Reviews - ACP Journal Club <1991 to March 2019>, EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>, EBM Reviews - Cochrane Clinical Answers <March 2019>, EBM Reviews - Cochrane Central Register of Controlled Trials <March 2019>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>

Search Strategy:

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1 Valve.af,ab,kw,ti. (8402)

2 Artificial.ab,kw,ti. (11951)

3 Mechanical.ab,kw,ti. (18547)

4 Prostheses.ab,kw,ti. (1641)

5 Prosthesis.ab,kw,ti. (5645)

6 Replacement.ab,kw,ti. (24066)

7 Heart.ab,kw,ti. (116322)

8 Cardiac.ab,kw,ti. (55124)

9 Heart Valve.ab,kw,ti. (1100)

10 Heart Valves.ab,kw,ti. (243)

11 Valve, Heart.ab,kw,ti. (29)

12 Valves, Heart.ab,kw,ti. (1)

13 Cardiac Valves.ab,kw,ti. (35)

14 Cardiac Valve.ab,kw,ti. (215)

15 Valve, Cardiac.ab,kw,ti. (12)

16 Valves, Cardiac.ab,kw,ti. (1)

17 mechanical valve.ab,kw,ti. (79)

18 valve replacement.ab,kw,ti. (2302)

19 heart valve prosthesis.ab,kw,ti. (233)

20 Heart Valve Prostheses.ab,kw,ti. (33)

21 Prostheses, Heart Valve.ab,kw,ti. (0)

22 Valve Prostheses, Heart.ab,kw,ti. (0)

23 Valve Prosthesis, Heart.ab,kw,ti. (20)

24 Prosthesis, Heart Valve.ab,kw,ti. (17)

25 Cardiac Valve Prosthesis.ab,kw,ti. (1)

26 Cardiac Valve Prostheses.ab,kw,ti. (0)

27 Prostheses, Cardiac Valve.ab,kw,ti. (0)

28 Prosthesis, Cardiac Valve.ab,kw,ti. (1)

29 Valve Prostheses, Cardiac.ab,kw,ti. (0)

30 Valve Prosthesis, Cardiac.ab,kw,ti. (1)

31 mechanical heart valves.ab,kw,ti. (71)

32 heart valve replacement.ab,kw,ti. (337)

33 artificial valve.ab,kw,ti. (19)

34 artificial heart valve.ab,kw,ti. (12)

35 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (190001)

36 Pregnant Women.ab,kw,ti. (11301)

37 Pregnant Woman.ab,kw,ti. (3078)

38 Woman, Pregnant.ab,kw,ti. (14)

39 Women, Pregnant.ab,kw,ti. (151)

40 Pregnant patient.ab,kw,ti. (49)

41 Pregnant.ab,kw,ti. (17827)

42 Pregnancy.ab,kw,ti. (42184)

43 Pregnancies.ab,kw,ti. (5993)

44 Gestation.ab,kw,ti. (10292)

45 Gravidity.ab,kw,ti. (245)

46 Gravidities.ab,kw,ti. (6)

47 Maternity.ab,kw,ti. (1721)

48 Fetation.ab,kw,ti. (0)

49 Conception.ab,kw,ti. (1602)

50 Pregnan.ab,kw,ti. (30)

51 Obstetric.ab,kw,ti. (5169)

52 Childbirth.ab,kw,ti. (3642)

53 Parturition.ab,kw,ti. (224)

54 Birth.ab,kw,ti. (24389)

55 Childbirth.ab,kw,ti. (3642)

56 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 (70390)

57 Fetus.ab,kw,ti. (5027)

58 Fetuses.ab,kw,ti. (888)

59 Fetal.ab,kw,ti. (9129)

60 Maternal-Fetal.ab,kw,ti. (1622)

61 Perinatal.ab,kw,ti. (5214)

62 Newborn.ab,kw,ti. (11850)
63 Infant.ab,kw,ti. (21930)
64 Newborns.ab,kw,ti. (4279)
65 Newborn.ab,kw,ti. (11850)
66 Neonate.ab,kw,ti. (1381)
67 Neonates.ab,kw,ti. (6955)
68 Placenta.ab,kw,ti. (1980)
69 Placentas.ab,kw,ti. (147)
70 Placentome.ab,kw,ti. (1)
71 Placentoma.ab,kw,ti. (0)
72 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 (45657)
73 56 or 72 (92693)
74 Warfarin.ab,kw,ti. (4486)
75 "4-Hydroxy-3-(3-oxo-1-phenylbutyl)-2H-1-benzopyran-2-one".ab,kw,ti. (43)
76 Apo-Warfarin.ab,kw,ti. (1)
77 Aldocumar.ab,kw,ti. (1)
78 Gen-Warfarin.ab,kw,ti. (1)
79 Warfant.ab,kw,ti. (0)
80 Coumadin.ab,kw,ti. (170)
81 Marevan.ab,kw,ti. (9)
82 Warfarin Potassium.ab,kw,ti. (2)
83 Potassium, Warfarin.ab,kw,ti. (1)
84 Warfarin Sodium.ab,kw,ti. (153)
85 Sodium, Warfarin.ab,kw,ti. (11)
86 Coumadine.ab,kw,ti. (9)
87 Tedicumar.ab,kw,ti. (0)
88 acenocoumarol.ab,kw,ti. (206)
89 Nicoumalone.ab,kw,ti. (6)
90 Acenocoumarin.ab,kw,ti. (11)
91 phenprocoumon.ab,kw,ti. (196)
92 Phenprocoumalol.ab,kw,ti. (0)

93 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 (4869)
94 heparin.ab,kw,ti. (10294)
95 heparins.ab,kw,ti. (653)
96 Unfractionated Heparin.ab,kw,ti. (1803)
97 UFH.ab,kw,ti. (744)
98 Heparin, Unfractionated.ab,kw,ti. (112)
99 Heparinic Acid.ab,kw,ti. (0)
100 Liquaemin.ab,kw,ti. (0)
101 Sodium Heparin.ab,kw,ti. (95)
102 Heparin, Sodium.ab,kw,ti. (150)
103 Heparin Sodium.ab,kw,ti. (150)
104 alpha-Heparin.ab,kw,ti. (4)
105 alpha Heparin.ab,kw,ti. (4)
106 enoxaparin.ab,kw,ti. (1924)
107 nadroparin.ab,kw,ti. (244)
108 fraxiparin.ab,kw,ti. (32)
109 low molecular weight heparin.ab,kw,ti. (3054)
110 LMWH.ab,kw,ti. (1427)
111 Heparin, Low Molecular Weight.ab,kw,ti. (409)
112 Low Molecular Weight Heparin.ab,kw,ti. (3054)
113 Low-Molecular-Weight Heparin.ab,kw,ti. (3054)
114 danaparoid.ab,kw,ti. (50)
115 danaproid.ab,kw,ti. (1)
116 danaparoid sodium.ab,kw,ti. (17)
117 danaproid sodium.ab,kw,ti. (1)
118 Aspirin.ab,kw,ti. (12027)
119 Acetylsalicylic Acid.ab,kw,ti. (3218)
120 Acid, Acetylsalicylic.ab,kw,ti. (54)
121 "2-(Acetyloxy)benzoic Acid".ab,kw,ti. (2)
122 Acylpyrin.ab,kw,ti. (129)
123 ASA.ab,kw,ti. (17266)
124 new oral anticoagulants.ab,kw,ti. (142)

125 NOACs.ab,kw,ti. (254)
126 Direct oral anticoagulants.ab,kw,ti. (236)
127 DOACs.ab,kw,ti. (179)
128 dabigatran.ab,kw,ti. (950)
129 rivaroxaban.ab,kw,ti. (1289)
130 apixaban.ab,kw,ti. (769)
131 edoxaban.ab,kw,ti. (459)
132 xarelto.ab,kw,ti. (57)
133 ximelagatran.ab,kw,ti. (207)
134 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 (3141)
135 118 or 119 or 120 or 121 or 122 or 123 (29601)
136 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 (11674)
137 Fondaparinux.ab,kw,ti. (405)
138 Fondaparinux Sodium.ab,kw,ti. (42)
139 137 or 138 (405)
140 Argatroban.ab,kw,ti. (151)
141 hirudin.ab,kw,ti. (195)
142 Hirudins.ab,kw,ti. (15)
143 bivalirudin.ab,kw,ti. (530)
144 lepirudin.ab,kw,ti. (28)
145 140 or 141 or 142 or 143 or 144 (877)
146 93 or 134 or 135 or 136 or 139 or 145 (44462)
147 35 and 73 and 146 (676)

SinoMed<to April,2019>

(妊娠[全字段] or 怀孕[全字段] or 孕期[全字段] or 孕妇[全字段]) and (抗凝[全字段] or 凝血[全字段] or 华法林[全字段] or 肝素 or[全字段] AND 抗凝药[全字段]) and (心脏瓣膜手术[全字段] or 心脏瓣膜[全字段] or 机械心脏瓣膜[全字段] or 人工心脏瓣膜[全字段] or 瓣膜[全字段] or 置换[全字段])

Clinical trial registry (www.ClinicalTrials.gov) < to April 3 ,2019>

(Pregnancy OR Pregnant OR Pregnancies OR Fetation OR Conception OR Newborn OR Infant OR Newborns OR Newborn OR Gestation OR Gravidity) AND (Heart Valve OR Heart Valves OR Cardiac Valves OR Valve OR Cardiac Valve OR Replacement OR Artificial)