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Cardiovascular and kidney outcomes of uric acid-lowering therapy in patients with different kidney functions: study protocol for a systematic review, pairwise and network meta-analysis

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ABSTRACT

Introduction Hyperuricaemia has been implicated in the development of kidney function in populations with chronic kidney disease; however, the benefits of urate-lowering therapy (ULT) remain uncertain in different clinical studies. The different kidney functions of enrolled populations and distinct pharmacokinetic characteristics of ULT might be of the essence for the contrasting results. In this study, we will synthesise all available data from randomised controlled trials (RCTs) and cohort studies, then evaluate the outcomes of ULT in patients stratified by different estimated glomerular filtration rate (eGFR) stratifications. Furthermore, we will attempt to explore a relatively optimal ULT regimen using a Bayesian network meta-analysis in different eGFRs.

Methods and analysis We searched published and unpublished data from MEDLINE, EMBASE, the Cochrane Central Register of Controlled trials and ClinicalTrials.gov website (before March 2022) for RCTs and cohort studies without language restriction. In the pairwise meta-analysis, all regimens of ULT will be pooled as a whole and compared with controls in different eGFRs. The random-effects model will be applied to generate the summary values using the software Stata V.12.0 (StataCorp). Network meta-analysis within a Bayesian framework will be conducted to explore the relative efficacy profiles of different ULTs and to find optimal ULT in different eGFRs. The software of WinBUGS V.1.4.3 and R2WinBUGS package of R V.3.1.1 will be used in the network meta-analysis. Primary outcomes will be the occurrence of major cardiovascular events and kidney failure events. Secondary outcomes will include the rate of change in eGFR per year, all-cause death, changes in serum uric acid level and major adverse events. Two authors will independently review study selection, data extraction and quality assessment.

Ethics and dissemination The meta-analysis does not require ethical certification. The results will be disseminated through publication in a peer-reviewed journal and through presentations at academic conferences.

PROSPERO registration number CRD42021226163.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Randomised controlled trials and cohort studies will be included.
⇒ Selection of studies, data extraction and bias assessment will be conducted by two independent reviewers.
⇒ Subgroup and meta-regression analyses will be performed.
⇒ The Grading of Recommendations Assessment, Development and Evaluation guidelines and the Confidence in Network Meta-analysis application will be used to grade the quality of evidence.
⇒ Traditional pairwise and network meta-analyses will be performed simultaneously.

BACKGROUND

Hyperuricaemia is common in people with chronic kidney disease (CKD) and increases along with the deterioration of kidney function. Initiating urate-lowering therapy (ULT) is recommended for patients experiencing their first flare when comorbid moderate-to-severe CKD by 2020 American College of Rheumatology (ACR) Guideline[1] and 2016 European Alliance of Associations for Rheumatology recommendations for the management of gout.[2] There was high certainty of evidence regarding the efficacy of ULT in reducing flare frequency,[3–5] tophi[3 6] and serum urate concentrations.[3] However, there is not a reliable body of evidence from which to recommend treatment of hyperuricaemia for the specific goal of delaying the progression of CKD. The role of hyperuricaemia in CKD, especially asymptomatic hyperuricaemia, has always been a controversial topic in nephrology. The possibility of increased cardiovascular risk with febuxostat and the threats of allopurinol withdrawal further undermine the ULT initiation.[7 8]

Prior studies have generally shown the benefit of ULT in populations with CKD and supported the viewpoint of treating asymptomatic hyperuricaemia to slow or delay the

progression of CKD.[9 10] However, another more sceptical account has emerged, which argues that the best available evidence from multicentre randomised controlled trials (RCTs) does not support the use of ULT in patients with asymptomatic hyperuricaemia and CKD, at least not to attenuate CKD progression.[11] The ACR Guideline of the Management of Gout also suggested that for most patients with asymptomatic hyperuricaemia (including those with comorbid CKD), the benefits of ULT would not outweigh potential treatment costs or risks for a large number of patients unlikely to progress to gout.[1]

In 2020, two critical negative RCTs were reported. The Controlled Trial of Slowing of Kidney Disease Progression from the Inhibition of Xanthine Oxidase (CKD-FIX) concluded that the renal function deterioration cannot be restrain throughout using ULT with allopurinol compared with placebo in patients with stage 3–4 CKD and no history of gout.[12] The result of Preventing Early Renal Loss in Diabetes (PERL) trial concluded that in the context of renin–angiotensin system inhibition, patients with early-stage diabetic nephropathy due to long-term type 1 diabetes did not benefit from allopurinol, as compared with placebo, which did not delay renal function decline, and reduce the incidence of cardiovascular events and hypertension.[13] Of note, subjects with a history of gout were both excluded, and these two studies did not include hyperuricaemia as a criterion because of the patients' higher baseline serum uric acid levels (6.1 mg/dL in PERL and 8.2 mg/dL in CKD-FIX). The generalisability of conclusions was limited in both studies due to the selected populations.

Subgroup analyses of Febuxostat vs Placebo Randomized Controlled Trial Regarding Reduced Kidney Function in Patients with Hyperuricemia Complicated by Chronic Kidney Disease Stage 3 Study showed an excellent efficacy in patients who were being treated without proteinuria and higher baseline renal function.[14] Sato *et al*[10] classified available RCTs based on the rate of CKD progression in the control group, identifying trials with an estimated glomerular filtration rate (eGFR) decline of >4 mL/min/1.73 m^2 in control subjects throughout the study period, and treatment with ULT conferred consistent clinical benefits.

Despite the contrasting results, a question was raised that duration of treatment and population enrolment might be critical in preventing deterioration of renal function, which might have contributed to the different conclusions reached in the PERL and CKD-FIX Studies. Recent animal experiments concluded that asymptomatic hyperuricaemia does not affect CKD progression unless uric acid crystallises in the kidney.[15] Uric acid crystals are more commonly observed in individuals with a history of gout, which affects at least one-third of patients with CKD.[16] Unfortunately, individuals with a history of gout are often excluded from RCTs of ULT because of the perception that assignment to placebo would be unethical. Several meta-analyses also included only the results of RCTs.[17 18] We need to summarise and analyse the studies in 'real world' to provide new insight into ULT, especially in subjects with CKD with either a history of gout, baseline hyperuricaemia and/or different levels of kidney function.

Furthermore, an increasing number of ULT drugs are available. We should recognise the distinct characteristics in pharmacology and pharmacokinetics of different ULTs especially when administrated in patients with impaired kidney function. The uricosuric drugs are usually limited to patients with renal impairment. The use of an inhibitor of the xanthine oxidase is the consensus first-line therapeutic strategy for ULT in populations with CKD. Febuxostat is commonly employed in ULT when allopurinol is not tolerated.[1 2] However, at present, it was still not clear whether renal impairment has any effect on the pharmacokinetics of febuxostat.[19] Some studies have shown that febuxostat achieves recommended target of serum urate levels more easily than allopurinol.[20–22] The Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities trial[23] suggested that febuxostat therapy might be associated with higher risks of all-cause death and cardiovascular death than allopurinol; however, the Febuxostat vs Allopurinol Streamlined Trial[24] with better ascertainment of events found no increase in these risks. Topiroxostat approved in Japan, a selective xanthine oxidase inhibitor, was reported an important protective effect against the progression of CKD and proteinuria.[25–28] The other treatment options, including lesinurad,[29] arhalofenate,[30] verinurad[31] and sodium glucose cotransporter 2 inhibitors,[32] are emerging and can inspire reperception and new understanding for ULT. Different drug classes, different doses of the same drug, their use alone or in combination, and distinct eGFRs introduce the complicated and difficult choice of prescription for the population with CKD with different kidney functions. Therefore, whether there is a relatively optimal ULT regimen in different eGFR stratifications is a prominent problem to be solved.

We will perform a systematic review, pairwise and network meta-analysis (NMA) of RCTs and cohort studies to search for the answers. The kidney outcomes and the cardiovascular events based on different eGFRs will be summarised in pairwise meta-analysis. Bayesian NMA will be applied to explore whether the optimal therapy agent exists in patients with different kidney functions.

METHODS

The protocol of this systematic review is developed and reported in accordance with the Preferred Reporting Item for Systematic Review and Meta-analysis Protocols guidelines, the extension statement for NMA and proposed additional considerations for protocols of systematic reviews including NMA.[33–36] We have followed the prespecified protocol registered at International Prospective Register of Systematic Reviews (PROSPERO) (CRD42021226163).[37]

Criteria for included studies

Types of studies

All RCTs and cohort studies comparing one drug with another or with a placebo in treatment for patients with hyperuricaemia will be included. The eligible studies need to report an assessment of the interesting outcomes, such as cardiovascular and kidney outcomes, without language restrictions. Every study must last 12 weeks at least. RCTs and cohort studies will be included in the pairwise meta-analysis, while the NMA will include only RCTs because of inevitable confounders and data not readily available for cohort studies.

Types of participants

Participants will include adults (≥18 years old) suffering from hyperuricaemia defined individually by each trial. Whether the patients accepted ULT before the study will not be considered. There is no limitation to initial renal function but the adults on dialysis will be excluded.

Types of interventions

We will include studies comparing the effects of ULT with placebo or another ULT intervention, and their combinations are also considered. The observation, which will give patients only usual care, will be included too. The interventions will be divided into seven groups: allopurinol, benzbromarone, probenecid, febuxostat, rasburicase, topiroxostat and pegloticase. If their different dosages or combined administrations exist, the groups can be added. We will assure the studies classified in the same group have homogeneity. An ideal network plot, which is a fully connected network with all the seven basic interventions, has been generated (figure 1).

Outcome measurements

We will include RCTs or cohort studies that reported at least one of the following outcomes:

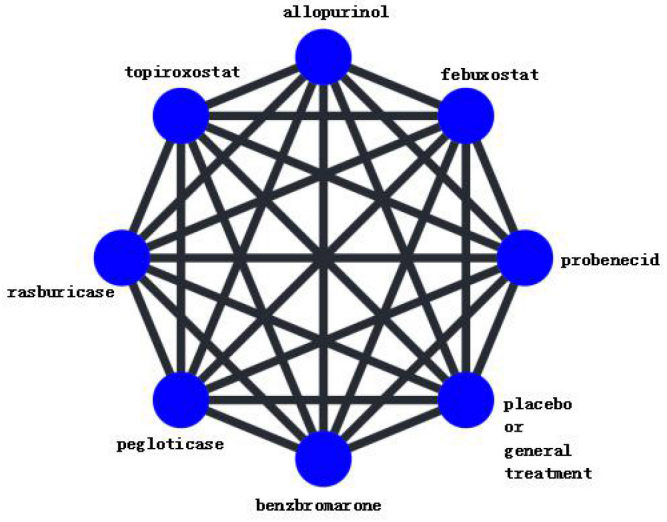

Figure 1 The ideal network structure based on expected eligible interventions.

Primary outcomes

1. Major cardiovascular events (as dichotomous outcome) will be defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, heart failure requiring hospitalisation and unstable angina requiring urgent coronary revascularisation, separately and combined.
2. Kidney failure events (as dichotomous outcome) will include more than 25% or 50% decrease in the eGFR, doubling of serum creatinine level or end-stage kidney disease as defined by the authors of each study during the follow-up period. If more than one method for defining kidney failure events is provided by a study, we will use that reporting more events for increased study power. End-stage kidney disease will be defined as eGFR <15 mL/min/1.73 m^2 or initiation of renal replacement therapy.

Secondary outcomes

1. The rate of change in eGFR per year (as a continuous outcome) will refer to the difference from baseline in eGFR divided by the number of years between eGFR measurements. We will pool eGFR data calculated by the Modification of Diet in Renal Disease Study formula, CKD Epidemiology Collaboration or Cockcroft-Gault equation and creatinine clearance (mL/min or mL/min/1.73 m^2).
2. All-cause death (as dichotomous outcome).
3. Change in serum uric acid level from baseline to end of follow-up (as a continuous outcome).
4. Major adverse events (as dichotomous outcome) will include rash, arthralgia, gastrointestinal symptoms and other drug-related adverse events as stated by the original investigators.

Search strategy and study selection

We will search for published, unpublished and ongoing studies in a range of research registries. Searches for published RCTs and cohort studies will be undertaken in the following electronic databases from the inception of databases to 1 March 2022: EMBASE, Ovid MEDLINE and Cochrane Central Register of Controlled trials. A detailed search strategy has been compiled, and the search terms will be combined using Boolean logic where appropriate (AND, OR). Relevant text words and medical subject headings included all spellings of “hyperuricemia”, “xanthine oxidase inhibitor” “allopurinol”, “benzbromarone”, “probenecid”, “febuxostat”, “rasburicase”, “topiroxostat” and “pegloticase”(online supplemental file 1). The ClinicalTrials.gov website, conference papers and reference lists from identified trials and review articles will be searched manually, and pharmaceutical companies will be consulted to identify any other relevant studies. No restrictions in terms of language, country or publication period are planned for all searches.

Preliminarily, one reviewer will sift out relevant pieces of literature by the established search strategy in the selected database, download and remove duplicates.

Then, two reviewers will screen titles and abstracts independently to figure out whether they meet the standard. After screening the studies that best met the criteria, the inclusion or exclusion of the studies was determined by reading the full text using the same criteria. In case of disagreement, a consensus will be sought; if disagreement persists, a third reviewer will take the decision.

Data extraction

A structured data extraction form will be used to ensure the consistency of extracted information and data. The following data will be extracted:

Publication and study details: research topic, authors, year of publication, funding source, possible conflicts of interest, inclusion and exclusion criteria, follow-up duration.

Methods: study design, randomisation in RCTs (ie, individual or cluster), the number of study centres, the adjusted factors in cohort studies and the statistical methods used.

Population: number of included patients, population characteristics for age, number of experimental group and control group, sex, the stage of CKD (the baseline level of eGFR) and baseline characteristics for outcome measures.

Interventions: experiment group: the kind of ULT, dosage, frequency of administration, duration of treatment; control group: placebo or general treatment.

Outcomes: definition, measures, imputation of missing data, primary and secondary outcomes, unintentional outcomes and the timing of assessment.

G3 data software (www.frantz.fi/software/g3data.php) will be used to make up for the lack of required quantitative data from published figures. The adjusted results were preferred for observational studies.[38]

Missing outcome data

Missing outcome data are sometimes imputed in the original trial report. We will try to contact the author by email to obtain the original data. The intention-to-treat principle will be used to deal with missing count data. The dropouts will be considered to be non-responders if they drop after the randomisation for the dichotomous efficacy outcome. If missing data are not available for continuous outcomes, this study will be excluded.

Risk of bias assessment

We will evaluate the methodological quality of the included RCTs using the updated Cochrane risk of bias.[39] The full guidance document includes the following five domains: bias arising from the randomisation process, bias due to deviations from intended interventions (effect of assignment to the interventions at baseline), bias due to missing outcome data, bias in the measurement of the outcome and bias in the selection of the reported result. Within each domain, the assessment comprises a series of signalling questions and a judgement about the risk of bias for the domain. The risk-of-bias judgements are 'low risk of bias', 'some concerns' or 'high risk of bias'. Judgements will be based on the summaries of the answers to signalling questions by an algorithm that maps responses to signalling questions to a proposed judgement.

To assess the risk of bias in cohort studies, we will follow the Cochrane Risk of Bias Tool for Non-Randomized Studies of Interventions.[40] Specifically, for included cohort studies, we will consider the following seven domains: pre-intervention ((1) bias due to confounding, (2) bias in selection of participants into the study); at intervention ((3) bias in measurement of interventions); post-intervention ((4) bias due to departures from intended interventions, (5) bias due to missing data, (6) bias in measurement of outcomes, (7) bias in selection of the reported result). Overall, risk-of-bias judgement for each study can be assessed as 'low risk of bias', 'moderate risk of bias', 'serious risk of bias' or 'critical risk of bias'.

Additionally, we will evaluate the influence of pharmaceutical industry funding and author–industry financial ties and/or employment according to the literature.[41] These two domains will not contribute towards the overall risk-of-bias judgements but will be addressed separately.

Grading the quality of evidence

For pairwise meta-analysis, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach will be used to summarise the strength of evidence for each outcome by two reviewers independently.[42] All processes will be implemented in GRADE software. Findings from large RCTs will be assigned the greatest weight. The brief procedures and standards of judgement are as follows.

- Starting point: if RCT forms the evidence base, the quality rating starts with high. If observational studies form the evidence base, the quality rating starts with low.
- Down rating: the quality rating may be rated down by −1 (serious concern) or −2 (very serious concern) for the following reasons: low risk of bias, inconsistency, indirectness, imprecision or publication bias.
- Up rating: rating up is typically applied only to observational studies; the most common reason is for a large or very large effect seen over a short period and altering a clear downward.

For NMA, the Confidence in Network Meta-analysis internet application (http://cinema.ispm.ch) will be used to clear and definite the confidence in network estimates by two reviewers independently.[43 44] Confidence was initially considered to be high and was maintained or downgraded to moderate, low or very low according to the assessment of the quality of the evidence. It covers six domains: (1) within-study bias, (2) across-studies bias (mainly reporting bias), (3)

indirectness, (4) imprecision, (5) heterogeneity and (6) incoherence.

Statistical synthesis of study data

Characteristics of included studies and information flow in the network

We will provide descriptive statistics based on population characteristics and available data across all eligible trials. The statistics and characteristics will summarise the types of comparisons and important clinical or methodological variables. Eligible comparisons for each outcome will be visually presented using the network diagrams.

Pairwise meta-analysis

Data will be classified according to different controls, including not using ULT or using another ULT as a control. Then, we will attempt to explore the risk of outcomes in patients with different kidney functions.

The random-effects models using a restricted maximum-likelihood method with CIs[45] modified by the Knapp-Hartung approach will be applied in the pairwise meta-analysis.[46] HR or risk ratio (RR) will be selected based on the data from the original study, and adjusted results of individual studies will be preferred for cohort studies. If HRs or RRs are unavailable in the original article, individual study HRs/RRs and 95% CIs will be calculated from event numbers and the total population at risk extracted from each trial before data pooling.

Mean differences will be used to pool rates of change in eGFRs and change of uric acid. When data for change from baseline are available in the included trials, we will directly extract them from the literature. When the change-from-baseline SD is missing, we will calculate it using correlations that are estimated from other included studies that have a similar follow-up period and report in considerable detail according to the imputed formulation and its related interpretations in Cochrane Handbook. We will replace the missing mean data with median data. As described in detail previously, missing SD data will be imputed using IQR (dividing by 1.35 only when large sample size), full range (dividing the range by values from the table of critical values for Pearson table) or reported p value. Summary estimates of mean differences will be also obtained using a random-effects model.[47]

I^2 statistics will be used to assess heterogeneity among studies. Values of I^2 <50% will indicate that heterogeneity is not salient for the cases that we explore. Subgroup analyses and meta-regression models will be used to explore the source of heterogeneity. Between-subgroup heterogeneity was assessed by χ^2 tests and meta-regression.[48]

All of the above operations will be performed using Stata software V.12.0 (StataCorp).

Assessment of the transitivity and consistency assumption

The transitivity assumption is the basic premise of NMA, which will be evaluated by comparing the distribution of clinical variables that could act as effect modifiers across treatment comparisons.[49 50] NMA will be considered to give valid results if additional evidence of intransitivity is lacking, and potential effect modifiers have similar distribution across the included studies. Descriptive transitivity analyses will show whether these clinical and methodological variables are relatively similar across treatment comparisons (arm level).[51] The selected effect modifiers will include the mean age; the percentage of females; basal uric acid level and eGFR; study design such as blind method and risk of bias; and interventions such as the types and dosages of therapy for lowering uric acid in the control group. The similar inclusion criteria of the eligible trials are also important, and we will summarise and present them.

Inconsistency will be assessed when three treatments are connected within a loop. The loop-specific approach will be used to check the local inconsistency.[52] For each closed loop, we will estimate the absolute difference between the direct and indirect comparisons, which is termed the inconsistency factor. Inconsistent loops will be identified by a significant disagreement (inconsistency factor and its 95% CI that excludes 0) between direct and indirect evidence. The tests for global inconsistency will be conducted using the design-by-treatment approach.[52]

Network meta-analysis

All ULTs will be analysed as a whole in the pairwise meta-analysis, and the possibility of distinction among them will be able to be ruled out. As described in detail previously, NMA within a Bayesian framework will be conducted to attempt to partly explain the source of heterogeneity in pairwise meta-analysis.[53] Given the inevitable confounding and the availability of data from observational studies, only RCTs will be included in Bayesian NMA for indirect comparisons between different ULTs. In NMA, event numbers and the total population at risk will be extracted from each RCT as original data. The results will be reported as OR and 95% credible interval by WinBUGS V.1.4.3 and the R2WinBUGS package of R V.3.1.1. We will use non-informative priors with vague normal (mean, 0; variance, 10 000) and uniform (0–5) prior distributions for parameters such as means and SDs, respectively.[53 54] We will generate 200 000 simulations for each of the two sets of different initial values and discard the first 80 000 simulations as the burn-in period for each analysis. Convergence will be reached when the potential scale reduction factor is close to 1 (using a cut-off of 1.05) for each of the parameters using the Brooks-Gelman-Rubin statistic.[53 55]

The correlation between the treatments can be induced since all effects are related to the same control arm when multiarm trials are included in the NMA.[56] In our analysis, the arm-level summaries, not the contrast-level summaries, will be used, where effect measures will be reported for each arm. The two primary outcomes are binomial. Accounting for the arm-level data and analysis under Bayesian frameworks, we will not induce the within-study correlation in fixed-effects models. We will further perform the NMA within the frequentist

framework as the sensitivity analysis. The correlation induced by multiarm trials will be handled by employing a multivariate normal distribution with covariances/2 with the structured model (setting all heterogeneity variances equal).

We will check whether a model's fit is satisfactory using the deviance information criterion (DIC).[57] DIC is the sum of Dbar (the posterior mean residual deviance) and the leverage, Pd (also termed the effective number of parameters). The model fits the data adequately when Dbar is approximative with the number of data points. Pd provides a measure of model complexity. Then, the DIC means a measure of model fit that penalises model complexity—lower values of the DIC suggest a more parsimonious model. To assess whether the model provided adequate fit, we will calculate the DICs of four models, including random consistency, random inconsistency, fixed consistency and fixed inconsistency model within a Bayesian framework using the WinBUGS and R software.

For the analysis of each outcome event, the surface area under the cumulative ranking curve (SUCRA) will be used to predict the optimal intervention, and the impact of different uric acid-lowering therapies on the kidney will be ranked by predicting probability.[58] SUCRA values will be applied carefully and presented along with 95% CIs to capture the uncertainty in the parameter values.[59]

Subgroup analysis and sensitivity analysis

Subgroup and meta-regression analyses for the pairwise or multitreatment comparisons will be conducted to address the potential heterogeneity and inconsistency by several major covariates.

1. Different CKD stages/kidney functions.
2. Baseline uric acid level and change of uric acid.
3. Patients with asymptomatic and symptomatic hyperuricaemia.
4. RCTs and cohort studies.
5. Single-centre and multicentre studies.
6. Whether the renal function in the control group is continuously progressive.
7. Different activities of xanthine oxidase.
8. Different quality of adjustment in observational studies.

The two primary outcomes will be used to carry out a sensitivity analysis to draw a robust conclusion.

1. Exclusion of studies with sample sizes less than 50.
2. Exclusion of studies evaluating only patients with normal kidney function.
3. Exclusion of studies reporting only RRs.
4. Exclusion of studies with very low quality. The very low-quality studies refer to the 'high' risk of bias in RCTs and 'serious' and 'critical' risk of bias in observational studies.
5. Exclusion of cohort studies without adjusted covariates.
6. Exclusion of studies written in other languages except English.

Assessment of publication bias

Selective outcome reporting will be rated regarding the two primary outcomes in the systematic review. The Outcome Reporting Bias in Trials classification system (http://www.outcome-reporting-bias.org) will be used to investigate reporting bias. It will be rated 'no risk', 'low risk' and 'high risk'.[60]

Patient and public involvement

Patients did not participate in the design of this systematic review and meta-analysis. However, the authors will communicate the findings to patients and public groups interested in the field.

ETHICS AND DISSEMINATION

This protocol is based on published data; thus, there is no requirement for ethics approval. An outline of the protocol has been published in the PROSPERO in 2021 (CRD42021226163). The results will be disseminated through publication in a peer-reviewed journal and through presentations at academic conferences.

Contributors YZ and XS conceived the study and drafted the protocol. RS, YH and LW revised it. YZ and RS developed the search strategies and will run them. YH and RS will select studies and extract data. YZ, XS and LW will analyse the data. All authors have approved the final edition of the protocol.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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