

INPLASY PROTOCOL

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submission:** The review has not
yet started.

Conflicts of interest:
The authors declare that they
have no conflict of interest.

INTRODUCTION

Review question / Objective: Our objective was to test whether hypothyroidism was independently predictive the cardiovascular risk in patients with CKD.

Rationale: Hypothyroidism has been shown to be associated with the progression of

Thyroid Dysfunction and cardiovascular events in patients with chronic kidney disease: A protocol of systematic review and meta-analysis

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Review question / Objective: Our objective was to test whether hypothyroidism was independently predictive the cardiovascular risk in patients with CKD.

Condition being studied: We have done a lot of literature research and clinical research on the relationship between hypothyroidism and cardiovascular risk in patients with chronic kidney disease. In addition, our team's previous research experience also focused on the cardiorenal damage in chronic kidney disease.

Information sources: Electronic databases, contact with authors, trial registers, or grey literature

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 07 October 2020 and was last updated on 07 October 2020 (registration number INPLASY2020100022).

many diseases, Studies have shown that hypothyroidism can lead to dyslipidemia, endothelial dysfunction and blood pressure changes, etc., which contribute to the increased long-term vascular risk. Hypothyroidism is a common complication in CKD, and the risk of renal function loss in CKD patients with hypothyroidism is significantly increased. However, the

correlation between hypothyroidism and cardiovascular risk in CKD patients has not been recognized and paid enough attention. We therefore conducted a systematic review and meta-analysis, based on the available studies, to address the association between hypothyroidism and cardiovascular events (CVE) in CKD patients.

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METHODS

Search strategy: Based on PubMed, Embase Database, Web of Science, China National Knowledge Infrastructure (CNKI), China Biology Medicine Database (CBM) and Wanfang Database, We conducted a systematic search of the literature on the association of hypothyroidism and the risk of CVD in patients with CKD. The retrieval strategy is the combination of Medical Subject Headings (MeSH) words and free-text terms. Additionally, We will review the relevant references of the retrieved literature to make the literature more comprehensive.

Participant or population: Patients with chronic kidney disease.

Intervention: Chronic kidney disease Patients with hypothyroidism.

Comparator: Chronic kidney disease Patients without hypothyroidism.

Study designs to be included: All cross-sectional, case-control or cohort studies that exploring the association of hypothyroidism and the risk of CVD in patients with CKD will be included in this meta- analysis.

Eligibility criteria: Literature that meets all of the above conditions will be included in

the study, and those with any of the following points will be excluded: (1) Repetitive literature, meta-analysis, case reports, reviews, conference abstracts, comments, protocols and practice guidelines; (2) Participants had acute or chronic diseases other than CKD; (3) Hypothyroidism is not the main influencing factor; (4) Study that cannot extract valid data.

Information sources: Electronic databases, contact with authors, trial registers, or grey literature.

Main outcome(s): CVE included acute myocardial infarction, angina pectoris, readmission for myocardial infarction or heart failure, need to undergo coronary artery bypass surgery and Cardiovascular death, etc.

Additional outcome(s): None.

Data management: The information extraction of selected literatures was carried out independently by two researchers (YJ GUAN and J LI). The contents of literature extraction include: (1) Basic information: First author, Author's unit (In order to avoid the superposition effect of multiple studies in the same unit and the same patient population), Year of publication and country, etc. (2) Characteristics of participants: diagnosis method, Sample size, average age, sex ratio, average disease course, Definition of hypothyroidism, etc. (3) Outcome indicators: Types of outcome indicators, measurement methods and values, etc. (4) quality assessment: Selection, Comparability, Exposure, etc. If there are multiple studies for the same population, we only select the latest one with the largest sample size.

Quality assessment / Risk of bias analysis: Two investigators (TT LIU and HM MAO) independently evaluated the quality of the included literature according to the Newcastle-Ottawa Scale (NOS). If there is inconsistency in the evaluation between the two researchers, the decision is made through consultation with the third

researcher (YL ZHAN). The main contents of the assessment are as follows: The accuracy of diagnosis in selected cases, the representativeness of selected cases, comparability between the observation group and the control group, the quality of factor exposure in case-control studies and follow up adequacy of outcome indicators in cohort studies.

Strategy of data synthesis: The risk ratio (RR) and 95% confidence intervals (CI) were used as the effect values of binary variables, and the mean difference (MD) and 95%CI were used as the effect values of continuous variables. The random effect model was select to calculate the effect size, as this method can better integrate the potential differences between studies, whether there is significant heterogeneity or not. chi-squared test and I² was used to evaluate the heterogeneity among the studies (low heterogeneity is defined as P >0.05, I² <50%, medium heterogeneity is defined as P close to 0.05 and I² close to 50%, high heterogeneity is defined as P 50%), If there is a high heterogeneity between studies, Sensitivity analysis and subgroup analysis were used to identify possible sources of heterogeneity, such as, age, gender, race, disease stage, type of study and quality of literature, etc. Additional contour funnel plot and egger's test were used to evaluate the possible publication bias qualitatively and quantitatively. Trial sequential analysis (TSA) will be used to evaluate the reliability and stability of the conclusions. Set type I error as 5%, and the power as 80% for the calculation of the required information size (RIS). If the cumulative Z curve crossed the traditional boundary value and RIS, it means that the results obtained by this meta-analysis have strong stability and credibility. We used the software of STATA (version 16.0) for meta-analysis and publication bias test. TSA (version 0.9.5.10) was used to conduct trial sequential analysis of this study. The significance of all statistical tests was set as P < 0.05.

Subgroup analysis: If there is a high heterogeneity between studies, subgroup analysis were used to identify possible

sources of heterogeneity, such as, age, gender, race, disease stage, type of study and quality of literature, etc.

Sensibility analysis: We will analyze the sensitivity of the study by eliminating the literature one by one.

Language: Search languages are English and Chinese only.

Country(ies) involved: China.

Other relevant information: The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was used independently by two researchers (TT LIU and HM MAO) to assess the quality of evidence for each outcome indicator, If there is inconsistency in the evaluation between the two researchers, the decision is made through consultation with the third researcher (YL ZHAN). All outcome indicators will be graded into four levels based on the quality of evidence: high, moderate, low, and very low quality. The reasons for the degradation of evidence quality of all outcome indicators will be commented in the form of comments.

Keywords: Hyroid Dysfunction; cardiovascular events; chronic kidney disease; protocol; systematic review; meta-analysis

Dissemination plans: The final results of this study will be published in journals and conferences

Contributions of each author:

Author 1 - Tongtong Liu - The author drafted the manuscript.

Author 2 - Yingjie Guan - The author provided statistical expertise.

Author 3 - Juan Li - The author provided statistical expertise.

Author 4 - Huimin Mao - The author contributed to the development of the selection criteria, and the risk of bias assessment strategy.

Author 5 - Yongli Zhan - The author read, provided feedback and approved the final manuscript.