INPLASY PROTOCOL

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

Conflicts of interest: **None.**

Efficacy and safety of thyroxine therapy on patients with heart failure and subclinical hypothyroidism: a protocol for systematic review and meta-analysis

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Review question / Objective: **1. Participant (1). Age ≥ 18; (2). Patients diagnosed with HF and SCH according to any of the diagnostic criteria are eligible to be included; (3). There are no restrictions on race, nationality, gender, or age; (4). Before inclusion in the study, patients were not treated with thyroxine; (5). Patients with cardiac resynchronization therapy or coronary artery bypass surgery, or with severe non-cardiovascular events were excluded. 2. Interventions and comparators The treatment group was treated with routine HF therapy plus thyroxine, while the control group was treated with HF routine therapy. The routine therapy in each study may not be the same, but treatment with thyroxine is the only difference between intervention and control. 3. Outcomes Main outcome measures effective rate and New York Heart Association classification (NYHA); Secondary outcome measures included: left ventricular ejection fraction (LVEF), quality of life (QOL) score, brain natriuretic peptide (BNP) / N-terminal pro brain natriuretic peptide (NT-proBNP), 6-minute walk test (6-MWT), and adverse events such as rash or itchy skin, dizziness, nausea, vomiting, dry cough, etc.**
Condition being studied: **Patients with subclinical hypothyroidism and heart failure. We will include randomized controlled trials (RCTs) for meta-analysis. At the same time, we will exclude the same studies, reviews, letters, abstracts or animal experiments.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 October 2020 and was last updated on 25 November 2020 (registration number INPLASY2020100062).

INTRODUCTION

Review question / Objective: **1. Participant (1). Age ≥ 18; (2). Patients diagnosed with HF and SCH according to any of the diagnostic criteria are eligible to be included; (3). There are no restrictions on race, nationality, gender, or age; (4). Before**

inclusion in the study, patients were not treated with thyroxine; (5). Patients with cardiac resynchronization therapy or coronary artery bypass surgery, or with severe non-cardiovascular events were excluded. 2. Interventions and comparators The treatment group was treated with routine HF therapy plus thyroxine, while the control group was treated with HF routine therapy. The routine therapy in each study may not be the same, but treatment with thyroxine is the only difference between intervention and control. 3. Outcomes Main outcome measures effective rate and New York Heart Association classification (NYHA); Secondary outcome measures included: left ventricular ejection fraction (LVEF), quality of life (QOL) score, brain natriuretic peptide (BNP) / N-terminal pro brain natriuretic peptide (NT-proBNP), 6-minute walk test (6-MWT), and adverse events such as rash or itchy skin, dizziness, nausea, vomiting, dry cough, etc.

Condition being studied: Patients with subclinical hypothyroidism and heart failure. We will include randomized controlled trials (RCTs) for meta-analysis. At the same time, we will exclude the same studies, reviews, letters, abstracts or animal experiments.

METHODS

Search strategy: #We searched PubMed, Cochrane Library, EMBASE, Chongqing VIP (CQVIP), China National Knowledge Infrastructure (CNKI), Chinese biomedical literature database (CBM), and Wan Fang database. We use the search strategy of MeSH terms combined with free-text. Pubmed database search terms: #1: (Subclinical[MeSH]) #2: (Hypothyroidism[MeSH]) #3: (Hypothyroidisms) OR ("Primary Hypothyroidism") OR ("Hypothyroidism, Primary") OR ("Primary Hypothyroidisms") OR ("Thyroid-Stimulating Hormone Deficiency") OR ("Deficiency, Thyroid-Stimulating Hormone") OR ("Hormone Deficiency, Thyroid-Stimulating") OR ("Thyroid Stimulating Hormone Deficiency") OR ("Thyroid-Stimulating Hormone Deficiencies") OR ("TSH Deficiency") OR ("Deficiency, TSH") OR ("TSH Deficiencies") OR ("Deficiency, TSH") OR ("TSH Deficiencies") OR ("Secondary Hypothyroidism") OR ("Hypothyroidism, Secondary") OR ("Secondary Hypothyroidisms") OR ("Central Hypothyroidism") OR ("Central Hypothyroidisms") OR ("Hypothyroidism, Central") #4: #2 OR #3 / #5: #1 AND #4 / #6: (Thyroxine[MeSH]) #7: ("O-(4-Hydroxy-3,5-diiodophenyl)-3,5-diiodotyrosine") OR ("T4 Thyroid Hormone") OR ("3,5,3',5'-Tetraiodothyronine") OR (Thyroxin) OR ("Thyroid Hormone, T4") OR (Synthrox) OR ("Levothyroxine Sodium") OR ("Sodium Levothyroxine") OR (Thyrax) OR (Tiroidine) OR ("Tiroxina Leo") OR (Unithroid) OR (Eferox) OR (Eltroxin) OR (Thevier) OR (Eltroxine) OR (Euthyrox) OR (Eutirox) OR ("L-Thyrox") OR ("L Thyrox") OR ("L-Thyroxin beta") OR ("L Thyroxin beta") OR ("L-Thyroxin Henning") OR ("L Thyroxin Henning") OR (Levothyroxine) OR ("O-(4-Hydroxy-3,5-diiodophenyl) 3,5-diiodo-L-tyrosine") OR ("L-Thyroxine") OR ("L Thyroxine") OR ("L-3,5,3',5'-Tetraiodothyronine") OR (Levoxine) OR (Levoxyl) OR (Lévothyrox) OR ("L-Thyroxine Roche") OR ("L Thyroxine Roche") OR ("Levo-T") OR ("Levo T") OR (Levothroid) OR (Novothyral) OR (Berlthyrox) OR (Dexnon) OR (Novothyrox) OR (Oroxine) OR (Synthroid) OR ("Levothyroxin Deladande") OR ("Levothyroxin Delalande") OR (Levothyroid) #8: #6 OR #7 / #9: ("Heart Failure"[Mesh]) #10: ("Heart Decompensation") OR ("Decompensation, Heart") OR ("Heart Failure, Right-Sided") OR ("Heart Failure, Right Sided") OR ("Right-Sided Heart Failure") OR ("Right Sided Heart Failure") OR ("Myocardial Failure") OR ("Congestive Heart Failure") OR ("Heart Failure, Congestive") OR ("Heart Failure, Left-Sided") OR ("Heart Failure, Left Sided") OR ("Left-Sided Heart Failure") OR ("Left Sided Heart Failure") OR ("Cardiac Failure") /#11: #9 AND #10 / #12: #5 AND #8 AND #11.

Participant or population: Patients diagnosed with heart failure according to the New York Classification of the American Heart Association (NY-HA) with subclinical hypothyroidism.

Intervention: Thyroxine treatment and HF routine therapy.

Comparator: HF routine therapy.

Study designs to be included: We will include randomized controlled trials (RCTs) for meta-analysis. At the same time, we will exclude the same studies, reviews, letters, abstracts or animal experiments.

Eligibility criteria: We will include randomized controlled trials (RCTs) which are about efficacy and safety of thyroxine therapy on patients with heart failure and subclinical hypothyroidism for meta-analysis. At the same time, we will exclude the same studies, reviews, letters, abstracts or animal experiments.

Information sources: We searched PubMed, Cochrane Library, EMBASE, Chongqing VIP (CQVIP), China National Knowledge Infrastructure (CNKI), Chinese biomedical literature database (CBM), and Wan Fang database.

Main outcome(s): Main outcome measures effective rate and New York Heart Association classification (NYHA).

Additional outcomes(s): Secondary outcome measures included: left ventricular ejection fraction (LVEF), quality of life (QOL) score, brain natriuretic peptide (BNP) / N-terminal pro brain natriuretic peptide (NT-proBNP), 6-minute walk test (6-MWT), and adverse events such as rash or itchy skin, dizziness, nausea, vomiting, dry cough, etc.

Data management: We will use Stata 14.0 software to conduct a meta-analysis of the included studies. Binary variables use relative risk (RR) and 95% CI as the statistical effect size. When continuous variables have the same measurement unit, they are expressed as weighted mean difference (WMD) with 95% CI. When the measurement unit is different, use standardized mean difference. (SMD) with 95% CI. $\chi 2$ was used for the heterogeneity test. When I250%, the random-effects model was used for meta-analysis.

Quality assessment / Risk of bias analysis: Two independent researchers will evaluate the included studies according to the guidelines in the Cochrane Handbook. We will assess the inclusion of the study from the following seven projects. They are random sequence generation, allocation hiding, participants and people blindness, results evaluation blind, results data incomplete, selective results report, and other deviations. The quality of each RCTs is classified as "high", "low" or "unclear" risk of bias. When there are differences, we will reach a consensus through discussions with third parties.

Strategy of data synthesis: The included studies were meta-analyzed by stata14.0 software. Count data is based on the relative risk (RR) and its 95% CI as the statistical effect size. The measurement data is expressed in terms of the weighted mean difference (WMD) and its 95% CI. When the measurement unit is different, the standardized mean difference (SMD) and 95% % CI representation. X2 was used for heterogeneity test. When P>0.05 and I2<50%, the fixed effects model was used for Meta analysis; when P50%, the random effects model was used for Meta analysis. At the same time, a funnel chart was drawn to evaluate the potential publication bias of the included studies. Finally, a general descriptive analysis of the adverse reactions occurred during the research process.

Subgroup analysis: We will make subgroup analysis according to age, gender, TSH level, intervention time, drug dosage, and other reasons, subgroup analysis is also an effective method to explore the source of heterogeneity.

Sensibility analysis: We perform a sensitivity analysis on the included studies one by one.

Country(ies) involved: China.

Keywords: heart failure; subclinical hypothyroidism; thyroxine; meta-analysis.

Contributions of each author:

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