INPLASY PROTOCOL

To cite: Shi et al. Efficacy and safety of thyroxine therapy on patients with heart failure and subclinical hypothyroidism: a protocol for systematic review and meta-analysis. Inplasy protocol 2020100062. doi: 10.37766/inplasy2020.10.0062

Received: 17 October 2020

Published: 17 October 2020

Corresponding author:
Tiantian Yang

ytt@bucm.edu.cn

Author Affiliation:
Department of Traditional Chinese Medicine, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan 25

Support: **This project is funded by the National Natural Science Foundation of China (no.81473631). The sponsors are not involved in design, execution, or writing the study.**

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

Shi, HS[1]; Kan, ZQ[2]; Liu, YF[3]; Li, WW[4]; Peng, M[5]; Yang, TT[6]

Review question / Objective: **1. Participant: (1). Age ≥ 18; (2). Patients with subclinical hypothyroidism(SCH) and heart failure(HF); (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 heart failure therapy plus thyroxine, while the control group was treated with heart failure 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 24 November 2020 (registration number INPLASY2020100062).

INTRODUCTION

Review question / Objective: **1. Participant: (1). Age ≥ 18; (2). Patients with subclinical hypothyroidism(SCH) and heart failure(HF); (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 heart failure therapy plus thyroxine, while the control group was treated with heart failure 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: #1: (Subclinical) #2: (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") OR (Hypothyroidism[MeSH]) #3: (Thyroxine[MeSH]) OR ("O-(4-Hydroxy-3,5-diiodophenyl)-3,5-diiodotyrosine") OR (Thyroxin) OR ("3,5,3',5'-Tetraiodothyronine") OR ("T4 Thyroid Hormone") 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 (Lévot hyrox) 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) #4: ("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") OR ("Heart Failure"[Mesh]) #5: #1 AND #2 #6: #3 AND #4 AND #5.

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: Thyroxin.

Comparator: Placebo or blank.

Study designs to be included: 1.All included studies are randomized controlled trials (RCTs); 2. All people included in the study are adults with Subclinical hypothyroidism

with heart failure (>18 years old); 3. No thyroxin was used before inclusion in the study; 4. In the results, each study reported LVEF, LVEDD, BNP, or 6MWT data before and after the intervention, or the change in these data; Or the effective rate or related adverse events are reported in the study.

Eligibility criteria: 1.All included studies are randomized controlled trials (RCTs); 2. All people included in the study are adults with Subclinical hypothyroidism with heart failure (>18 years old); 3. No thyroxin was used before inclusion in the study; 4. In the results, each study reported LVEF, LVEDD, BNP, or 6MWT data before and after the intervention, or the change in these data; Or the effective rate or related adverse events are reported in the study.

Information sources: PubMed database, Cochrane trials database, and Embase 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.

Quality assessment / Risk of bias analysis: We used the Cochrane Collaboration Tool to evaluate the quality of RCTs, Including randomization sequence generation, allocation concealment, selective reporting, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and other forms of bias.

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 conduct a subgroup analysis of the included population based on gender, age, and cardiac function classification.

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

Country(ies) involved: China.

Keywords: thyroxin; subclinical hypothyroidism; heart failure.

Contributions of each author:
Author 1 - Hongshuo Shi.
Author 2 - Zunqi Kan.
Author 3 - Yufan Liu.
Author 4 - Wenwen Li.
Author 5 - Min Peng.
Author 6 - Tiantian Yang.