

# Herbs of rich-iodine for Graves' Hyperthyroidism Trial (the HIGHT trial): a study protocol for a randomized, double-blind, placebo-controlled, multicentre clinical trial

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## Study protocol

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# Abstract

## Background

Graves' hyperthyroidism is one of the refractory diseases in endocrinology. Thionamides are known to be effective and its common side-effects are markedly reduced when starting with low dose. Iodine-rich Chinese herbal decoction (IRH) is a frequently prescribed Chinese herbal medicine in patients with Graves' hyperthyroidism. However, high quality clinical evidence is still very scarce, which made the Traditional Chinese Medical (TCM) management of Graves' hyperthyroidism remains controversial. The objective of this study is to prove that IRH might get faster and longer lasting remission and improved quality of life (QoL) in Graves' hyperthyroidism patients compared with methimazole (MMI) .

## Methods/design

This study is a randomized, double-blind, placebo-controlled and multicentre clinical trial. We will recruit a total of 240 participants with Graves' hyperthyroidism who have any common ATD-associated side-effects. They will be randomized (1:1:1) to receive (☒) IRH *plus* MMI placebo, (☒) IRH placebo *plus* MMI and (☒) IRH *plus* MMI for 12 weeks. The primary outcome measures will be the serum free triiodothyronine (FT3), free thyroxine (FT4) levels and serum thyroid-stimulating hormone (TSH) level. Secondary outcome measures will include the level of thyroid stimulating hormone-receptor antibodies (TRAb), thyroid ultrasound (US) and Thyroid-specific Patient Reported Outcome(ThyPRO39).

## Discussion

The outcomes of this study will provide new evidence for the efficacy and safety of IRH for the treatment of Graves' hyperthyroidism and will also guide physicians at clinics more clearly in prescribing IRH.

Trial registration number:

ChiCTR, ChiCTR2000032706. Registered 7 May 2020, <http://www.chictr.org.cn>

## Background

Graves' hyperthyroidism is an organ-specific autoimmune disease whose major manifestations including hyperthyroidism and goiter, characterized by the infiltration of thyroid antigen-specific T cells into thyroid-stimulating hormone receptor (TSH-R)-expressing tissues. Graves' hyperthyroidism has a population prevalence of 1-1.5% [1], and is associated with the increasing of the risk of coronary heart disease mortality, atrial fibrillation, heart failure, fractures, and mortality in patients with serum TSH levels < 0.1 mIU/L [2–5]. The treatment of graves' hyperthyroidism comprise: 1) anti-thyroid drugs (ATD) (mainly including methimazole, MMI or propylthiouracil, PTU); 2) thyroidectomy and 3) radioactive iodine (RAI) treatment. In China, the primary treatment is usually ATD, which leads to resolution of hyperthyroidism in 85–90% of patients within 12 weeks.[6] The ATD treatment is usually lasts for a period of 12 to 18 months and then tapered off. The common side effects of ATD contain skin rash, urticaria, arthralgia,

polyarthritis, fever and leukopenia [1]. Rare but major side effects include hepatitis, a lupus-like syndrome, and agranulocytosis (neutrophil count < 500/mL), which occurs in 0.1-1.0% of the Graves' hyperthyroidism patients [7–9]. The above mentioned side effects of ATD are the main reason for the withdrawal of ATD. In addition, patients with Graves' hyperthyroidism suffer from a wide range of symptoms and have major impairments in most areas of quality of life (QoL). Therefore, a better therapy is desperately needed.

The administration of stable iodide to hyperthyroid patients has been known to produce clinical benefit. Plummer utilized 10 drops of Lugol's solution containing 5% I<sub>2</sub> and 10% potassium iodide (KI), once or four times a day (approximately 80–320 mg iodine daily) to hyperthyroidism with good effect [10–13]. Starting from the 1930s, Thompson et al reported satisfactory results after giving hyperthyroid patients approximately 6 mg of iodine daily in 64% of the mild cases and 10% of the severe cases [14]. In recent years, treatment of Graves' hyperthyroidism with KI is widely accepted by Japanese thyroid specialists, and its efficacy has been reported in 2016 ATA guideline [15–19].

Currently, Traditional Chinese Medicine (TCM) is widely used to treat patients with Graves' hyperthyroidism in China and has accumulated rich experience [20–22]. Rich-Iodine herbs are those of their main representatives. The granules used in this trial contains eight Chinese herbs, algae, including kelp, spica prunellae, oldenlandia, and so on. Our studies have confirmed that the iodine content of algae and kelp are much higher than other herbs, therefore, we call them iodine-rich herbs [23–25]. Our small sample, iodine-rich Chinese herbal decoction (IRH) showed safety and effectiveness in patients with Graves' hyperthyroidism [26]. However, there have been few high-quality trials and more evidence is needed to prove the therapeutic effect of IRH.

We set up this study, which is a randomized, double-blind, placebo-controlled, multicentre clinical trial to clarify that IRH might get faster and longer lasting remission and improved QoL in Graves' hyperthyroidism patients compared with MMI, to provide high-quality data.

## Methods/design

### Objectives

The aim of this trial is to assess the efficacy and safety of IRH in patients with Graves' hyperthyroidism who have any common ATD-associated side-effects.

### Design

The HIGHT trial (Herbs of rich-iodine for Graves' Hyperthyroidism Trial) is a randomized, double-blind, placebo-controlled and multicentre clinical trial in patients with Graves' hyperthyroidism who have any common ATD-associated side-effects. The trial has a multi-arm design with 1:1:1 allocation to the experimental intervention group (A group), the control intervention group (B group) and combined intervention group (C group), and involving five clinical trial centers in China (The affiliated hospital of

Liaoning Traditional Chinese Medicine University, Xinjiang Uygur Autonomous Region Hospital of Traditional Chinese Medicine, The affiliated Shuguang hospital of Shanghai Traditional Chinese Medicine University, Liaoning Armed Police Corps Hospital, The 2nd affiliated hospital of Liaoning Traditional Chinese Medicine University). Figure 1 briefly shows the study flow chart, and the time-point of assessment is shown in Table 1. The development of the protocol of this study is per Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) guideline.[27]

Table 1  
SPIRIT schedule for enrollment, treatment, and assessments

Item	Enrolment/Baseline	Intervention period			
	-within 1 week	Week 2	Week 4	Week 8	Week 12
Visit	1	2	3	4	5
Informed consent	×				
Demographic information	×				
Record of medical history	×				
General physical examination	×	×	×	×	×
ThyPRO39	×	×	×	×	×
Pregnancy Test	×				×
FT3, FT4, TSH	×	×	×	×	×
TRAb	×	×	×	×	×
TgAb, TPOAb	×	×	×	×	×
Serum iodine	×				×
Iodine /creatinine ratio in spot urine	×				×
Thyroid Ultrasound (US.)	×		×		×
Blood and urine regulation*	×	×	×	×	×
ALT, AST,TBIL,ALP,γ-GT*	×	×	×	×	×
BUN, Cr, K, Ca	×	×	×	×	×
Electrocardiogram	×	×	×	×	×
Selection/exclusion criteria	×				

All assessments must be made at the time points specified above. If the assessment is not possible at the specified time, the assessment shall still be conducted, and the time shall be noted in the electronic case report form (eCRF). Following this, deviations from the protocol can be assessed. ThyPRO39: Thyroid-specific Patient Reported Outcome; FT3: free triiodothyronine; FT4: free thyroxine; TSH: levels and serum thyroid-stimulating hormone; TRAb: TSH-receptor Antibody; TPOAb: Thyroid peroxidase antibody; US: Ultrasound; TgAb: Thyroglobulin antibody. \*Patients should be informed of potential side effects of ATD and the necessity of informing the physician promptly if they should develop jaundice, light-colored stools, dark urine, fever, pharyngitis, or cystitis. In patients taking ATD, a differential white blood cell count should be obtained during febrile illness and/or pharyngitis, and liver function should be assessed in those who experience jaundice, light-colored stools, or dark urine. Full Blood Count every week for 4 weeks and then every 4 weeks; Liver Function Tests (LFT) every 2 weeks for 4 weeks and then every 4 weeks. # Adverse reactions of former treatment of ATD. ##That is, thyroid surgery or RAI therapy.

Item	Enrolment/Baseline		Intervention period		
Drugs of prohibition	x		x	x	x
Drug Distribution and record	x			x	x
Drug combination	x		x	x	x
Adverse reactions/Adverse events	x#		x	x	x
Referral to ablative therapy##			x	x	x

All assessments must be made at the time points specified above. If the assessment is not possible at the specified time, the assessment shall still be conducted, and the time shall be noted in the electronic case report form (eCRF). Following this, deviations from the protocol can be assessed. ThyPRO39: Thyroid-specific Patient Reported Outcome; FT3: free triiodothyronine; FT4: free thyroxine; TSH: levels and serum thyroid-stimulating hormone; TRAb: TSH-receptor Antibody; TPOAb: Thyroid peroxidase antibody; US: Ultrasound; TgAb: Thyroglobulin antibody. \*Patients should be informed of potential side effects of ATD and the necessity of informing the physician promptly if they should develop jaundice, light-colored stools, dark urine, fever, pharyngitis, or cystitis. In patients taking ATD, a differential white blood cell count should be obtained during febrile illness and/or pharyngitis, and liver function should be assessed in those who experience jaundice, light-colored stools, or dark urine. Full Blood Count every week for 4 weeks and then every 4 weeks; Liver Function Tests (LFT) every 2 weeks for 4 weeks and then every 4 weeks. # Adverse reactions of former treatment of ATD. ##That is, thyroid surgery or RAI therapy.

Figure 1 Trial flow chart

Table 1 SPIRIT schedule for enrollment, treatment, and assessments

## Sample size

According to the previous studies, we assumed an effective rate would be 90%. The sample was estimated according to the parameters: a significance level of 5%, power of 80%.

$$n = 2\pi(1-\pi) (\mu_{\alpha} + U_{1-\beta/2})^2 / \delta^2 = 66.355$$

Thus, the sample size was 80 subjects in each group with drop-out rate of 20%. A total of 240 subjects will be recruited and divided into three groups of 80 subjects each.

## Participants

### Diagnosis criteria

The diagnostic criteria for Graves' hyperthyroidism are based on the criteria set by the European Thyroid Association Guideline in 2018.[1]

#### Inclusion criteria

1. Patients between the age of 18 and 70 years, either male or female;

2. Fulfill Graves' hyperthyroidism diagnostic criteria (elevated FT3 and/or FT4, suppressed TSH and positive TRAb according to local laboratory results);
3. Intolerance to MMI or PTU (such as liver function injury, agranulocytosis, rash and urticaria and so on) and refuse thyroidectomy or RAI;
4. Willingness to provide written informed consent.

#### Exclusion criteria

1. Hyperthyroidism crisis;
2. Symptomatic compression or large goiter;
3. Those whose FT4 exceeds the measuring range, and/or TRAb exceeds the measuring range;
4. Subjects who allergy to the components in TCM and/or placebo;
5. Those who have thiocarbamides-associated major side effects including of severe hepatitis (elevation of AST or ALT more than double the normal upper limit), agranulocytosis (neutrophil count < 500/mL), severe exfoliative dermatitis;
6. Women who are pregnant or lactating, or preparing for pregnancy and lactating women;
7. Subjects with a history of alcohol abuse, drug abuse, or mental diseases;
8. Those who are in seriously unstable medical condition, such as cardiovascular disease, cerebrovascular disease, hepatobiliary disease, renal disease or problems in the urinary reproductive system, or neoplasms, or whose treatment with any medication potentially influencing thyroid function (IFN-gama, amiodarone, lithium, corticosteroids, etc.);
9. Subjects who have taken other clinical trial drugs within 3 months;
10. Subjects who are thought to be inappropriate for this study.

## Intervention

Study recruits receive respectively IRH plus placebo MMI (A group), placebo IRH *plus* MMI (B group), or IRH *plus* MMI (C group). Participants in three groups will take either IRH or the placebo IRH twice daily (10 g/packet at a time), plus either MMI or placebo MMI once daily (5–10 mg at a time) for 12 weeks. The drugs will be distributed to Graves' hyperthyroidism patients per month.

Both IRH and placebo granules are manufactured by Jingyin Pharmaceutical (Jingyin, China) according to good manufacturing practice guidelines. Drugs will be prepared in the form of brown granules. The constituents of IRH are kelp, spica prunellae, oldenlandia, and so on. The placebo will consist of corn starch, lactose hydrate, citric acid, and caramel color. The placebo and IRH will have the same size, appearance, smell and taste. They are packaged in the same packet, labelled as trial-specific Investigational Medicinal Products (IMPs) as the IRH granules, and then distributed to the 5 centres.

MMI tablets (Thyrozol, 10mg × 50) are produced by Merck KGaA, Germany. The placebo MMI tablets are made for the trial by Beijing Chengyou Pharmacy Manufacturing Unit in accordance with good manufacturing practice and exactly match the size, appearance, taste, smell of the active MMI tablets,

which are removed from their blister-packs and re-packaged in the same bottles as the placebos. Both active and placebo drugs are then labeled as trial-specific IMPs and distributed to the 5 centres.

## **Randomization and allocation concealment**

Randomization using Statistics Analysis System (SAS) software will be performed by independent staff statisticians. Participants will be randomly assigned to either the A or B or C group in a 1:1:1 ratio. The study coordinator will be blinded to the group assignment and will give participants the numbered package of intervention according to their visiting time sequence at baseline visit. Thus, the allocation concealment will be maintained throughout the study. The allocation for each subject will be sealed in an opaque envelope and will not be disclosed until the clinical trial is completely over, unless serious adverse events (SAEs) happen.

## **Blindness**

Double-blinding method is adopted in this study. Both participants and investigators will be blinded to the allocation until completion of the trial. The each placebo drug was confirmed in advance that the size, appearance, taste and flavor were similar. According to the randomization sequence, drugs will be packed in the same form and will be delivered to the hospital. At the end of the study, the blinding codes will be revealed. In case of SAEs, an administrator will unblind the patient information as an emergency and provide relevant treatment.

## **Concomitant medication or treatment**

The use of any traditional medicine designed to treat Graves' hyperthyroidism, except for the intervention of this trial, will be prohibited during the study. During the treatment, the clinician can decide whether to combine with  $\beta$ -adrenergic blocker, antihistamine agents, hepatoprotective agents and leukocytopoiesis-promoting agents according to the specific condition. All concomitant medication and treatment (that is, treatment drugs / treatment measures for other diseases) during the study period will be recorded in the combined medication table in detail.

## **Discontinuation**

Participants may withdraw from the trial at any time for any reason, and the reason will be recorded in the electronic case report forms (eCRFs). In order to conduct intention-to-treat analyses with as few missing data as possible, the investigator may ask the participants which aspects of the trial, they wish to withdraw from. These can include the following: receipt of the trial intervention, participation in the remaining follow-up assessments, or use of already collected data in the data analyses. The investigators will discontinue a participant's taking of the trial intervention at any time, if the participant: experiences intolerable adverse reactions; is diagnosed with any of the exclusion criteria during the intervention period; is referred for ablative therapy (RAI or thyroid surgery) during the intervention period. In all three cases, the investigator and/or the treating physician will encourage the participant to continue with follow up assessment and to allow the use of collected data in the analyses.

# Safety assessment

Safety will be assessed in terms of the routine physical examination consists of breath rate, heart rate, temperature, blood pressure, weight, and routine kidney function, liver function, blood, urine, and electrocardiogram test results obtained at 2, 4, 8 and 12 weeks of treatment, respectively. Adverse events, vital signs, and laboratory examinations will be recorded on eCRFs before and after patients take their medication at every visit. Adverse events (AEs) are defined as any unexpected sign or symptom during the treatment period, and participants will be asked to inform clinicians about the occurrence of any AEs while taking their medication. The researchers will then comprehensively evaluate the relation between these AEs and the experimental drugs according to the records, including the occurrence time, duration, manifestation, cause, and treatment measures. If SAEs occur that may lead to death or require extended hospitalization, the participants will be asked to quit the clinical trial as soon as possible, and proper treatment will be provided.

## Outcomes

Outcomes will be assessed four times during the trial.

## Primary outcome

The primary outcome will be the change in serum FT3, FT4 levels and serum TSH level results from baseline to the end of the 12-week intervention.

### Secondary outcomes

1. The proportion of euthyroidism participants at the study visits at 2, 4, 8 and 12 weeks of treatment, respectively;
2. The serum level of TRAb at 2, 4, 8 and 12 weeks of treatment, respectively;
3. The change in thyroid imaging (thyroid color Doppler ultrasound) from baseline to the end of the 12-week intervention.
4. Proportion of participants who have been referred to ablative therapy (RAI or thyroid surgery) at some point during the entire intervention period;
5. Thyroid-specific Patient Reported Outcome (ThyPRO39) and hyperthyroid symptoms during 12 weeks after randomization, and at the end of the intervention period. ThyPRO39 will be measured by the global score in the questionnaire;
6. Number of patients with ARs and / or SARs during the intervention period.

## Data management and Monitoring

All researchers involved in the study will be qualified physicians. All source documents, such as informed consent forms, signature of participants and questionnaires, will be collected and conserved in compliance with standard operating procedures (SOP). The data will be collected via an electronic data

capture system through eCRFs using the OpenClinical EDC management system. The main data will be locked up until research completed. For the questions in the eCRFs, data manager should inquire the researchers through clinical supervisor and make data modification, affirmation and record according to the reply of researchers. The principal investigator will coordinate dissemination of data.

The administrators of the Affiliated Hospital of Liaoning Traditional Chinese Medicine University will visit each unit regularly (once a month) to confirm the quality of data collection and facilitate problem-solving and the Ethics Committee will monitor for protocol violations. The safety, progress, study integrity, and design aspects will be monitored by the research team involved in this study.

## Statistical Analysis Plan

### Analysis of data sets

1. Intention to treat (ITT): The ITT principle will include subjects who meet the full analysis set criteria, including subjects who had the primary outcome assessed once or more except for the baseline measures and who took the test drug at least once.
2. Full analysis set (FAS): According to the principle of analysis for ITT, participants will be rejected by smallest and reasonable method.
3. Per-protocol set (PPS): PPS should be used in the patients who satisfied with the following characters: case of completed observation; fit with inclusion criteria; not using prohibited drugs.
4. Safety analysis set (SAS): All information of safety record will be assessed, including subjects who took the test drug at least once.

### Statistical analysis method

1. All parameters will be analyzed by SPSS version 25.0 software package.
2. The significance level will be set to 0.05 in a two tailed test.
3. The last observation carried forward (LOCF) method will be used for the missing data supplement.
4. Dropping analysis: The chi-square test, or Fisher exact probability method.
5. The model will include baseline values and gender as covariates and treatment as a fixed effect. The independent t test or Wilcoxon rank-sum test will be used for continuous variables, and the chi-square test or Fisher's exact test will be used for categorical variables.
6. Comparison within each group: Student's t test or Wilcoxon's signed-rank test will be used to compare data before and after the treatment between the groups. Categorical data will be analyzed using the chi-square test or Fisher's exact test.
7. Comparison between groups: The chi-square test for enumeration data; Wilcoxon rank sum test for non-normal distribution of measurement data; Student's t-test for normal distribution of measurement data; ANOVA for repeated measurement data; Ridit test for ranked data.
8. CMH test for the center effect.
9. Compliance analysis: The incidence of SAEs and AEs related to the treatment will be analyzed. The percentage of subjects who experience one or more side effects during the study will be analyzed

and presented using a descriptive analysis for each group.

## Ethical considerations

The HIGHT trial will be conducted in accordance with the principles of the Declaration of Helsinki (2013 version). The trial design will follow the principles set out in the Good Clinical Practice guidelines for the appropriate clinical use of TCM. The trial is approved by the Ethics Committee of Affiliated Hospital of Liaoning Traditional Chinese Medicine University (H-4-2012-026). The trial was registered at the Chinese Clinical Trial Registry (ChiCTR2000032706). The trial will fully comply with the SPIRIT reporting guidelines. After the clinicians provide a complete explanation to the participants, written informed consent will be obtained from the participants before treatment intervention. The trial will help to demonstrate if IRH is effective and safe for patients with Graves' hyperthyroidism and the results will be published in peer-reviewed journals to ensure widespread dissemination. All protocol amendments will be approved by the Institutional Review Board prior to execution.

## Discussion

This study is a randomized, double-blind, placebo-controlled multicentre clinical trial designed to prove that IRH might get faster and longer lasting remission and improved QoL compared with MMI in Graves' hyperthyroidism patients who have any common ATD-associated side-effects.

TCM is beneficial to Chinese thyroid patients for thousands of years. Our previous study have shown that IRH may be an alternative therapy for Graves' hyperthyroidism patients who suffer from common ATD-associated side-effects, but its quality is not enough [26]. In addition, we hope to establish a standard IRH scheme, given that there is, to date, no such consensus in Graves' hyperthyroidism patients. To the best of our knowledge, this is the first randomized, double-blind, placebo-controlled multicentre clinical trial that will determine the efficacy and safety of IRH in the therapy of Graves' hyperthyroidism patients, which is why we intend to perform this study.

The strength of this study is the rigorous design, which is a randomized, double-blind, placebo-controlled multicentre clinical trial. The outcomes derived from this study include objective parameters, such as the serum FT3, FT4, TSH levels, TRAb, TgAb, TPOAb and thyroid imaging, as well as subjective parameters obtained from questionnaires (ThyPRO-39). To ensure the quality of this study and reach a reliable conclusion, the experimental design and study performance are under strict quality control. At each center, training sessions will be provided to explain the study protocol, and the standard operating procedures.

The short study period is the limitation of this study. Nevertheless, this study is reasonably well designed. The results are expected to provide new evidence for the effectiveness and safety of IRH treatment in patients with Graves' hyperthyroidism and guide physicians more clearly in prescribing IRH.

# Abbreviations

The HIGHT trial: The Herbs of rich-Iodine for Graves' Hyperthyroidism Trial; IRH: Iodine-rich Chinese herbal decoction; TCM: Traditional Chinese Medical; QoL: quality of life; ThyPRO39: Thyroid-specific Patient Reported Outcome; MMI: methimazole; FT3: free triiodothyronine; FT4: free thyroxine; TSH: thyroid-stimulating hormone; TSH-R-Ab: thyroid stimulating hormone-receptor antibodies; US: Ultrasound; ATD: Anti-thyroid drugs; PTU: propylthiouracil; RAI:radioactive iodine; KI: potassium iodide; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; TRAb: TSH-receptor Antibody; TPOAb: Thyroid peroxidase antibody; TgAb: Thyroglobulin antibody; SAS: Statistics Analysis System; SAEs: serious adverse events; eCRFs: electronic case report forms; AEs: adverse events; SOP: standard operating procedures; ITT: Intention to treat; FAS: Full analysis set; PPS: Per-protocol set; SAS: Safety analysis set; LOCF: last observation carried forward.

# Declarations

## Trial status

The protocol version date is November 9, 2019. The protocol version number is LNZYXZK201902. Patient recruitment was began in December 1, 2019 and it will be completed by May 2021.

## Competing interest

None of the investigators have any financial or non-financial competing interest.

## Author contributions

All authors contributed to the design of the trial, preparation and review of the manuscript and all authors read and approved the final manuscript.

## Funding

Capacity building project of TCM clinical (specialty) department in Liaoning Province (LNZYXZK201902).

## Ethics approval and consent to participate

We confirm that the trial will obtain the informed consent of all study participants. The full name of the ethics committee that approved the study is IRB of The Affiliated Hospital of Liaoning University of Traditional Chinese Medicine. The committee's reference number is 2019063FS(KT)-039-02.

## Consent for publication

Not Applicable.

## Availability of data and materials

All data and materials for this trial are available.

## Acknowledgements

Not Applicable.

## References

1. George J, Kahaly L, Bartalena L, Hegedüs L, Leenhardt K, Poppe SH. Pearce: 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. *Eur Thyroid J.* 2018;7:167–86.
2. Collet TH, Gussekloo J, Bauer DC, den Elzen WP, Cappola AR, Balmer P, Iervasi G, Asvold BO, Sgarbi JA, Volzke H, Gencer B, Maciel RM, Molinaro S, Bremner A, Luben RN, Maisonneuve P, Cornuz J, Newman AB, Khaw KT, Westendorp RG, Franklyn JA, Vittinghoff E, Walsh JP, Rodondi N. Thyroid Studies Collaboration: Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. *Arch Intern Med.* 2012;172:799–809.
3. Biondi B, Kahaly GJ. Cardiovascular involvement in patients with different causes of hyperthyroidism. *Nat Rev Endocrinol.* 2010;6:431–43.
4. Gencer B, Collet TH, Virgini V, Bauer DC, Gussekloo J, Cappola AR, Nanchen D, den Elzen WP, Balmer P, Luben RN, Iacoviello M, Triggiani V, Cornuz J, Newman AB, Khaw KT, Jukema JW, Westendorp RG, Vittinghoff E, Aujesky D, Rodondi N. Thyroid Studies Collaboration: Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. *Circulation.* 2012;126:1040–9.
5. Blum MR, Bauer DC, Collet TH, Fink HA, Cappola AR, da Costa BR, Wirth CD, Peeters RP, Asvold BO, den Elzen WP, Luben RN, Imaizumi M, Bremner AP, Gogakos A, Eastell R, Kearney PM, Strotmeyer ES, Wallace ER, Hoff M, Ceresini G, Rivadeneira F, Uitterlinden AG, Stott DJ, Westendorp RG, Khaw KT, Langhammer A, Ferrucci L, Gussekloo J, Williams GR, Walsh JP, Juni P, Aujesky D, Rodondi N. Thyroid Studies Collaboration: Subclinical thyroid dysfunction and fracture risk: a meta-analysis. *JAMA.* 2015;313:2055–65.
6. Compilation group of Chinese Society of Endocrinology for. Chinese thyroid disease diagnosis and treatment guide: Guidelines for diagnosis and treatment of thyroid diseases in China. *Chinese Journal of Internal Medicine.* 2007;46(10):876–82.
7. Pearce SH. Spontaneous reporting of adverse reactions to carbimazole and propylthiouracil in the UK. *Clin Endocrinol.* 2004;61:589–94.
8. Yang J, Zhu YJ, Zhong JJ, Zhang J, Weng WW, Liu ZF, Xu Q, Dong MJ. Characteristics of antithyroid drug-induced agranulocytosis in patients with hyperthyroidism: a retrospective analysis of 114 cases in a single institution in China involving 9690 patients referred for radioiodine treatment over 15 years. *Thyroid.* 2016;26:627–33.

9. Nakamura H, Miyauchi A, Miyawaki N, Imagawa J. Analysis of 754 cases of antithyroid drug-induced agranulocytosis over 30 years in Japan. *J Clin Endocrinol Metab.* 2013;98:4776–83.
10. Volpe R, Johnston MW. The effect of small doses of stable iodine in patients with hyperthyroidism. *Ann Intern Med.* 1962;56:577–89.
11. Plummer HS: Results of administering iodine to patients having exophthalmic goiter. *JAMA* 1923, 80:1955.
12. Plummer HS, Boothby WM. The value of iodine in exophthalmic goiter. *J Iowa Med Soc.* 1924;14:66–73.
13. Astwood EB. Thyroid and antithyroid drugs. In: Goodman LS, Gilman A, editors *The Pharmacological Basis of Therapeutics*. 3rd ed. New York: The Macmillan Company 1965:1466–1503.
14. Thompson WO, Thompson PK, Brailey AG, Cohen AC. Prolonged treatment of exophthalmic goiter by iodine alone. *JAMA Internal Medicine.* 1930;45(4):481–502.
15. Okamura K, Sato K, Fujikawa M, Bandai S, Ikenoue H, Kitazono T. Remission After Potassium Iodide Therapy in Patients With Graves' Hyperthyroidism Exhibiting Thionamide-Associated Side Effects. *The Journal of Clinical Endocrinology Metabolism.* 2014;99(11):3995–4002.
16. Yoshihara A, Noh JY, Watanabe N, Kunii Y, Suzuki M, Matsumoto M, Suzuki N, Hiruma M, Morisaki M, Kawaguchi A, Sugino K, Ito K. Characteristics of Patients with Graves' Disease Whose Thyroid Hormone Levels Increase After Substituting Potassium Iodide for Methimazole in the First Trimester of Pregnancy. *Thyroid.* 2020;30(3):451–6.
17. Sato S, Noh JY, Sato S, Suzuki M, Yasuda S, Matsumoto M, Kunii Y, Mukasa K, Sugino K, Ito K, Nagataki S, Taniyama M. Comparison of Efficacy and Adverse Effects Between Methimazole 15 mg + Inorganic Iodine 38 mg/Day and Methimazole 30 mg/Day as Initial Therapy for Graves' Disease Patients with Moderate to Severe Hyperthyroidism. *Thyroid.* 2015;25:43–50.
18. Yoshihara A, Noh JY, Watanabe N, Mukasa K, Ohye H, Suzuki M, Matsumoto M, Kunii Y, Suzuki N, Kameda T, Iwaku K, Kobayashi S, Sugino K, Ito K. Substituting Potassium Iodide for Methimazole as the Treatment for Graves' Disease During the First Trimester May Reduce the Incidence of Congenital Anomalies: A Retrospective Study at a Single Medical Institution in Japan. *Thyroid.* 2015;25(10):1155–61.
19. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, Rivkees SA, Samuels M, Sosa JA, Stan MN, Walter MA. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid.* 2016;26:1343–421.
20. Zhou CY, Gao TS. Clinical efficacy of Traditional Chinese Medicine in treatment of Graves disease: A Meta Analysis. *Journal of Liaoning University of TCM.* 2020;47(2):29–32.
21. Liu QY, Gao TS. Effect of Nourishing-Yin Removing -Fire and Dissipating -Stagnation Decoction on intrathyroid vascularity and VEGF levels in patients with Graves disease. *Chinese Journal of Biochemical Pharmaceuticals.* 2015;35(3):76–71.
22. Liu QY, Gao TS. Effect of Nourishing-Yin Removing-Fire and Dissipating-Stagnation Decoction in Combination with Western Medicine Treatment on Thyroid Volumes and Interleukin Induced Protein-

10(IP-10) Levels in Patients with Graves Disease. Journal of Liaoning University of TCM. 2015;17(6):23–6.

23. Cui P, Gao TS. To Mensurate the Content of Iodine in Herbal Medicine and Compound Prescription Used in Softening Hard Mass and Disintegrating Masses. Chinese Archives of Traditional Chinese Medicine. 2007;25(7):1396–8.
24. Zheng Q, Gao TS. Determination of iodine content of iodine-rich herbal and analysis of effective factors. Chinese Journal of Biochemical Pharmaceuticals. 2014;34(7):171–3 + 176.
25. Xiang PP, Zhao YJ, Chen GF, Liu KM, Wang X, Liu C. Determination of Iodine Content in Chinese Decoction and Herbal for Thyroid Diseases. Guiding Journal of Traditional Chinese Medicine Pharmacy. 2019;25(13):94–6,120.
26. Hong YT, Gao TS. Clinical efficacy and safety evaluation of Chinese Medicine compound containing iodine in the treatment of Graves' disease. Asia-Pacific Traditional Medicine. 2019;15:146–9.
27. Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleza-Jeric K, Laupacis A, Moher D. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ. 2013;346:e7586.

## Figures

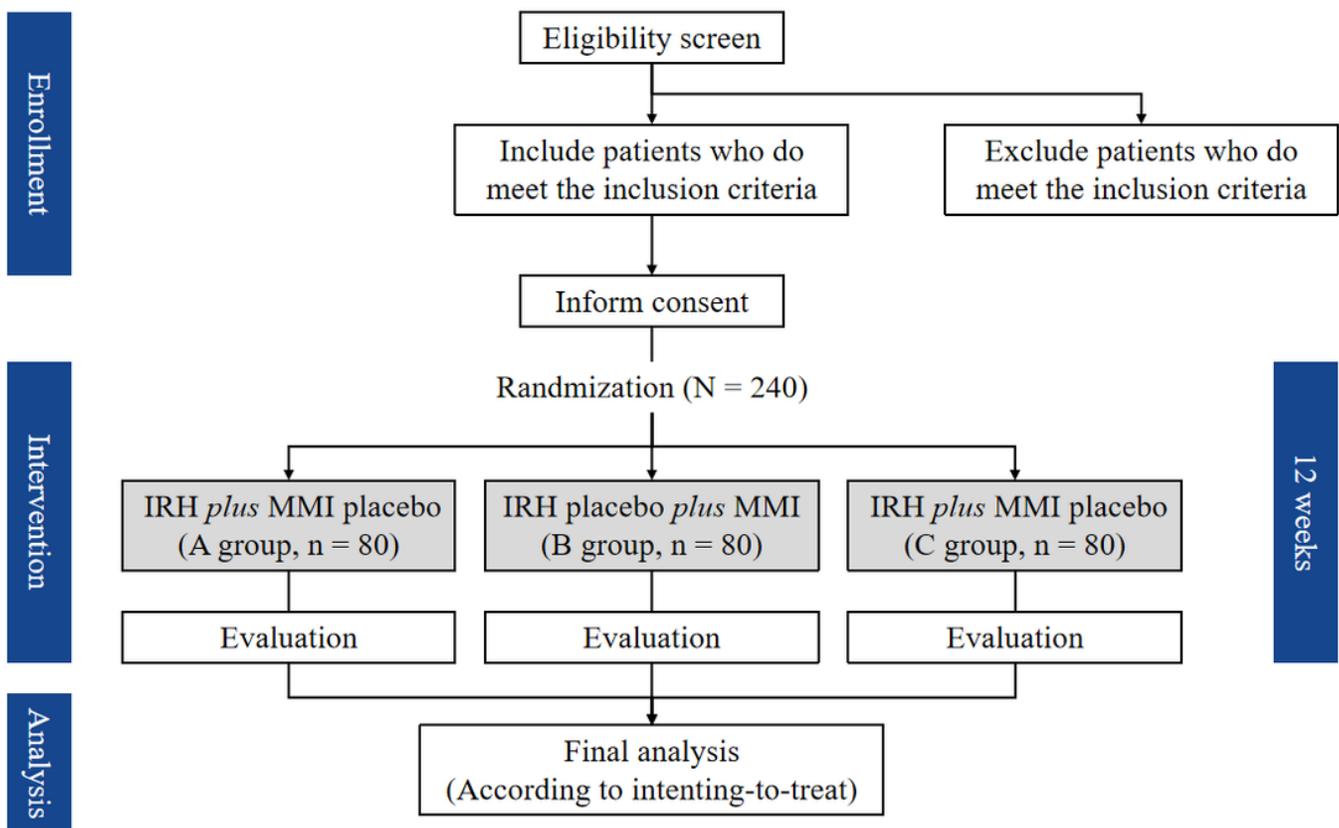


Figure 1

Trial flow chart

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