IEMO 80-plus thyroid trial.

Gepubliceerd: 12-02-2013 Laatst bijgewerkt: 18-08-2022

1. Does Levothyroxine treatment for subclinical hypothyroidism give multi-modal benefits for the oldest old people with subclinical hypothyroidism? 2. Are benefits seen across a wide range of outcomes, including prevention of cardiovascular disease...

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON22581

Bron
Nationaal Trial Register

Verkorte titel
IEMO 80-plus

Aandoening

Subclinical hypothyroidism
Levothyroxin
Older adults
Randomized placebo-controlled trial
Subklinische hypothyreoidie
Levothyroxine
Ouderen
Gerandomiseerd placebo-gecontrolleerde trial

Ondersteuning

Primaire sponsor: Leids Universitair Medisch Centrum
Overige ondersteuning: ZonMw project no 627001001

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

The main study endpoint is change in thyroid-specific quality of life and symptom burden assessed using the hypothyroid symptoms scale score and tiredness symptoms scale score on the thyroid-specific quality of life (ThyPRO) questionnaire at baseline, six to eight weeks and 12 months after recruitment and at the close-out visit are included.

Toelichting onderzoek

Achtergrond van het onderzoek

Background of the study:

Subclinical hypothyroidism is a common condition (8-18%) among older men and women. Although by definition subclinical hypothyroidism comprises biochemically mild thyroid hormone deficiency, it is a possible contributor to multiple problems in older age. Thyroid hormone has effects

on numerous physiological systems, including the vascular tree, heart, skeletal muscle and brain. Therefore, thyroxine substitution to overcome thyroid hormone deficiency has the potential to give multisystem benefits to older people with subclinical hypothyroidism. Small studies have reported reduced atherosclerosis and improved heart function with thyroxine replacement, but no large clinical trials have been performed. Therefore the available evidence is limited, leading to major variations in guidelines and clinical practice, with uncertainty regarding the indications for screening and treatment. This is especially the case for the oldest old, because observational studies are conflicting and very few oldest old are included in clinical trials, although they have the highest prevalence of subclinical hypothyroidism and its potentially related symptoms and diseases.

Objective of the study:

1. Does Levothyroxine treatment for subclinical hypothyroidism give multi-modal benefits for the oldest old people with subclinical hypothyroidism?

2. Are benefits seen across a wide range of outcomes, including prevention of cardiovascular disease, and improving health- related quality of life, muscle function and cognition?

3. Are benefits seen in specific subgroups of oldest old people with SCH, including women, and those with mild degrees of subclinical hypothyroidism (TSH 4.6-10 mU/L)?

4. Are any benefits offset by adverse effects, such as atrial fibrillation or heart failure?

5. To store study blood samples in a repository of blood samples from which potential biomarkers and/or genes may be identified that better predict those older people with SCH who are at risk of dying or developing ill-health, including cardiovascular and cerebrovascular disease.

Study design:

Randomised double-blind placebo-controlled parallel group trial. The IEMO 80-plus thyroid trial was set up as a an independent randomised double-blind placebo-controlled parallel group trial of levothyroxine for oldest old persons with subclinical hypothyroidism. From the outset the study was designed jointly and in parallel with the TRUST trial and both trials share a near identical design and infrastructure including study protocols, standard operating procedures, independent data monitoring and endpoint committees, databases, statisticians and study nurses.

Study population:

145 community-dwelling patients aged >80 years with subclinical hypothyroidism, diagnosed on the basis of persistently elevated TSH levels, measured on a minimum of two occasions at least 3 months apart, over 2 years.

Intervention:

Oral Levothyroxine 50 µg daily (reduced to 25 mcg daily in

subjects < 50 kg body weight or if known coronary heart disease) versus matching placebo.

Primary study parameters/outcome of the study:

The main study endpoint is change in thyroid-specific quality of life and symptom burden assessed using the hypothyroid symptoms scale score and tiredness symptoms scale score on the thyroid-specific quality of life (ThyPRO) questionnaire at baseline, six to eight weeks and 12 months after recruitment and at the close-out visit are included.

Secundary study parameters/outcome of the study:

1. General quality of life;

2. Handgrip strength;

3. Cognitive function, particularly executive function;

4. Total mortality and cardiovascular mortality;

5. Functional ability (basic Activities of Daily Living (ADL);

extended activities of daily living);

6. Gait speed;

7. Haemoglobin;

8. Depressive symptoms ;

9. Fatal and non-fatal cardiovascular events (this will include acute myocardial infarction; stroke; amputations for peripheral vascular disease; revascularisations for atherosclerotic vascular disease, including for acute coronary syndrome and heart failure hospitalisations).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

Adverse events (atrial fibrillation, heart failure and fractures in particular) are likely to occur only in the context of over replacement of Levothyroxine. Our dose titration scheme and study processes of careful monitoring of thyroid function tests are designed to ensure we avoid prolonged periods of thyroid hormone excess.For the group allocated to placebo, there is risk of developing overt clinical hypothyroidism; however, our study processes of careful monitoring of thyroid function tests are designed to avoid this scenario.

Statistical analysis:

The participants of the present project will be included in a pre-planned combined analysis with the international TRUST consortium, of which the LUMC is the Dutch member (protocol number P12.203), who includes a total number of 738 participants over the age of 65 years. The present project adds 145 80-plus year old participants to perform an adequately powered sub-group analysis in the over eighties age group. The main analysis will be the association between thyroid specific quality of life and treatment in the combined study population of IEMO and the 80-plus participants of TRUST. Treatment effects will be assessed using analysis of covariance (ANCOVA) adjusting for gender and baseline levels of the same variable. To assess for associations with cardiovascular events, time to first event Cox regression analysis are used stratified by gender in models containing the randomised treatment allocation as a covariate (intention-to- treat). Tests of treatment effect will be based on the Wald test and corresponding point estimates and 95% confidence intervals for the hazard ratio for treatment will be calculated. The assumption of proportionality of hazards will be tested. Additional end points relevant to older people will be assessed for the present study alone and in combination with the 80-plus participants in TRUST.

Doel van het onderzoek

1. Does Levothyroxine treatment for subclinical hypothyroidism give multi-modal benefits for the oldest old people with subclinical hypothyroidism?

2. Are benefits seen across a wide range of outcomes, including prevention of cardiovascular disease, and improving health-related quality of life, muscle function and cognition?

3. Are benefits seen in specific subgroups of oldest old people with subclinical

hypothyroidism, including women, and those with mild degrees of subclinical hypothyroidism (TSH 4.6-10 mU/L)?

4. Are any benefits offset by adverse effects, such as atrial fibrillation or heart failure?

5. To store study blood samples in a repository of blood samples from which potential biomarkers and/or genes may be identified that better predict those older people with SCH who are at risk of dying or developing ill-health, including cardiovascular and cerebrovascular disease.

Onderzoeksopzet

The primary outcome will be assessed at baseline, six to eight weeks and 12 months after recruitment and eventually at 24 and 36 months.

Onderzoeksproduct en/of interventie

Oral Levothyroxine 50 µg daily (reduced to 25 mcg daily in subjects < 50 kg body weight or if known coronary heart disease) versus matching placebo. The intervention will have a maximum of 3 years.

Contactpersonen

Publiek

P.O.Box 9600
Simon Mooijaart
Leiden University Medical Center
Dept. of Gerontology and Geriatrics
C-02-R
Leiden 2300 RC
The Netherlands
+31 (0)71 5266640

Wetenschappelijk

P.O.Box 9600
Simon Mooijaart
Leiden University Medical Center
Dept. of Gerontology and Geriatrics
C-02-R
Leiden 2300 RC
The Netherlands

+31 (0)71 5266640

Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

Community-dwelling patients aged >80 years with SCH.

SCH is defined as persistently elevated TSH levels (>4.6 and ≤19.9 mU/L) and free thyroxine (fT4) in reference range measured on a minimum of two occasions at least 3 months apart.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Subjects currently on Levothyroxine or antithyroid medication (e.g. Carbimazole, methimazole, propylthiouracil, potassium percholate), amiodarone or lithium;

2. Recent thyroid surgery or radio-iodine therapy (within 12 months);

3. Grade IV NYHA heart failure;

4. Prior clinical diagnosis of dementia;

5. Recent hospitalisation for major illness (within 4 weeks);

6. Recent acute coronary syndrome, including myocardial infarction or unstable angina (within 4 weeks);

7. Acute myocarditis ore acute pancarditis;

8. Untreated adrenal insufficiency;

9. Terminal illness;

10. Patients known to have rare hereditary problem of galactose intolerance;

11. Subjects who are participating in ongoing RCTs of therapeutic interventions (including clinical trials of investigational medicinal products [CTIMPs]);

12. Plan to move out of the region in which the trial is being conducted within the next 2 years (proposed minimum follow-up period).

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Dubbelblind
Controle:	Placebo

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	13-05-2014
Aantal proefpersonen:	145
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Ethische beoordeling

Positief advies

Datum:	12-02-2013
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL3681
NTR-old	NTR3851
Ander register	EudraCT : 2012-004160-22
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Resultaten

Samenvatting resultaten
Trial Results
Mooijaart SP, Du Puy RS, Stott DJ, Kearney PM, Rodondi N, Westendorp RGJ, den Elzen WPJ, Postmus I, Poortvliet RKE, van Heemst D, van Munster BC, Peeters RP, Ford I, Kean S, Messow CM, Blum MR, Collet TH, Watt T, Dekkers OM, Jukema JW, Smit JWA, Langhorne P, Gussekloo J. Association Between Levothyroxine Treatment and Thyroid-Related Symptoms Among Adults Aged 80 Years and Older With Subclinical Hypothyroidism. JAMA. 2019 Oct 30:1-11. doi: 10.1001/jama.2019.17274. [Epub ahead of print] PubMed PMID: 31664429; PubMed Central PMCID: PMC6822162.

Methods paper
Du Puy RS, Postmus I, Stott DJ, Blum MR, Poortvliet RKE, Den Elzen WPJ, Peeters RP, van Munster BC, Wolffenbuttel BHR, Westendorp RGJ, Kearney PM, Ford I, Kean S, Messow CM, Watt T, Jukema JW, Dekkers OM, Smit JWA, Rodondi N, Gussekloo J, Mooijaart SP. Study protocol: a randomised controlled trial on the clinical effects of levothyroxine treatment for subclinical hypothyroidism in people aged 80 years and over. BMC Endocr Disord. 2018 Sep 19;18(1):67. doi: 10.1186/s12902-018-0285-8. PubMed PMID: 30231866; PubMed Central PMCID: PMC6146605.