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PROJECT FINAL REPORT

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Project acronym: TRUST

Project title: Multi-modal effects of Thyroid hormone Replacement for Untreated older adults with Subclinical hypothyroidism; a randomised placebo-controlled Trial

Funding Scheme: THEME [HEALTH.2011.2.2.2-1]; Investigator-driven clinical trials for therapeutic interventions in elderly populations

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Project website Error! Bookmark not defined. **address:**

Public website - www.trustthyroidtrial.com; investigators web portal - www.trusttrial.org

[1] Usually the contact person of the coordinator as specified in Art. 8.1. of the Grant Agreement.

4.1 Final publishable summary report

Executive summary (1 page):

Background

The use of levothyroxine to treat subclinical hypothyroidism is controversial. We aimed to determine if levothyroxine gives clinical benefits for older people with this condition.

Methods

We screened 2647 subjects with biochemical evidence of subclinical hypothyroidism for possible participation in a double-blind randomised placebo-controlled parallel group trial. We randomised 737 adults aged ≥65 years with persisting subclinical hypothyroidism (thyroid stimulating hormone (TSH) 4.60-19.99 mIU/L and free thyroxine levels within laboratory reference range); 368 were allocated to levothyroxine, starting dose 50 µg daily (25 µg if weight <50Kg or coronary heart disease) with dose titration according to TSH level; 369 were allocated to placebo with mock titration. Co-primary outcomes were change in Hypothyroid Symptoms and Tiredness scales of the thyroid-related quality of life questionnaire (ThyPRO) at one year.

Results

Mean age of recruits was 74.4 years with 396 (53.7%) women. Baseline TSH was 6.40 (SD 2.01) mIU/L, reducing to 5.48 at 1 year in the placebo group, and 3.63 mU/L in the levothyroxine group ($p<0.001$) with median dose of 50 µg. We found no differences in the 1-year change in Hypothyroid Symptoms scores (0.2, SD [14.4] in the placebo group versus 0.2 [14.4] with levothyroxine, 95% CI for between-group difference -2.03, 2.06) or Tiredness scores (3.2 [17.7] and 3.8 [18.4], 95% CI: -2.11, 2.87). No beneficial effects of levothyroxine were seen on secondary outcome measures and there was no significant excess of Serious Adverse Events pre-designated as of special interest. A study biobank (blood samples at baseline and 1 year) was established

Conclusions

Levothyroxine gave no benefits for older people with subclinical hypothyroidism; we concluded that this intervention should not be routinely prescribed to older people with this condition. The primary manuscript arising from this work is published in the New England Journal of Medicine, 4th April 2017, and the results were launched the same day at the Endocrine Society Meeting in Orlando USA. This work has attracted considerable media attention including the New York Times in the USA. The study biobank will support future research on the biology of ageing and thyroid disease.

Summary description of project context and objectives (not exceeding 4 pages).

Subclinical hypothyroidism (SCH) is a common condition (8-18%) among European older men and women. Although by definition SCH comprises biochemically mild thyroid hormone deficiency without overt symptoms, it is a likely contributor to multiple problems in older age. Thyroid hormone has multiple pleiotropic effects on numerous physiological systems, including the vascular tree, heart, skeletal muscle and brain. Therefore, levothyroxine substitution to overcome thyroid hormone deficiency has the potential to give multi-system benefits to older people with SCH. Small studies have reported reduced atherosclerosis and improved cardiac 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.

We have completed a multicentre randomised placebo-controlled trial to assess the impact of levothyroxine in older adults with persisting SCH (excluding those in whom it is a temporary phenomenon who are less likely to benefit).

Principle research questions and objectives:

- Does thyroxine treatment for SCH give multimodal benefits for older people with SCH?
- Are benefits seen across a wide range of outcomes, including improving health-related quality of life, prevention of cardiovascular disease, and muscle function and cognition?
- Are benefits seen in specific subgroups of older people with SCH, including women, very elderly and those with mild degrees of SCH?
- Are any benefits offset by adverse effects, such as atrial fibrillation or heart failure?

Secondary research questions and objectives:

- To establish a strong European network of complementary research expertise on SCH in older people, including geriatric medicine, endocrinology and metabolic medicine, primary care, cardiovascular disease and biostatistics.
- To link this research expertise with strong focus on patient perspective and needs.
- To provide the necessary evidence to properly inform best practice for treatment of SCH in older people.
- To disseminate this evidence to healthcare practitioners and patients.

- To improve clinical practice in management of SCH in older people.
- To improve health and wellbeing of older people with SCH.
- To establish a blood biobank, to be used in future research into causes and mechanisms of health, disease and disability in later life.
- To determine the association of thyroid function with long-term risk of future illness and mortality in older people, using record linkage for the screenees.

Description of the work performed since the beginning of the project and the main results:

Work package 1: Consortium Management

The study was coordinated from an administrative office (in Glasgow). The central steering committee met regularly over the course of the grant funding period.

Membership was established, charters put in place and systems of working established for both the Endpoint committee and the Independent Data and Safety Monitoring Committee (IDMC).

Systems were put in place to ensure all ethics and drug regulatory authority and sponsor approvals were secured and up to date.

Work package 2: Screening and recruitment

Systems were established in all four member / associated states to use laboratory databases to identify potential study patients (over 65s with biochemical test results consistent with persisting SCH). Over 3000 General Practices were invited to participate in the study, and over 1000 agreed to take part. At the close of recruitment in December 2015 we had screened 2,647 patients and enrolled 737 patients into the TRUST trial.

Work package 3: Patient randomisation, treatment and follow up

The randomisation schedule was prepared and maintained by the Robertson Centre for Biostatistics in Glasgow; it was communicated to and implemented by Mawdsley Brooks (who packaged and labelled levothyroxine and placebo). Patient allocation was conducted by the trial web portal by study nurses at the time of the baseline study visit.

A total of 369 patients were assigned to receive placebo, and 368 to receive levothyroxine. Of these 337 and 332 respectively were included in the 12 month follow up, with median dose of levothyroxine 50μg; 187 patients in the placebo group and 194 in the levothyroxine group continued in the trial beyond 12 months with follow-up of median duration of 24.2 months from study baseline.

Electronic record systems (approved by the study sponsors) were established for pharmacovigilance reporting to appropriate regulatory authorities within each Member / Associated State.

Work package 4: Data management and biostatistics

A trial web portal was established, including functionality for data handling (including electronic clinical record forms), data query resolution, drug supply management, endpoint adjudication facilitation and documentation and report dissemination.

The trial web portal is in English, however, for patient questionnaires these were also prepared in local languages (Dutch, German and French). The electronic clinical record forms (eCRF) were developed to allow direct data entry by the study research assistants / nurses onto networked laptops or PCs. Data were transferred to the data centre in Glasgow via the trial web portal. Systems were put in place to allow data queries to be flagged to the sites for correction.

After full checking of study data, the database was closed on 12th January.

The initial statistical analysis was performed in time for discussion of the results at the Investigator conference on 16-17 January 2017, and was further refined as per the New England Journal of Medicine requirements, enabling publication of the primary manuscript on 4th April 2017.

Work package 5: Thyroid function analysis

A general system and process of information transfer for thyroid function tests (TFTs) results from participating laboratories to the data centre was established.

In total 2647 screening TFTs of patients with previously elevated TSH (4.6-19.99 mIU/litre) were performed by the close of recruitment in December 2015. Of these 1645 (62%) showed reversion of TSH level to <4.60 mIU/litre; this was the main reason that screened patients were excluded from the trial.

In those randomised to the trial mean TSH level was 6.40 (SD 2.01) mIU per litre at baseline. Treatment with levothyroxine was associated with a persistent reduction in the serum TSH level of approximately 2 mIU per liter, as compared with placebo, with the maximum effects seen at time of first review (6 to 8 weeks). At 1 year, the TSH level had decreased to 5.48 mIU per litre in the placebo group, as compared with 3.63 mIU per litre in the levothyroxine group (P<0.001). A similar reduction persisted at extended follow-up (at median of 24.2 months). Free thyroxine level was 2.3 pmol per litre higher in the levothyroxine group than in the placebo group both at 6 to 8 weeks and at 12 months (P<0.001 for both comparisons).

Work package 6: Medicine manufacture, packaging and distribution

Medicines were manufactured and provided by Merck KGaA (donation free of charge). Packaging, labelling and distribution is performed by Mawdsley Brooks (approved subcontract). Technical Agreements with both of these companies were put in place. Pharmacy support was arranged in all countries, supported by an electronic drug management system (developed by the Robertson Centre for Biostatistics). Resupply of blistered and packaged medicines, and appropriate regulatory approvals were put in place in time to ensure no gaps in supply throughout the study. Supplies of medicines were put in place to enable treatment until date of last patient out of the study (17th November 2016).

Work package 7: Dissemination and transfer of knowledge

Language-specific website content was developed and posters and newsletters produced in English, Dutch, French and German.

The TRUST study protocol has been published (Stott et al. BMC Endocrine Disorders 2017;17:6 DOI 10.1186/s12902-017-0156-8) and the primary manuscript was published in the New England Journal of Medicine on 4th April 2017, at the same time as the launch of the results at the Endocrine Society Meeting in Orlando USA.

There has been substantial media interest in the results of the study, due to the major implications for clinical guidelines and practice.

Description of the main S&T results/foregrounds (not exceeding 25 pages)

Methods

Study overview

We conducted the clinical phase of the research between 11th March 2013 and 17th November 2016 in primary care practices and academic centres in 4 countries (United Kingdom, Ireland, the Netherlands and Switzerland). The lead study sponsor was University of Glasgow / Greater Glasgow Health Board (UK), with each other country also having their individual sponsor.
The trial protocol was approved by the relevant ethics committees and regulatory authorities in all countries. All subjects provided written informed consent for participation.
The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The Robertson Centre for Biostatistics at the University of Glasgow was the study data and biostatistics centre.
The European Union (FP7) provided the primary financial support for the conduct of the study. Supplies of levothyroxine and matching placebo were provided free of charge by Merck KGaA.

Participants

Potential subjects were identified from clinical laboratory and General Practice databases and records; inclusion criteria were age ≥65 years with persistent subclinical hypothyroidism defined as elevated TSH levels (4.60-19.99 mIU/L) measured on a minimum of two occasions 3 months to 3 years apart with free thyroxine fT4 levels within the reference range.
The main exclusion criteria for the study were; subjects currently prescribed levothyroxine, anti-thyroid drugs, amiodarone or lithium; thyroid surgery or radio-iodine within 12 months; clinical diagnosis of dementia; hospitalisation for major illness or elective surgery within 4 weeks; acute coronary syndrome (including myocardial infarction or unstable angina) within 4 weeks; terminal illness.

Study Design and treatment

This was a randomised double-blind parallel group trial of levothyroxine versus placebo (allocated 1:1) with stratification by national site, sex and starting dose, using randomly permuted blocks. Randomisation was performed by an independent party at the data centre using a web-based algorithm. Implementation was also by an independent party, Mawdsley Brooks UK, who were

responsible for packaging and labelling of the study medication. Allocation of study number was performed by central computer, with the decision triggered by study nurses using a dedicated website following entry of eligibility data on an electronic clinic record form. Patients, their usual medical providers, study personnel, investigators, adjudicators and statisticians were blinded to treatment allocation.

The active intervention started with levothyroxine 50 µg daily (reduced to 25 µg in subjects <50 kg body weight or if known coronary heart disease (previous myocardial infarction or symptoms of angina pectoris) versus matching placebo for 6-8 weeks. The dose was adjusted to achieve TSH level within the reference range (0.40-4.59 mIU/L) as follows; 6-8 weeks after randomisation a blood sample was taken for serum TSH, with three possible actions:

- TSH < 0.40 mIU/L: levothyroxine dose reduced to 25 µg in those starting on 50 µg and replaced with placebo in those starting on 25 µg; if TSH remained < 0.40 mIU/L after 4-6 weeks, the patient was withdrawn from randomised treatment.
- TSH 0.40-4.59 mIU/L: no change to the levothyroxine dose; patient to be reviewed at 12 months.
- TSH ≥ 4.60 mIU/L: additional 25 µg levothyroxine.

Titration of levothyroxine dose (in 25 µg increments or decrements) against serum TSH was repeated up to a maximum of two occasions at 6-8 week intervals, with a check of serum TSH performed at 6-8 weeks after all dose titrations. A mock titration was performed in the placebo group using an adaptive schedule, in which the data centre allocated (by computer algorithm) the same proportion of placebo patients to dose adjustment (up or down) as required in the levothyroxine group (followed by check of TSH at 6-8 weeks as above). The above process (but with only a single titration step) was repeated at the 12-month review, then annually. The maximum dose of levothyroxine that could be prescribed was 150 µg. All dose titrations were generated and executed by computer, without intervention of a physician. The participants, investigators, and treating physicians remained blinded to the results of TSH measurements throughout the course of the study, as TSH results at each visit were directly sent to the data centre, without being available to the local investigators.

Study procedures and endpoints

The co-primary outcomes for the study were change from baseline to 12 months in the Thyroid-related quality of life Patient-Reported Outcome measure (ThyPRO) Hypothyroid Symptoms score (4 items) and Tiredness scores (7 items) (range 0-100, more symptoms and tiredness with higher scores). The ThyPRO and other instruments were administered in English, French, German or Dutch as appropriate. Initially we planned for cardiovascular events and thyroid specific quality of life to be co-primary outcomes, however this was modified during the study (as per the latest version of Annex 1 in June 2016) to thyroid specific quality of life as primary outcome and cardiovascular events as a secondary outcome when it became apparent that the study would be underpowered for cardiovascular events due to delays and difficulties in recruitment. Fatal and non-fatal cardiovascular events were recorded (acute myocardial infarction; stroke; amputations for peripheral vascular disease; revascularisations for atherosclerotic vascular disease, including for acute coronary syndrome; and heart failure hospitalisations), as were total and cardiovascular mortality. Clinical endpoints were judged by an independent Endpoints Committee blinded to treatment allocation.

Other secondary study outcomes included changes from baseline in generic health-related quality of life (EuroQol-5D), comprehensive thyroid-related quality of life (ThyPRO-39 scores – available only at final follow-up), handgrip strength (Jamar isometric dynamometer - best of 3 measures in dominant hand), executive cognitive function (letter digit coding test), blood pressure (systolic and diastolic), weight, body mass index, waist circumference, activities of daily living as measured by the Barthel index, Instrumental Activities of Daily Living and fatal and non-fatal cardiovascular events. Minimum follow-up was 1 year and maximum 3 years.

Laboratory methods

All TSH and free thyroxine assays were undertaken in accredited clinical laboratories in each country with adherence to external quality controls schemes, using conventional methods and quality control systems which conform to international standards. A total of 18 laboratories performed thyroid function tests for the study (baseline and in-trial measures); this included one laboratory in the UK, 2 in Switzerland, 2 in Ireland and 13 in Netherlands. All measures of TSH and free thyroxine were made by immunoassay, using established methods. A total of 10 laboratories used a Cobas (Roche) method (6000 or 8000 and e601 or e602); 6 laboratories used Architect (Abbott); one laboratory used UniCel DxL (Beckman); one used Immulite 2000XPI (Siemens; for TSH) and Vitros ECiQ (Ortho Clinical Diagnostics; for free thyroxine).

Repeated TSH (and free thyroxine when available) measurements within one patient were always performed using the same method for that individual.

Statistical Analysis

All efficacy and safety analyses were carried out on a modified intention to treat population as the primary analyses; this population was defined as those participants randomised (excluding those randomised in error), for whom data was available on the outcome of interest. For analyses at the 12 month visit to be valid, they must have been conducted at 12 months ± 31 days after randomisation. These analyses were supported with sensitivity analyses for missing data using mixed effects models and multiple imputation. Analyses were repeated on the per protocol population as exploratory analyses.

Per-protocol populations consisted of all participants in the modified intention to treat population who fulfilled the following criteria;

- Data were available for the outcome variable of interest.
- Subject was on treatment at the time of the analysis being conducted, i.e. they had not withdrawn from treatment and, if they are in the active treatment group, they have not been down-titrated to 0µg dose.
- Subjects had their 12 month visit at 12 months ± 31 days after randomisation.
- There was no other major protocol violation identified prior to database lock.

The methods of analysis of continuous efficacy outcomes involving measurements at baseline and follow-up were analysed at each time point comparing treatment groups and adjusting for stratification variables (site, sex and starting dose of levothyroxine) and baseline levels of the same variable using multivariate linear regression. In addition, data items measured at more than one time point (including at the final assessment) were analysed using repeated measures regression analyses. Time-to-event outcomes were compared between groups using Cox proportional hazards regression models adjusting for stratification variables. Time-to-event curves were based on the Kaplan-Meier method.

Patients withdrawn from treatment continued to be followed up for the modified intention to treat analysis. These analyses were supported with sensitivity analyses using mixed effects models and multiple imputations for missing data. The primary and secondary outcomes at 12 months were also analysed for pre-defined subgroups by sex and baseline TSH. Analyses were repeated on the per-protocol population (subjects who remained on trial medication as per study protocol).

The Hypothyroid Symptoms and Tiredness scores from the ThyPRO were co-primary outcomes, with the required p-value for statistical significance split equally to each (0.05/2=0.025 to each test). We assumed standard deviations (SDs) for data at 1 year (adjusted for baseline) of 13.3 and 18.3 (100-unit scales) respectively; this gave us 80% power to detect a change with levothyroxine treatment (versus placebo) of 3.0 on the Hypothyroid Symptoms score and 4.1 on the Tiredness score with our revised maximum expected number of subjects recruited of 750, and 3.5 and 4.9 respectively with our minimum expected number of 540.

Patient safety and adverse events recording

Adverse events were assessed, managed, recorded, reported, notified and analysed in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended). Adverse events of special interest included new atrial fibrillation, heart failure, fractures and new diagnosis of osteoporosis. The ThyPRO Hyperthyroid Symptoms scale was recorded as a possible adverse event.

Summary of changes to protocol during the running of the trial

Reduction in study sample size and removal of incident vascular events as a co-primary outcome measure:

In the initial study plans we aimed to recruit 3,000 community dwelling subjects aged 65 years or over with SCH. This sample size was justified by power calculations based on a reduction of vascular events. At the start of the clinical trial vascular events were designated as a co-primary outcome along with the Hypothyroid Symptom and Fatigue domains from the Thyroid-related Quality of Life patient-reported outcome measure (ThyPRO).

Due to a combination of factors we were unable to achieve 3,000 recruits. Study recruitment targets therefore were revised in October 2014 (by when 290 patients randomised) with an anticipated minimum of 540 to be randomised; with an upscaling of geographical areas for recruitment in all countries we anticipated an increase up to a maximum of 750 patients randomised. Given the projections for recruitment, revised power calculations were calculated for the Hypothyroid Symptom and Fatigue domains from ThyPRO. We determined the study power for a minimum total recruitment number of 540 and a maximum number of 750. Incident cardiovascular disease was demoted to a secondary outcome as there was limited statistical power for this outcome with the

reduced recruitment numbers. The EU was fully informed of these amendments, which were approved in a revised Annex 1 submitted in June 2016.

Hypothyroid Symptom and Fatigue domains from the Thyroid-related Quality of Life patient-reported outcome measure (ThyPRO) remained as primary efficacy outcomes. In view of their importance for the trial, power calculations for the trial were revised for these outcomes. We calculated 80% power to detect a change with Levothyroxine treatment (versus placebo) of 3.5 or 3.0 points on the hypothyroid scale and 4.9 or 4.1 points on the fatigue / vitality scale with total sample sizes of 540 or 750 respectively, with the required p-value for statistical significance split equally to each (0.05/2=0.025 to each test).

Thyroid-specific quality of life:

ThyPRO-39 was added to the study protocol as a secondary outcome, late in the conduct of the trial but prior to conduct of subject final visits. This measure was made at subject final visit only. It provides a short validated generic assessment of thyroid-specific quality of life.

All these amendments were approved by the relevant local ethics committees.

Results

Trial population

We screened 2647 community-dwelling individuals aged ≥65 years identified as having biochemical subclinical hypothyroidism for possible inclusion; 737 subjects were randomised into the trial, of whom 369 were allocated to placebo and 368 to levothyroxine. Baseline characteristics were similar in the two groups.

A total of 337 (91.3%) subjects randomized to the placebo group completed 12-month follow-up, compared to 332 (90.2%) in the levothyroxine group. Median follow-up duration for all randomised subjects (including withdrawals) was 17.3 months (Lower Quartile 12.0, Upper Quartile 24.4) in the placebo group, and 18.0 months (11.0, 25.4) in the levothyroxine group.

Thyroid function tests

Mean baseline TSH was 6.40 (SD 2.01) mIU/L. TSH levels were significantly reduced from baseline in the levothyroxine group compared to placebo at all time points of review with a mean difference of 2.29 miU/L at 6-8 weeks after randomization ($p<0.001$). At 12 months TSH was 5.48 (2.48) in the placebo group, and 3.63 (2.11) in the levothyroxine group, a between group difference

of 1.92 miU/L (p<0.001). There was a significant treatment by visit interaction (p=0.03) with reduction in TSH greatest at 6-8 weeks.
Free thyroxine levels were not routinely measured in-study, however data were available for a subset of patients; between group differences were 2.3 pmol/L higher levels in the levothyroxine group at both 6-8 weeks and 12 months (both p<0.001).

Thyroid-specific quality of life

Hypothyroid Symptoms score at 12 months (adjusted for baseline) was 16.7 (SD 17.5) in the placebo group and 16.6 (16.9) in the levothyroxine group (p=0.99); respective Tiredness scores were 28.6 (19.5) and 28.7 (20.2) (p=0.77). There were also no significant between group differences in either of these measures at 6-8 weeks. There was a small magnitude reduction in Tiredness score with levothyroxine (-3.49; p=0.05) at the extended follow-up review. Pre-specified analyses by sex and baseline TSH did not reveal any subgroups who benefited from treatment. Per-protocol analyses and sensitivity analyses using multiple imputation of missing values showed no statistically significant differences between levothyroxine and placebo.

Other outcome measures

The EuroQol 5-D showed a small deterioration at 12 months (mean difference -0.025; p=0.05), but a minor improvement at extended follow-up (mean difference 0.040; p=0.026) in the levothyroxine group compared to the placebo group, but with no between-group differences at 6-8 weeks. There were no significant between-group differences in the EuroQol visual analogue scale.
No significant effects were seen in any of the other secondary outcome measures, either in the modified intention to treat or per protocol analyses or for pre-specified subgroups.

Adverse effects and events

We found no change in hyperthyroid symptoms (ThyPRO) with levothyroxine compared to placebo, at any time-point. The incidence of Serious Adverse Events of special interest (atrial fibrillation, cardiac failure, fractures or new diagnosis of osteoporosis) was similar in the two groups. The number of patients with at least one Serious Adverse Events was slightly higher in the placebo group (p=0.049) as was the total number of Serious Adverse Events, however we observed no pattern of event type that contributed to this difference; the proportion of patients withdrawing from treatment or follow-up were similar in the two groups.

Discussion

In this large multi-center double-blind randomised placebo-controlled parallel group trial of older subjects with subclinical hypothyroidism, treatment with levothyroxine achieved a persistent reduction in serum TSH levels of around 2 mIU/L compared to placebo with maximum effects seen at time of first review (6-8 weeks). Despite these biochemical changes we found levothyroxine had no consistent beneficial effect on thyroid symptomatology. This was true for both older men and women, and for different levels of baseline TSH. Our study had good statistical power to detect a clinically meaningful effect on thyroid-related health-related quality of life, with 95% confidence intervals excluding a beneficial effect greater than 2.1 points (0-100 scale) in either of our co-primary outcomes. If symptom benefit was to have occurred, it would be expected to be seen at 12 months. The subsequent small magnitude reduction in tiredness with levothyroxine in the subgroup who had extended follow-up is likely to be a chance finding.

Levothyroxine treatment yielded no significant beneficial effects on a range of secondary outcome measures. We found a slight deterioration (of borderline statistical significance) in the EuroQol 5D score with levothyroxine at 12 months, but an improvement in the subgroup who completed extended follow-up (at median of 24.5 months). The effects seen were in opposite directions at these different time-points, and were of very small magnitude (-0.025, 0.040 respectively) and therefore these are likely to be random chance findings. No effect of treatment was seen on the EuroQol visual analogue scale. Therefore, it appears that levothyroxine had no clinically significant effects on generic health-related quality of life.

Muscle function has been claimed to be adversely affected by underactive thyroid. However, we found handgrip strength showed no change with levothyroxine treatment. Similarly it has been suggested that speed of information processing is slowed in subclinical hypothyroidism, however we found no benefit on executive cognitive function as measured by the letter digit coding test. There also was no effect of treatment on blood pressure, weight, waist circumference, body mass index, Barthel Index or Instrumental Activities of Daily Living scores.

Patients were monitored closely for adverse effects from levothyroxine treatment. We found no increase in hyperthyroid symptoms after starting treatment, and there was no significant excess of Serious Adverse Events of special interest including atrial fibrillation, cardiac failure, fractures or

new diagnosis of osteoporosis. The slight excess of patients with Serious Adverse Events in the placebo group we believe to be a chance finding, spread amongst a range of body systems with no particular pattern observed.

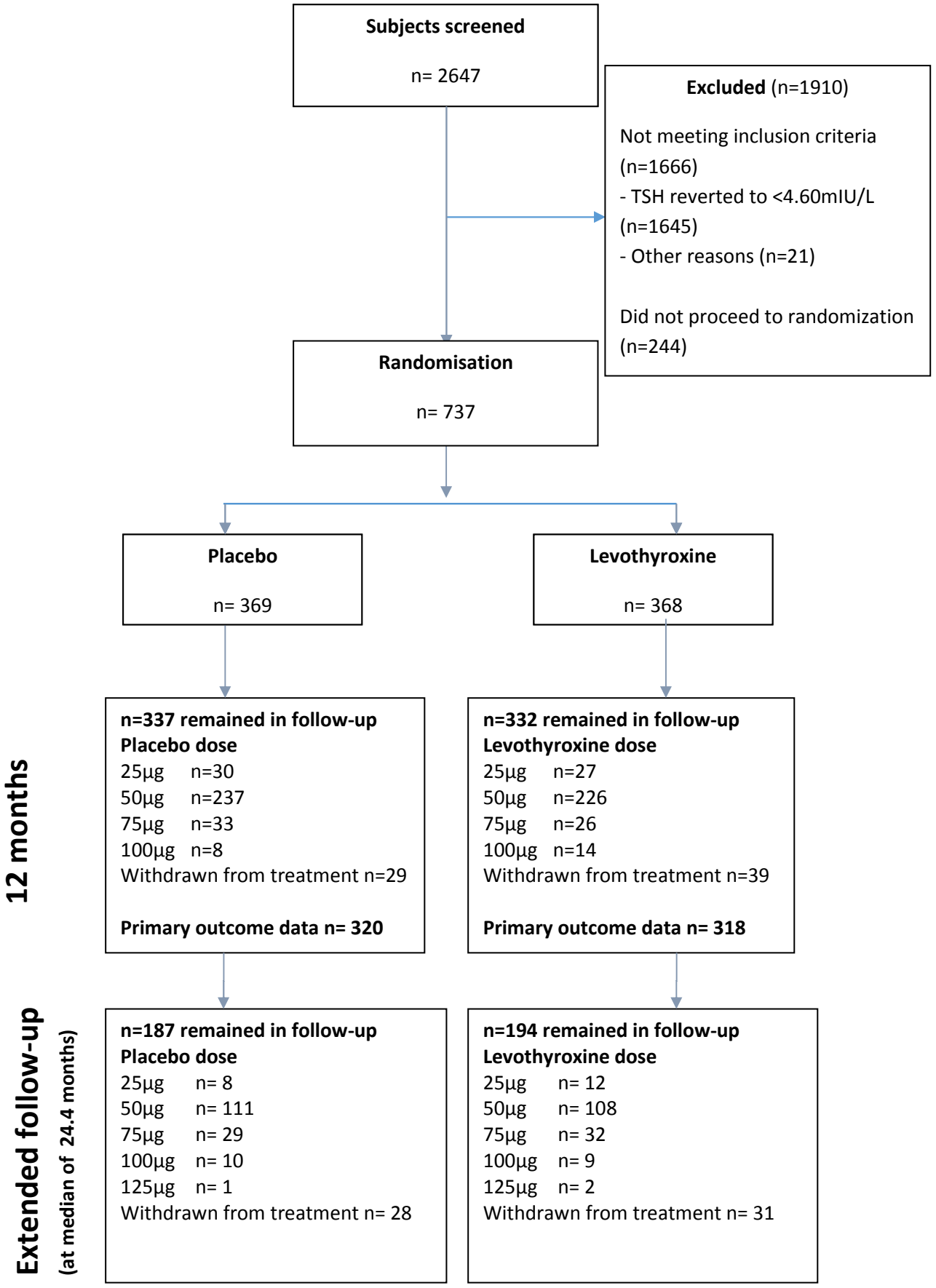
It is clear that many older people with biochemistry consistent with subclinical hypothyroidism will revert to euthyroid state if followed-up without treatment. In total around three-in-five of those that we screened for entry to the study on the basis of previously elevated TSH levels reverted to normal thyroid biochemistry and were therefore excluded from the trial. These data are consistent with several other observational and trial cohorts showing a high proportion of subjects with elevated TSH reverting to biochemical euthyroidism during follow-up.

Our study has a number of strengths. We recruited by far the largest study cohort to-date and our study has good statistical power to exclude symptomatic benefit. We used validated measures of thyroid-specific quality of life that have been shown to be sensitive to change as well as a range of secondary outcomes of clinical relevance. However, there are also a number of limitations. There were few participants with baseline TSH >10mIU/L and so we cannot address whether there are benefits from treatment in this subgroup. The symptom levels at study entry were low, and so we cannot exclude the possibility of benefit in individuals with more marked complaints. We do not have measurements of thyroid antibody levels, which might help identify a subgroup of patients who would benefit from treatment. Lastly, our trial was underpowered to detect any impact of levothyroxine on cardiovascular events or mortality. Therefore, we cannot exclude the possibility that treatment with levothyroxine may provide cardiovascular protection (or cause harm).

Conclusions

We found that treatment with levothyroxine for elderly patients with subclinical hypothyroidism gave no symptomatic benefits. This study provides evidence that levothyroxine should not be routinely prescribed to older people with this condition.

Figure. Flow of participants through the study and doses of levothyroxine

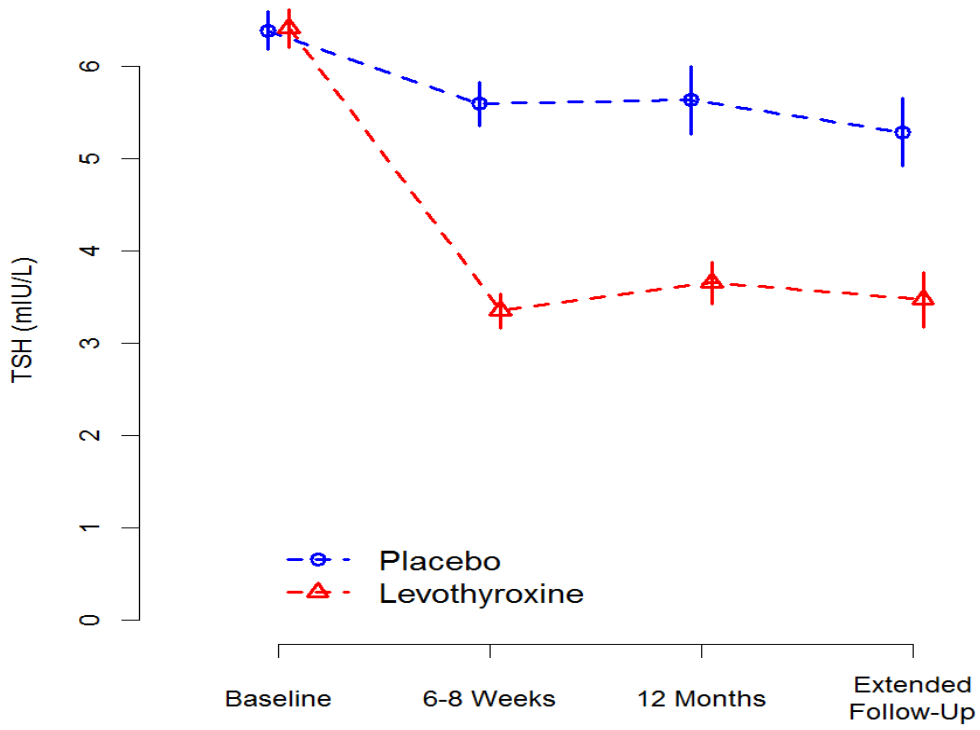


Footnotes

Exclusions for 'other reasons' included; 17 – anti-thyroid medication, 1 – recent thyroid surgery, 1 recent acute coronary syndrome, 1 – currently in trial, 1 – adrenal insufficiency; 2 patients excluded as TSH reverted to <4.60mIU/L also had an additional exclusion of galactose intolerance.

Extended study follow-up beyond 12 months was in a subgroup of patients, in the placebo group at a median of 24.2 months (lower quartile, upper quartile 18.4, 30.3) from study baseline, and in the levothyroxine group at 24.5 months (IQR 18.4, 30.5).

Figure. TSH in placebo and levothyroxine groups (modified intention to treat analysis).



Number of patients with TSH results				
Placebo	369	355	313	180
Levothyroxine	368	350	317	191

Footnotes:

Data are mean and 95% CI.

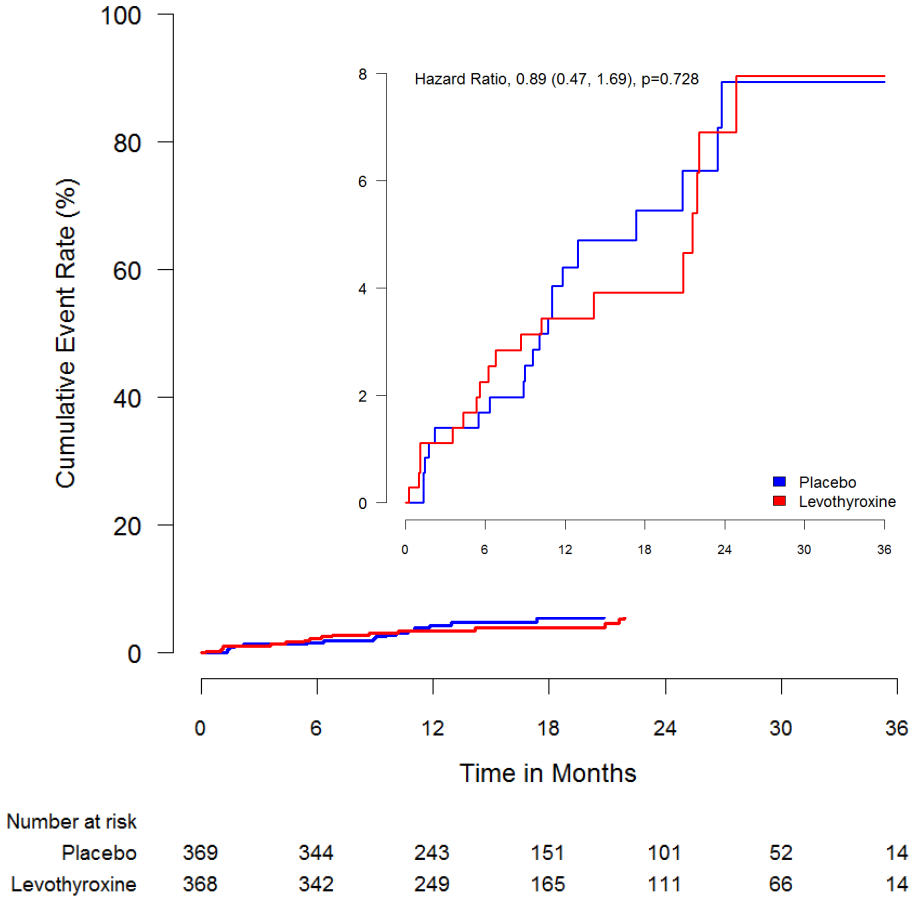
Extended study follow-up beyond 12 months was in a subgroup of patients, in the placebo group at a median of 24.2 months (lower quartile, upper quartile 18.4, 30.3) from study baseline, and in the levothyroxine group at 24.5 months (IQR 18.4, 30.5).

Table. Baseline characteristics of the study participants.

	Placebo (n=369)	Levothyroxine (n=368)
Demographics		
Age (years) [mean, SD and range]	74.8 (6.8) [65.1-93.4]	74.0 (5.8) [65.2-93.0]
Female sex	198 (53.7%)	198 (53.8%)
White race	362 (98.1%)	362 (98.4%)
Standard housing	356 (96.5%)	358 (97.3%)
Previous medical conditions / clinical descriptors		
Ischaemic heart disease	50 (13.6%)	50 (13.6%)
Atrial fibrillation	44 (12.0%)	45 (12.4%)
Hypertension	183 (50.0%)	192 (52.2%)
Diabetes mellitus	54 (14.7%)	63 (17.1%)
Osteoporosis	47 (12.8%)	41 (11.3%)
Current smokers	33 (8.9%)	29 (7.9%)
Number of concomitant medicines [median and lower quartile, upper quartile]	4 (2, 6)	4 (2, 6)
Mini-mental state examination [median (lower quartile, upper quartile)]	29 (28, 30)	29 (27, 30)
Weight <50Kg	5 (1.4%)	5 (1.4%)
Laboratory results		
TSH (mIU/L) [mean (SD); median (lower and upper quartiles); and range]	6.38 (2.01) 5.76 (5.10, 6.94) [4.60-17.60]	6.41 (2.01) 5.73 (5.12, 6.83) [4.60-17.60]
fT4 (pmol/L)	13.3 (1.9)	13.4 (2.1)
Outcome measures		
ThyPRO Hypothyroid Symptoms (0-100)	16.9 (17.9)	17.5 (18.8)
ThyPRO Tiredness (0-100)	25.5 (20.3)	25.9 (20.6)
EuroQol-5D	0.847 (0.171)	0.846 (0.187)
EuroQol visual analogue scale	76.5 (16.3)	78.4 (15.3)
Handgrip strength (Kg)	27.5 (11.3)	28.0 (10.2)
Letter Digit Coding Test	25.2 (8.3)	24.9 (7.4)
Systolic Blood Pressure (mmHg)	140.4 (18.9)	141.2 (18.7)
Diastolic Blood Pressure (mmHg)	74.8 (11.7)	74.1 (11.6)
Body Mass Index (kg/m^2)	27.7 (4.6)	28.1 (5.3)
Waist circumference (cm)	97.5 (12.8)	98.5 (13.6)
Barthel index [median and range]	20 (14, 20)	20 (13, 20)
Instrumental Activities of Daily Living [median and range]	14 (7, 14)	14 (7, 14)

Footnotes: Results for continuous variables are expressed as mean (SD), categorical variables as number (percent), unless otherwise stated. No statistically significant between-group differences were seen in baseline characteristics. **Abbreviations:** fT4, free thyroxine; IQR, interquartile range; SD, Standard Deviation; TSH, thyroid-stimulating hormone.

Figure. Time course of incident fatal plus nonfatal cardiovascular events in placebo and levothyroxine groups (modified intention to treat population).



Number at risk							
Placebo	369	344	243	151	101	52	14
Levothyroxine	368	342	249	165	111	66	14

Table. Study outcomes at 12 months and extended follow-up (at median of 24.4 months, IQR 18.4-30.5) (modified intention to treat analysis).

	Baseline		12 months		Between group difference at 12 months (95% CI);	Extended follow-up visit		Between group difference at extended follow-up visit (95% CI);
	Placebo	Levothyroxine	Placebo	Levothyroxine	Levothyroxine-placebo difference	Placebo	Levothyroxine	Levothyroxine-placebo difference
TSH (mIU/L) Mean (SD) Median (lower quartile, upper quartile)	6.38 (2.01) 5.76 (5.10,6.94) n=369	6.41 (2.01) 5.7 (5.12,6.83) n=368	5.48 (2.48) 4.90 (3.91,6.46) n=313	3.63 (2.11) 3.16 (2.45,4.22) n=317	-1.92 (-2.24, -1.59)***	5.28 (2.5) 4.94 (3.78,6.26) n=180	3.47 (2.08) 3.00 (2.26,4.16) n=191	-1.88 (-2.32,-1.45) ***
Primary outcomes								
ThyPRO Hypothyroid Symptoms (0-100)	16.9 (17.9) n=369	17.5 (18.8) n=368	16.7 (17.5) n=320	16.6 (16.9) n=318	0.2 (-2.03, 2.06)	15.2 (15.9) n=187	17.9 (19.1) n=194	0.99 (-1.88, 3.87)
ThyPRO Tiredness (0-100)	25.5 (20.3) n=369	25.9 (20.6) n=368	28.6 (19.5) n=320	28.7 (20.2) n=318	0.38 (-2.11, 2.87) p=0.77	31.9 (22.1) n=187	30.2 (20.5) n=194	-3.49 (-7.00, 0.01) p=0.05
Secondary outcomes								
EuroQol 5D	0.847 (0.171) n=369	0.846 (0.187) n=368	0.853(0.191) n=320	0.833 (0.212) n=318	-0.025(-0.050,0.000)*	0.829(0.209) n=187	0.864(0.188) n=193	0.040 (0.005,0.075)**
EuroQol visual analogue scale	76.5 (16.3) n=369	78.4 (15.3) n=368	77.4 (13.7) n=319	77.3 (15.65) n=318	-1.3 (-3.2, 0.6)	77.2 (13.5) n=187	76.8 (14.2) n=193	-0.75 (-3.23, 1.73)
Handgrip strength (kg)	27.5 (11.3) n=358	28.0 (10.2) n=358	27.1 (11.2) n=298	27.5 (10.5) n=302	-0.08 (-0.91, 0.74)	24.9 (10.6) n=173	24.4 (10.1) n=186	-0.56 (-1.70,0.58)
Systolic blood pressure (mmHg)	140.4 (18.9) n=368	141.2 (18.7) n=368	138.4 (17.8) n=319	138.3 (18.7) n=318	0.14 (-2.12, 2.41)	137.5 (19.2) n=182	136.8 (17.6) n=189	1.05 (-4.14,2.05)
Diastolic blood pressure (mmHg)	74.8 (11.7) n=368	74.1 (11.6) n=368	73.5 (11.1) n=319	72.8 (11.4) n=318	-0.06 (-1.46, 1.33)	72.3 (11.4) n=182	72.0 (11.5) n=189	0.51 (-1.35, 2.37)
Body mass index (kg/m^2)	27.7 (4.6) n=368	28.1 (5.3) n=367	27.7 (4.6) n=318	27.9 (5.1) n=317	-0.01 (-0.19, 0.17)	27.2 (4.5) n=185	27.9 (4.9) n=190	0.16 (-0.14,0.46)
Waist circumference (cm)	97.5 (12.8) n=368	98.5 (13.6) n=367	96.8 (13.1) n=319	98.0 (13.2) n=316	0.41 (-0.44, 1.26)	96.0 (13.8) n=185	97.6 (13.4) n=190	0.27 (-0.92,1.47)
Adverse symptoms								
ThyPRO Hyperthyroid Symptoms (0-100)	10.5 (11.2) n=369	10.5 (11.2) n=368	10.3 (11.3) n=320	10.5 (10.8) n=318	0.60 (-0.67, 1.87)	9.8 (11.0) n=187	11.1 (11.7) n=194	0.69 (-1.15, 2.52)

Footnotes:

* p=0.05, **p<0.05; Results are expressed as mean (SD) unless otherwise stated.

The modified intention to treat population was defined as those participants randomised (excluding those randomised in error) for whom data was available on the outcome of interest. For analyses at the 12 month visit to be valid, they must have been conducted at 12 months ± 31 days after randomisation.

Results at 12 months, at the extended follow-up visit and between-group differences are adjusted for stratification variables (country, sex and starting dose of levothyroxine) and baseline levels of the same variable using linear regression; data for the extended follow-up visit are additionally adjusted for time to visit.

Extended study follow-up beyond 12 months was in a subgroup of patients, in the placebo group at a median of 24.2 months (lower quartile, upper quartile 18.4, 30.3) from study baseline, and in the levothyroxine group at 24.5 months (IQR 18.4, 30.5).

The body mass index is the weight in kilograms divided by the square of the height in metres.

The co-primary outcomes were the Hypothyroid Symptoms and Tiredness scores from the ThyPRO questionnaire, at 12 months (adjusted as above). The minimum clinically important difference for both these scores has been estimated as 9 points (0-100 scale). Higher scores indicate more symptoms.

Abbreviations: CI, confidence interval; IQR, interquartile range; TSH, thyroid-stimulating hormone; ThyPRO, Thyroid-Related quality of life Patient-Reported Outcome questionnaire.

Table. Clinical outcomes and Adverse Events (including Serious Adverse Events and Adverse Events of special interest) in the modified intention to treat population, and withdrawals from trial medication and study follow-up.

	All patients n=737	Placebo n=369	Levothyroxine n=368	Treatment effect Hazard Ratio (95% CI)
Clinical outcomes				
Fatal plus non-fatal cardiovascular events	38 (5.2%)	20 (5.4%)	18 (4.9%)	0.89 (0.47, 1.69)
Cardiovascular death	3 (0.4%)	1 (0.3%)	2 (0.5%)	n/a
All-cause mortality	15 (2.0%)	5 (1.4%)	10 (2.7%)	1.91 (0.65, 5.60)
SAEs				
Number of patients with 1 or more SAE (number of events)	181 (24.6%) (343 events)	103 (27.9%) (201 events)	78 (21.2%) (142 events)	0.94 (0.88, 1.00)*
AEs of special interest				
New onset atrial fibrillation	24 (3.3%)	13 (3.5%)	11 (3.0%)	0.80 (0.35, 1.80)
Heart failure	9 (1.2%)	6 (1.6%)	3 (0.8%)	n/a
Fracture	17 (2.3%)	8 (2.1%)	9 (2.4%)	1.06 (0.41, 2.76)
New diagnosis of osteoporosis	7 (0.9%)	4 (1.1%)	3 (0.8%)	n/a
Withdrawals				
Permanent withdrawal from trial medication	160 (21.7%)	79 (21.4%)	81 (22.0%)	1.06 (0.78, 1.44)
Withdrawal from study follow-up	41 (5.6%)	22 (6.0%)	19 (5.2%)	0.84 (0.46, 1.56)

**Footnotes: ***p=0.05. Hazard ratio for treatment obtained from a Cox proportional hazards regression model predicting survival from randomised treatment group and stratification variables (site, gender, dose at randomisation).
Abbreviations: SAEs are Serious Adverse Events; AEs of special interest were pre-defined as new atrial fibrillation, heart failure, fracture and new diagnosis of osteoporosis

- The potential impact (including the socio-economic impact and the wider societal implications of the project so far) and the main dissemination activities and exploitation of results (not exceeding 10 pages).

Guidelines for thyroid disorders in older people outdated:

A mildly underactive thyroid gland (subclinical hypothyroidism) is a common condition in older age, affecting up to one-in-ten older men and women. According to current guidelines, nine of every ten women with the condition receive thyroid hormone tablets, typically levothyroxine, which has become the most prescribed drug in the USA and the third most prescribed drug in the UK. Our large 5-year European study now shows that the common treatment of this condition with levothyroxine provides no apparent benefits, calling for a re-evaluation of the guidelines. The main results of the study were launched on the 3rd April 2017 with a publication in The New England Journal of Medicine along with simultaneous presentation at the Endocrine Society meeting (ENDO 2017) in Orlando, USA.

European 5-year study of 737 older adults

Our team of researchers from four European Universities have followed 737 older adults (average age 74 years) to determine if levothyroxine provides clinical benefits for older people with subclinical hypothyroidism. This condition has been linked to various health problems in later life, such as tiredness or lethargy, problems with the blood circulation, muscle weakness, slowed speed of thinking, and increasing blood pressure and weight, but it is also argued that the condition causes little harm. Half of the older adults in the trial were allocated to a placebo and half to levothyroxine, and participants were followed up for at least a year. The 5-year study found that treatment with levothyroxine tablets did effectively restore a normal balance of thyroid function, but did not give any symptomatic benefits. There was also no improvement of muscle strength, speed of thinking or any effect on body weight or blood pressure. Specific advice for the oldest old (over 80 years old) will be available next year, when TRUST results will be combined with the ongoing IEMO trial among over 80s.

No worthwhile benefits from levothyroxine treatment

Based on these findings, we concluded that there is now convincing evidence that older people with a mildly underactive thyroid do not get worthwhile benefits from levothyroxine treatment. Our aim was to significantly improve the health and well-being of older people with subclinical hypothyroidism, by resolving uncertainties about how best to manage this condition. Treatment with levothyroxine is common in clinical practice, but controversial. Our study concludes this treatment provides no apparent benefits for older adults and should therefore no longer be started routinely for this condition. An update of the guidelines is necessary.

- The address of the project public website, if applicable as well as relevant contact details.

Public website - www.trustthyroidtrial.com; investigators web portal - www.trusttrial.org

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List of Investigators

TRUST Study Group

TRUST Executive Group, Steering Committee and National Organising Committees

The main decision making group for the study is an Executive group of principle investigators;

- Professor David J Stott (chair).
- Professor Ian Ford.
- Professor Jacobijn Gussekloo.
- Professor Patricia M Kearney.
- Professor Nicolas Rodondi.
- Professor Rudi GJ Westendorp.

The strategic planning and conduct of the study was supervised by a Steering Committee (Chair Professor David J Stott) which included the above PIs, plus key ancillary partners, including Yvonne Andersson Lakwijk of Thyroid Federation International (Sweden). The PIs approved additional members of the steering committee as required through the study. National organising committees (chaired by the national Principal Investigators) supervised the conduct of the trial in each of the 4 participating countries. Lead for UK, Professor David J Stott; Ireland, Professor Patricia M Kearney; Netherlands, Professor Jacobijn Gussekloo, Ireland, Switzerland, Professor Nicolas Rodondi.

Independent Data Monitoring Committee

The trial was subject to supervision by an Independent Data Monitoring Committee. Members were as follows;

- Professor Gary Ford (Chair; Chief Executive Officer of the Oxford Academic Health Science Network, Oxford University Hospitals NHS Foundation Trust Division of Medical Sciences, University of Oxford, Oxford, UK).
- Professor Thompson G Robinson (University Hospitals of Leicester NHS Trust, Department of Cardiovascular Sciences, Leicester Royal Infirmary, Leicester, UK).
- Professor Colin Dayan (Institute of Molecular and Experimental Medicine, Cardiff University School of Medicine, Heath Park, Cardiff, UK).
- Professor Kathleen Bennett (Population Health Sciences Division of the Royal College of Surgeons in Ireland, Ireland).

Endpoint Committee

Members of the study Endpoint Committee were;

- Professor Peter Langhorne (chair).

- Professor J Wouter Jukema (vice-chair).
- Dr Tinh-Hai Collet.
- Professor Olaf M Dekkers.
- Dr Anne Marie O'Flynn.

Dr Eleanor Dinnett acted as Endpoints Committee coordinator.

Central laboratory support

Charlotte Syme, Clinical Scientist, Biochemistry Macewen Building, Glasgow Royal Infirmary UK.

TRUST Biobank committee

This committee consists of the following members;

- Professor Patricia M Kearney (chair).
- Professor Naveed Sattar.
- Dr H Anette van Dorland.
- Dr Wendy PJ den Elzen.
- Dr Anton JM de Craen (deceased).

Biostatistics Data Management and Informatics

The Study Data and Biostatistics Centre (Robertson Centre for Biostatistics, University of Glasgow, UK): Biostatistics;

- Professor Ian Ford.
- Dr Martina Messow.
- Dr Alex McConnachie.
- Mrs Paula McSkimming.

Data Management and Informatics;

- Ms Sharon Kean.
- Mr Robbie Wilson.
- Mr Alan Stevenson.
- Dr Lorna Gillespie.

Pharmacy

The lead pharmacist for the trial was Dr Elizabeth Douglas, Senior Clinical Trials Pharmacist, Clinical Research & Development, NHS Greater Glasgow & Clyde.

4.2 Use and dissemination of foreground

Section A

The dissemination measures, including any scientific publications relating to foreground. To be made available in the public domain thus demonstrating the added-value and positive impact of the project on the European Union.

The results of the EU funded, 5-year TRUST study were launched on 3 April 2017 with the publication of the article Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism in The New England Journal of Medicine (NJEM). As per 1 May, the online version of this article has generated over 85,000 page views: 50 per cent from the US, the other half coming from all over the world. On the day of the NJEM publication, the main findings of the study were presented by Professor David Stott (University of Glasgow) on behalf of the TRUST study team at the 99th Annual Meeting and Expo of the Endocrine Society (ENDO 2017) in Orlando, USA. The conference was attended by 7,500 scientists, physicians and students in the field of endocrinology.

The study results and the NJEM article attracted attention in various international media. On 25 April, The New York Times featured the article Could Be the Thyroid; Could Be Ennui. Either Way, the Drug Isn't Helping in the Science section of the print edition (column The New Old Age). The online article made the New York Times 'most emailed'-list and caused a lively discussion in the comments section between readers, both patients and doctors (314 comments). The study was also covered in media such as the British Medical Journal (Research News and Richard Lehman's journal review), Medscape, Clinical Correlations and the Journal of the American Pharmacist Association.

The European Universities involved in the TRUST study also undertook various activities in their respective countries to disseminate the study results. There were publications and interviews in British, Swiss, Irish, Dutch and Danish national news and healthcare media (print, online, and radio). Trial participants were informed by post and patient events, for instance three lunchtime events in Ireland. The University of Cork also hosted an 'educational evening' for general practitioners. In The Netherlands, a meeting was organised at the Leiden University Medical Centre for researchers, participants and physicians to share and discuss the main findings of the study. In Denmark, the study and recommendations regarding the treatment of subclinical hypothyroidism were presented to Dr. Søren Brostrøm, Director General of the Danish Health Authority. He passed on the material to his staff working with national guidelines and rational pharmacotherapy, to explore how these findings can be included in their recommendations for general practitioners. In Ireland, the TRUST findings were shared with the Health Products Regulatory Authority.

- Section B

Exploitable foreground and the plans for exploitation. These data are public and will be made available in the public domain thus demonstrating the added-value and positive impact of the project on the European Union.

The TRUST trial database is owned jointly by the beneficiaries (UGla, LUMC, UBerne, UCC, LAVA). It provides a valuable resource for further research. It will be augmented with laboratory analyses of the TRUST biobank, sub-study data, and long-term-follow-up data post-trial. This work will be supervised by the trial Steering Committee, which will continue to supervise exploitation of the intellectual property arising from the study after completion of the grant funding period.

The Steering Committee has collaborative associations with 2 main groups;

- The IEMO trial of over-80s, led by Dr Simon Mooijaart.
- The EU funded THYRAGE project, led by Diana van Heemst