Impact of Thyroid Hormone Therapy on Atherosclerosis in the Elderly With Subclinical Hypothyroidism: A Randomized Trial

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Context: Subclinical hypothyroidism (SHypo) has been associated with atherosclerosis, but no conclusive clinical trials assessing the levothyroxine impact on carotid atherosclerosis exist.

Objective: To assess the impact of treatment of SHypo with levothyroxine on carotid atherosclerosis.

Design and Setting: Randomized, double-blind, placebo-controlled trial nested within the Thyroid Hormone Replacement for Subclinical Hypothyroidism trial.

Participants: Participants aged ≥65 years with SHypo [thyroid-stimulating hormone (TSH), 4.60 to 19.99 mIU/L; free thyroxine level within reference range].

Intervention: Levothyroxine dose-titrated to achieve TSH normalization or placebo, including mock titrations.

Main Outcome Measures: Carotid intima media thickness (CIMT), maximum plaque thickness measured with ultrasound.

Results: One hundred eighty-five participants (mean age 74.1 years, 47% women, 96 randomized to levothyroxine) underwent carotid ultrasound. Overall mean TSH ± SD was 6.35 ± 1.95 mIU/L at baseline and decreased to 3.55 ± 2.14 mIU/L with levothyroxine compared with 5.29 ± 2.21 mIU/L with placebo ($P < 0.001$). After a median treatment of 18.4 months (interquartile range 12.2 to 30.0 months), mean CIMT was 0.85 ± 0.14 mm under levothyroxine and 0.82 ± 0.13 mm under placebo [between-group difference = 0.02 mm; 95% CI, −0.01 to 0.06; $P = 0.30$]. The proportion of carotid plaque was similar (n = 135; 70.8% under levothyroxine and 75.3% under placebo; $P = 0.46$). Maximum carotid plaque thickness was 2.38 ± 0.92 mm under levothyroxine and 2.37 ± 0.91 mm

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Abbreviations: CIMT, carotid intima media thickness; CV, cardiovascular; FT4, free thyroxine; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; RCT, randomized controlled trial; SHypo, subclinical hypothyroidism; TRUST, Thyroid Hormone Replacement for Subclinical Hypothyroidism; TSH, thyroid-stimulating hormone.

under placebo (between-group difference −0.03; 95% CI, −0.34 to 0.29; $P = 0.86$). There were no significant interactions between levothyroxine treatment and mean CIMT, according to sex, baseline TSH (categories 4.6 to 6.9, 7.0 to 9.9, and ≥10 mIU/L), or established cardiovascular disease (all P for interaction ≥ 0.14).

Conclusion: Normalization of TSH with levothyroxine was associated with no difference in CIMT and carotid atherosclerosis in older persons with SHypo. (***J Clin Endocrinol Metab*** **103: 2988–2997, 2018)**

Subclinical hypothyroidism (SHypo), defined as thyroid-stimulating hormone (TSH) above the reference range with normal free thyroxine (FT4) levels, is common with increasing age (1). Coronary heart disease is among the leading causes of morbidity and mortality, particularly within the context of a growing aging population (2). Meta-analyses have linked SHypo with an increased risk of coronary heart disease events and mortality (3, 4). No large randomized controlled trial (RCT) has assessed the impact of thyroid hormone replacement on cardiovascular (CV) outcomes. The Thyroid Hormone Replacement for Subclinical Hypothyroidism (TRUST) trial ("Multi-Modal Effects of Thyroid Hormone Replacement for Untreated Older Adults With Subclinical Hypothyroidism"; synopsis of the trial is provided in Methods), the largest multinational RCT comparing levothyroxine with placebo in older individuals with SHypo, was not powered to assess clinical CV outcomes (5, 6). Validated surrogate markers are therefore valuable to assess the CV impact of treating SHypo (7).

Carotid intima media thickness (CIMT) is a well-known marker for atherosclerosis. A meta-analysis of eight relevant observational studies showed CIMT to be a strong predictor of future CV events, with each increase of 0.10 mm of CIMT corresponding to an increased risk of myocardial infarction with a relative risk of 1.15 [95% CI, 1.12 to 1.17] (8, 9). CIMT has therefore been used in a number of clinical trials as the outcome to assess the effects of statin and other lipid-lowering treatments (10–12). In cross-sectional studies, CIMT was significantly higher in participants with SHypo compared with euthyroid controls (13). Small interventional studies suggested that the restoration of euthyroidism in patients with SHypo is associated with regression of carotid atherosclerosis (13, 14). However, these trials had major limitations, with small sample sizes (the largest included only 45 participants with SHypo) (14) and/or non-controlled study designs. Therefore, in a substudy of the TRUST trial, we aimed to assess the effect of thyroid hormone replacement therapy on CIMT in older adults with SHypo, hypothesizing that normalization of TSH with levothyroxine is associated with lower CIMT and carotid atherosclerosis.

Methods

This trial was registered on ClinicalTrials.gov (number NCT02832934) as a substudy of the TRUST trial [ClinicalTrials.gov (number NCT01660126)], conducted at the two Swiss study centers (Inselspital, University Hospital of Bern, and Centre Hospitalier Universitaire Vaudois, Lausanne University Hospital). The trial was approved by the local Institutional Review Boards, and written, informed consent was obtained from all participants.

The TRUST trial

The protocol and the main results of the TRUST trial have been published elsewhere (5, 6). In brief, community-dwelling adults, aged ≥65 years with untreated SHypo, were included into a randomized, blinded (blinded patients, physicians, and outcome assessors), placebo-controlled, parallel group trial in four European countries (Scotland, Ireland, the Netherlands, and Switzerland). With the use of central web-based, computer-generated, randomly permuted blocks, participants were allocated in a 1:1 ratio, stratified according to country, sex, and treatment starting dose. SHypo was defined as persistently elevated TSH values (4.6 to 19.9 mIU/L, at least twice, at least 3 months apart) with FT4 levels within the reference range. The intervention consisted of levothyroxine with a starting dose of 50 μg daily [25 μg in participants with known coronary heart disease (defined as previous myocardial infarction or symptoms of angina pectoris) or a body weight <50 kg] that was regularly dose titrated to achieve a TSH level within the reference range. There were several mock titrations in the placebo group.

Outcomes

The primary outcome was the mean CIMT, calculated as the average of the left and right common carotid artery mean intima media thickness, at the final study visit (end of trial visit) (15). Comparing outcomes at the end of the trial between both treatment groups has been performed in previous trials, as baseline values should be equally distributed as a result of randomization (16, 17). For the secondary outcomes of maximum CIMT, plaque presence, and maximum carotid plaque thickness, the larger value of the measurements on each side was retained (15).

Carotid ultrasound

We performed a carotid ultrasound exam at the final visit of all Swiss participants of the TRUST trial. The exam was performed by four blinded operators trained in the field of carotid ultrasound, according to the consensus guideline on CIMT measurement (15). CIMT was measured bilaterally on the far wall of the common carotid artery using a linear transducer (11 MHz at the University Hospital of Bern and 5 to 13 MHz at

the University Hospital of Lausanne), with a machine-specific setting for carotid imaging. The measurement was performed 0 to 10 mm proximal to the carotid bulb flare on a plaque-free, straight segment of at least 10 mm at the end of diastole. Concomitant three-point ECG was recorded to identify end of diastole. A machine-specific, automated edge-detection software was used to measure mean and maximum CIMT (Hitachi EUB-7500/EZU-IM1 at the University Hospital of Bern and Aloka ProSound Alpha 10/M'Ath Std 3.1.0 at the University Hospital of Lausanne). CIMT was measured with two decimal precision. In addition, the common, internal, and external carotid, including the carotid bulb, were assessed for plaque burden. Following the consensus guideline (15), a plaque was defined as a focal structure that encroaches into the arterial lumen of at least 0.5 mm or at least 50% of the surrounding CIMT value or is >1.5 mm thick from the intima-lumen interface to the media-adventitia interface. Maximal plaque thickness of the largest plaque was measured with single decimal precision on longitudinal and cross-sectional images.

To assess inter-observer reliability of carotid measurements, we performed blinded, independent measurements of CIMT in a subset of eight consecutive participants by three operators and of maximum plaque thickness by two of the same operators, and the intraclass correlation coefficient was calculated using a two-way, mixed-effects model (18). The achieved intraclass correlation was 0.81 (95% CI, 0.51 to 0.94) for mean CIMT and 0.93 (95% CI, 0.70 to 0.99) for maximum plaque thickness, both of which are deemed excellent (19). A blinded, second reading of the stored ultrasound images was performed by two experienced angiology specialists (J.D. and L.A.) to assess the validity of the measurements.

Biochemical parameters

TSH and FT4 were measured from plasma samples at the accredited study center laboratories by immunoassay (Electrochemiluminescence Immunoassay, Roche Diagnostics), with participants, general practitioners, and investigators/outcome assessors blinded to the results. Baseline and 12-month follow-up fasting lipid profile (total cholesterol, high-density lipoprotein cholesterol, and triglyceride concentrations), the inflammation marker high-sensitivity C-reactive protein (hsCRP), and creatinine levels were measured after trial end from stored EDTA plasma samples on a Cobas 8000 system (Roche Diagnostics) using enzymatic colorimetric analysis at the University Institute of Clinical Chemistry, Inselspital, University of Bern. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation if the triglyceride concentration was <4.6 mM (20). Levels of hsCRP >10 mg/dL were discarded (21).

Statistical analysis

The primary analysis was conducted according to a modified intention-to-treat principle on a population defined as those participants randomized with available data on the outcome of interest, as in the protocol of the main trial analysis (5). We compared the outcomes between both groups with adjustment for stratification variables (sex, study center, starting dose of levothyroxine) and time to visit using multivariable linear regression. Model fit was assessed for the main analysis using distribution plots of residuals and scatter plots of standardized residuals against predicted values. Prespecified subgroup analyses were performed according to sex, TSH levels, medication compliance, and pre-existing CV disease, using multivariable linear regression models with an interaction term for treatment group and stratification group. In sensitivity analyses, multiple imputation by chained equations was performed for the mean CIMT and maximum CIMT outcomes, with age, sex, baseline thyroid function (TSH and FT4), CV risk factors (body mass index, blood pressure, smoking status, diabetes mellitus, and history of CV disease), and intervention data (treatment allocation, date of randomization, and study center) included in the imputation procedure, and 20 sets of imputed datasets (22, 23). The analysis was repeated as an exploratory analysis on the per-protocol population, as previously defined (5). An exploratory analysis—comparing the difference in CV risk factors, including LDL cholesterol and hsCRP, between treatment groups at follow-up at 12 months—was performed using multivariable linear regression, adjusting for the baseline value of the outcome of interest, in addition to the previously mentioned stratification variables.

Power calculation

Power calculation was performed for the primary outcome (mean CIMT) and was based on raw differences using a two-sample means test. Based on results from small interventional studies assessing the impact of thyroid replacement on CIMT (13, 14, 24) and 185 expected participants (217 participants included, with an expected 15% for dropouts/deaths/losses to follow-up), we calculated a statistical power of 88% to detect a mean CIMT difference of 0.06 mm [a difference based on assessment of clinical relevance (8) and at the lower end of the range found in previous interventional trials (13, 14, 24)] at a two-sided αlevel of 0.05, assuming an SD of 0.13 mm from an expected distribution of CIMT in a population of elderly (25).

All analyses were performed using Stata Statistical Software (Stata 14; StataCorp).

Results

Trial population

Figure 1 shows the study flowchart. Participants were enrolled from April 2013 through December 2015 when the recruitment target was reached. The last participant completed the study follow-up in November 2016. In total, 603 participants were screened, and 217 were randomized with 109 in the intervention group. Reversion to euthyroidism accounted for 90% of exclusions during screening. Thirteen (12%) participants in the intervention group and 19 (18%) in the control group were excluded from the primary analysis. Fourteen of the 16 withdrawals from follow-up were patient decisions, and two were a result of adverse events. In one subject, the primary outcome was not measurable as a result of heavy carotid calcification. This resulted in a modified intention-to-treat population of 96 in the intervention group and 89 in the control group.

Baseline characteristics are shown in Table 1 (all participants, n = 217) and Supplemental Table 1 (participants in primary analysis, n = 185) and were well balanced except for a higher prevalence of diabetes in the

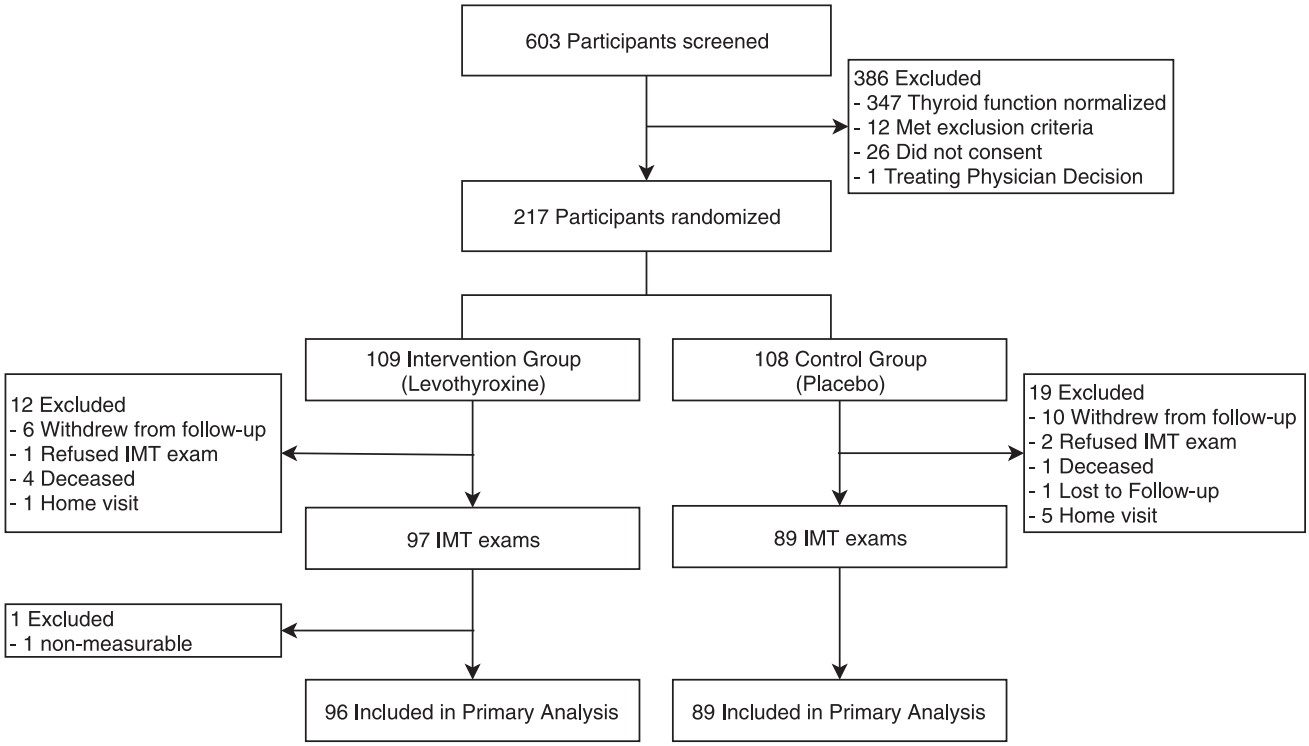

Figure 1. Study flowchart. Home visit indicates participants that were visited by the study personnel at their home for the final visit, where it was not possible to perform a carotid ultrasound exam. IMT, intima media thickness.

intervention group. Median time from baseline until carotid ultrasound exam was 18.5 months (interquartile range 12.2 to 30.4) in the levothyroxine group and 18.3 months (interquartile range 12.2 to 25.2) in the placebo group ($P = 0.26$). In the levothyroxine group, 14 participants were started at a lower dose of 25 μg (12 participants, as a result of known coronary heart disease, and two, as a result of body weight <50 kg). Mean treatment dose in the levothyroxine group was 47 μg (range 25 to 50 μg) at baseline and 43 μg (range 0 to 100 μg) at final visit.

Thyroid function tests

The course of TSH levels by treatment group is shown in Fig. 2. The overall mean TSH ± SD was 6.35 ± 1.95 (range 4.6 to 17.0) mIU/L at baseline. At 6 to 8 weeks after randomization, TSH decreased to 2.92 ± 1.06 (range 0.9 to 5.4) mIU/L in the levothyroxine group and to 5.36 ± 2.03 (range 1.9 to 12.6) mIU/L in the placebo group ($P < 0.001$). At trial end, the mean TSH was 3.55 ± 2.14 (range 0.03 to 13.3) mIU/L in the levothyroxine group and 5.29 ± 2.21 (range 1.4 to 16.4) mIU/L in the placebo group (adjusted between-group difference 1.64 mIU/L, $P < 0.001$).

CIMT

The mean CIMT was 0.85 ± 0.14 mm in the levothyroxine group and 0.82 ± 0.13 mm in the placebo group (adjusted between-group difference 0.02 mm; 95% CI, −0.01 to 0.06; $P = 0.30$). Maximum CIMT was 1.10 ± 0.22 mm in the levothyroxine group and 1.07 ± 0.18 mm in the placebo group (adjusted between-group difference 0.03 mm; 95% CI, −0.03 to 0.09; $P = 0.35$; Fig. 3). Model fit was good (data not shown). Prespecified stratification, according to sex, baseline TSH level, and history of prior CV disease, as well as *post hoc* stratification according to baseline use of lipid-lowering medication, did not reveal any statistically significant differences among subgroups in favor of levothyroxine (Fig. 3). Exploratory analyses, including per-protocol analysis and multiple imputation of missing outcome data, did not show statistically significant differences for mean or maximum CIMT between treatment groups. As a result of baseline imbalances, exploratory sensitivity analyses, excluding participants with diabetes mellitus and adjusting for the presence of diabetes mellitus, were conducted and did not show statistically significant between-group differences (Table 2). Furthermore, no significant effects were seen in a sensitivity analysis using a central second reading of the stored ultrasound images by two blinded angiology specialists (Table 2), where one participant was excluded from the control group, as the original measurement was not done at end of diastole, and four CIMT measurements were reassessed (Supplemental Table 2).

Maximum carotid plaque thickness

The presence of carotid plaque was assessed bilaterally in the common, internal, and external carotid artery and was similar in both arms (n = 135, 70.8% in the levothyroxine group and 75.3% in the placebo group,

Table 1. Baseline Characteristics[a]

	Levothyroxine, n = 109	Placebo, n = 108
Demographics		
Age, y, mean ± SD	74.5 ± 5.4	74.6 ± 6.2
Female, n (%)	49 (45.0)	49 (45.4)
White race, n (%)	107 (98.2)	106 (98.2)
CV risk factors		
BMI, kg/m^2, mean ± SD[b]	27.9 ± 5.3	26.9 ± 4.6
Blood pressure, mmHg, mean ± SD		
Systolic	137.6 ± 18.2	138.5 ± 20.0
Diastolic	74.1 ± 11.2	77.4 ± 12.3
Currently smoking, n (%)[c]	8 (7.3)	10 (9.3)
Diabetes mellitus, n (%)	17 (15.6)	11 (10.2)
Prior CV disease, n (%)[d]	26 (23.9)	30 (27.8)
Estimated creatinine clearance, n (%)[e]		
Normal, ≥90 mL/min	7 (6.4)	6 (5.6)
Mild, 60–<90 mL/min	61 (56.0)	70 (64.8)
Moderate, 30–<60 mL/min	38 (34.9)	28 (25.9)
Severe, <30 mL/min	3 (2.8)	4 (3.7)
Lipid profile		
Total cholesterol, mM, mean ± SD[f]	5.08 ± 1.09	5.18 ± 1.11
LDL cholesterol, mM, mean ± SD[g]	2.84 ± 0.99	2.88 ± 0.93
HDL cholesterol, mM, mean ± SD[h]	1.45 ± 0.47	1.49 ± 0.46
Triglycerides, mM, mean ± SD[i]	1.80 ± 1.13	1.78 ± 0.87
Concomitant medication		
Antiplatelets, n (%)	33 (30.3)	36 (33.3)
Lipid lowering, n (%)	49 (45.0)	42 (38.9)
Statin, n (%)	47 (43.2)	41 (38.0)
Antihypertensives, n (%)	70 (64.2)	59 (54.6)
Antidiabetics, n (%)	17 (15.6)	8 (7.4)
Insulin, n (%)	5 (4.6)	1 (0.9)
Thyroid function		
TSH, mIU/L, mean ± SD	6.40 ± 2.02	6.51 ± 2.12
FT4, pM, mean ± SD	13.5 ± 2.0	13.7 ± 1.9

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein.

[a]Baseline characteristics of participants in the primary analysis (n = 185) are provided in Supplemental Table 1.

[b]Calculated as weight (kilograms) divided by squared height (meters).

[c]Defined as currently smoking at the time of baseline exam.

[d]Defined as one or more of the following: acute coronary syndrome (myocardial infarction or stable or unstable angina), coronary or other arterial revascularization, stroke, transient ischemic attack, peripheral arterial disease.

[e]Calculated using the Chronic Kidney Disease-Epidemiology Collaboration equation (26).

[f]Missing for two participants in the placebo group.

[g]Calculated using the Friedewald equation if triglycerides lower than 4.6 mM. Missing for four participants in the levothyroxine group and four participants in the placebo group.

[h]Missing for one participant in the levothyroxine group and three participants in the placebo group.

[i]Missing for two participants in the placebo group.

P = 0.46). Maximum carotid plaque thickness was 2.38 ± 0.92 mm in the levothyroxine group and 2.37 ± 0.91 mm in the placebo group (adjusted between-group difference −0.03; 95% CI, −0.34 to 0.29; P = 0.86; Fig. 3). There were no significant differences in stratified analyses (Fig. 3), per-protocol analysis, or any sensitivity analysis (Table 2).

Change of cointerventions and CV risk factors over time

CV medications were nearly unchanged between the baseline visit and the 12-month visit between both treatment groups (Supplemental Table 3). In an exploratory analysis, there was no significant between-group difference in CV risk factors, including levels of LDL cholesterol and the inflammation marker hsCRP at follow-up after 12 months, after adjustment for baseline values.

Clinical outcomes and adverse events

Thirty of 109 (28%) participants in the levothyroxine group experienced at least one serious adverse event, as did 35 of 108 (32%) participants in the placebo group (P = 0.43), and the total number of serious adverse events was 54 and 67, respectively (Supplemental Table 4). A

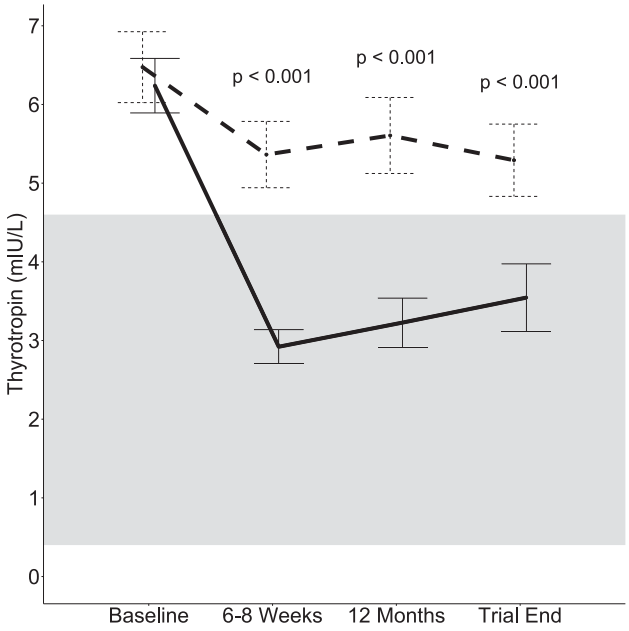

Figure 2. Course of TSH levels over time. Data show mean TSH levels, and error bars indicate 95% CIs (solid line for the levothyroxine group and dashed line for the placebo group). *P* values shown are for between-group differences in TSH levels and were calculated using linear regression models adjusting for baseline TSH, sex, study center, and starting dose of levothyroxine (with additional adjustment for time to visit for the end-of-trial visit). The gray, shaded area denotes the target reference range of TSH.

fatal or nonfatal CV event occurred in seven (6.4%) participants in the levothyroxine group and six (5.6%) participants of the placebo group. Five participants (four in the levothyroxine group and one in the placebo group) died (two deaths in the levothyroxine group were from a CV cause, and none in the placebo group). Proportions of participants permanently discontinuing the study drug and withdrawing from follow-up were similar between treatment groups. Of the participants with outcome assessment, 14 (14.6%) in the levothyroxine group and seven (7.9%) in the placebo group had withdrawn from treatment at the time of the final study visit.

Discussion

In this double-blind, randomized, placebo-controlled trial of 185 participants over 65 years of age, normalization of TSH with levothyroxine did not show any evidence of a relevant impact on CIMT and plaque burden in older persons with SHypo after a median follow-up of 18.4 months. We found no differences according to sex, baseline TSH, and history of prior CV disease.

These results contrast with a previous, smaller randomized, placebo-controlled trial of 45 participants with SHypo, which after 6 months of stable euthyroidism found a decrease of CIMT of 0.09 mm (95% CI, 0.06 to 0.11) (14). However, participants in this past trial were considerably younger (mean age 37 ± 11 years), and definition of SHypo differed (TSH > 3.6 mIU/L). In addition, a before-after interventional study of 28 participants with SHypo after 12 months of treatment with levothyroxine showed a regression of CIMT from 0.67 ± 0.11 to 0.60 ± 0.10 mm ($P = 0.021$) but was limited by a nonrandomized, noncontrolled study design and small sample size (13). Comparability is further limited by higher baseline TSH levels (12.32 ± 5.90 mIU/L vs 6.35 ± 1.95) and higher mean dose of levothyroxine (67 vs 43 μg) than in our trial. Furthermore, neither of these studies included participants taking drugs that affect the lipid profile. Whereas a large proportion of participants in our trial was on lipid-lowering medication, a *post hoc* stratified analysis showed no statistically significant interaction between levothyroxine and CIMT, according to baseline use of lipid-lowering medication.

One potential explanation for our negative findings is the lack of between-group differences in CV risk factors, including LDL cholesterol and hsCRP, at 12 months after adjustment for baseline values, even though our trial is the largest and with the longest follow-up assessing CV risk factors in SHypo (27). Moreover, changes in LDL cholesterol levels in previous smaller, randomized placebo-controlled trials in SHypo (maximum number of participants = 99, duration of follow-up 4 to 12 months) were small (mean differences in these trials ranged from 0.0 to 0.6 mM) (27). Another potential explanation for our negative findings might be that the follow-up time may have been too short to show a substantial impact of levothyroxine treatment on CIMT. However, median follow-up time was 18.4 months compared with 6 to 12 months of treatment in previous interventional studies, which found a mean decrease of CIMT in the range of 0.07 to 0.09 mm under treatment with levothyroxine (13, 14, 24), and our study was powered to detect such a difference. For comparison, in interventional trials assessing the impact of statin therapy, the decrease of CIMT varied greatly and ranged from 0.015 (0.009 to 0.020) mm per year in low-risk participants of the Measuring Effects on Intima-Media Thickness: An Evaluation of Rosuvastatin (28) trial, over 0.05 ± 0.001 mm after 36 months in the Stop Atherosclerosis in Native Diabetics Study trial (29), to 0.29 mm after 12 months in uncontrolled trials (30).

Our trial has several strengths. In the absence of any ongoing RCT large enough to be powered for clinical CV outcomes, this study comprises the largest RCT assessing the effect of thyroxine replacement in SHypo on surrogate CV outcomes. Second, our sample size was four times larger than all available previous trials of thyroid replacement and CIMT [the largest one included 45 participants (14)], was comparable in size with statin

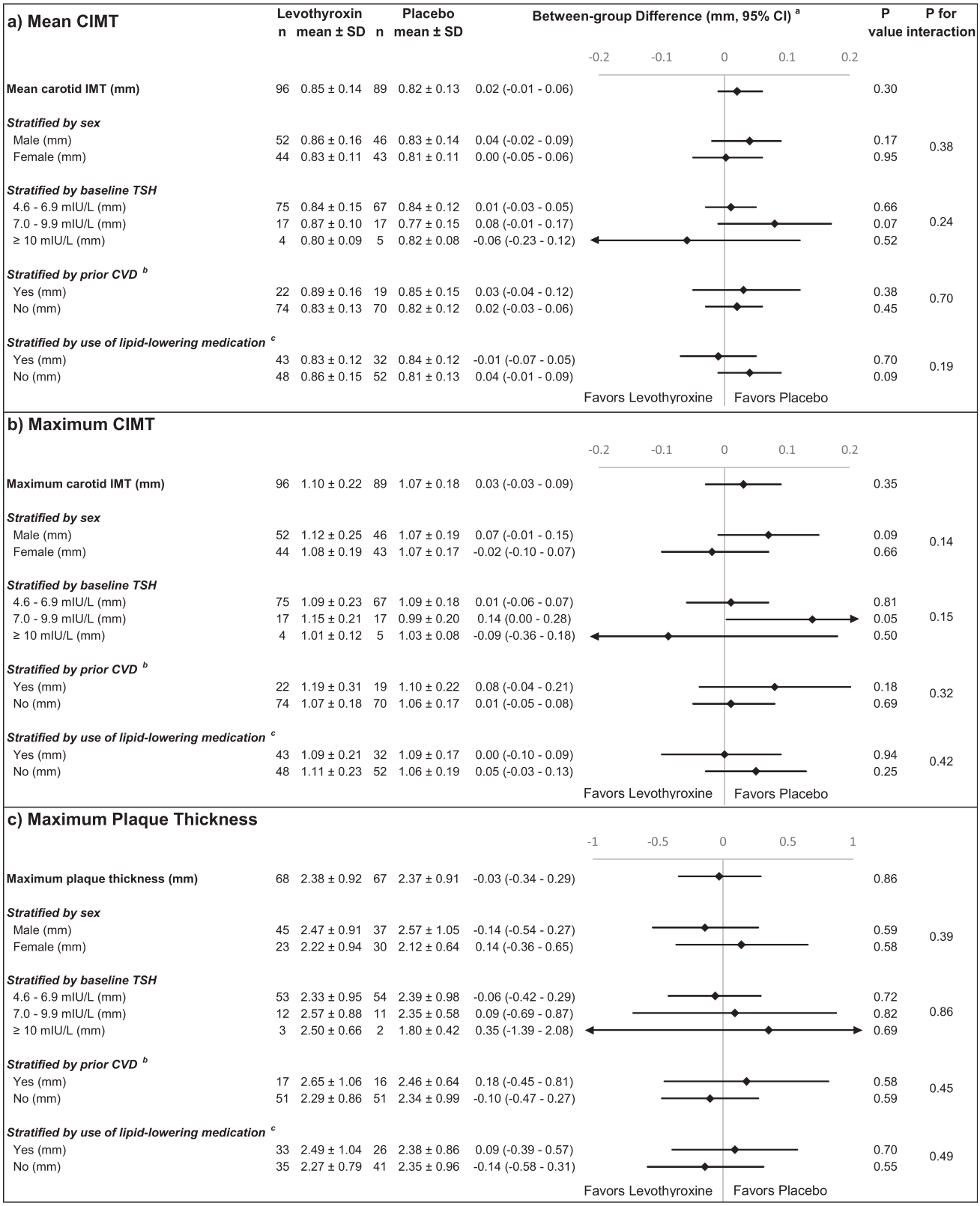

Figure 3. Main outcomes and stratified analyses. (a) Mean CIMT. (b) Maximum CIMT. (c) Maximum plaque thickness. [a]Adjusted for stratification variables (sex, study center, starting dose of levothyroxine) and time to visit, using linear regression. For stratified analyses, an interaction term between the stratification variable and the treatment group was added. [b]Defined as at least one of the following: acute coronary syndrome (myocardial infarction or stable or unstable angina), coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease. [c]Defined as use of statin and/or fibrate at baseline. CVD, CV disease. IMT, intima media thickness.

Table 2. Sensitivity Analyses

	Levothyroxine		Placebo		Difference[a]	
	n	Mean ± SD	n	Mean ± SD	Mean (95% CI)	*P*
Centralized second reading						
Mean CIMT, mm	96	0.85 ± 0.14	88	0.82 ± 0.13	0.02 (−0.02 to 0.06)	0.31
Maximum CIMT, mm	96	1.10 ± 0.22	88	1.07 ± 0.18	0.03 (−0.03 to 0.09)	0.34
Maximum carotid plaque thickness, mm	68	2.39 ± 0.85	66	2.34 ± 0.79	0.02 (−0.27 to 0.30)	0.90
Multiple imputation of missing outcomes[b]						
Mean CIMT, mm	109	0.85 ± 0.14	108	0.83 ± 0.13	0.02 (−0.02 to 0.06)	0.38
Maximum CIMT, mm	109	1.10 ± 0.22	108	1.08 ± 0.19	0.02 (−0.04 to 0.08)	0.44
Per-protocol analysis,[c]						
Mean CIMT, mm	82	0.83 ± 0.12	82	0.82 ± 0.13	0.01 (−0.03 to 0.05)	0.70
Maximum CIMT, mm	82	1.09 ± 0.19	82	1.07 ± 0.19	0.01 (−0.05 to 0.07)	0.66
Maximum carotid plaque thickness, mm	57	2.35 ± 0.91	62	2.35 ± 0.92	−0.03 (−0.37 to 0.31)	0.86
Excluding participants with diabetes mellitus						
Mean CIMT, mm	81	0.84 ± 0.12	82	0.82 ± 0.12	0.01 (−0.03 to 0.05)	0.52
Maximum CIMT, mm	81	1.09 ± 0.19	82	1.06 ± 0.18	0.01 (−0.04 to 0.07)	0.62
Maximum carotid plaque thickness, mm	56	2.28 ± 0.84	63	2.37 ± 0.94	−0.14 (−0.48 to 0.19)	0.39
Adjusting for diabetes mellitus						
Mean CIMT, mm	96	0.85 ± 0.14	89	0.82 ± 0.13	0.02 (−0.02 to 0.05)	0.42
Maximum CIMT, mm	96	1.10 ± 0.22	89	1.07 ± 0.18	0.02 (−0.04 to 0.08)	0.48
Maximum carotid plaque thickness, mm	68	2.38 ± 0.92	67	2.37 ± 0.91	−0.07 (−0.38 to 0.25)	0.68

[a]Adjusted for stratification variables (sex, study center, starting dose of levothyroxine) and time to visit, using linear regression.

[b]The outcome of mean CIMT and maximum CIMT was imputed in 32 of 217 (14.7%) participants.

[c]Defined as outcome of interest measured on study drug at final visit and not down titrated to 0 μg in the levothyroxine group.

trials showing a positive impact on CIMT (12), and did not have methodological and statistical limitations of previous trials (13, 14, 24). Third, ultrasound scans were performed according to a standardized protocol with excellent inter-rater reliability, and a second reading of measurements further improved internal validity.

Our study also has several limitations. First, participants with TSH > 10 mIU/L accounted for only 5% of the study population (although this is within an expected range for this age category) (31), and our results may thus not be generalizable to this subgroup of more pronounced SHypo. Second, we titrated levothyroxine to reach a TSH between 0.40 and 4.60 mIU/L. The latest guidelines from the European Thyroid Association recommend the targeting of a TSH between 0.4 and 2.5 mIU/L, although a higher TSH between 1 and 5 mIU/L may be considered for older adults >70 years (32). We cannot rule out that the targeting of a lower TSH might have an important effect. Furthermore, at the study end, the adjusted between-group difference in TSH was 1.64 mIU/L, and the mean levothyroxine dose was 43 μg. It is possible that substantial differences in carotid atherosclerosis would have been found if there were a larger difference in TSH, and/or a higher dose of levothyroxine had been used. Third, although the proportion of participants with carotid atherosclerosis in our study population was in line with previous reports from European populations in this age range (33–36), the baseline CV disease burden was relatively low. Therefore, we cannot rule out that the effects of levothyroxine treatment could differ in a population with a more pronounced baseline CV burden. Fourth, there was no baseline measurement of CIMT. Paired outcome data would have increased power to detect differences, as within-participant variation is reduced (37). However, baseline participant characteristics were evenly distributed, and previous RCTs similarly added outcome measurements at the end of the trial, comparing both randomized groups (16, 17). As previously described, in the case of continuous outcomes, a trial with ~100 participants per treatment arm is considered a large trial, where baseline variables can be expected to be evenly distributed between treatment arms (38). In addition, a *post hoc* calculation of the detectable mean difference varying the assumed correlation coefficient between baseline and follow-up mean CIMT from 0.6 to 0.9, whereas otherwise retaining the same estimates and assumptions from our power calculation, resulted in a detectable mean difference in mean CIMT, ranging from 0.03 to 0.05 mm, which is larger than what we observed (37). Fourth, whereas the overall drop rate was 14.7%, with a slightly higher dropout rate in the placebo group (17.6%) than in the levothyroxine group (11.9%), results from the modified intention-to-treat analysis, the per-protocol analysis, and the multiple imputation analysis were virtually the same.

Conclusion

Compared with placebo, normalization of TSH with levothyroxine did not show any evidence of a relevant

impact on CIMT and plaque burden in community-dwelling persons, aged 65 years or older, with SHypo after a median follow-up of 18.4 months. The TRUST trial, the largest RCT on treatment of SHypo, was underpowered to detect any effect of levothyroxine on the incidence of CV events or mortality (5), and our results provide no evidence in favor of using levothyroxine to treat older adults with mild SHypo, with the goal of lowering CV risk. Whereas CIMT is a predictor of future CV events (8), larger and longer-duration, randomized trials assessing clinical CV events would be needed to determine definitively the clinical effect of levothyroxine replacement in SHypo.

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