




---

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

Manuel R. Blum, Baris Gencer, Luise Adam, Martin Feller, Tinh-Hai Collet, Bruno R. da Costa, Elisavet Moutzouri, Jörn Dopheide, Michèle Depairon, Gerasimos P. Sykiotis, Patricia Kearney, Jacobijn Gussekloo, Rudi Westendorp, David J. Stott, Douglas C. Bauer, Nicolas Rodondi

*The Journal of Clinical Endocrinology & Metabolism*  
Endocrine Society

Submitted: February 03, 2018

Accepted: May 23, 2018

First Online: May 28, 2018

---

Advance Articles are PDF versions of manuscripts that have been peer reviewed and accepted but not yet copyedited. The manuscripts are published online as soon as possible after acceptance and before the copyedited, typeset articles are published. They are posted "as is" (i.e., as submitted by the authors at the modification stage), and do not reflect editorial changes. No corrections/changes to the PDF manuscripts are accepted. Accordingly, there likely will be differences between the Advance Article manuscripts and the final, typeset articles. The manuscripts remain listed on the Advance Article page until the final, typeset articles are posted. At that point, the manuscripts are removed from the Advance Article page.

---

DISCLAIMER: These manuscripts are provided "as is" without warranty of any kind, either express or particular purpose, or non-infringement. Changes will be made to these manuscripts before publication. Review and/or use or reliance on these materials is at the discretion and risk of the reader/user. In no event shall the Endocrine Society be liable for damages of any kind arising references to, products or publications do not imply endorsement of that product or publication.

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

Manuel R. Blum,<sup>1</sup> Baris Gencer,<sup>2</sup> Luise Adam,<sup>1,3</sup> Martin Feller,<sup>1,4</sup> Tinh-Hai Collet,<sup>5</sup> Bruno R. da Costa,<sup>4,6</sup> Elisavet Moutzouri,<sup>1,4</sup> Jörn Dopheide,<sup>3</sup> Michèle Depairon,<sup>7</sup> Gerasimos P. Sykiotis,<sup>5</sup> Patricia Kearney,<sup>8</sup> Jacobijn Gussekloo,<sup>9</sup> Rudi Westendorp,<sup>10</sup> David J. Stott,<sup>11</sup> Douglas C. Bauer,<sup>12</sup> Nicolas Rodondi<sup>1,4</sup>.

<sup>1</sup> Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland; <sup>2</sup> Cardiology Division, University Hospital of Geneva, University of Geneva, Switzerland; <sup>3</sup> Clinic for Angiology, Swiss Cardiovascular Center, Inselspital, University of Bern, Switzerland; <sup>4</sup> Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland; <sup>5</sup> Service of Endocrinology, Diabetes and Metabolism, Lausanne University Hospital, University of Lausanne, Switzerland; <sup>6</sup> Applied Health Research Centre (AHRC), Li Ka Shing Knowledge Institute of St. Michael's Hospital, Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, Ontario, Canada; <sup>7</sup> Service of Angiology, Department of Heart and Vessels, Lausanne University Hospital, University of Lausanne, Switzerland; <sup>8</sup> University College Cork, Cork, Ireland; <sup>9</sup> Leiden University Medical Center, Leiden, Netherlands; <sup>10</sup> Center for Healthy Aging, University of Copenhagen, Copenhagen, Denmark; <sup>11</sup> Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom; <sup>12</sup> University of San Francisco, San Francisco, CA, USA

Received 03 February 2018. Accepted 23 May 2018.

**Trial registration:** Clinicaltrials.gov number NCT02832934.

**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/Setting:** Randomized, double-blind, placebo-controlled trial nested within the TRUST trial.

**Participants:** Participants aged  $\geq 65$  years with SHypo (thyroid-stimulating hormone, TSH, 4.60-19.99 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:** 185 participants (mean age 74.1 years, 47% women, 96 randomized to levothyroxine) underwent carotid ultrasound. Overall mean TSH $\pm$ SD was 6.35 $\pm$ 1.95 mIU/L at baseline and decreased to 3.55 $\pm$ 2.14 mIU/L with levothyroxine, as compared to 5.29 $\pm$ 2.21 mIU/L with placebo ( $p < 0.001$ ). After a median treatment of 18.4 months (interquartile range 12.2-30.0 months), mean CIMT was 0.85 $\pm$ 0.14 mm under levothyroxine and 0.82 $\pm$ 0.13 mm under placebo (between-group difference=0.02 mm, 95% confidence interval (CI)-0.01 to 0.06,  $p = 0.30$ ). 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 $\pm$ 0.92 mm under levothyroxine and 2.37 $\pm$ 0.91 mm 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 4.6-6.9, 7.0-9.9, and  $\geq 10$  mmol/L) or established cardiovascular disease (all  $p$  for interaction  $\geq 0.14$ ).

**Conclusion:** Normalization of TSH with levothyroxine was associated with no difference in CIMT and carotid atherosclerosis in older persons with SHypo.

Older adults with subclinical hypothyroidism were randomized to levothyroxine or placebo. No relevant difference in carotid atherosclerosis was found after a median follow-up of 18.4 months.

## Introduction

Subclinical hypothyroidism, 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 subclinical hypothyroidism 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 TRUST trial (“Multi-Modal Effects of Thyroid Hormone Replacement for Untreated Older Adults with Subclinical Hypothyroidism”; synopsis of the trial is provided in the Methods section), the largest multinational RCT comparing levothyroxine versus placebo in older individuals with subclinical hypothyroidism, was not powered to assess clinical CV outcomes.(5,6) Validated surrogate markers are therefore valuable to assess the CV impact of treating subclinical hypothyroidism.(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 relative risk of 1.15 (95% confidence interval, CI, 1.12-1.17).(8,9) CIMT has therefore been used in a number of clinical trials as 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 subclinical hypothyroidism compared to euthyroid controls.(13) Small interventional studies suggested that restoring euthyroidism in patients with subclinical hypothyroidism 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 subclinical hypothyroidism(14)) and/or non-controlled study designs. Therefore, in a sub-study of the TRUST trial, we aimed to assess the effect of thyroid hormone replacement therapy on CIMT in older adults with subclinical hypothyroidism, 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 sub-study 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  $\geq 65$  years with untreated subclinical hypothyroidism 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, Switzerland). Using 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. Subclinical hypothyroidism was defined as persistently elevated TSH values (4.6-19.9 mIU/L at least twice at least three months apart) with FT4 levels within the reference range. The intervention consisted of levothyroxine with a starting dose of 50 $\mu$ g daily (25 $\mu$ g 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 CIMT, at the final study visit (end of trial visit).(15) Comparing outcomes at the end of the trial between both treatment groups have been performed in previous trials, as baseline values should be equally distributed due to randomization, as done in other trials.(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 5–13 MHz at the University Hospital of Lausanne) with a machine-specific setting for carotid imaging. The measurement was performed zero 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 intra-class correlation coefficient was calculated using a two-way mixed-effects model.(18) The achieved intra-class correlation was 0.81 (95%CI 0.51-0.94) for mean CIMT and 0.93 (95%CI 0.70-0.99) 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 (Roche ECLIA), 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 Roche cobas 8000 system using enzymatic colorimetric analysis in 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 mmol/l.(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), cardiovascular risk factors (BMI, blood pressure, smoking status, diabetes mellitus and history of cardiovascular disease), and intervention data (treatment allocation, date of randomisation 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 cardiovascular 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 above-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% drop-outs/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 alpha level of 0.05, assuming a standard deviation of 0.13 mm from an expected distribution of CIMT in a population of elderly.(25)

All analyses were performed using Stata 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

## Results

### Trial population

Figure 1 shows the study flow-chart. 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. 13 (12%) participants in the intervention group and 19 (18%) in the control group were excluded from the primary analysis. 14 of the 16 withdrawals from follow-up were patient decisions, and two were due to adverse events. In one subject the primary outcome was not measurable due to 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 Appendix Table 1 (participants in primary analysis, n = 185), and were well balanced except for a higher prevalence of diabetes in the intervention group. Median time from baseline until carotid ultrasound exam was 18.5 months (interquartile range 12.2–30.4) in the levothyroxine group and 18.3 months (interquartile range 12.2–25.2) in the placebo group (p = 0.26). In the

levothyroxine group, 14 participants were started at a lower dose of 25 µg (12 participants due to known coronary heart disease and 2 due to 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 Figure 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 randomisation, 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,  $p<0.001$ ).

### **Carotid intima media thickness**

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,  $p = 0.35$ ) (Figure 3). Model fit was good (data not shown). Prespecified stratification according to sex, baseline TSH level and history of prior cardiovascular disease as well as post-hoc stratification according to baseline use of lipid-lowering medication did not reveal any statistically significant differences among sub-groups in favour of levothyroxine (Figure 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. Due to baseline imbalances, exploratory sensitivity analyses excluding participants with diabetes mellitus and adjusting for presence of diabetes mellitus were conducted and did not show statistically significant between-group differences (Table 2). Also, 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 re-assessed (Appendix 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,  $p = 0.46$ ). 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,  $p = 0.86$ ) (Figure 2). There were no significant differences in stratified analyses (Figure 2), per-protocol analysis or any sensitivity analysis (Table 2).

### **Change of co-interventions and cardiovascular risk factors over time**

Cardiovascular medications were nearly unchanged between the baseline visit and the 12 months visit between both treatment groups (Appendix Table 3). In an exploratory analysis, there was no significant between-group difference in cardiovascular 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, 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 (Appendix Table 4). A fatal or

non-fatal cardiovascular event occurred in 7 (6.4%) participants in the levothyroxine group and 6 (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 cardiovascular 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 7 (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 carotid intima media thickness and plaque burden in older persons with subclinical hypothyroidism after a median follow-up of 18.4 months. We found no differences according to sex, baseline TSH and history of prior cardiovascular disease.

These results contrast with a previous smaller randomized placebo-controlled trial of 45 participants with subclinical hypothyroidism, which after 6 months of stable euthyroidism found a decrease of CIMT of 0.09 mm (95%CI 0.06 to 0.11).<sup>(14)</sup> However, participants in this past trial were considerably younger (mean age  $37\pm 11$  years), and definition of subclinical hypothyroidism differed (TSH  $>3.6$  mIU/L). In addition, a before-after interventional study of 28 participants with subclinical hypothyroidism after 12 months of treatment with levothyroxine showed a regression of CIMT from  $0.67\pm 0.11$  to  $0.60\pm 0.10$  mm ( $p=0.021$ ), but was limited by a non-randomized non-controlled study design and small sample size.<sup>(13)</sup> Comparability is further limited by higher baseline TSH levels ( $12.32\pm 5.90$  mIU/L vs.  $6.35\pm 1.95$ ) and higher mean dose of levothyroxine (67 vs 43  $\mu\text{g}$ ) than in our trial. Also, neither of these studies included participants taking drugs that affect the lipid profile. While 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 cardiovascular 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 cardiovascular risk factors in subclinical hypothyroidism.<sup>(26)</sup> Moreover, changes in LDL cholesterol levels in previous smaller randomized placebo-controlled trials in subclinical hypothyroidism (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 mmol/l).<sup>(26)</sup> Another potential explanation for our negative findings might be that the follow-up time may have been too short to show a significant impact of levothyroxine treatment on CIMT. However, median follow-up time was 18.4 months compared to 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<sup>(13,14,24)</sup>, 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 METEOR<sup>(27)</sup> trial, over  $0.05\pm 0.001$  mm after 36 months in the SANDS trial<sup>(28)</sup> to 0.29mm after 12 months in uncontrolled trials.<sup>(29)</sup>

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 subclinical hypothyroidism 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 to statin 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)(30), and our results may thus not be generalizable to this subgroup of more pronounced subclinical hypothyroidism. 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 targeting 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.(31) We cannot rule out that targeting a lower TSH might have a significant effect. Also, at 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 significant 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,(32-35) the baseline cardiovascular 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 cardiovascular 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.(36) 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 approximately 100 participants per treatment arm is considered a large trial, where baseline variables can be expected to be evenly distributed between treatment arms.(37) 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 while 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.(36) Fourth, while 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 to placebo, normalization of TSH with levothyroxine did not show any evidence of a relevant impact on carotid intima media thickness and plaque burden in community-dwelling persons aged 65 years or older with subclinical hypothyroidism after a median follow-up of 18.4 months. The TRUST trial, the largest RCT on treatment of subclinical hypothyroidism, was underpowered to detect any effect of levothyroxine on the incidence of CV events or mortality,(5) and our results provide no evidence in favour of using levothyroxine to treat older adults with mild subclinical hypothyroidism with the goal of lowering CV risk. While CIMT is a predictor of future CV events,(8) larger and longer-duration randomized trials assessing clinical CV events would be needed to definitively determine the clinical effect of levothyroxine replacement in subclinical hypothyroidism.



## Disclosures, Acknowledgements, Funding

This study was supported by a grant of the Swiss National Science Foundation to Dr. Rodondi (SNSF 320030-150025 and 320030-172676), and an investigator-driven grant of the Velux Stiftung (974a, to Dr. Rodondi). The TRUST Trial was supported by a research grant (grant agreement number 278148) from the European Union FP7-HEALTH-2011 program and by grants from the Swiss National Science Foundation (SNSF 320030-150025, to Dr. Rodondi), the Swiss Heart Foundation (to Dr. Rodondi) and Velux Stiftung (974a, to Dr. Rodondi).

Dr. Blum's work was supported by an intramural personal grant by the Clinical Trials Unit of the Bern University Hospital at the University of Bern, Switzerland (grant number 84801053) and by a grant from the Swiss National Science Foundation (P2BEP3\_175289). Dr. Collet's research is supported by grants from the Swiss National Science Foundation (PZ00P3-167826).

Merck KGaA provided study medication as an investigator grant free of any cost or charges. Merck played no role in the design, analysis, or reporting of the trial. Merck KGaA reviewed the manuscript for medical accuracy only before journal submission. The authors are fully responsible for the content of this manuscript, and the views and opinions described in the publication reflect solely those of the authors.

Medications were classified using the WHO Collaborating Centre for Drug Statistics Methodology, ATC classification index with DDDs, 2017. Oslo, Norway 2016.

The Robertson Biostatistics Center at the University of Glasgow, UK, was the trial data center and prepared the trial data for analysis.

Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung <http://dx.doi.org/10.13039/501100001711>, 320030-150025, Nicolas Rodondi; Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung <http://dx.doi.org/10.13039/501100001711>, 320030-172676, Nicolas Rodondi; Velux Stiftung <http://dx.doi.org/10.13039/100007214>, 974a, Nicolas Rodondi; European Union FP7-HEALTH-2011, 278148, Not Applicable; Schweizerische Herzstiftung <http://dx.doi.org/10.13039/501100004362>, Nicolas Rodondi; Clinical Trials Unit, Bern, University Hospital, University of Bern, Switzerland, 84801053, Manuel Raphael Blum; Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung <http://dx.doi.org/10.13039/501100001711>, P2BEP3\_175289, Manuel Raphael Blum; Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung <http://dx.doi.org/10.13039/501100001711>, P3SMP3-155318, Tinh-Hai Collet; Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung <http://dx.doi.org/10.13039/501100001711>, PZ00P3-167826, Tinh-Hai Collet

**Corresponding author:** Nicolas Rodondi, MD, MAS, Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, 3010 Bern, Switzerland; Email: [nicolas.rodondi@insel.ch](mailto:nicolas.rodondi@insel.ch); Phone: +41 31 632 41 63; Fax +41 31 632 18 81

Disclosure:

The authors report no conflicts of interest in this work.

## References

1. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. *Endocr Rev* 2008; 29:76-131

2. Moran AE, Forouzanfar MH, Roth GA, Mensah GA, Ezzati M, Flaxman A, Murray CJ, Naghavi M. The global burden of ischemic heart disease in 1990 and 2010: the Global Burden of Disease 2010 study. *Circulation* 2014; 129:1493-1501
3. Rodondi N, den Elzen WP, Bauer DC, Cappola AR, Razvi S, Walsh JP, Asvold BO, Iervasi G, Imaizumi M, Collet TH, Bremner A, Maisonneuve P, Sgarbi JA, Khaw KT, Vanderpump MP, Newman AB, Cornuz J, Franklyn JA, Westendorp RG, Vittinghoff E, Gussekloo J. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *Jama* 2010; 304:1365-1374
4. Gencer B, Collet TH, Virgini V, Bauer DC, Gussekloo J, Cappola AR, Nanchen D, den Elzen WP, Balmer P, Luben RN, Iacoviello M, Triggiani V, Cornuz J, Newman AB, Khaw KT, Jukema JW, Westendorp RG, Vittinghoff E, Aujesky D, Rodondi N. Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. *Circulation* 2012; 126:1040-1049
5. Stott DJ, Rodondi N, Kearney PM, Ford I, Westendorp RG, Mooijaart SP, Sattar N, Aubert CE, Aujesky D, Bauer DC, Baumgartner C, Blum MR, Browne JP, Byrne S, Collet TH, Dekkers OM, den Elzen WP, Du Puy RS, Ellis G, Feller M, Floriani C, Hendry K, Hurley C, Jukema JW, Kean S, Kelly M, Krebs D, Langhorne P, McCarthy G, McCarthy V, McConnachie A, McDade M, Messow M, O'Flynn A, O'Riordan D, Poortvliet RK, Quinn TJ, Russell A, Sinnott C, Smit JW, Van Dorland HA, Walsh KA, Walsh EK, Watt T, Wilson R, Gussekloo J. Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism. *N Engl J Med* 2017;
6. Stott DJ, Gussekloo J, Kearney PM, Rodondi N, Westendorp RG, Mooijaart S, Kean S, Quinn TJ, Sattar N, Hendry K, Du Puy R, Den Elzen WP, Poortvliet RK, Smit JW, Jukema JW, Dekkers OM, Blum M, Collet TH, McCarthy V, Hurley C, Byrne S, Browne J, Watt T, Bauer D, Ford I. Study protocol; Thyroid hormone Replacement for Untreated older adults with Subclinical hypothyroidism - a randomised placebo controlled Trial (TRUST). *BMC Endocr Disord* 2017; 17:6
7. Tardif JC, Heinonen T, Orloff D, Libby P. Vascular biomarkers and surrogates in cardiovascular disease. *Circulation* 2006; 113:2936-2942
8. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation* 2007; 115:459-467
9. Lorenz MW, Schaefer C, Steinmetz H, Sitzer M. Is carotid intima media thickness useful for individual prediction of cardiovascular risk? Ten-year results from the Carotid Atherosclerosis Progression Study (CAPS). *Eur Heart J* 2010; 31:2041-2048
10. Smilde TJ, van Wissen S, Wollersheim H, Trip MD, Kastelein JJ, Stalenhoef AF. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. *Lancet* 2001; 357:577-581
11. Lind L, Peters SA, den Ruijter HM, Palmer MK, Grobbee DE, Crouse JR, 3rd, O'Leary DH, Evans GW, Raichlen JS, Bots ML. Effect of rosuvastatin on the echolucency of the common carotid intima-media in low-risk individuals: the METEOR trial. *J Am Soc Echocardiogr* 2012; 25:1120-1127.e1121
12. Taylor AJ, Villines TC, Stanek EJ, Devine PJ, Griffen L, Miller M, Weissman NJ, Turco M. Extended-release niacin or ezetimibe and carotid intima-media thickness. *N Engl J Med* 2009; 361:2113-2122
13. Kim SK, Kim SH, Park KS, Park SW, Cho YW. Regression of the increased common carotid artery-intima media thickness in subclinical hypothyroidism after thyroid hormone replacement. *Endocr J* 2009; 56:753-758

14. Monzani F, Caraccio N, Kozakowa M, Dardano A, Vittone F, Viridis A, Taddei S, Palombo C, Ferrannini E. Effect of levothyroxine replacement on lipid profile and intima-media thickness in subclinical hypothyroidism: a double-blind, placebo- controlled study. *J Clin Endocrinol Metab* 2004; 89:2099-2106
15. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, Csiba L, Desvarieux M, Ebrahim S, Hernandez Hernandez R, Jaff M, Kownator S, Naqvi T, Prati P, Rundek T, Sitzer M, Schminke U, Tardif JC, Taylor A, Vicaut E, Woo KS. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. *Cerebrovasc Dis* 2012; 34:290-296
16. Grady D, Yaffe K, Kristof M, Lin F, Richards C, Barrett-Connor E. Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/progestin Replacement Study. *Am J Med* 2002; 113:543-548
17. Zanchetta JR, Bogado CE, Ferretti JL, Wang O, Wilson MG, Sato M, Gaich GA, Dalsky GP, Myers SL. Effects of teriparatide [recombinant human parathyroid hormone (1-34)] on cortical bone in postmenopausal women with osteoporosis. *J Bone Miner Res* 2003; 18:539-543
18. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull* 1979; 86:420-428
19. Cicchetti DV, Sparrow SA. Developing criteria for establishing interrater reliability of specific items: applications to assessment of adaptive behavior. *Am J Ment Defic* 1981; 86:127-137
20. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972; 18:499-502
21. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, 3rd, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC, Jr., Taubert K, Tracy RP, Vinicor F. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003; 107:499-511
22. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM, Carpenter JR. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *Bmj* 2009; 338:b2393
23. Altman DG. Missing outcomes in randomized trials: addressing the dilemma. *Open Med* 2009; 3:e51-53
24. Nagasaki T, Inaba M, Henmi Y, Kumeda Y, Ueda M, Tahara H, Sugiguchi S, Fujiwara S, Emoto M, Ishimura E, Onoda N, Ishikawa T, Nishizawa Y. Decrease in carotid intima-media thickness in hypothyroid patients after normalization of thyroid function. *Clin Endocrinol (Oxf)* 2003; 59:607-612
25. Sillesen H, Muntendam P, Adourian A, Entekin R, Garcia M, Falk E, Fuster V. Carotid plaque burden as a measure of subclinical atherosclerosis: comparison with other tests for subclinical arterial disease in the High Risk Plaque BioImage study. *JACC Cardiovasc Imaging* 2012; 5:681-689
26. Rugge JB, Bougatsos C, Chou R. Screening and treatment of thyroid dysfunction: an evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2015; 162:35-45
27. Crouse JR, 3rd, Raichlen JS, Riley WA, Evans GW, Palmer MK, O'Leary DH, Grobbee DE, Bots ML. Effect of rosuvastatin on progression of carotid intima-media

thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. *Jama* 2007; 297:1344-1353

28. Fleg JL, Mete M, Howard BV, Umans JG, Roman MJ, Ratner RE, Silverman A, Galloway JM, Henderson JA, Weir MR, Wilson C, Stylianou M, Howard WJ. Effect of statins alone versus statins plus ezetimibe on carotid atherosclerosis in type 2 diabetes: the SANDS (Stop Atherosclerosis in Native Diabetics Study) trial. *J Am Coll Cardiol* 2008; 52:2198-2205
29. Riccioni G, Vitulano N, Mancini B, Zanasi A, D'Orazio N. One-year treatment with rosuvastatin reduces intima-media thickness in 45 hypercholesterolemic subjects with asymptomatic carotid artery disease. *Pharmacology* 2010; 85:63-67
30. Surks MI, Hollowell JG. Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. *J Clin Endocrinol Metab* 2007; 92:4575-4582
31. Pearce SH, Brabant G, Duntas LH, Monzani F, Peeters RP, Razvi S, Wemeau JL. 2013 ETA Guideline: Management of Subclinical Hypothyroidism. *Eur Thyroid J* 2013; 2:215-228
32. Liao X, Norata GD, Polak JF, Stehouwer CD, Catapano A, Rundek T, Ezhov M, Sander D, Thompson SG, Lorenz MW, Balakhonova T, Safarova M, Grigore L, Empana JP, Lin HJ, McLachlan S, Bokemark L, Ronkainen K, Schminke U, Lind L, Willeit P, Yanez DN, Steinmetz H, Poppert H, Desvarieux M, Ikram MA, Johnsen SH, Iglseeder B, Frier A, Xie W, Plichart M, Su TC, Srinivasan SR, Schmidt C, Tuomainen TP, Volzke H, Nijpels G, Willeit J, Franco OH, Suarez C, Zhao D, Ducimetiere P, Chien KL, Robertson C, Bergstrom G, Kauhanen J, Dorr M, Dekker JM, Kiechl S, Sitzer M, Bickel H, Sacco RL, Hofman A, Mathiesen EB, Gabriel R, Liu J, Berenson G, Kavousi M, Price JF. Normative values for carotid intima media thickness and its progression: Are they transferrable outside of their cohort of origin? *Eur J Prev Cardiol* 2016; 23:1165-1173
33. Engelen L, Ferreira I, Stehouwer CD, Boutouyrie P, Laurent S. Reference intervals for common carotid intima-media thickness measured with echotracking: relation with risk factors. *Eur Heart J* 2013; 34:2368-2380
34. Baldassarre D, Hamsten A, Veglia F, de Faire U, Humphries SE, Smit AJ, Giral P, Kurl S, Rauramaa R, Mannarino E, Grossi E, Paoletti R, Tremoli E. Measurements of carotid intima-media thickness and of interadventitia common carotid diameter improve prediction of cardiovascular events: results of the IMPROVE (Carotid Intima Media Thickness [IMT] and IMT-Progression as Predictors of Vascular Events in a High Risk European Population) study. *J Am Coll Cardiol* 2012; 60:1489-1499
35. Sturlaugsdottir R, Aspelund T, Bjornsdottir G, Sigurdsson S, Thorsson B, Eiriksdottir G, Gudnason V. Prevalence and determinants of carotid plaque in the cross-sectional REFINE-Reykjavik study. *BMJ Open* 2016; 6:e012457
36. Friedman LM, Furberg CD, DeMets DL, Reboussin DM, Granger CB. *Fundamentals of Clinical Trials*. Fifth ed: Springer International Publishing; 2015:181.
37. Nuesch E, Trelle S, Reichenbach S, Rutjes AW, Tschannen B, Altman DG, Egger M, Juni P. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. *BMJ* 2010; 341:c3515
38. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150:604-612

Figure 1: Study flow-chart. Legend: 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. Abbreviations: IMT, intima media thickness

Figure 2: Course of TSH levels over time. Legend: Data show mean TSH levels, and error bars indicate 95% confidence intervals, in 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, starting dose of levothyroxine (with additional adjustment for time to visit for the end of trial visit). The grey shaded area denotes the target reference range of TSH. Abbreviations: TSH, thyroid-stimulating hormone

Figure 3: Main outcomes and stratified analyses. Legend: <sup>a</sup> 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. Abbreviations: CI, confidence interval; CIMT, carotid intima media thickness; CVD, cardiovascular disease; n, number of participants included in the analysis; SD, standard deviation; TSH, thyroid-stimulating hormone. <sup>b</sup> Defined as at least one of the following: acute coronary syndrome (myocardial infarction, stable or unstable angina), coronary or other arterial revascularization, stroke, transient ischemic attack, peripheral arterial disease. <sup>c</sup> Defined as use of statin and/or fibrate at baseline.

Table 1: Baseline characteristics <sup>a</sup>

	Levothyroxine n = 109	Placebo n = 108
<b>Demographics</b>		
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)
<b>Cardiovascular risk factors</b>		
BMI (kg/m <sup>2</sup> , mean ± SD) <sup>b</sup>	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, %) <sup>c</sup>	8 (7.3)	10 (9.3)
Diabetes mellitus (n, %)	17 (15.6)	11 (10.2)
Prior CVD <sup>d</sup>	26 (23.9)	30 (27.8)
Estimated creatinine clearance (n, %) <sup>e</sup>		
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)
<b>Lipid profile</b>		
Total cholesterol (mmol/L, mean ± SD) <sup>f</sup>	5.08 ± 1.09	5.18 ± 1.11
LDL cholesterol (mmol/L, mean ± SD) <sup>g</sup>	2.84 ± 0.99	2.88 ± 0.93
HDL cholesterol (mmol/L, mean ± SD) <sup>h</sup>	1.45 ± 0.47	1.49 ± 0.46
Triglycerides (mmol/L, mean ± SD) <sup>i</sup>	1.80 ± 1.13	1.78 ± 0.87
<b>Concomitant medication</b>		
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)
<b>Thyroid function</b>		
TSH (mIU/L, mean ± SD)	6.40 ± 2.02	6.51 ± 2.12
FT4 (pmol/L, mean ± SD)	13.5 ± 2.0	13.7 ± 1.9

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; FT4, free thyroxine; HDL, high density lipoprotein; LDL, low density lipoprotein; n, number; SD, standard deviation; TSH, thyroid stimulating hormone; y, years

<sup>a</sup> Baseline characteristics of participants in the primary analysis (n=185) are provided in the Appendix Table 1.

<sup>b</sup> Calculated as weight (kg) divided by squared height (m)

<sup>c</sup> Defined as currently smoking at the time of baseline exam.

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

<sup>e</sup> Calculated using the CKD-EPI equation.(38)

<sup>f</sup> Missing for two participants in the placebo group.

<sup>g</sup> Calculated using the Friedewald equation if triglycerides lower than 4.6 mmol/L. Missing for four participants in the levothyroxine group and four participants in the placebo group.

<sup>h</sup> Missing for one participant in the levothyroxine group and three participants in the placebo group.

<sup>i</sup> Missing for two participants in the placebo group.

Table 2: Sensitivity analyses

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

Legend:

<sup>a</sup> Adjusted for stratification variables (sex, study center, starting dose of levothyroxine) and time to visit, using linear regression.

<sup>b</sup> The outcome of mean CIMT and maximum CIMT were imputed in 32 of 217 (14.7%) participants.

<sup>c</sup> Defined as: Outcome of interest measured, on study drug at final visit and not down-titrated to 0 µg in levothyroxine group.

Abbreviations: CI, confidence interval; CIMT, carotid intima media thickness; n, number of participants included in the analysis; SD, standard deviation.







