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The Impact of Levothyroxine on Cardiac Function in Older Adults With Mild Subclinical Hypothyroidism: A Randomized Clinical Trial

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ABSTRACT

BACKGROUND: Subclinical hypothyroidism has been associated with heart failure, but only small trials assessed whether treatment with levothyroxine has an impact on cardiac function.

METHODS: In a randomized, double-blind, placebo-controlled, trial nested within the TRUST trial, Swiss participants ages ≥65 years with subclinical hypothyroidism (thyroid-stimulating hormone [TSH] 4.60-19.99 mIU/L; free thyroxine level within reference range) were randomized to levothyroxine (starting dose of 50 μg daily) to achieve TSH normalization or placebo. The primary outcomes were the left ventricular ejection fraction for systolic function and the ratio between mitral peak velocity of early filling to early diastolic mitral annular velocity (E/e′ ratio) for diastolic function. Secondary outcomes included e′ lateral/septal, left atrial volume index, and systolic pulmonary artery pressure.

RESULTS: A total of 185 participants (mean age 74.1 years, 47% women) underwent echocardiography at the end of the trial. After a median treatment duration of 18.4 months, the mean TSH decreased from 6.35 mIU/L to 3.55 mIU/L with levothyroxine (n = 96), and it remained elevated at 5.29 mIU/L with placebo (n = 89). The adjusted between-group difference was not significant for the mean left ventricular ejection fraction (62.7% vs 62.5%, difference = 0.4%, 95% confidence interval −1.8% to 2.5%, $P = 0.72$) and the E/e′ ratio (10.6 vs 10.1, difference 0.4, 95% confidence interval −0.7 to 1.4, $P = 0.47$). No differences were found for the secondary diastolic function parameters or for interaction according to sex, baseline TSH, preexisting heart failure, and treatment duration (P value >0.05).

CONCLUSION: Systolic and diastolic heart function did not differ after treatment with levothyroxine compared with placebo in older adults with mild subclinical hypothyroidism.

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INTRODUCTION

Subclinical hypothyroidism, defined as thyroid-stimulating hormone (TSH) above the reference range with free thyroxine (FT4) levels within the defined reference range, is a common condition affecting up to 10%-20% of persons older than 65 years of age.[1] An individual participant data meta-analysis of large prospective cohorts showed an increased risk of heart failure events for both subclinical hypothyroidism and hyperthyroidism compared with euthyroidism,[2] and another large populational study pointed out an increased risk of heart failure in subclinical hyperthyroidism only.[3] In the Cardiovascular Health Study, participants with TSH ≥10mIU/L had a greater risk of heart failure compared to individuals with euthyroidism.[4] Baseline mitral peak velocity of early filling (E), an echo parameter of diastolic dysfunction, was greater in participants with TSH ≥10 mIU/l compared to participants with euthyroidism.[4]

The TRUST trial ("Multi-Modal Effects of Thyroid Replacement for Untreated Older Adults with Subclinical Hypothyroidism"), the largest available multicenter randomized controlled trial (RCT) comparing levothyroxine to placebo in older individuals with subclinical hypothyroidism, was not powered for clinical cardiovascular outcomes.[5] In this context E echocardiographic endpoints of cardiac function are relevant to evaluate the impact of treating subclinical hypothyroidism.[6] Several small interventional studies suggested a potential improvement of systolic and diastolic function with the treatment of subclinical hypothyroidism.[1] However, these trials had limitations (ie, small sample sizes [the largest included only 30 participants], a higher risk of overestimation or underestimation of treatment effects associated with small, underpowered trials, or non-controlled study designs).[7-11] Therefore, we aimed to assess the effect of thyroid hormone therapy on cardiac function in older adults with subclinical hypothyroidism and hypothesized that thyroid hormone therapy would preserve cardiac function.

CLINICAL SIGNIFICANCE

- In this double-blind randomized placebo-controlled trial of 185 participants older than 65 years of age with subclinical hypothyroidism, cardiac function did not differ with a treatment of levothyroxine after a median follow-up of 18.4 months.
- The mean left ventricular ejection fraction was similar in both arms, for systolic function, and no significant differences were found for the ratio between mitral peak velocity of early filling to early diastolic mitral annular velocity for diastolic function.

METHODS

This trial was registered on ClinicalTrials.gov, number NCT02832960, as a nested study within the TRUST trial (ClinicalTrials.gov, number NCT01660126), that included TRUST participants included at the 2 Swiss study centers (Inselspital, Bern University Hospital, and Centre Hospitalier Universitaire Vaudois, Lausanne University Hospital). The protocol was approved by the local institutional review boards, and written informed consent obtained from all participants.

The TRUST Trial

The TRUST was a 2-arm, parallel, placebo-controlled, double-blind, superiority, multicenter, randomized clinical trial.[5] A detailed description of the design and main results of the TRUST trial have been published previously.[5] The inclusion criteria were an age of 65 years or older and persistent subclinical hypothyroidism, defined as an elevated thyrotropin level (4.60-19.99 mIU/L) that was measured on at least 2 occasions that were 3 months to 3 years apart, with the FT4 level within the reference range. The relevant exclusion criteria for this analysis were an acute coronary syndrome (including myocardial infarction or unstable angina) within the previous 4 weeks and severe heart failure, defined as New York Heart Association stage IV. Using central web-based computed-generated randomly permuted blocks, participants were allocated in a 1:1 ratio and stratified according to sex and treatment starting dose. The intervention consisted of levothyroxine with a starting dose of 50 μg daily, or 25 μg for participants with a body weight of <50 kg or with a history of coronary heart disease. The medication was dose-titrated every 6-8 weeks to achieve a TSH level within the reference range (0.40-4.59 mIU/L).[12] The following algorithm was used: 1) TSH <0.40 mIU/L meant 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 4-6weeks, the patient was withdrawn from randomized treatment; 2) TSH 0.40-4.59 mIU/L meant no change to the levothyroxine dose; patient to be reviewed at 12 months; and 3) TSH ≥4.60 mIU/L meant additional 25 μg levothyroxine. A mock titration was performed in the placebo group using an adaptive schedule, in which the data center allocated (by computer algorithm) the same proportion of patients on placebo to dose adjustment (up or down) as required in the levothyroxine group (followed by check of TSH at 6-8 weeks). The participants, investigators, and treating physicians remained blinded to the results of TSH measurements and for treatment allocation.

Outcomes

We performed an echocardiography at the final visit of the Swiss participants included in the TRUST trial. The primary outcome was the ratio (E/e′ ratio) between mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e′) for diastolic function and left ventricular ejection fraction for systolic function, using the biplane Simpson rule.[6,13] The E/e′ ratio was validated as a strong predictor of cardiac events in high-risk patients.[14] We used

the same approach that previous trials have by comparing imaging outcomes between treatment groups at the end of the trial.[15,16] Secondary measurements of diastolic function were: 1) Doppler-derived transmitral inflow patterns (E and A peak velocity, E/A ratio, E velocity deceleration time, ratio of transmitral E velocity to tissue Doppler-derived early diastolic velocity of the mitral annulus, deceleration time), 2) left atrial volume index using the Biplane Area-Length Methods, and 3) tricuspid regurgitation velocity.[13] To define the presence of diastolic dysfunction in patients with normal left ventricular ejection fraction, the algorithm for the diagnosis of diastolic dysfunction was based on: 1) average E/e′ >14, 2) septal e′ velocity <7 cm/s or lateral e′ velocity <10 cm/s, 3) tricuspid regurgitation velocity >2.8 m/s, and 4) left atrial volume index > 34mL/m^2.[13] Participants were classified as 1) having diastolic dysfunction if >2 positive criteria, 2) having indeterminate function if 2 positive criteria, and 3) having normal diastolic function if <2 positive criteria.[13] Additional secondary measurements comprised systolic pulmonary pressure and longitudinal global strain.[17] The standard acquisition protocol for transthoracic echocardiography was performed by certified operators.[6] The definition of outcome was prespecified before the acquisition and the plausibility of entered values was checked by a certified cardiologist (BG).

Statistical Analysis

The primary analysis was conducted according to a modified intention-to-treat principle on a population of participants randomized with echocardiography data.[5] We compared the outcomes between groups with adjustment for variables (sex, starting dose of levothyroxine, study center, and time to visit), using multivariable linear regression. Prespecified subgroup analyses were performed according to sex, TSH levels, preexisting cardiovascular disease or heart failure, and use of antihypertensive medication. We also compared the difference in cardiovascular risk factors, medications and biomarkers (N-terminal pro b-type natriuretic peptide [NT-proBNP]) between treatment groups at follow-up at 12 months using multivariable linear regression adjusting for the baseline value. Finally, we examined whether the missing of the primary endpoints were different in both arms.

Power Calculation

With 185 participants with echocardiography, we had a statistical power of 92% to detect a between-group difference of the mean of E/e′ ratio and left ventricular ejection fraction of 0.5 standard deviation (SD) units with an alpha = 0.05 (2-sided).[14] Our sample size was able to detect differences of 5% in left ventricular ejection fraction (considering 10% as a SD) and 1.25 in E/e′ ratio (considering 2.5 as a SD). All analyses were performed using Stata statistical software (Version 14, StataCorp LP, College Station, Tex).

RESULTS

Studied Population

Figure depicts the study flowchart. Participants were enrolled from April 2013 through December 2015. In total, 603 participants were screened, and 217 were randomized to the intervention group (n = 109) or the control group (n = 108). Thirteen (12%) participants in the intervention group and 19 (18%) in the control group did not have echocardiography. Four participants in the intervention group

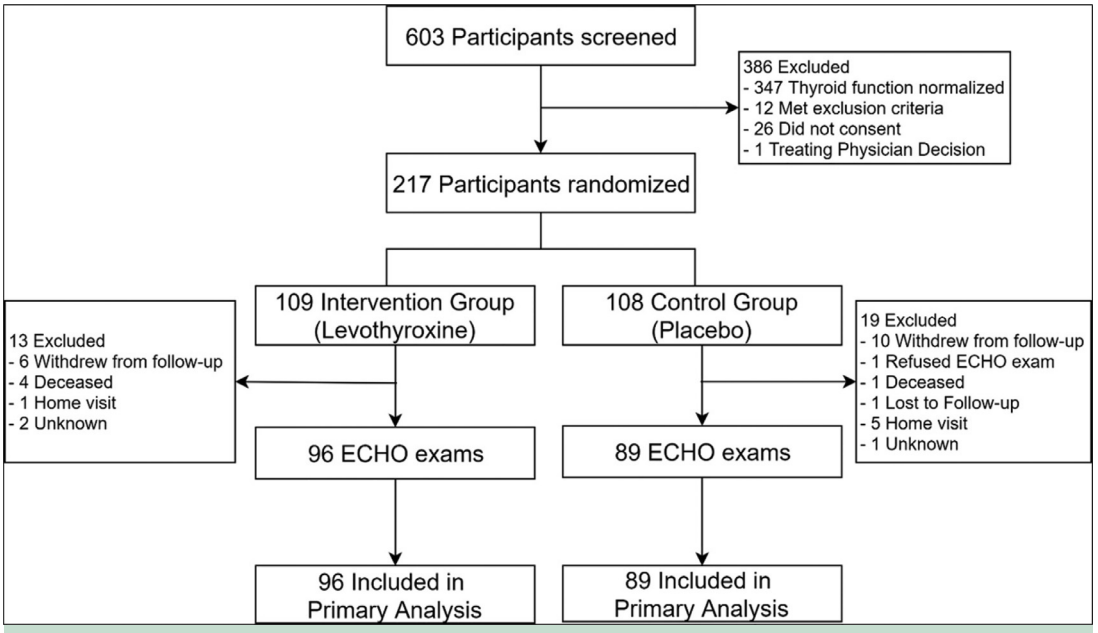

Figure Study flowchart. Home visit indicates participants that requested, usually for mobility issues, to do the final study visit at home, where it was not possible to perform an echocardiography.

Table 1 Baseline Characteristics for Participants With Echocardiography

	Levothyroxine n = 96	Placebo n = 89
Demographics*		
Age (y, mean ± SD)	74.4 ± 5.3	73.8 ± 5.9
Female (n, %)	44 (45.8)	43 (48.3)
White (n, %)	95 (99.0)	87 (97.8)
Cardiovascular risk factors		
BMI (kg/m^2, mean ± SD)†	27.6 ± 4.9	26.9 ± 4.7
Blood pressure (mm Hg, mean ± SD)		
Systolic	138.6 ± 18.0	139.1 ± 20.0
Diastolic	74.3 ± 10.9	77.4 ± 12.9
Currently smoking (n, %)‡	8 (8.3)	9 (10.1)
Diabetes mellitus (n, %)	14 (14.6)	6 (6.7)
Preexisting CVD (n, %)§	28 (25.7)	32 (29.6)
Preexisting HF (n, %)	1 (1.0)	5 (5.6)
Estimated creatinine clearance (n, %)¶		
Normal (≥90 mL/min)	5 (5.2)	6 (6.7)
Mild (60-89 mL/min)	53 (55.2)	58 (65.2)
Moderate (30-59 mL/min)	35 (36.5)	22 (24.7)
Severe (< 30 mL/min)	3 (3.1)	3 (3.4)
History of atrial fibrillation (n, %)	14 (14.6)	9 (10.1)
Lipid profile		
Total cholesterol (mmol/L, mean ± SD)**	5.11 ± 1.11	5.31 ± 1.10
LDL cholesterol (mmol/L, mean ± SD)††	2.88 ± 1.01	2.98 ± 0.94
HDL cholesterol (mmol/L, mean ± SD)‡‡	1.46 ± 0.48	1.51 ± 0.46
Triglycerides (mmol/L, mean ± SD)§§	1.78 ± 1.14	1.79 ± 0.91
Concomitant medication		
Antiplatelets (n, %)	30 (31.3)	27 (30.3)
Lipid-lowering (n, %)	44 (45.9)	32 (36.0)
Statin (n, %)	43 (44.8)	32 (36.0)
Antihypertensives (n, %)	58 (60.4)	47 (52.8)
Diuretics (n, %)	16 (16.7)	9 (10.1)
ACE inhibitor/ARB (n, %)	45 (46.9)	35 (39.3)
Beta-blockers (n, %)	29 (30.2)	20 (22.5)
Antidiabetics (n, %)	14 (14.6)	4 (4.5)
Insulin (n, %)	4 (4.2)	1 (1.1)
Cardiac function		
NT-pro BNP (pg/mL; median, IQR)¶¶	148 (158)	101 (114)
Baseline thyroid function		
TSH (mIU/L, mean ± SD)	6.26 ± 1.75	6.47 ± 2.17
FT4 (pmol/L, mean ± SD)	13.6 ± 2.0	13.7 ± 1.8

ACE = angiotensin-converting enzyme; ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; BMI = body mass index; CKD-EPI = chronic kidney disease epidemiology collaboration; CVD = cardiovascular disease; FT4 = free thyroxine; HDL = high-density lipoprotein; HF = heart failure; IQR = interquartile range; LDL = low-density lipoprotein; n = number; NT-pro BNP = N-terminal pro b-type natriuretic peptide; SD = standard deviation; TSH = thyroid-stimulating hormone; y = years.

*Baseline characteristics of all participants (n = 217) are provided in Supplemental Table 2, available online.

†Calculated as weight (kg) divided by squared height (m).

‡Defined as currently smoking at the time of baseline examination.

§Defined as 1 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.

¶Calculated using the CKD-EPI equation.

**Missing for 2 participants in the placebo group.

††Calculated using the Friedewald equation if triglycerides were lower than 4.6 mmol/L (400 mg/dL). Missing for 4 participants in the levothyroxine group and 4 participants in the placebo group.

‡‡Missing for 1 participant in the levothyroxine group and 3 participants in the placebo group.

§§Missing for 2 participants in the placebo group.

¶¶Missing for 5 participants in the placebo group and 3 participants in the levothyroxine group.

Table 2 Outcomes for Echocardiographic Systolic and Diastolic Cardiac Functions

	Levothyroxine		Placebo		Difference*	*P* Value
	N	Mean (SD)	N	Mean (SD)	Mean (95% CI)	
Systolic Function						
Left ventricular ejection fraction (%)†	95	62.9 (7.9)	89	62.5 (7.4)	0.4 (−1.8 to 2.5)	0.72
Global longitudinal strain (%)	58	−17.8 (3.5)	58	−18.5 (3.7)	0.5 (−0.8 to 1.8)	0.43
Diastolic Function						
E/e′	85	10.6 (3.7)	84	10.1 (3.3)	0.4 (−0.7 to 1.4)	0.47
e′ lateral (cm/s)	77	7.8 (1.8)	76	8.1 (2.5)	−0.2 (−0.9 to 0.5)	0.54
e′ septal (cm/s)	86	5.8 (1.3)	85	5.9 (1.9)	−0.1 (−0.6 to 0.4)	0.75
Left atrial volume index (mL/m^2)	90	34.7 (15.9)	85	32.9 (11.7)	1.2 (−3.0 to 5.5)	0.57
Systolic pulmonary artery pressure (mm Hg)	62	36.6 (12.2)	51	32.5 (10.0)	5.1 (0.9 to 9.2)	0.02
E/A ratio	81	0.8 (0.3)	81	0.8 (0.2)	0.00 (−0.1 to 0.1)	0.94
E deceleration time (ms)	78	225.5 (56.8)	78	216.22 (53.3)	9.7 (−7.5 to 26.9)	0.27

CI = confidence interval; n = number; SD = standard deviation.

*Calculated using multivariable linear regression adjusted for sex, center, treatment starting dose, and length of follow-up.

†The range (min-max) of the left ventricular ejection fraction was 38%-80% in the levothyroxine arm and 20%-77% in the placebo arm.Missing values for primary and secondary endpoints: 1 participant had not measurable left ventricular ejection fraction. A total of 16 participants (11 in the levothyroxine group and 5 in the placebo group) had E/e′ outcomes not measurable with the recorded examinations. The systolic pulmonary artery pressure was not measurable in 72 participants (34 in the levothyroxine group and 38 in the placebo group). A total of 10 participants had not measurable left atrial volume (6 in the levothyroxine group and 4 in the placebo group). Global longitudinal strain was performed only if the quality of images allowed to perform speckle tracking.

died (2 of them from cardiovascular causes) as did 1 in the placebo group (Supplemental Table 1, available online). This resulted in a modified intention-to-treat population of 96 in the intervention group and 89 in the control group. Missing data for the primary echocardiographic outcome were equally distributed between the randomized arms ($P = 0.61$ for left ventricular ejection fraction and $P = 0.55$ for E/e′).

Baseline characteristics were well balanced except for a higher prevalence of diabetes in the intervention group (Table 1 and Supplemental Table 2, available online). The median time from baseline until echocardiography examination was 18.4 months (interquartile range 12.2-30.4) in the levothyroxine group and 18.2 months (interquartile range 12.2-24.7) in the placebo group.

Thyroid Function Tests

At 6 to 8 weeks after randomization, TSH decreased to 2.95 ± 1.08 (range 0.9-5.4) mIU/L in the levothyroxine group and to 5.37 ± 2.04 (range 1.9-12.6) mIU/L in the placebo group ($P < 0.001$). At 12 months, the mean TSH was 3.48 ± 2.12 mIU/L in the levothyroxine group and 5.25 ± 2.23 mIU/L in the placebo group (adjusted between-group difference 1.74 mIU/L, $P < 0.001$; Supplemental Figure 1, available online). There was no patient with a TSH between 0.4 and 0.6 mIUL/L at 12 months in both arms, whereas 2 participants had a TSH <0.4 mIU/L at 12 months in the levothyroxine arm.

Systolic and Diastolic Cardiac Function

The mean left ventricular ejection was 62.7% ± 7.9 in the levothyroxine group and 62.5% ± 7.4 in the placebo group (adjusted between-group difference 0.4%, 95% confidence interval [CI] -1.8% to 2.5%, $P = 0.72$, Table 2). The range (min-max) of the left ventricular ejection fraction was 38%-80% in the levothyroxine arm and 20%-77% in the placebo arm. Regarding diastolic function, no statistically significant differences were found for the E/e′ ratio (10.6 vs 10.1, adjusted between-group difference 0.4, 95%CI -0.7 to 1.4, $P = 0.47$). For secondary outcomes, no significant differences were observed in longitudinal systolic function (-17.8% ± 3.5 vs -18.5% ± 3.7, adjusted between-group difference 0.5%, 95% CI -0.8% to 1.8%, $P = 0.43$). Regarding diastolic function, no statistically significant differences were found for E wave, lateral and septal e′, E/A ratio, E-wave deceleration time, left atrial volume indexed (all $P > 0.25$), except for systolic pulmonary artery pressure (37 mm Hg in the levothyroxine group vs 33 mm Hg in the placebo group, $P = 0.02$ in intention-to-treat, but $P = 0.06$ in per protocol, Supplemental Table 3, available online). In sensitivity analyses, results were similar after excluding 16 patients with atrial fibrillation or nonsinus rhythm at the time of examination (Supplemental Table 4, available online). There was no significant difference between treatment groups in heart rate at the time of echocardiography ($P = 0.69$). The proportions of patients with normal systolic function (93.7% vs 97.8%, $P = 0.24$) and according to diastolic function classification (normal function 54.3% vs 58.1%, indeterminate 16.1% vs 16.3% and diastolic dysfunction 29.6% vs 25.6%, $P = 0.57$) were similar in the levothyroxine group and the placebo group (Table 3).

Prespecified stratification for primary endpoints according to sex, baseline TSH level, or history of prior cardiovascular disease or heart failure, as well as post hoc stratification according to baseline use of antihypertensive medication and treatment duration did not reveal any statistically significant differences among subgroups in favor of levothyroxine

Table 3 Classification of Echocardiographic Cardiac Function Abnormalities

	Levothyroxine N (%)	Placebo N (%)	*P* Value*
Ejection fraction	95	89	0.24
Normal (%)	89 (93.7)	87 (97.8)	
Reduced (defined as ≤50%)	6 (6.3)	2 (2.3)	
Diastolic dysfunction in patients with normal LVEF	81	86	0.57
Normal function (%)	44 (54.3)	50 (58.1)	
Indeterminate (%)	13 (16.1)	14 (16.3)	
Diastolic dysfunction (%)	24 (29.6)	22 (25.6)	

*Calculated using logistic or ordinal logistic regression models, adjusting for sex, center, treatment starting dose, and length of follow-up.

(Table 4 and Table 5). Due to baseline imbalances, exploratory sensitivity analyses excluding participants with diabetes mellitus (Supplemental Table 5, available online) and adjusting for presence of diabetes mellitus (Supplemental Table 6, available online) did not show statistically significant between-group differences. Similar findings were observed when excluding the 9 participants who had a baseline TSH ≥10 mIU/L (Supplemental Table 7, available online) or excluding those with preexisting heart failure (Supplemental Table 8, available online). The assessment of cardiovascular risk factors (blood pressure and cholesterol), biomarkers (high-sensitivity C-reactive protein [hs-CRP] and NT-proBNP) and cardiovascular medication at baseline and after 12 months did not show any significant differences over time in the levothyroxine and placebo groups (Supplemental Table 9, available online). At baseline, the median NT-proBNP levels were slightly higher in the group randomized to levothyroxine compared with placebo (156 vs 110 pg/mL, $P = 0.014$), but between-group changes over time were not statistically significant (38 pg/mL, 95% CI −14 to 91, $P = 0.15$).

DISCUSSION

In this double-blind randomized placebo-controlled trial of 185 participants older than 65 years with mild subclinical hypothyroidism, systolic and diastolic cardiac function did not differ after treatment of levothyroxine compared to placebo after a median follow-up of 18.4 months.

Although the measurement of TSH is recommended in the assessment and management of heart failure,[18] few studies have assessed the impact of thyroid hormone therapy on cardiac function in patients with subclinical hypothyroidism.[19] The available evidence was from young adults with mild subclinical hypothyroidism and moderate-sized studies.[9-11] In a nonrandomized study of 26 subjects (mean age 32.6 years old) with subclinical hypothyroidism and 30 controls, echo-Doppler parameters of diastolic dysfunction were

Table 4 Stratified Analyses for Echocardiographic Systolic Function

LVEF	Levothyroxine		Placebo		Between-group difference, 95% CI*	*P* Value	*P* for interaction
	n	Mean ± SD	n	Mean ± SD			
LVEF (% ± SD)	95	62.7 ± 7.9	89	62.5 ± 7.4	0.4 (−1.8 to 2.5)	0.72	
Stratified by sex							
Male	52	61.3 ± 8.8	46	63 ± 6.0	−0.7 (−3.7 to 2.2)	0.62	0.27
Female	43	64.3 ± 6.2	43	62 ± 8.7	1.7 (−1.5 to 4.8)	0.30	
Stratified by baseline TSH							
4.6-6.9 mIU/L	73	62.6 ± 7.6	67	62.9 ± 8.0	−0.1 (−2.5 to 2.4)	0.96	0.71
7.0-9.9 mIU/L	18	63.2 ± 9.3	17	61.4 ± 5.8	1.6 (−3.4 to 6.5)	0.53	
≥10 mIU/L	4	66.3 ± 6.0	5	61.6 ± 4.3	3.3 (−6.6 to 13.2)	0.51	
Stratified by prior CVD†							
Yes	23	60.1 ± 8.5	20	59.2 ± 10.5	1.6 (−2.8 to 6.1)	0.47	0.51
No	72	63.5 ± 7.5	69	63.5 ± 6.0	0.0 (−2.4 to 2.4)	0.98	
Stratified by use of antihypertensive medication‡							
Yes	57	61.6 ± 8.8	47	62.0 ± 8.4	0.3 (−2.5 to 3.2)	0.24	0.86
No	38	64.3 ± 6.0	42	63.1 ± 6.1	0.7 (−2.5 to 4.0)	0.44	
Stratified by treatment duration							
< median (18.4 months)	45	62.2 ± 7.5	46	62.6 ± 8.6	0.3 (−2.7 to 3.4)	0.84	0.96
≥ median (18.4 months)	50	63.2 ± 8.2	43	62.5 ± 6.0	0.4 (−2.6 to 3.5)	0.79	

CI = confidence interval; CVD = cardiovascular disease; LVEF = left ventricular ejection fraction; n = number; SD = standard deviation; TSH = thyroid-stimulating hormone.

Analyses were 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.

*Calculated using multivariable linear regression adjusted for sex, center, treatment starting dose, and length of follow-up and including an interaction term for each stratification variable with treatment allocation

†Defined as at least 1 of the following: acute coronary syndrome (myocardial infarction, stable or unstable angina), coronary or other arterial revascularization, heart failure, stroke, transient ischemic attack, peripheral arterial disease.

‡Defined as use of angiotensin-converting enzyme II inhibitor, angiotensin receptor blocker, beta-blocker, or diuretic at baseline.

Table 5 Stratified Analyses for Echocardiographic Diastolic Function

E/e' (ratio ± SD)	Levothyroxine		Placebo		Between-group difference, 95% CI*	*P* Value	*P* for interaction
	N	Mean ± SD	N	Mean ± SD			
E/e' (ratio ± SD)	85	10.6 ± 3.7	84	10.1 ± 3.3	0.4 (−0.7 to 1.4)	0.47	
Stratified by sex							
Male	47	10.7 ± 3.6	42	10.1 ± 2.7	0.7 (−0.8 to 2.1)	0.37	0.60
Female	38	10.4 ± 3.9	42	10.2 ± 3.9	0.1 (−1.5 to 1.7)	0.91	
Stratified by baseline TSH							
4.6-6.9 mIU/L	65	10.4 ± 3.3	62	10.2 ± 3.3	0.2 (−1.0 to 1.4)	0.72	0.86
7.0-9.9 mIU/L	16	11.4 ± 4.8	17	10.4 ± 3.7	0.9 (−1.5 to 3.3)	0.47	
≥10 mIU/L	4	9.8 ± 5.7	5	8.0 ± 1.0	1.0 (−3.7 to 6.0)	0.67	
Stratified by prior CVD/HF†							
Yes	21	12.2 ± 3.3	17	11.2 ± 3.6	1.0 (−1.3 to 3.2)	0.41	0.57
No	64	10.1 ± 3.7	67	9.8 ± 3.2	0.2 (−1.0 to 1.4)	0.72	
Stratified by use of antihypertensive medication‡							
Yes	48	11.4 ± 4.0	42	11.0 ± 2.9	0.3 (−1.2 to 1.7)	0.69	0.93
No	37	9.6 ± 2.9	42	9.2 ± 3.5	0.4 (−1.2 to 2.0)	0.63	
Stratified by treatment duration							
< median (18.4 months)	41	10.6 ± 3.6	43	9.6 ± 3.5	1.1 (−0.4 to 2.6)	0.15	0.19
≥ median (18.4 months)	44	10.5 ± 3.8	41	10.7 ± 3.0	−0.3 (−1.8 to 1.2)	0.69	

CI = confidence interval; CVD = cardiovascular disease; E/e' = ratio between mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e'); HF = heart failure; n = number; SD = standard deviation; TSH = thyroid-stimulating hormone.

Analyses were 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.

*Calculated using multivariable linear regression adjusted for sex, center, treatment starting dose, and length of follow-up and including an interaction term for each stratification variable with treatment allocation.

†Defined as at least 1 of the following: acute coronary syndrome (myocardial infarction, stable or unstable angina), coronary or other arterial revascularization, heart failure, stroke, transient ischemic attack, peripheral arterial disease.

‡Defined as use of angiotensin-converting enzyme II inhibitor, angiotensin- receptor blocker, beta-blocker, or diuretic at baseline.

significantly different among both groups: prolongation of isovolumetric relaxation time, increased A wave, and reduced E/A ratio.[10] Thyroid hormone replacement of subclinical hypothyroidism was associated with a shortening of isovolumetric relaxation time, a reduction of the A wave, and an increase of the E/A ratio.[10] Among 20 patients with subclinical hypothyroidism, those randomized to levothyroxine compared to placebo presented changes in diastolic dysfunction (reduction of peak A and isovolumetric relaxation time).[9] Regarding the effect of levothyroxine in patients with heart failure, a retrospective cohort study reported an increased risk of cardiovascular death and major adverse cardiovascular events with thyroxine therapy.[20]

Our findings suggest that treating subclinical hypothyroidism with levothyroxine had no effect on systolic and diastolic cardiac function. The only difference was observed for a secondary endpoint of diastolic function with slightly higher values of systolic pulmonary pressure in the levothyroxine group. The reason of this finding could be an error type I because the *P* value was not significant in per protocol analysis. Subjects allocated to the levothyroxine might have been at higher risk of heart failure by chance, as suggested by higher NT-pro BNP levels, in the levothyroxine group compared to placebo group at the 2 different time points (at baseline and at 12-month follow-up). However, the lack of between-group differences in cardiovascular risk factors, NT-pro BNP levels, and other biomarkers and cardiovascular treatments at 12 months after adjustment for baseline values rather supported that thyroid replacement had no effect on heart function after a median follow-up of 18.4 months in patients with subclinical hypothyroidism. Our data confirm the statement of the 2019 clinical practice recommendation that concluded that most adults with subclinical hypothyroidism would not benefit from treatment with thyroid hormones.[21]

Our study also has some limitations. First, because of the low number of older patients with TSH ≥10 mIU/L (n = 9), our study findings are mainly applicable to patients with mild hypothyroidism. No significant effect modification of levothyroxine was observed by baseline prespecified TSH levels, and the overall results did not change after excluding those with TSH ≥10 mIU/L (Supplemental Table 7, available online), but we could not address with appropriate power the effect of levothyroxine in those with more pronounced subclinical hypothyroidism. The proportion of older participants with TSH ≥10 mIU/L in our study was representative of the reality because the prevalence of such abnormality at this age category accounts only for about 5% of the patients with subclinical hypothyroidism.[22] Second, we designed the TRUST trial in 2011[23], so we chose to set a thyrotropin target of 0.40 to 4.60 mIU/L with levothyroxine treatment, which was the usual approach at this time[24] and the range used to define euthyroidism in the

Thyroid Studies Collaboration.[25] The 2013 European Thyroid Association guidelines have even recommended a lower thyrotropin target (eg, 0.40-2.50 mIU/L),[12] although a higher TSH target between 1 and 5 mIU/L may be considered for adults >70 years of age,[12] as well as the use of age-specific reference range for the diagnosis of subclinical hypothyroidism in the elderly.[22,26] The latest guidelines from the American Thyroid Association also recommended to raise the target serum TSH in older adults.[27] Third, we did not have available measurement for triiodothyronine (T3), which has been previously associated with diastolic function.[28] Fourth, we did not have baseline echocardiography. In randomized design, baseline participant characteristics (including unmeasured confounding factors) should be evenly distributed, and the addition of the primary outcome measurement at the end of the trial is a frequent design in imaging studies [15,16] and in other RCTs.[29,30] Our data suggest that the studied population had likely no major underlying systolic heart failure at enrolment (no baseline echocardiography) because 93.7% in the levothyroxine arm and 97.8% in the placebo arm had a normal ejection fraction at the end of the trial. Therefore, our study does not preclude a beneficial or detrimental effect of thyroxine replacement in individuals with preexisting echocardiographic abnormalities. Finally, the ethnic diversity of the study population was limited (white race was 99.0% in the levothyroxine arm and 97.8% in the placebo arm).

Our trial has several strengths. The sample size was larger than those of previous trials of thyroid replacement and cardiac function.[9,10] In the absence of any previous or ongoing adequately powered RCT regarding major cardiovascular outcomes, this study is the largest RCT to date assessing the effect of thyroid hormone therapy in subclinical hypothyroidism using recommended surrogate outcomes of heart failure.

CONCLUSION

Systolic and diastolic function did not differ after treatment with levothyroxine compared to placebo in older adults with mild subclinical hypothyroidism.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2020.01.018.

Supplemental Table 1 Summary of Adverse Events

	All Participants n = 217	Levothyroxine n = 109	Placebo n = 108
Clinical Outcome			
Fatal or nonfatal cardiovascular event, n (%)	13 (6.0)	7 (6.4)	6 (5.6)
Cardiovascular death, n (%)	2 (0.9)	2 (1.8)	0 (0.0)
All-cause death, n (%)	5 (2.5)	4 (3.7)	1 (0.9)
Serious adverse event*			
Participants with ≥1 serious adverse event, n (%)	65 (30%)	30 (27.5)	35 (32.4)
Number of events, n	121	54	67
Withdrawal			
Permanent withdrawal from study drug, n (%)	45 (20.7)	22 (20.2)	23 (21.3)
Withdrawal from follow-up, n (%)	16 (7.4)	6 (5.5)	10 (9.3)

n = number.

*Serious adverse event was defined as any untoward medical occurrence that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability/incapacity.

Supplemental Table 2 Baseline Characteristics of All Participants (N = 217)

	Levothyroxine n = 109	Placebo n = 108
Demographics*		
Age (y, mean ± SD)	74.5 ± 5.4	74.6 ± 6.2
Female (n, %)	50 (45.9)	50 (46.3)
White race (n, %)	107 (98.2)	106 (98.2)
Cardiovascular risk factors		
BMI (kg/m^2, mean ± SD)†	27.9 ± 5.3	26.9 ± 4.6
Blood pressure (mm Hg, mean ± SD)		
Systolic	137.6 ± 18.2	138.5 ± 20.0
Diastolic	74.1 ± 11.2	77.4 ± 12.3
Currently smoking (n, %)‡	8 (7.3)	10 (9.3)
Diabetes mellitus (n, %)	17 (15.6)	11 (10.2)
Prior CVD (n, %)§	26 (23.9)	30 (27.8)
Prior heart failure (n, %)	3 (2.8)	7 (6.5)
Estimated creatinine clearance (n, %)¶		
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)
History of atrial fibrillation (n, %)	16 (14.7)	13 (12.0)
Lipid profile		
Total cholesterol (mmol/L, mean ± SD)**	5.08 ± 1.09	5.18 ± 1.11
LDL cholesterol (mmol/L, mean ± SD)††	2.84 ± 0.99	2.88 ± 0.93
HDL cholesterol (mmol/L, mean ± SD)‡‡	1.44 ± 0.47	1.49 ± 0.46
Triglycerides (mmol/L, mean ± SD)§§	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)
Diuretics (n, %)	21 (19.3)	12 (11.1)
ACEII/ARB (n, %)	55 (50.5)	43 (39.8)
Beta-blockers (n, %)	32 (29.4)	26 (24.1)
Antidiabetics (n, %)	17 (15.6)	8 (7.4)
Insulin (n, %)	5 (4.6)	1 (0.9)

Supplemental Table 2 (*Continued*)

	Levothyroxine n = 109	Placebo n = 108
Cardiac function		
NT-pro BNP (pg/mL; median, IQR)¶¶	156 (175)	110 (144)
Thyroid function		
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

ACEII = angiotensin-converting enzyme II; ARB = angiotensin-receptor blocker; BMI = body mass index; CKD-EPI = chronic kidney disease epidemiology collaboration; CVD = cardiovascular disease; FT4 = free thyroxine; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein; n = number; NT-pro BNP = N-terminal pro b-type natriuretic peptide; SD = standard deviation; TSH = thyroid-stimulating hormone; y = years.

*Baseline characteristics of participants in the primary analysis (n = 186) are provided in the Table 1.

†Calculated as weight (kg) divided by squared height (m)

‡Defined as currently smoking at the time of baseline examination.

§Defined as 1 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

¶Calculated using the CKD-EPI equation.

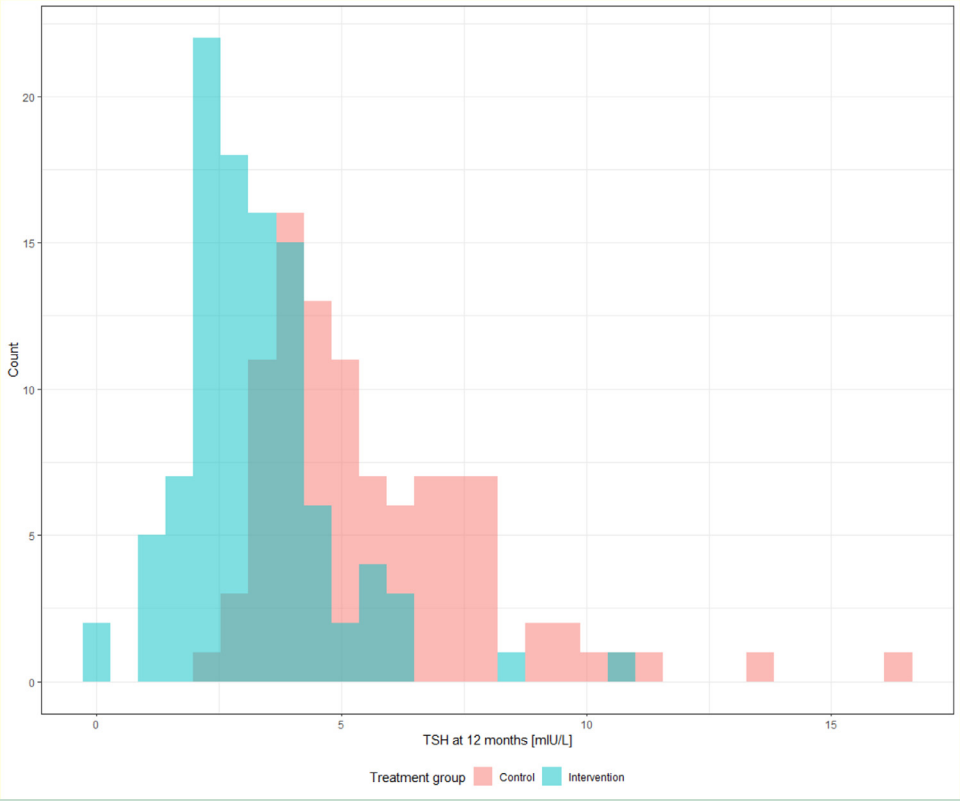
**Missing for 2 participants in the placebo group.

††Calculated using the Friedewald equation if triglycerides lower than 4.6 mmol/L. Missing for 4 participants in the levothyroxine group and 4 participants in the placebo group.

‡‡Missing for 1 participant in the levothyroxine group and 3 participants in the placebo group.

§§Missing for 2 participants in the placebo group.

¶¶Missing for 5 participants in the placebo group and 3 participants in the levothyroxine group.



Supplemental Figure 1 Distribution of the TSH at 12 months (mIU/L) in the placebo (red) and in the treatment arm (blue). TSH = thyroid-stimulating hormone.

Supplemental Table 3 Per Protocol Analysis for Outcomes for Echocardiographic Systolic and Diastolic Cardiac Functions

	Levothyroxine		Placebo		Difference*	*P* Value
	N	Mean ± SD	N	Mean ± SD	Mean (95% CI)	
Left ventricular ejection fraction (%)	80	62.5 ± 8.0	81	62.8 ± 7.6	0.2 (−2.1 to 2.6)	0.84
E/e′	71	10.5 ± 3.8	76	9.9 ± 3.0	0.5 (−0.6 to 1.6)	0.39
Systolic Pulmonary artery pressure (mm Hg)	54	36.7 ± 12.9	44	33.3 ± 10.4	4.5 (−0.2 to 9.3)	0.06

CI = confidence interval; n = number; SD = standard deviation.
*Calculated using multivariable linear regression adjusted for sex, center, treatment starting dose, and length of follow-up.

Supplemental Table 4 Outcomes for Echocardiographic Systolic and Diastolic Cardiac Functions After Excluding Patients With Atrial Fibrillation

	Levothyroxine		Placebo		Difference*	*P* Value
	N	Mean (SD)	N	Mean (SD)	Mean (95% CI)	
Systolic Function						
Left ventricular ejection fraction (%)	74	64.0 ± 6.3	74	63.2 ± 5.6	0.7 (−1.2 to 2.5)	0.46
Global longitudinal strain (%)	48	−18.5 ± 3.0	50	−19.0 ± 3.2	0.5 (−0.8 to 1.8)	0.46
Diastolic Function						
E/e′	71	10.2 ± 3.6	73	9.9 ± 3.4	0.2 (−0.9 to 1.3)	0.72
e′ lateral (cm/s)	63	7.9 ± 1.7	68	8.1 ± 2.6	−0.2 (−0.9 to 0.6)	0.63
e′ septal (cm/s)	71	5.9 ± 1.2	74	5.9 ± 2.0	0.0 (−0.5 to 0.6)	0.89
Left atrial volume index (mL/m^2)	72	31.7 ± 11.3	71	30.6 ± 9.9	1.1 (−2.4 to 4.5)	0.54
Systolic pulmonary artery pressure (mm Hg)	48	34.7 ± 10.0	39	29.9 ± 5.7	5.4 (1.8 to 9.0)	0.003
Maximal tricuspid regurgitation velocity (cm/s)	36	259.7 ± 39.9	29	240.7 ± 27.5	22.6 (5.1 to 40.2)	0.01
E/A ratio	72	0.81 ± 0.25	73	0.81 ± 0.22	0.0 (−0.1 to 0.1)	0.99
E deceleration time (ms)	71	219.9 ± 53.0	68	216.5 ± 55.2	3.8 (−14.2 to 21.8)	0.68

CI = confidence interval; n = number; SD = standard deviation.
*Calculated using multivariable linear regression adjusted for sex, center, treatment starting dose, and length of follow-up.

Supplemental Table 5 Outcomes for Echocardiographic Systolic and Diastolic Cardiac Functions After Excluding Patients With Diabetes

	Levothyroxine		Placebo		Difference*	*P* Value
	N	Mean (SD)	N	Mean (SD)	Mean (95% CI)	
Systolic Function						
Left ventricular ejection fraction (%)	81	63.7 ± 7.0	83	62.3 ± 7.5	1.3 (−0.8 to 3.5)	0.23
Global longitudinal strain (%)	50	−18.2 ± 3.2	50	−18.5 ± 3.7	0.1 (−1.3 t0 1.4)	0.93
Diastolic Function						
E/e′	72	10.5 ± 3.8	81	10.1 ± 3.4	0.4 (−0.8 to 1.5)	0.53
e′ lateral (cm/s)	64	8.0 ± 1.7	73	8.1 ± 2.5	−0.1 (−0.8 to 0.7)	0.86
e′ septal (cm/s)	73	5.9 ± 1.2	81	6.0 ± 1.9	0.0 (−0.6 to 0.5)	0.87
Left atrial volume index (mL/m^2)	77	34.5 ± 16.9	79	32.7 ± 14.0	1.0 (−3.7 to 5.7)	0.67
Systolic pulmonary artery pressure (mm Hg)	56	37.0 ± 12.7	39	30.9 ± 7.2	6.9 (2.9 to 10.9)	0.001
Maximal tricuspid regurgitation velocity (cm/s)	40	261.8 ± 38.3	29	241.4 ± 25.5	22.6 (7.5 to 37.7)	0.004
E/A ratio	69	0.9 ± 0.3	73	0.82 ± 0.21	0.03 (−0.05 to 0.11)	0.49
E deceleration time (ms)	68	223.4 ± 57.6	68	215.9 ± 52.6	7.6 (−10.5 to 25.6)	0.41

CI = confidence interval; n = number; SD = standard deviation.
*Calculated using multivariable linear regression adjusted for sex, center, treatment starting dose, and length of follow-up.

Supplemental Table 6 Outcomes for Echocardiographic Systolic and Diastolic Cardiac Functions After Adjusting For Diabetes

	Levothyroxine		Placebo		Difference*	*P* Value
	N	Mean (SD)	N	Mean (SD)	Mean (95% CI)	
Systolic Function						
Left ventricular ejection fraction (%)	95	62.7 ± 7.7	83	62.5 ± 7.4	0.6 (−1.5 to 2.8)	0.55
Global longitudinal strain (%)	58	−17.8 ± 3.5	58	−18.5 ± 3.7	0.2 (−1.1 to 1.5)	0.76
Diastolic Function						
E/e'	85	10.6 ± 3.7	84	10.1 ± 3.3	0.4 (−0.7 to 1.5)	0.49
e' lateral (cm/s)	77	7.8 ± 1.8	76	8.1 ± 2.5	−0.1 (−0.8 to 0.6)	0.83
e' septal (cm/s)	86	5.8 ± 1.3	85	5.9 ± 1.9	0.0 (−0.5 to 0.5)	0.87
Left atrial volume index (ml/m^2)	90	34.7 ± 15.9	85	32.9 ± 11.7	1.1 (−3.2 to 5.4)	0.62
Systolic pulmonary artery pressure (mm Hg)	62	36.6 ± 12.2	51	32.5 ± 10.0	4.9 (0.8 to 9.0)	0.02
Maximal tricuspid regurgitation velocity (cm/s)	43	262.2 ± 38.1	38	246.6 ± 34.7	18.2 (2.7 to 33.7)	0.02
E/A ratio	81	0.8 ± 0.3	81	0.82 ± 0.22	0.02 (−0.06 to 0.09)	0.65
E deceleration time (ms)	78	225.5 ± 56.8	78	216.2 ± 53.3	8.7 (−8.7 to 26.1)	0.33

CI = confidence interval; n = number; SD = standard deviation.
*Calculated using multivariable linear regression adjusted for sex, center, treatment starting dose, and length of follow-up.

Supplemental Table 7 Outcomes for echocardiographic systolic and diastolic Cardiac Functions After Excluding Those With a Baseline TSH ≥10 mUI/L

	Levothyroxine		Placebo		Difference*	*P* Value
	N	Mean (SD)	N	Mean (SD)	Mean (95% CI)	
Systolic Function						
Left ventricular ejection fraction (%)	91	62.5 ± 7.9	84	62.6 ± 7.6	0.3 (−2.0 to 2.5)	0.82
Global longitudinal strain (%)	54	−17.8 ± 3.5	53	−18.4 ± 3.8	0.4 (−0.9 to 1.8)	0.53
Diastolic Function						
E/e'	81	10.6 ± 3.6	79	10.3 ± 3.4	0.4 (−0.7 to 1.4)	0.53
e' lateral (cm/s)	73	7.8 ± 1.8	71	8.0 ± 2.5	−0.1 (−0.8 to 0.6)	0.73
e' septal (cm/s)	82	5.8 ± 1.3	80	5.9 ± 1.9	−0.1 (−0.6 to 0.5)	0.83
Left atrial volume index (ml/m^2)	86	34.8 ± 16.2	80	32.7 ± 14.0	1.9 (−2.5 to 6.3)	0.40
Systolic pulmonary artery pressure (mm Hg)	59	36.9 ± 12.4	50	32.6 ± 10.0	5.4 (1.2 to 9.6)	0.01
Maximal tricuspid regurgitation velocity (cm/s)	41	263.2 ± 38.6	37	247.2 ± 34.9	20.3 (3.5 to 37.2)	0.02
E/A ratio	77	0.8 ± 2.7	76	0.8 ± 0.22	0.02 (−0.06 to 0.10)	0.64
E deceleration time (ms)	74	219.9 ± 51.7	73	218.0 ± 54.0	3.2 (−14.0 to 20.)	0.72

CI = confidence interval; n = number; SD = standard deviation; TSH = thyroid-stimulating hormone.
*Calculated using multivariable linear regression adjusted for sex, center, treatment starting dose, and length of follow-up.

Supplemental Table 8 Outcomes for Echocardiographic Systolic and Diastolic Cardiac Functions After Excluding Those Preexisting Heart Failure

	Levothyroxine		Placebo		Difference*	*P* Value
	N	Mean (SD)	N	Mean (SD)	Mean (95% CI)	
Systolic Function						
Left ventricular ejection fraction (%)	94	62.8 ± 7.8	84	63.1 ± 6.0	0.0 (−2.0 to 2.0)	0.98
Global longitudinal strain (%)	57	−17.8 ± 3.5	55	−18.8 ± 3.4	0.6 (−0.7 to 2.)	0.34
Diastolic Function						
E/e'	84	10.6 ± 3.7	80	10.0 ± 3.3	0.5 (−0.6 to 1.5)	0.41
e' lateral (cm/s)	76	7.8 ± 1.8	72	8.1 ± 2.5	−0.3 (−1.0 to 0.4)	0.46
e' septal (cm/s)	85	5.8 ± 1.3	81	5.9 ± 2.0	−0.1 (−0.6 to 0.4)	0.73
Left atrial volume index (ml/m^2)	89	34.4 ± 15.7	82	31.7 ± 10.7	2.2 (−1.7 to 6.1)	0.26
Systolic pulmonary artery pressure (mm Hg)	61	36.3 ± 12.1	48	31.7 ± 9.2	5.1 (1.1 to 9.2)	0.01
Maximal tricuspid regurgitation velocity (cm/s)	43	262.2 ± 38.1	36	245.0 ± 34.9	19.7 (3.2 to 36.2)	0.02
E/A ratio	81	0.83 ± 0.27	79	0.82 ± 0.22	0.00 (−0.08 to 0.07)	0.94
E deceleration time (ms)	78	225.5 ± 56.8	75	215.3 ± 53.4	10.3 (−7.1 to 27.7)	0.25

CI = confidence interval; n = number; SD = standard deviation.
*Calculated using multivariable linear regression adjusted for sex, center, treatment starting dose, and length of follow-up.

Supplemental Table 9 Control of Cardiovascular Risk Factors, Biomarkers, and Medication From Baseline to 12-months Follow-Up

	Baseline		Follow-Up		Difference	*P* Value
	Levothyroxine	Placebo	Levothyroxine	Placebo	(95% CI)	
Cardiovascular risk factors*						
Systolic blood pressure (mm Hg, mean ± SD)†	137.8 ± 18.2	139.0 ± 19.9	134.8 ± 18.4	134.8 ± 16.9	0.6 (−3.3 to 4.5)	0.76
Diastolic blood pressure (mm Hg, mean ± SD)‡	74.1 ± 11.2	77.6 ± 12.4	73.1 ± 10.9	75.1 ± 11.6	−0.2 (−2.8 to 2.5)	0.89
LDL cholesterol (mmol/L, mean ± SD)§,¶	2.85 ± 1.00	2.90 ± 0.95	2.67 ± 0.95	2.74 ± 0.98	−0.02 (−0.19 to 0.15)	0.82
Inflammation marker						
High-sensitivity CRP (mg/L, mean ± SD)**	2.31 ± 1.69	2.50 ± 2.05	2.30 ± 1.77	2.35 ± 1.85	0.06 (−0.36 to 0.48)	0.78
Cardiac function						
NT-proBNP (pg/mL, median ± IQR)††	156 (175)	110 (144)	201 (252)	118 (146)	38 (−14 to −91)	0.15
Medications‡‡						
Antiplatelets (n, %)	31 (32.0)	34 (37.4)	30 (30.9)	37 (40.7)	−0.04 (−0.08 to 0.00)	0.04
Lipid-lowering (n, %)	46 (47.4)	37 (40.7)	47 (48.5)	39 (42.9)	−0.01 (−0.07 to 0.04)	0.68
Statin (n, %)	45 (46.4)	36 (39.6)	46 (47.4)	38 (41.8)	−0.01 (−0.07 to 0.04)	0.68
Antihypertensives (n, %)	64 (66.0)	54 (59.3)	63 (65.0)	55 (60.4)	−0.02 (−0.08 to 0.04)	0.48
Antidiabetics (n, %)	16 (16.6)	7 (7.7)	16 (16.5)	8 (8.8)	−0.01 (−0.05 to 0.02)	0.55
Insulin (n, %)	5 (5.2)	1 (1.1)	5 (5.2)	1 (1.1)	—	1.00

CI = confidence interval; CRP = C-reactive protein; LDL = low-density lipoprotein; n = number; NT-pro BNP = N-terminal pro b-type natriuretic peptide; SD = standard deviation.

*Analyses conducted in the modified intention-to-treat population (all correctly randomized participants with the respective outcome available). Results are adjusted for stratification variables (sex, treatment starting dose, study center) and baseline level of the same variable using linear regression. Between-group difference is the value in the levothyroxine group minus the value in the placebo group.

†N = 202 Missing in placebo|levothyroxine group: 0|0 at baseline, 8|7 at 12 months.

‡N = 202. Missing in placebo|levothyroxine group: 0|0 at baseline, 8|7 at 12 months.

§N = 191. Missing in placebo|levothyroxine group: 4|4 at baseline, 12|9 at 12 months.

¶Sensitivity analysis excluding participants on lipid-lowering medications (statins, fibrates; n = 89) yielded similar results.

**N = 183. Missing in placebo|levothyroxine group: 5|3 at baseline, 14|15 at 12 months.

††N = 190. Missing in placebo|levothyroxine group: 5|3 at baseline, 11|11 at 12 months.

‡‡Complete (baseline and 12-month follow-up) medication information was unavailable for 29 participants. Data shown is for complete case (n = 188). Between-group difference (levothyroxine compared to placebo) in change of proportions of participants using a medication were calculated using generalized estimating equation models, with an interaction term for treatment group and time.