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Effect of Levothyroxine on Left Ventricular Ejection Fraction in Patients With Subclinical Hypothyroidism and Acute Myocardial Infarction
A Randomized Clinical Trial

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IMPORTANCE Thyroid hormones play a key role in modulating myocardial contractility. Subclinical hypothyroidism in patients with acute myocardial infarction is associated with poor prognosis.

OBJECTIVE To evaluate the effect of levothyroxine treatment on left ventricular function in patients with acute myocardial infarction and subclinical hypothyroidism.

DESIGN, SETTING, AND PARTICIPANTS A double-blind, randomized clinical trial conducted in 6 hospitals in the United Kingdom. Patients with acute myocardial infarction including ST-segment elevation and non–ST-segment elevation were recruited between February 2015 and December 2016, with the last participant being followed up in December 2017.

INTERVENTIONS Levothyroxine treatment (n = 46) commencing at 25 µg titrated to aim for serum thyrotropin levels between 0.4 and 2.5 mU/L or identical placebo (n = 49), both provided in capsule form, once daily for 52 weeks.

MAIN OUTCOMES AND MEASURES The primary outcome measure was left ventricular ejection fraction at 52 weeks, assessed by magnetic resonance imaging, adjusted for age, sex, type of acute myocardial infarction, affected coronary artery territory, and baseline left ventricular ejection fraction. Secondary measures were left ventricular volumes, infarct size (assessed in a subgroup [n = 60]), adverse events, and patient-reported outcome measures of health status, health-related quality of life, and depression.

RESULTS Among the 95 participants randomized, the mean (SD) age was 63.5 (9.5) years, 72 (76.6%) were men, and 65 (69.1%) had ST-segment elevation myocardial infarction. The median serum thyrotropin level was 5.7 mU/L (interquartile range, 4.8-7.3 mU/L) and the mean (SD) free thyroxine level was 1.14 (0.16) ng/dL. The primary outcome measurements at 52 weeks were available in 85 patients (89.5%). The mean left ventricular ejection fraction at baseline and at 52 weeks was 51.3% and 53.8%, respectively, in the levothyroxine group compared with 54.0% and 56.1%, respectively, in the placebo group (adjusted difference in groups, 0.76% [95% CI, −0.93% to 2.46%]; P = .37). None of the 6 secondary outcomes showed a significant difference between the levothyroxine and placebo treatment groups. There were 15 (33.3%) and 18 (36.7%) cardiovascular adverse events in the levothyroxine and placebo groups, respectively.

CONCLUSIONS AND RELEVANCE In this preliminary study involving patients with subclinical hypothyroidism and acute myocardial infarction, treatment with levothyroxine, compared with placebo, did not significantly improve left ventricular ejection fraction after 52 weeks. These findings do not support treatment of subclinical hypothyroidism in patients with acute myocardial infarction.

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Visual Abstract

Supplemental content

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Advances in pharmacological and mechanical reperfusion strategies to restore coronary artery blood flow have led to improved mortality in patients with acute myocardial infarction.[1] However, a significant proportion of patients with acute myocardial infarction develop subsequent heart failure.[2] Consequently, the numbers of patients living with chronic heart failure due to ischemic cardiomyopathy have been increasing.[3] Impaired left ventricular function is the strongest predictor of morbidity and mortality after acute myocardial infarction.

Thyroid hormones play a key role in regulating cell metabolism and, in the heart, have powerful inotropic and chronotropic effects.[4] Subclinical hypothyroidism, a mild form of thyroid failure, is diagnosed when serum thyrotropin level is high and circulating thyroid hormones are within the reference range, and may be graded as mild or severe based on degree of thyrotropin elevation.[5] Subclinical hypothyroidism is associated with an increased risk of cardiovascular disease[6] and, in high-risk patients, is associated with worse cardiovascular outcomes.[7-10] This apparent increased risk could be due to the fact that thyroid hormone levels influence both the pathogenesis of atherosclerosis and recovery and myocardial repair after acute myocardial infarction.[11] Recent clinical practice guidelines have highlighted the lack of high-quality data to inform their recommendations regarding the management of mild subclinical hypothyroidism, particularly in patients with existing cardiovascular disease.[12,13] It is unknown whether treatment of subclinical hypothyroidism in patients with acute myocardial infarction is safe and whether it has prognostic benefits on postacute myocardial infarction left ventricular (LV) function.

The Thyroxine in Acute Myocardial Infarction (ThyrAMI-2) trial[14] was designed to assess the effect of levothyroxine treatment on LV function in patients with acute myocardial infarction and subclinical hypothyroidism.

Key Points

Question Does levothyroxine treatment improve left ventricular function in patients with subclinical hypothyroidism presenting with acute myocardial infarction?

Findings In this randomized clinical trial that included 95 participants with subclinical hypothyroidism and acute myocardial infarction, treatment with levothyroxine, compared with placebo, did not significantly improve left ventricular ejection fraction after 52 weeks (mean left ventricular ejection fraction, 53.8% vs 56.1%, respectively).

Meaning These findings do not support treatment of subclinical hypothyroidism in patients with acute myocardial infarction.

Methods

Study Population

This was a randomized, double-blind, placebo-controlled trial of levothyroxine for 52 weeks' duration in patients with acute myocardial infarction and persistent mild subclinical hypothyroidism. Individuals admitted with acute myocardial infarction provided written informed consent for their thyroid function to be assessed and their long-term health followed up. Ethical approval was granted by the North East Tyne and Wear South Research Ethics Committee. The trial was conducted as per the Helsinki Declaration guidelines.[15]

Eligible participants were identified from 6 acute UK hospitals between February 2015 and December 2016. The trial design and protocol have been published and are available in Supplement 1,[14] and the statistical analysis plan is available in Supplement 2. Briefly, inclusion criteria were men and women older than 18 years with serum thyrotropin levels greater than 4.0 mU/L with normal free thyroxine (FT_4) levels on 2 occasions 7 to 10 days apart and with 1 thyrotropin value being below 10 mU/L, and either ST-elevation myocardial infarction (STEMI) or non-STEMI (NSTEMI) diagnosed on admission as per standard criteria.[16] Exclusion criteria were patients taking medications affecting thyroid function, those with advanced malignancy, those with sustained ventricular tachycardia requiring treatment occurring more than 24 hours after myocardial reperfusion/revascularization, those who were unable to provide written informed consent, those who were unlikely or unwilling to attend study-specific visits, those participating in another interventional trial, and those with standard contraindications for magnetic resonance imaging (MRI) (eAppendix 1 in Supplement 3).

Study Procedures

Participants had standard laboratory assessment plus their thyroid profile and standard physical examination parameters, including blood pressure, heart rate, and body mass index, evaluated on admission. Coronary angiography was performed using standard techniques and the need for and technique of revascularization was left to the discretion of the local clinician. The coronary angiographic findings and ischemia time (calculated from onset of symptoms to the time of the coronary intervention) for patients with STEMI were noted. All patients received standard medication according to current guidelines, were offered rehabilitation programs, and were given lifestyle advice.

Patients who met the trial criteria on admission were provided with an information sheet and reconsented to have their thyroid function test repeated 7 to 10 days after the initial screening. Those whose serum thyrotropin and FT_4 levels at the repeat test were within the trial inclusion range were invited to participate in the clinical trial. The day of admission to hospital was defined as the day of acute myocardial infarction.

Participants were randomized using a computerized algorithm, stratified by type of acute myocardial infarction (STEMI or NSTEMI), in a 1:1 ratio using permuted random blocks of variable length (maximum, 8) to either levothyroxine therapy or visually matching placebo, both administered once daily as capsules for 52 weeks of treatment. The trial medication was prescribed as container numbers, with the aim to start the first dose within 21 days of the acute myocardial infarction. The starting dose of levothyroxine was 25 µg and was amended at subsequent visits based on thyroid function tests. The target serum thyrotropin level ranged between 0.4 and 2.5 mU/L because the median thyrotropin

levels of euthyroid individuals lie within this range.[17] Participants had their thyrotropin levels checked at 4, 8, 12, and 24 weeks (±7 days, for all visits) and concomitant dose of their levothyroxine altered by 25 µg daily, if required (eAppendix 2 in Supplement 3). Independent clinicians performed the dose adjustment by instructing the blinded study team to prescribe specific container numbers.

Manufacturing and packaging of the study medication was performed by Newcastle upon Tyne Hospitals Pharmacy Production Unit, United Kingdom, according to the Good Manufacturing Practice standards of the European Union. Study drug adherence was assessed by tablet count at each follow-up visit. The 52 weeks' duration of treatment was chosen to provide the best possible chance to detect efficacy and toxicity signals. Standard laboratory assessment, electrocardiograms, and thyroid function tests were repeated at the end of the trial.

The Newcastle Clinical Trials Unit performed trial monitoring, data management, and validation. Members of the independent trial steering committee reviewed the trial protocol and analysis plan, monitored collection and quality of data, and reviewed the manuscript. An independent data and safety monitoring committee regularly monitored the recruitment and safety data in the trial and advised the trial steering committee whether the trial should be stopped due to safety concerns.

Biochemical Analyses

Serum thyrotropin, FT_4, free triiodothyronine (FT_3), highly sensitive troponin T or I, total cholesterol, and creatinine were analyzed using either the Roche (ecobas, Roche Diagnostics, United Kingdom) or Advia Centaur (Siemens Healthineers, United Kingdom) assays for 4 and 2 centers, respectively. Reference ranges were applied uniformly across both assays: 0.4 to 4.0 mU/L for thyrotropin, 0.70 to 1.94 ng/dL for FT_4, 1.95 to 4.56 pg/mL for FT_3, 0 to 14 ng/L for highly sensitive troponin T, 0 to 45 ng/L for highly sensitive troponin I, and 0.79 to 1.24 mg/dL for creatinine (eAppendix 3 in Supplement 3).

Trial Outcomes

The primary outcome measure was left ventricular ejection fraction (LVEF) at 52 weeks assessed by 3-T whole-body MRI scanners (Philips Medical Systems, Best, the Netherlands) using a phased array cardiac receiver coil at 2 centers (Newcastle and Leeds), following the same protocol (eAppendix 4 in Supplement 3).[18] All MRI analyses were performed at a core laboratory (Newcastle University MRI center, United Kingdom) using the IntelliSpace workstation (Philips Medical Systems) by a study team member blinded to the participant's allocation status or time point.

The main prespecified secondary outcomes of cardiac MRI were LV volumes (end-systolic and end-diastolic per meter-squared body surface area) at 52 weeks. A gadolinium-based contrast agent (Dotarem) was intravenously administered and late gadolinium-enhanced images acquired after 10 minutes (eAppendix 4 in Supplement 3). Additional prespecified secondary outcomes, such as infarct size (both in grams and as percentage of total LV mass), were evaluated from the late gadolinium-enhanced images in participants with normal or mildly reduced kidney function (estimated glomerular filtration rate>50 mL/min/1.73 m^2). The IntelliSpace workstation (Philips Medical Systems) was used to quantify the infarct size by the 5SD technique[18] (eAppendix 4 in Supplement 3).

Other prespecified secondary outcomes included patient-reported outcome measures, evaluated by validated questionnaires, at baseline and at 52 weeks. Health status was assessed by the Short Form 12 4-week recall (SF-12v2) Physical and Mental Health Composite scores (range, 0-100, wherein a 0 score indicates the lowest level of health measured by the scales and 100 indicates the highest level of health, and a minimal clinically important difference [MCID] of 1.8 and 1.5, respectively),[19] heart failure–specific quality of life by the Minnesota Living With Heart Failure Questionnaire (score range, 0-105, with higher scores indicating worse health status, and MCID of 5.0),[20] and depression by the Center for Epidemiologic Studies Depression Scale (possible range of scores from 0 to 60, with higher scores indicating greater depressive symptoms, and MCID is not established).[21]

There were other prespecified secondary vascular and thrombotic outcomes that were evaluated in the trial but are not reported here (described in the protocol and analysis plan in Supplement 1 and Supplement 2, respectively).

Adverse events were assessed throughout the study by reporting of serious adverse events as defined in the protocol,[14] and regularly reviewed by the independent data and safety monitoring committee. In addition, electrocardiogram recordings and New York Heart Assessment categories were evaluated. Adherence to study medication was assessed by recording the number of returned capsules at each visit, and was classed as good if greater than 80%.

Post hoc measures of LV function (stroke volume, stroke index, cardiac output, and cardiac index) and LV mass were analyzed.

Sample Size

Previous randomized trials in patients with acute myocardial infarction have demonstrated that an absolute difference between treatment groups in LVEF of 3% or more is associated with improved morbidity and mortality.[22,23] The standard deviation of LVEF was anticipated to be 6%, as previously reported.[24] Consequently, this trial was designed with 90% power to detect an overall difference of 3% in LVEF between the 2 groups (mean 3% improvement in the placebo group and mean 6% in the levothyroxine group, equating to a standardized effect size of 0.5) at 52 weeks after acute myocardial infarction, at a 2-sided significance level of 5%.[25] With these parameters, this trial required 47 patients to be enrolled in each group, assuming 10% drop out, based on analysis of covariance assuming a correlation between baseline and follow-up of 0.75.

Statistical Analyses

Data analyses were performed according to a prespecified analysis plan,[26] which was finalized prior to unblinding of the randomization code and reviewed by the independent trial steering committee (Supplement 2). The primary statistical

analysis was performed by retaining patients in their assigned treatment groups and including protocol violators. Missing data for all outcomes were low, hence a complete case analysis was conducted. For baseline variables, categorical data are expressed as numbers and percentages, whereas continuous variables are expressed as means (SDs) or as medians with their interquartile ranges (IQRs), depending on distribution. The relationship of clinical and treatment variables with outcomes was assessed by multiple linear regression analysis. The regression model included the outcome at 12 months as the dependent variable and treatment (levothyroxine or placebo), baseline value, age, sex, type of acute myocardial infarction (STEMI or NSTEMI), and coronary artery affected (left anterior descending, right coronary artery, circumflex, or other) as independent variables.

Assumptions of linearity between the dependent and independent continuous variables were confirmed by visual inspection of scatter plots. Normal probability plots and residual predictor plots were explored to confirm model goodness of fit. Multicollinearity was assessed by variance inflation factor. We performed prespecified subgroup analyses to explore subgroups by treatment interactions to investigate potential differential estimated treatment effects (Supplement 2 and eAppendix 5 in Supplement 3). In addition, a post hoc analysis assessing the primary outcome measure with an additional adjustment for site was performed.

All reported *P* values are 2-sided and a value less than .05 was deemed as indicative of statistical significance. Analyses of secondary end points were not powered and due to potential for type I error caused by multiple comparisons, findings should be interpreted as exploratory. Analyses were performed using the statistical software package SPSS version 24 (IBM).

Results

Study Population

During the study enrolment period, 2147 patients were admitted to the participating hospitals with acute myocardial infarction and 1966 consented to have their thyroid function screened. Of these, 314 participants (16%) were identified with subclinical hypothyroidism, and after assessments of trial inclusion and exclusion criteria, 95 participants were recruited to the trial with 46 randomized to the levothyroxine group and 49 to the placebo group (**Figure 1**). Ten randomized participants did not have the baseline, final visit, or both cardiac MRI scans (7 in the levothyroxine group and 3 in the placebo group), leaving 85 participants for the analysis of the primary outcome (Figure 1) (details in eTable 1 in Supplement 3). In addition, results for serum FT_3 levels were missing in 15 participants at baseline and 9 participants at 52 weeks.

Baseline characteristics demonstrated balanced samples across both treatment groups (**Table 1**). The mean age of participants was 64.1 and 62.9 years, 80% and 74% were men, and 70% and 67% presented with STEMIs in the levothyroxine and placebo groups, respectively. The use of antiplatelet and other secondary preventive medications was similar in both groups and study medication was commenced after similar number of days after acute myocardial infarction (17.0 and 16.0 days, respectively). Furthermore, revascularization procedure (eTable 2 in Supplement 3) and baseline mean LVEF (**Table 2**) were comparable in the levothyroxine and placebo groups.

Primary Outcome Measure

In both groups, LVEF improved in the 52 weeks following acute myocardial infarction: from a mean (SD) of 51.3% (9.1%) to 53.8% (9.7%) in the levothyroxine group and from 54.0% (7.9%) to 56.1% (7.9%) in the placebo group. Levothyroxine did not significantly alter LVEF at 52 weeks, with an adjusted between-group mean difference of 0.76% (95% CI, −0.93% to 2.46%; *P* = .37) (Table 2). Treatment effect was adjusted by the inclusion of baseline LVEF (regression coefficient, 0.89 [95% CI, 0.79 to 0.99]; *P* < .001), age (−0.12 [95% CI, −0.20 to −0.03]; *P* = .01), sex (−2.42 [95% CI, −4.43 to −0.39]; *P* = .02), type of acute myocardial infarction (−0.22 [95% CI, −2.16 to 1.73]; *P* = .83), and coronary artery affected (−0.26 [95% CI, −1.23 to 0.71]; *P* = .59). Continuous independent variables (age and baseline LVEF) appeared to be linearly related to outcome so were included in the model without transformation. Residual plots confirmed model goodness of fit. The variance inflation factor for all independent variables was less than 2.5.

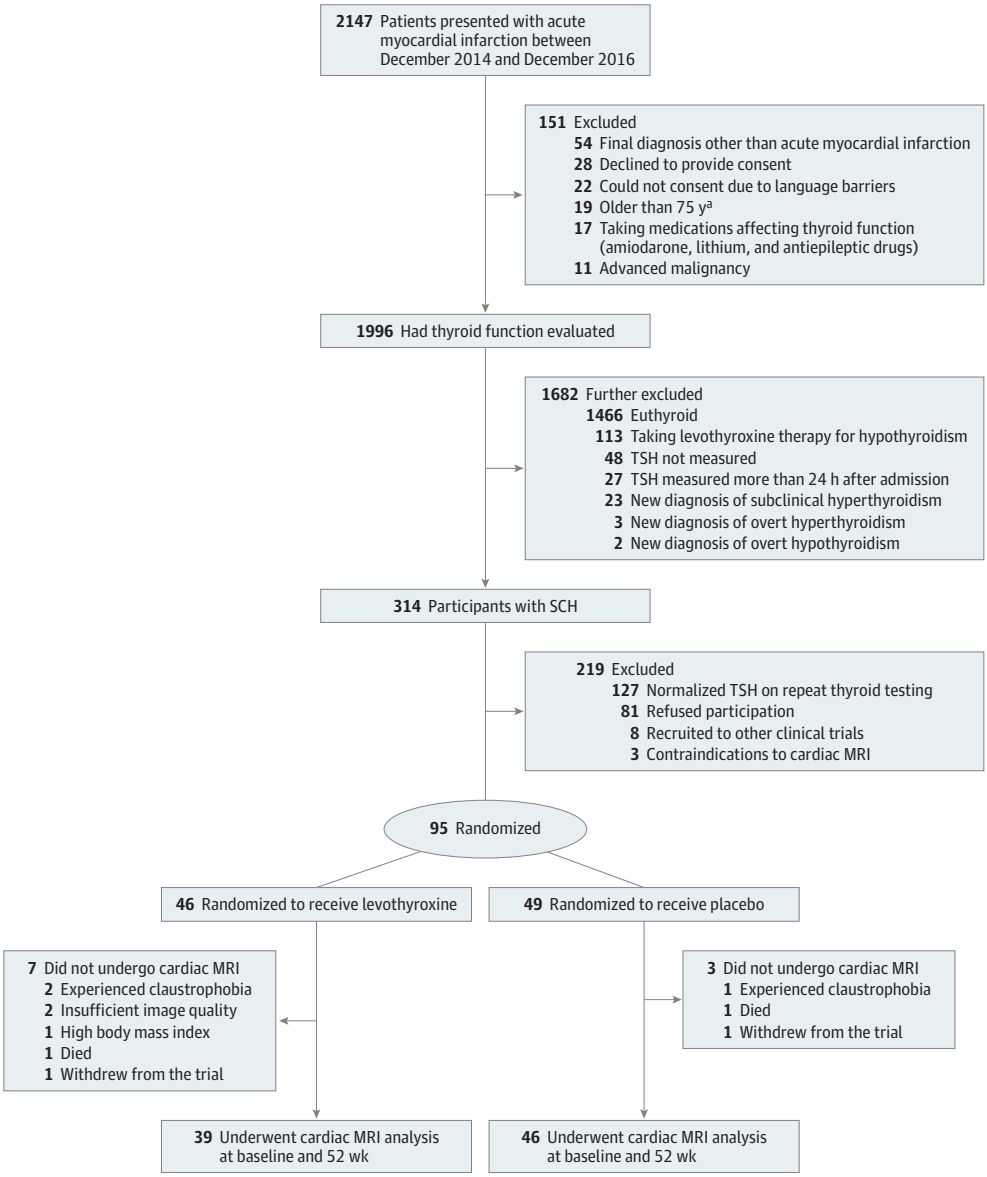
Subgroup analyses suggested that the result obtained was not influenced by sex, STEMI or NSTEMI presentation, or baseline thyroid function (all *P* for interactions >.40). In the subgroup of participants with baseline reduced LVEF (<55%), the adjusted between-group difference in LVEF associated with levothyroxine treatment was 2.46% (95% CI, 0.28% to 4.60%), and the *P* value for interaction (compared with those with normal LVEF [≥55%]) was nonsignificant (*P* = .44) (**Figure 2**). Post hoc analysis with site as an additional variable did not change the result (adjusted between-group mean difference in LVEF, 0.66% [95% CI, −1.10% to 2.39%]; *P* = .45).

Secondary Outcomes

Left Ventricular Volumes and Infarct Size Assessment

LV end-diastolic volume per body surface area (66.7 mL/m^2 in the levothyroxine group and 70.4 mL/m^2 in the placebo group), end-systolic volume per body surface area (31.1 mL/m^2 in the levothyroxine group and 31.4 mL/m^2 in the placebo group), and cardiac output (4.1 L/min in the levothyroxine group and 4.6 L/min in the placebo group) at 52 weeks were not significantly different in both study groups, with adjusted between-group differences of −4.27 mL/m^2 (95% CI, −9.03 to 0.49), −2.44 mL/m^2 (95% CI, −5.46 to 0.58), and −0.14 L/min (95% CI, −0.47 to 0.18), respectively (Table 2). Thirty patients in the levothyroxine group and 30 patients in the placebo group had their mass of infarct and LV mass assessed. The remaining participants did not have late gadolinium-enhanced imaging due to impaired kidney function (estimated glomerular filtration rate ≤50 mL/min/1.73 m^2). There were no significant differences at 52 weeks in either the infarct size (5.8% vs 8.4%) or the LV mass between the levothyroxine and placebo groups (adjusted between-group difference, 0.02% [95% CI, −1.34% to 1.38%] and 1.97 g [95% CI, −4.43 to 8.37], respectively) (Table 2).

Figure 1. Flow of Participants Through the Thyroxine in Acute Myocardial Infarction (ThyrAMI-2) Randomized Clinical Trial



MRI indicates magnetic resonance imaging; TSH, serum thyrotropin.

[a] Age older than 75 years was an exclusion criteria for the first 3 months of recruitment until the protocol was amended.

Quality of Life and Depression

Measures of patient-reported outcomes at 52 weeks were not significantly different between the levothyroxine and placebo groups: SF-12v2 mean Physical and Mental Component scores of 46.0 vs 45.6 and 50.4 vs 52.8, respectively (adjusted between-group differences, −0.14 [95% CI, −4.54 to 4.23] and −3.03 [95% CI, −7.30 to 1.24], respectively); median Minnesota Living With Heart Failure Questionnaire scores of 13.0 vs 15.0 (adjusted between-group difference, −3.74 [95% CI, −10.60 to 3.08]); and median Center for Epidemiologic Studies Depression Scale scores of 10.0 vs 5.0 (adjusted between-group difference, 3.13 [95% CI, 0 to 6.27]), respectively; all *P* values for adjusted between-group differences were ≥.05 (Table 2).

Thyroid Profile and Levothyroxine Dose Throughout the Study

Serum thyrotropin levels declined over the 52 weeks of study in both groups (**Table 3**). However, the median thyrotropin level was lower in the levothyroxine group (1.8 mU/L [IQR, 1.3-2.2]) compared with the placebo group (3.2 mU/L [IQR, 2.7-4.2]) after 52 weeks. Furthermore, the median thyrotropin level was consistently lower in the levothyroxine group at all study time points compared with the corresponding values in the placebo group. Conversely, FT_4 levels were higher in the levothyroxine group at the end of the study: mean (SD) levels of 1.34 (0.21) ng/dL vs 1.13 (0.16) ng/dL in the placebo group at 52 weeks. The median daily dose of levothyroxine at the end of

Table 1. Baseline Characteristics

Characteristic	No. (%)[a] Levothyroxine (n = 46)	Placebo (n = 49)
Age, mean (SD), y	64.1 (9.4)	62.9 (9.7)
Sex		
Men	36 (80)	36 (74)
Women	10 (20)	13 (26)
Blood pressure, median (IQR), mm Hg		
Systolic	122.5 (117.3-134.3)	124.0 (114.3-138.3)
Diastolic	76.0 (69.3-80.0)	74.5 (64.0-82.3)
Heart rate, median (IQR), bpm	61.0 (53.3-65.0)	61.5 (57.5-66.8)
Body mass index, median (IQR)[b]	27.7 (25.5-30.8)	28.9 (25.9-31.2)
Current smoker	14 (30.4)	11 (22.9)
STEMI	32 (70)	33 (67)
Interval between AMI and starting treatment, median (IQR), d	17.0 (14.5-20.0)	16.0 (14.0-19.5)
NYHA class[c]		
1 (Least severe)	8 (17)	8 (16)
2 (Moderately severe)	36 (80)	38 (78)
3 (Markedly severe)	2 (4)	3 (6)
Thyroid function		
Thyrotropin, median (IQR), mU/L	5.8 (5.0-7.1)	5.7 (4.7-7.3)
FT_4, mean (SD), ng/dL	1.14 (0.16)	1.13 (0.19)
FT_3, mean (SD), pg/mL (n = 80)	2.99 (0.52)	2.86 (0.52)
Total cholesterol, mean (SD), mg/dL	185.3 (50.2)	185.3 (46.3)
Creatinine, median (IQR), mg/dL	0.95 (0.81-1.13)	0.93 (0.80-1.11)
Preexisting medical conditions		
Hypertension	18 (39)	19 (39)
Dyslipidemia	13 (28)	14 (29)
Type 2 diabetes	8 (17)	10 (20)
Ischemic heart disease	3 (7)	4 (8)
Cerebrovascular disease	2 (4)	3 (6)
Secondary prevention medication use		
Aspirin	46 (100)	49 (100)
Second antiplatelet agent	46 (100)	49 (100)
Prasugrel	21 (46)	23 (47)
Clopidogrel	13 (28)	14 (29)
Ticagrelor	12 (26)	12 (25)
β-Blocker	43 (94)	48 (98)
ACE inhibitor or ARB	44 (96)	48 (98)
Statin	46 (100)	49 (100)

Abbreviations: ACE, angiotensin-converting enzyme; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; bpm, beats per minute; FT_4, thyroxine; FT_3, triiodothyronine; IQR, interquartile range; NYHA, New York Heart Association; STEMI, ST-elevation myocardial infarction.

SI conversion factors: To convert creatinine to μmol/L, multiply by 88.4; FT_4 to pmol/L, multiply by 12.87; FT_3 to pmol/L, multiply by 1.54; and total cholesterol to mmol/L, multiply by 0.0259.

[a] Unless otherwise specified.

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

[c] NYHA is a classification of the severity of heart failure depending on symptoms: class 1 indicates no limitation of physical activity; class 2, slight limitation; and class 3, marked limitation.

the study was 50 μg (IQR, 50-75). Adherence to study medication was good over the course of the study (94%).

Adverse and Serious Adverse Events

There were 10 reported serious adverse events (SAEs) in 8 patients in the levothyroxine group and 17 SAEs in 10 patients in the placebo group (Table 2). The SAEs were categorized as cardiovascular and noncardiovascular events. In the levothyroxine and placebo groups, there were 2 and 6 cardiovascular SAEs, respectively. One patient in each group died (cardiovascular disease–related deaths) during follow-up. The definition and details of all adverse events are provided in eAppendix 7 and eTable 3 in Supplement 3.

Discussion

In this double-blind, randomized, placebo-controlled trial, treatment with levothyroxine for 52 weeks did not significantly improve LV function in patients with subclinical hypothyroidism presenting with acute myocardial infarction. On the basis of these findings, screening for and subsequent treatment of subclinical hypothyroidism in patients with acute myocardial infarction to preserve LV function is not justified.

Patients with cardiac disease who have subclinical hypothyroidism experience worse outcomes.[9,27,28] For example, the presence of subclinical hypothyroidism in patients admitted with an acute cardiac event is associated with a 3.6-fold and a 2.3-fold greater risk of cardiac and all-cause mortality, respectively.[9] In animal models of acute myocardial infarction, administration of thyroid hormone augments myocardial remodeling and improves LV function.[29] In older individuals with subclinical hypothyroidism, treatment with levothyroxine is associated with a 72% lower risk of heart failure events.[30] Trials with small numbers of participants (ranging between 10 and 30) have shown that treatment of subclinical hypothyroidism with levothyroxine improves LV function.[25,31,32] Thus, subclinical hypothyroidism following acute myocardial infarction is an important marker for poor outcome, and one that is suitable for a cost-effective intervention, if evidence of efficacy can be proven. However, it remains unknown whether the relationship between subclinical hypothyroidism with poor prognosis in cardiac patients is causal.

One of the strengths of this study is that MRI, considered as the reference-standard technique, was used to assess cardiac volumes and function.[33] Despite the null findings, a greater risk of mortality in patients with subclinical hypothyroidism after acute myocardial infarction highlights the need for ongoing studies to reduce vascular event rates to levels seen in euthyroid patients. One of the reasons for the discrepancy detected in the previous observational studies of poor prognosis in individuals with subclinical hypothyroidism and the lack of efficacy of levothyroxine shown in this trial could be because many observational studies diagnosed subclinical hypothyroidism based on a single blood test. Up to half of raised serum thyrotropin levels in individuals with subclinical hypothyroidism and acute myocardial infarction

Table 2. Primary and Secondary Outcomes

Outcome	Levothyroxine		Placebo		Adjusted difference between levothyroxine and placebo (95% CI)[a]	*P* value
	Baseline	52 wk	Baseline	52 wk		
Primary outcome						
No.	39		46			
LVEF, mean (SD), %	51.3 (9.1)	53.8 (9.7)	54.0 (7.9)	56.1 (7.9)	0.76 (−0.93 to 2.46)	.37
Secondary outcomes, mean (SD)						
LV volumes and function, No.	39		46			
EDV/BSA, mL/m^2	68.6 (17.2)	66.7 (16.6)	70.5 (13.8)	70.4 (13.1)	−4.27 (−9.03 to 0.49)	.08
ESV/BSA, mL/m^2	34.4 (14.1)	31.1 (12.1)	32.9 (9.9)	31.4 (10.2)	−2.44 (−5.46 to 0.58)	.11
Stroke volume, mL[b]	67.2 (13.1)	75.4 (16.7)	68.7 (16.1)	78.9 (15.9)	−3.76 (−8.45 to 0.94)	.12
Stroke index, mL/m^2[b]	34.4 (6.6)	34.9 (7.8)	37.6 (7.9)	38.9 (6.9)	−1.74 (−4.11 to 0.64)	.15
Cardiac output, L/min[b]	3.9 (0.7)	4.1 (0.87)	4.6 (1.1)	4.6 (0.96)	−0.14 (−0.47 to 0.18)	.38
Cardiac index, L/min/m^2[b]	2.0 (0.3)	2.1 (0.43)	2.3 (0.5)	2.3 (0.38)	−0.07 (−0.22 to 0.09)	.39
Infarct size and LV mass, No.	30		30			
Infarct size, median (IQR), g	7.9 (2.5 to 20.3)	5.6 (1.3 to 15.2)	8.9 (1.9 to 16.1)	7.0 (1.0 to 13.3)	0.23 (−1.31 to 1.77)	.77
Infarct size, median (IQR), %	7.8 (2.7 to 14.7)	5.8 (2.1 to 12.9)	8.5 (1.7 to 16.2)	8.4 (1.0 to 14.8)	0.02 (−1.34 to 1.38)	.98
LV mass, mean (SD), g[b]	106.4 (33.4)	99.2 (29.9)	102.1 (22.9)	94.0 (18.2)	1.97 (−4.43 to 8.37)	.54
Patient-reported outcomes, No.	45		49			
SF12						
Physical[c]	39.9 (10.6)	46.0 (10.1)	38.5 (10.9)	45.6 (10.6)	−0.14 (−4.54 to 4.23)	.95
Mental[d]	49.6 (10.5)	50.4 (11.7)	51.6 (10.8)	52.8 (7.9)	−3.03 (−7.30 to 1.24)	.16
MLWHF, median (IQR)[e]	27.0 (12.3 to 40.0)	13.0 (6.8 to 24.3)	23.0 (11.5 to 37.5)	15.0 (6.0 to 30.0)	−3.74 (−10.6 to 3.08)	.28
CES-D, median (IQR)[f]	9.0 (4.0 to 16.0)	10.0 (2.0 to 18.0)	8.0 (2.5 to 15.0)	5.0 (2.0 to 14.0)	3.13 (−0.0 to 6.27)	.05
Clinical outcomes, No. (%)						
No.	45		49			
Cardiovascular events						
Serious adverse events[g]		2 (4.4)		6 (12.2)		
Adverse events[g]		15 (33.3)		18 (36.7)		
Noncardiovascular events						
Serious adverse events[g]		8 (17.8)		11 (22.4)		
Adverse events[g]		32 (64.4)		27 (55.1)		
Death		1 (2.2)		1 (2.0)		

Abbreviations: BSA, body surface area; CES-D, Centre for Epidemiologic Studies Depression Scale; EDV, end-diastolic volume; ESV, end-systolic volume; IQR, interquartile range; LVEF, left ventricular ejection fraction; MLWHF, Minnesota Living With Heart Failure questionnaire; SF12, Short Form 12 Health Status questionnaire.

[a] Primary and secondary outcomes were compared using linear regression adjusting for age, sex, type of acute myocardial infarction, infarct territory, and baseline levels.

[b] Post hoc analysis.

[c] SF12 Physical: scores range from 20 to 56, with higher scores indicating better physical health; the mean score of approximately 40 suggests that the average participant in this trial scored their physical health as being good or very good.

[d] SF12 Mental: scores range from 41 to 61, with higher scores indicating perceived better mental health; the mean score of approximately 50 suggests that the average participant in this trial rated their mental health as being good or very good.

[e] MLWHF: scores range from 0 to 105, with higher scores indicating increase in symptoms of heart failure; the median scores of trial participants at baseline in both groups were suggestive of moderate symptoms of heart failure but improved to being self-rated as good over the subsequent 52 weeks.

[f] CES-D: scores range from 0 to 60, with higher scores indicating greater depressive symptoms; the median scores of the participants in both groups suggest low risk of clinical depression (using a cut-off of 16.0).

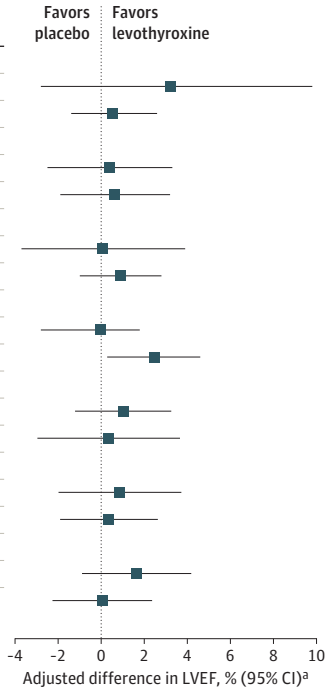
[g] The definition of adverse events and serious adverse events are provided in eAppendix 7 in Supplement 3. All serious adverse events are also included in the adverse events.

normalize over time.[34] Furthermore, thyrotropin levels are known to rise during the recovery phase of nonthyroidal illness or could be affected by the iodine content in the angiographic contrast media.[35] In this trial, only patients with sustained subclinical hypothyroidism were included and had their baseline thyroid function assessed prior to coronary angiography. In addition, patients with mild subclinical hypothyroidism (at least 1 thyrotropin value below 10.0 mU/L) were recruited because this group constitutes most patients with subclinical hypothyroidism and where the greatest uncertainty of treatment efficacy prevails.[12,13] It remains unknown whether targeting treatment in individuals with more severe disease (thyrotropin >10.0 mU/L) may or may not be beneficial.

This trial does address an important uncertainty regarding the potential safety profile of levothyroxine replacement therapy in a postacute myocardial infarction setting. These results suggest levothyroxine replacement therapy does not appear to

Figure 2. Effect of Levothyroxine Compared With Placebo on Left Ventricular Ejection Fraction (LVEF) According to Prespecified and Post Hoc Subgroups

Variable	No. of patients: Levothyroxine (n = 39)	No. of patients: Placebo (n = 46)	Adjusted difference in LVEF, % (95% CI)[a]	*P* for interaction[b]
Sex				
Female	8	11	3.21 (-2.8 to 9.8)	.68
Male	31	35	0.55 (-1.4 to 2.6)	
Age, y[c]				
Above median (>62.7)	21	21	0.37 (-2.5 to 3.3)	.91
Below median (≤62.7)	18	25	0.64 (-1.9 to 3.2)	
Type of AMI				
NSTEMI	10	13	0.08 (-3.7 to 3.9)	.92
STEMI	29	33	0.9 (-0.99 to 2.8)	
Baseline LVEF, %				
Normal (≥55)	13	19	-0.05 (-2.80 to 1.79)	.44
Reduced (<55)	26	27	2.46 (0.28 to 4.60)	
Baseline thyrotropin level, mU/L				
Above median (>5.7)	22	22	1.02 (-1.21 to 3.25)	.47
Below median (≤5.7)	17	24	0.35 (-2.96 to 3.66)	
Baseline FT_4 level, ng/dL[c]				
Above median (>1.12)	17	25	0.87 (-1.98 to 3.72)	.95
Below median (≤1.12)	22	21	0.36 (-1.91 to 2.63)	
Baseline FT_3 level, pg/mL[c]				
Above median (>2.93)	15/36	20/44	1.65 (-0.89 to 4.18)	.39
Below median (≤2.93)	21/36	24/44	0.05 (-2.26 to 2.36)	



AMI indicates acute myocardial infarction; FT_4, free thyroxine; FT_3, free triiodothyronine; NSTEMI, non–ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction. To convert FT_4 to pmol/L, multiply by 12.87; and FT_3 to pmol/L, multiply by 1.54.

[a] The difference in LVEF between the levothyroxine and placebo groups was adjusted for baseline age, sex, type of AMI, baseline LVEF, and infarct territory.

[b] The *P* for interaction was calculated by the addition of the interaction term (independent variable × allocation to levothyroxine or placebo) to the fully adjusted model above.

[c] Post hoc subgroup.

Table 3. Post Hoc Analysis of Thyroid Function and Dose of Levothyroxine During the Course of the Study

	Mean (SD)					
	Visit 1 (baseline)	Visit 2 (4 wk)	Visit 3 (8 wk)	Visit 4 (12 wk)	Visit 5 (24 wk)	Visit 6 (52 wk)
Levothyroxine group						
Thyrotropin, median (IQR), mU/L	5.8 (5.0-7.1)	2.6 (1.8-3.5)	1.8 (1.4-2.3)	2.2 (1.6-2.9)	1.8 (1.4-2.3)	1.8 (1.3-2.2)
FT_4, ng/dL	1.14 (0.16)					1.34 (0.21)
FT_3, pg/mL	2.99 (0.52)					3.06 (0.39)
Dose of levothyroxine, median (IQR), µg/d		25 (25-25)	50 (25-50)	50 (25-68.8)	50 (25-75)	50 (50-75)
Placebo group						
Thyrotropin, median (IQR), mU/L	5.7 (4.7-7.3)	3.4 (2.8-4.2)	3.8 (3.0-4.9)	3.9 (3.3-4.7)	3.8 (3.0-4.9)	3.2 (2.7-4.2)
FT_4, ng/dL	1.13 (0.19)					1.13 (0.16)
FT_3, pg/mL	2.86 (0.52)					3.12 (0.39)

Abbreviations: FT_4, free thyroxine; FT_3, free triiodothyronine; IQR, interquartile range.

SI conversion factors: To convert FT_4 to pmol/L, multiply by 12.87; and FT_3 to pmol/L, multiply by 1.54.

increase adverse effects, particularly cardiovascular adverse effects, in patients with acute myocardial infarction.

Limitations

This trial has several limitations. First, the therapeutic efficacy of levothyroxine replacement may have been blunted due to the delay between coronary occlusion and initiation of levothyroxine therapy (median of 17 days). This was considered necessary as patients with sustained subclinical hypothyroidism were to be recruited in this trial. It remains unknown whether earlier treatment or treatment for a longer period may be beneficial.

Second, due to the unknown safety profile of levothyroxine in this group of patients, levothyroxine was initiated at a small dose (25 µg daily) and titrated over several weeks. The median dose of levothyroxine at the end of the study (50 µg

daily) is lower than that used in other trials that have demonstrated benefit of treatment on endothelial function and lipid profiles.[36,37] This may have reduced the therapeutic efficacy of levothyroxine on cardiac remodeling and ventricular function. However, serum thyrotropin levels in the levothyroxine group were within the target range (0.4-2.5 mU/L) and FT_4 levels were higher at the end of the trial compared with baseline and the placebo group.

Third, the bioavailability of cardiac T3 could have been low in patients recruited in this trial due to impaired conversion of T4 to T3 despite treatment with levothyroxine due to changes in the activating and inactivating thyroid hormone enzymes (deiodinases).[38] These findings raise the possibility that further research may be useful to investigate alternative thyroid hormone treatments in patients with a low thyroid hormone state. An open-label trial of oral T3 in patients with STEMI and low serum T3 levels demonstrated no significant improvement in LVEF.[39]

Fourth, nearly 40% of patients recruited in this trial had evidence of preserved LV function and the effect of treatment in patients with worse LVEF remains unknown. Additional research might be useful to evaluate efficacy in this group of patients.

Fifth, individuals with chronic persistent subclinical hypothyroidism may be a different population than the population studied here and it is not possible to exclude whether levothyroxine might improve LV function in this population outside the situation of recent acute myocardial infarction.

Sixth, LVEF represents the percentage change of LV chamber size and not myocardial contractility and other markers of LV contractility (such as global longitudinal strain) are independent of LVEF and may offer greater prognostic information.[40] Thus, because there were no significant changes in LV end-systolic or end-diastolic volumes with treatment, no change in LVEF was to be expected.

Conclusions

In this preliminary trial involving patients with subclinical hypothyroidism and acute myocardial infarction, treatment with levothyroxine, compared with placebo, did not significantly improve LVEF after 52 weeks. These findings do not support treatment of subclinical hypothyroidism in patients with acute myocardial infarction.

ARTICLE INFORMATION

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