ORIGINAL ARTICLE

Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism

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ABSTRACT

BACKGROUND

The use of levothyroxine to treat subclinical hypothyroidism is controversial. We aimed to determine whether levothyroxine provided clinical benefits in older persons with this condition.

METHODS

We conducted a double-blind, randomized, placebo-controlled, parallel-group trial involving 737 adults who were at least 65 years of age and who had persisting subclinical hypothyroidism (thyrotropin level, 4.60 to 19.99 mIU per liter; free thyroxine level within the reference range). A total of 368 patients were assigned to receive levothyroxine (at a starting dose of 50 μg daily, or 25 μg if the body weight was <50 kg or the patient had coronary heart disease), with dose adjustment according to the thyrotropin level; 369 patients were assigned to receive placebo with mock dose adjustment. The two primary outcomes were the change in the Hypothyroid Symptoms score and Tiredness score on a thyroid-related quality-of-life questionnaire at 1 year (range of each scale is 0 to 100, with higher scores indicating more symptoms or tiredness, respectively; minimum clinically important difference, 9 points).

RESULTS

The mean age of the patients was 74.4 years, and 396 patients (53.7%) were women. The mean (±SD) thyrotropin level was 6.40±2.01 mIU per liter at baseline; at 1 year, this level had decreased to 5.48 mIU per liter in the placebo group, as compared with 3.63 mIU per liter in the levothyroxine group (P<0.001), at a median dose of 50 μg. We found no differences in the mean change at 1 year in the Hypothyroid Symptoms score (0.2±15.3 in the placebo group and 0.2±14.4 in the levothyroxine group; between-group difference, 0.0; 95% confidence interval [CI], −2.0 to 2.1) or the Tiredness score (3.2±17.7 and 3.8±18.4, respectively; between-group difference, 0.4; 95% CI, −2.1 to 2.9). No beneficial effects of levothyroxine were seen on secondary-outcome measures. There was no significant excess of serious adverse events prespecified as being of special interest.

CONCLUSIONS

Levothyroxine provided no apparent benefits in older persons with subclinical hypothyroidism. (Funded by European Union FP7 and others; TRUST ClinicalTrials.gov number, NCT01660126.)

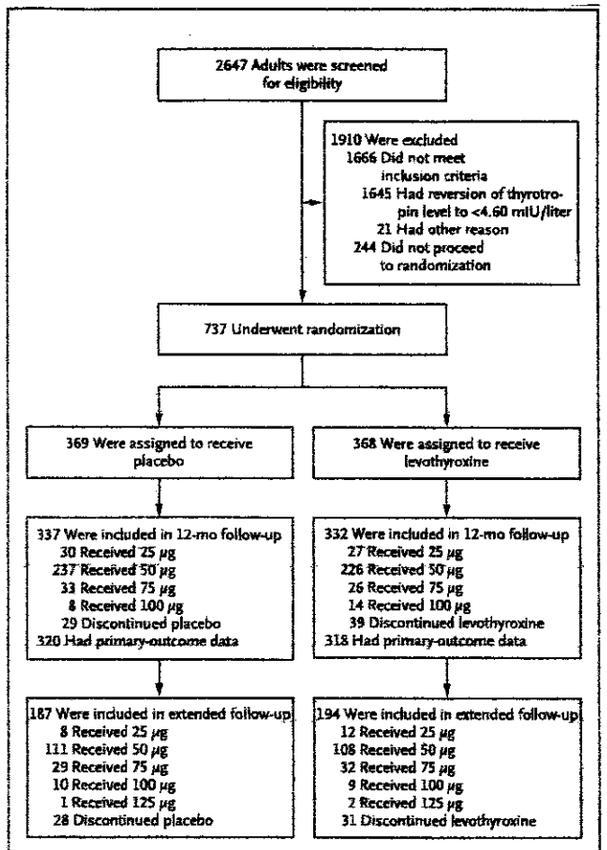

Figure 1. Randomization, Follow-up, and Dose Levels.

Exclusions for other reasons included use of antithyroid medication (in 17 persons), recent thyroid surgery (in 1), recent acute coronary syndrome (in 1), current participation in another trial (in 1), and adrenal insufficiency (in 1). Two patients who were excluded because the thyrotropin level reverted to less than 4.60 mIU per liter also had an additional exclusion of galactose intolerance. Extended follow-up beyond 12 months was conducted in a subgroup of patients, with a median duration of follow-up from baseline of 24.2 months (interquartile range, 18.4 to 30.3) in the placebo group and 24.5 months (interquartile range, 18.4 to 30.5) in the levothyroxine group.

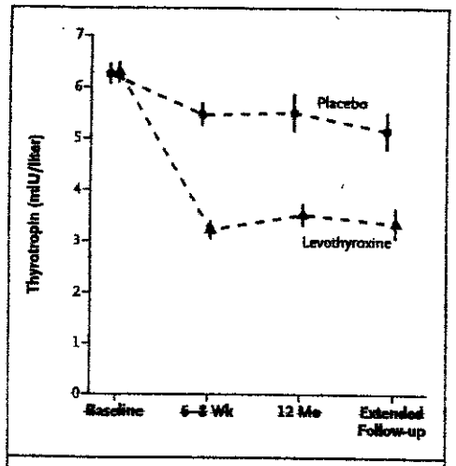

Figure 2. Thyrotropin Levels in the Placebo Group and Levothyroxine Group.

Shown are the results of a modified intention-to-treat analysis. Data are means, and error bars indicate 95% confidence intervals. Extended follow-up beyond 12 months was conducted in a subgroup of patients, with a median duration of follow-up from baseline of 24.2 months (interquartile range, 18.4 to 30.3) in the placebo group and 24.5 months (interquartile range, 18.4 to 30.5) in the levothyroxine group. P<0.001 for between-group differences in the thyrotropin level at 6 to 8 weeks, 12 months, and extended follow-up. Analyses were adjusted for stratification variables (country, sex, and starting dose of levothyroxine) and baseline thyrotropin level with the use of linear regression; data for the extended follow-up visit were additionally adjusted for time to visit.

Table 3. Clinical Outcomes and Adverse Events.*

Variable	All Patients (N=737)	Placebo Group (N=369)	Levothyroxine Group (N=368)	Hazard Ratio (95% CI)
Clinical outcome				
Fatal or nonfatal cardiovascular event — no. (%)	38 (5.2)	20 (5.4)	18 (4.9)	0.89 (0.47–1.69)
Cardiovascular death — no. (%)	3 (0.4)	1 (0.3)	2 (0.5)	—
Death from any cause — no. (%)	15 (2.0)	5 (1.4)	10 (2.7)	1.91 (0.65–5.60)
Serious adverse event				
No. of patients with ≥1 serious adverse event	181 (24.6)	103 (27.9)	78 (21.2)	0.94 (0.88–1.00)†
No. of events	343	201	142	—
Adverse event of special interest				
New-onset atrial fibrillation — no. (%)	24 (3.3)	13 (3.5)	11 (3.0)	0.80 (0.35–1.80)
Heart failure — no. (%)	9 (1.2)	6 (1.6)	3 (0.8)	—
Fracture — no. (%)	17 (2.3)	8 (2.2)	9 (2.4)	1.06 (0.41–2.76)
New diagnosis of osteoporosis — no. (%)	7 (0.9)	4 (1.1)	3 (0.8)	—
Withdrawal				
Permanent discontinuation of trial regimen — no. (%)	160 (21.7)	79 (21.4)	81 (22.0)	1.06 (0.78–1.44)
Withdrawal from follow-up — no. (%)	41 (5.6)	22 (6.0)	19 (5.2)	0.84 (0.46–1.56)

* This table includes serious adverse events and adverse events of special interest in the modified intention-to-treat population and data on withdrawals from trial regimen and follow-up. Hazard ratios were not calculated for cardiovascular death, heart failure, or new diagnosis of osteoporosis owing to the small number of events.

† P=0.05. Hazard ratios for treatment were obtained from a Cox proportional-hazards regression model predicting survival from randomized trial group and stratification variables (country, sex, and dose at randomization).