Long-Term Outcome in Levothyroxine Treated Patients With Subclinical Hypothyroidism and Concomitant Heart Disease

Mette Nygaard Andersen, Anne-Marie Schjerning Olsen, Jesper Clausager Madsen, Søren Lund Kristensen, Jens Faber, Christian Torp-Pedersen, Gunnar H. Gislason, and Christian Selmer

Department of Cardiology (M.N.A., A.-M.S.O., S.L.K., G.H.G.), Gentofte University Hospital, 2900 Hellerup, Denmark; Elective Laboratory of the Capital Region (J.C.M.), 1112 Copenhagen, Denmark; Department of Endocrinology (J.F.), Herlev University Hospital, 2730 Herlev, Denmark; Faculty of Health Sciences (J.F., G.H.G.), University of Copenhagen, 1165 Copenhagen, Denmark; Department of Health Science and Technology (C.T.-P.), University of Aalborg, 9100 Aalborg, Denmark; The Danish Heart Foundation (G.H.G.), 1120 Copenhagen, Denmark; The National Institute of Public Health (G.H.G.), University of Southern Denmark, 1399 Copenhagen, Denmark; and Department of Endocrinology (C.S.), Amager and Hvidovre University Hospital, 2650 Copenhagen, Denmark

Context: Subclinical hypothyroidism is a common condition that may lead to impaired cardiac function.

Objective: This study sought to examine the effects of levothyroxine treatment in patients with subclinical hypothyroidism and heart disease.

Design: This was a register-based historical cohort study.

Setting and Participants: The study was composed of Danish primary care patients and hospital outpatients age 18 years and older with established heart disease who were diagnosed with subclinical hypothyroidism in 1997–2011. Patients were stratified according to whether they claimed a subsequent prescription of levothyroxine. Event rates and incidence rate ratios (IRR) were calculated by use of time-dependent multivariable Poisson regression models.

Main Outcome Measures: Measures included all-cause mortality and major adverse cardiac events (MACEs), defined as cardiovascular death, fatal or nonfatal myocardial infaction and stroke, and all-cause hospital admissions.

Results: Of 61 611 patients with a diagnosis of cardiac disease having their first time thyroid function testing, 1192 patients with subclinical hypothyroidism (mean age 73.6 [SD ± 13.3] y, 63.8% female) were included, of whom 136 (11.4%) were treated with levothyroxine. During a median follow-up time of 5.6 y (interquartile range, 6.5 y), 694 (58.2%) patients died. Patients treated with levothyroxine displayed no significantly increased risk of all-cause mortality (adjusted IRR, 1.17; 95% confidence interval [CI], 0.90–1.52), MACE (adjusted IRR, 1.08; 95% CI, 0.80–1.45), or hospital admission (adjusted IRR, 0.94; 95% CI, 0.71–1.24), when compared with patients not treated with levothyroxine.

Conclusion: Levothyroxine treatment in patients with subclinical hypothyroidism and heart disease was not associated with a significant benefit nor risk of all-cause mortality, MACE, or hospital admission in this large real-world cohort study. **(*J Clin Endocrinol Metab* 101: 4170–4177, 2016)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received May 27, 2016. Accepted August 22, 2016.
First Published Online August 29, 2016

Abbreviations: ATC, Anatomical Therapeutic Chemical; CI, confidence interval; ICD, International Classification of Diseases; IQR, interquartile range; IRR, incidence rate ratio; MACE, major adverse cardiac event; MI, myocardial infarction; py, person year.

Subclinical hypothyroidism is typically an asymptomatic condition, biochemically defined by a raised serum TSH concentration combined with a normal level of free T_4 (FT_4) (1). The prevalence of the condition is approximately 5–10% in the adult population, and it is more common in women and elderly (2, 3). Furthermore, subclinical hypothyroidism can be divided into a mild and a severe grade depending on whether the TSH level is below or above 10 mIU/L, respectively (4, 5). The condition is associated with an increased risk of dyslipidemia (6, 7), but also coronary heart disease (8, 9) and ischemic heart disease (10–14). Furthermore, subclinical hypothyroidism has been associated with an increased mortality in patients with established cardiovascular disease (15, 16). It is unclear whether treatment with levothyroxine holds any benefit in terms of preventing cardiovascular events in patients with subclinical hypothyroidismand controversy prevails regarding need for treatment (17–19). Levothyroxine treatment in this setting has not been adequately studied and the issue of treatment remains debated (20). Current guidelines recommend that patients with established cardiovascular disease and subclinical hypothyroidism should be started in a lower dose of levothyroxine than subclinical hypothyroid patients without cardiac comorbidities (21) due to fear of potentially harmful effects of levothyroxine. The present register-based cohort study was conducted with the aim to examine the effects of levothyroxine treatment in patients with subclinical hypothyroidism and heart disease.

Materials and Methods

Setting and data sources

In Denmark, each resident is provided with a permanent personal identification number that enables individual-level linkage between national administrative registers holding information on health care usage (22). Five of these registers were used in this study: 1) The Danish National Patient Register holds records of all hospital admissions since 1977. All admissions have been registered with one main discharge diagnosis, and, if applicable, one or more supplementary discharge diagnoses coded according to the International Classification of Diseases (ICD-8 until 1994 and from 1994 ICD-10) (23). 2) The Civil Registration system records deaths and migration for all Danish citizens provided information regarding vital status (22). 3) The Danish Register of Causes of Death provided information regarding specific causes of death (24). 4) The Danish Register of Medicinal Product Statistics contains information on all claimed prescriptions (coded according to the international Anatomical Therapeutic Chemical [ATC] Classification) from pharmacies in Denmark since 1994 (25). The register also holds information regarding quantity, strength, and date of dispensation as well as formulation and the affiliation of the physician issuing the prescription. Annual incomes were retrieved from 5) The Danish registers on personal income and transfer payments—The Danish Labor Market (26). Socioeconomic status was defined by the average yearly gross household income in a 5-year period prior to inclusion in the study.

The study population

The study cohort comprised citizens of three distinct regions of Denmark age at least 18 years with known heart disease who underwent a thyroid function test in the period of 1997–2011. The population comprised primary care patients from the Copenhagen region and hospital outpatients in Copenhagen, Roskilde, and the North Region of Denmark. The presence of heart disease was defined by one or more prior hospital discharge diagnosis of acute myocardial infarction (MI), chronic ischemic heart disease, arrhythmia, or heart failure (HF), see Table 1. for ICD codes.

Each subject entered the cohort on date of first thyroid function screening if they fulfilled the criteria of subclinical hypothyroidism and was followed until death, emigration, or end of study (December 31, 2012). Patients were categorized according to their thyroid status at the time of their first thyroid function test. Biochemically, we defined subclinical hypothyroidism as TSH greater than 5.0 mIU/L and FT_4, 9–22 pmol/L. Patients with indication of previous thyroid dysfunction (ie, a history of prescriptions of thyroid hormones, antithyroid drugs or any thyroid related hospital diagnoses) were excluded from the study. Furthermore, patients who had received treatment with medication known to affect thyroid function, such as amiodarone, lithium, and glucocorticoids, were also excluded, (Table 1).

Table 1. Diagnoses (ICD-8 and ICD-10) and Medication (ATC) Codes Used in the Study

Diseases and Medication	ICD and ATC Codes
Thyroid disease and medication	
Hypothyroidism	ICD-10: E02–03, E063
Hyperthyroidism	ICD-10: E05, E062
Any thyroid related disease	ICD-8: 240–246, ICD-10: E00–E06, O905
Levothyroxine	ATC: H03AA01
Methimazole	ATC: H03BB01, H03BB02
Propylthiouracil (PTU)	ATC: H03BA02
Cardiovascular disease	
Ischemic heart disease	ICD-10: I20, I23–I25, ICD-8: 411–414
MI	ICD-10: I21–I22, ICD-8: 410
Cardiomyopathy	ICD-10: I42–I43
Arrhythmia	ICD-10: I44–I49
HF	ICD-10: I50–I51, J819
Stroke	ICD-8: 433–434, 436, ICD-10: I60–I62
Loop diuretics	ATC: C03C
Amiodarone	ATC: C01BD01
β blockers	ATC: C07
ACE inhibitors	ATC: C09A
Statins	ATC: C10AA
Other disease and medication	
Diabetes	CD-8: 250, ICD-10: E10–E11, E14
Lithium	ATC: N05AN01
Corticosteroids	ATC: H02AB

Study design

Patients were divided into groups according to whether they initiated levothyroxine treatment during followup. Furthermore, patients were divided into two grades of subclinical hypothyroidism: Grade I with mildly increased TSH, 5.0–10 mIU/L; and Grade II with severely increased TSH, greater than 10 mIU/L. The treated patients contributed with risk time in the untreated group until they were prescribed with levothyroxine treatment, at which point they were shifted to the treated group using a method validated previously (27).

Comorbidity and concomitant medical therapy

Comorbidities such as ischemic heart disease, stroke, MI and diabetes, were identified by hospitalizations from The Danish National Patient Register (see Table 1 for complete list). Charlson Comorbidity Index was calculated on basis of prespecified diagnoses up to 5 years prior to cohort entry (28, 29). Concomitant medical treatment was defined by any cashed prescriptions prior to thyroid tests, for the following drugs; amiodarone, glucocorticoids, lithium, beta blockers, ACE-inhibitors, loop diuretics, and statins.

Dose and duration of levothyroxine treatment

The Danish Register of Medical Product Statistics does not include information on prescribed daily dosage of the medication. We therefore used an algorithm for levothyroxine in which a minimum, maximum, and typical daily dosage range of the used medication was defined. For each prescription, treatment periods were calculated for levothyroxine by dividing the number of tablets dispensed by the estimated daily dosage. The estimated daily dose for each individual was calculated by comparing the cumulated dosage and the elapsed time between seven successive prescriptions for levothyroxine. This algorithm allowed the dosage to change when a new prescription was dispensed. This method, used to determine the average treatment time and dosage, has previously been described (30, 31).

Outcomes

The primary outcome of interest was all-cause mortality, with the secondary outcomes being all-cause hospital admissions and major adverse cardiac events (MACE), determined as cardiovascular death, fatal or nonfatal MI, and stroke.

Statistical analysis

Baseline characteristics are presented as numbers with percentages for categorical variables and as means ± SD for continuous variables. Median follow-up time and average treatment time is reported with interquartile range (IQR). Incidence rates were calculated as number of events per 1000 person-years (py) stratified by levothyroxine treatment status. Incidence rate ratios (IRRs; with 95% confidence intervals [CIs]) for each study outcome were estimated by time-dependent Poisson regression models and adjusted for age, sex, and Charlson Comorbidity Index. The model therefore included three time scales: calendar time with bands split in 1-year periods after January 1, 1997 and duration since the first thyroid function testing. Age was calculated at the beginning of each interval. Individuals were censored at the time of fatal or nonfatal event, emigration or end of study (December 31, 2012). A 95% significance level was used in all analyses including the test of interactions.

A number of sensitivity analyses were performed to test the primary findings. First, we adjusted the main model for socioeconomic status at baseline. Second, the model was stratified by sex. Third, different run-in-periods of 3, 9, 6, and 12 months from the date of the first thyroid function test until the time of the first prescription of levothyroxine, were used. Fourth, patients were censored at the time of amiodarone prescription. Fifth, time was divided into smaller intervals to ensure a constant rate in time division (bands were split every 3- and 6 months from January 1, 1997). Sixth, we obtained results from a second thyroid function test to verify the thyroid function status of the patient group initially classified with subclinical hypothyroidism. We then conducted an analysis in which we used patients with no known comorbidities besides the heart disease and an analysis where we adjusted the main model for loop diuretics, β blockers, ACE inhibitors, and statins. Furthermore, we conducted a new analysis using only patients who had their subclinical hypothyroid status confirmed by a second thyroid function test. Then we adjusted the main model for atrial fibrillation. Finally, we repeated the analyses using only primary care patients in Copenhagen who underwent a thyroid function test between January 1, 2000 and January 31, 2009. This was done to ensure that the results were not influenced by factors including severity of comorbidities that might differ between patients in primary care facilities and outpatient clinics.

All statistical analyses were performed with the SAS Statistical Software package version 9.4 (SAS Institute, Inc.) and Stata Software version 11 (StataCorp).

Ethics

Register-based studies do not require ethical approval in Denmark. The Danish Data protection Agency approved this study (Ref. No. 2007-58-0015/GEH-2014-018; I-Suite No. 02736) and data were made available for this study in an anonymized format preventing identification of individuals.

Results

Population

The total study cohort comprised 61 611 patients with a diagnosis of cardiovascular disease defined by one or more prior hospital discharge diagnosis of acute MI, chronic ischemic heart disease, arrhythmia or heart failure (HF), over the age of 18 years who had a first-time thyroid function test. One thousand, one hundred ninety-two of these patients were classified with subclinical hypothyroidism of whom 975 had mild subclinical hypothyroidism (TSH level between 5 and 10 mIU/L), whereas the remaining 217 patients were classified with severe subclinical hypothyroidism (TSH level above 10 mIU/L). Selection of the study cohort is illustrated in Figure 1, and the baseline characteristics of the cohort are presented in Table 2. The study cohort was composed mainly of women (63.8%) and the mean age was 73.6 years (SD ± 13.3 y). The levothyroxine-treated patient group was ~4 years younger and had more concomitant medications prescribed than the untreated group. There were no major

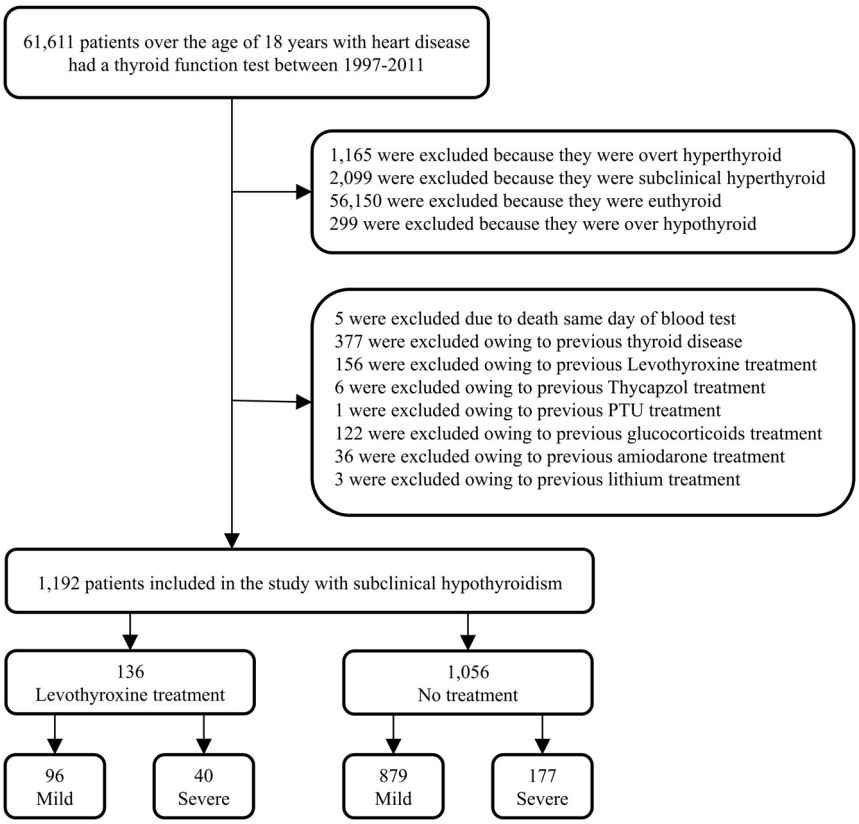

Figure 1. Flowchart. Selection of the study population.

differences in terms of comorbidity and socioeconomic status.

During the study, 136 (11.4%) patients claimed a prescription for levothyroxine. The median treatment time was 1306 (IQR, 1710) days and the average daily dosage prescribed was 76.6 (SD ± 32.1) micrograms.

Outcomes

During a median follow-up time of 5.6 (IQR, 6.5) years, 694 deaths, 585 MACEs, and 1064 hospital admissions occurred. Thirty patients were lost to followup due to emigration and were censored. The unadjusted incidence rates (for all-cause mortality were 96.8/1000 py for the treated group and 95.9/1000 py for the untreated group. Considering patients with Grade I subclinical hypothyroidism, the unadjusted incidence rates were 90.7/1000 py and 96.8/1000 py for the treated and untreated group, respectively, whereas the unadjusted rates for Grade II were 111.8/1000 py and 91.6/1000 py for the treated and untreated group, respectively. The adjusted IRR did not show any statistically significant effect of levothyroxine treatment for neither the overall group of patients (IRR, 1.17; 95% CI, 0.90–1.52), nor the patients with Grade I (IRR, 1.11; 95% CI, 0.81–1.52), nor the patients with Grade II (IRR, 1.23; 95% CI, 0.75–2.02) (Figure 2). The results from the Poisson model did not show any statistically significant effect of levothyroxine treatment when considering neither MACE (IRR, 1.08; 95% CI, 0.80–1.45) nor hospital admissions (IRR, 0.94; 95% CI, 0.71–1.24). Stratifying the model by the two grades of subclinical hypothyroidism did not change the main results, neither did the analyses performed only for patients age 65 years or older (Figure 2).

Sensitivity analysis

The main results were not altered when we adjusted the main model for socioeconomic status at baseline. The sex-stratified analysis showed a decrease in IRR for women and an increase in IRR for men. These alterations, however, were not significant. Using different run-in-periods between thyroid function test and initiation of levothyroxine (3, 6, 9, and 12 mo) did not change the overall results from the main model, nor did the analysis where patients were censored when they were prescribed amiodarone. Also, the main results were not altered when time was divided into smaller intervals, nor when using only individuals with no known comorbidities besides the heart disease or when the main model was adjusted for loop diuretics, β blockers, ACE inhibitors, and statins. Of the 1192 patients initially classified with subclinical hypothyroidism and concomitant heart disease, 952 patients (79.9%) had the subclinical hypothyroidism diagnosis confirmed in a second thyroid function test. The median time between the first and second thyroid function test was 146 (IQR ± 467) days. Conducting the same analysis using only these 952 patients with a confirmed subclinical hypothyroidism in the second thyroid function test yielded no differences from the main results, neither did the analysis adjusted for atrial fibrillation nor using only primary care patients (Table 3). Interactions of levothyroxine treatment with age and sex were examined, and no clinical important interactions were found.

Discussion

In the present study we found no association between levothyroxine treatment and risk of all-cause mortality, MACE, and hospital admissions in patients with concomitant cardiovascular disease. Data on the potential long-

Table 2. Baseline Characteristics

	Cardiac Patients With Subclinical Hypothyroidism		
	Untreated (n = 1056)	**Treated (n = 136)**	**Total Population (n = 1192)**
Age, y (±SD)			
Mean age, y	74.0 (13.2)	70.1 (13.4)	73.6 (13.3)
Min.–max. age	22–101	28–92	22–101
Mean age, Women	75.4 (13.2)	70.7 (13.2)	74.8 (13.4)
Mean age, Men	71.7 (12.6)	68.0 (14.2)	71.4 (12.8)
Sex, No. (%)			
Women	656 (62.1)	104 (76.5)	760 (63.8)
Men	400 (37.9)	32 (23.5)	432 (36.2)
Comorbidity, No (%)			
Ischemic heart disease	719 (68.1)	86 (63.2)	805 (67.5)
Stroke	108 (10.2)	9 (6.6)	117 (9.8)
MI	366 (34.7)	51 (37.5)	417 (35.0)
Atrial fibrillation	308 (29.2)	30 (22.1)	338 (28.4)
Diabetes	116 (11.0)	16 (11.8)	132 (11.1)
Concomitant medical treatment, No. (%)			
β blockers	199 (18.8)	58 (42.6)	257 (21.6)
ACE inhibitors	120 (11.4)	35 (25.7)	155 (13.0)
Statins	85 (8.0)	35 (25.7)	120 (9.1)
Loop diuretics	197 (18.7)	40 (29.4)	237 (19.9)
Charlson comorbidity index, No. (%)			
0	627 (59.4)	84 (61.8)	711 (59.6)
1	246 (23.3)	28 (20.6)	274 (23.0)
2	102 (9.6)	15 (11.6)	117 (9.8)
3+	81 (7.7)	9 (6.6)	90 (7.6)
Socioeconomic factors, No. (%)			
Yearly income on quintiles			
0 (lowest)	243 (23.0)	26 (19.1)	269 (22.6)
1	390 (36.9)	50 (36.8)	440 (36.9)
2	212 (20.1)	28 (20.6)	240 (20.1)
3	124 (11.8)	14 (10.3)	138 (11.6)
4 (highest)	87 (8.2)	18 (13.2)	105 (8.8)

The treated patient group was ~4 y younger and had more concomitant medications prescribed than the untreated group. Otherwise, there were no major distinctions in comorbidities and socioeconomic status.

term effects of levothyroxine treatment in cardiovascular patients with subclinical hypothyroidism are sparse, and there has been concern over the issue of thyroid hormone replacement therapy with data limited to only a few studies, most of which are concentrated on T_3 treatment (32). It is known that patients with HF have low levels of T_3, which remains unaltered or even might decrease further during levothyroxine (T_4) treatment due to impaired conversion of the inactive T_4 to the active T_3 (33, 34). HF can be a complication to severe hypothyroidism and it has been speculated whether T_3 treatment could improve cardiac function in HF patients with low T_3. However, this hypothesis is not supported in a recent randomized, double-blind, crossover, placebo-controlled, 3-month intervention study by Holmager et al (35). Interestingly, a placebo-controlled study by Moruzzi et al (36) on 20 patients with idiopathic dilated cardiomyopathy showed that levothyroxine treatment improved cardiac and exercise performance. However, we were not able in the present study to find an association between levothyroxine treatment and a reduction in risk of all-cause mortality, MACE, and hospital admissions in patients with cardiovascular disease and subclinical hypothyroidism.

A recent study by Shatynska-Mytsyk et al (37) showed an improvement in left ventricular diastolic function in patients with subclinical hypothyroidism substituted with low-doses (6.25–25 μg/d) of levothyroxine. These findings suggest that a low-dose levothyroxine treatment might have a beneficial effect on the cardiovascular system. The average daily dosage of levothyroxine administered to the treated patients in the present study was 76.5 (SD ± 32.0) μg. This dosage might be too high considering the cardiovascular health and comorbidities of the treated patients, and the well-known fact that overtreatment of levothyroxine affects the cardiovascular system (38). A British cohort study by Razvi et al (39) investigating 4735 primary care patients with subclinical hypothyroidism, showed that levothyroxine treatment in younger patients (age 40–70 y) was associated with fewer ischemic heart disease events, an effect which was not evident in older

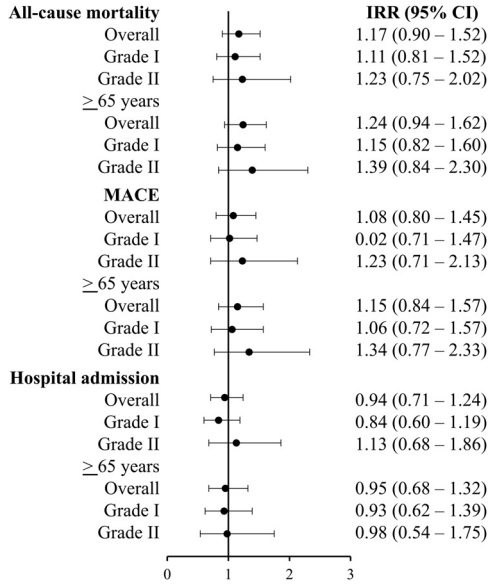

Figure 2. Risk of all-cause mortality, MACE, and hospital admissions in levothyroxine-treated vs untreated individuals with subclinical hypothyroidism and heart disease. Forrest-plot and IRR with 95% CI.

patients (age > 70 y). However, the present study was unable to demonstrate the same beneficial effects of levothyroxine treatment when observing patients with subclinical hypothyroidism and concomitant heart disease (39).

The neutral findings from the present study could also be explained by confounding by indication. The levothyroxine treated patients had more concomitant cardiovascular pharmacotherapy than the untreated patients, which could both point to more severe heart disease or an overall better treatment in the group of levothyroxine-treated patients than in the group of untreated patients. Alternatively, the results of this study could also be explained by nontreated patients experiencing spontaneous normalizations of TSH values and therefore regress to a euthyroid state without treatment, which could underestimate the treatment effect. In contrast, some nontreated patients could progress to overt hypothyroidism, which could potentially overestimate the calculated risk (40). In the ~90% of patients who had their thyroid function status confirmed in a second thyroid function test we observed no significantly increased risk of the examined endpoints.

The results of the present study might be interpreted in two ways: the treatment is either harmless or the physicians carefully choose to prescribe levothyroxine to the low-risk patients and treat them properly with the correct dose of medicine.

Strengths and limitations

The main strengths of this study is the large cohort of 61 611 individuals with heart disease who had thyroid function tests, the use of real-world data from primary care and hospital outpatient departments, and that fact that the study had access to complete follow-up data. It is however, essential to notice that we did not have knowledge of the indication for thyroid function testing, how

Table 3. Sensitivity Analyses

	Outcome		
	All-Cause Mortality	**MACE**	**Hospital Admission**
Main Results	1.17 (0.90–1.52)	1.08 (0.80–1.45)	0.94 (0.71–1.24)
Adjusted for socioeconomic status at baseline	1.16 (0.89–1.51)	1.07 (0.80–1.44)	0.88 (0.66–1.17)
Stratified by sex			
Women	1.08 (0.80–1.48)	0.99 (0.70–1.40)	0.92 (0.67–1.25)
Men	1.43 (0.87–2.34)	1.36 (0.79–2.35)	1.03 (0.54–1.94)
Time from thyroid function test to first levothyroxine prescription			
3 mo	0.83 (0.50–1.37)	0.80 (0.47–1.37)	1.03 (0.71–1.50)
6 mo	0.99 (0.65–1.50)	1.01 (0.64–1.59)	1.13 (0.80–1.59)
9 mo	1.04 (0.70–1.55)	0.97 (0.62–1.51)	1.12 (0.80–1.55)
12 mo	1.18 (0.82–1.70)	0.96 (0.62–1.48)	1.05 (0.76–1.45)
Censored at amiodarone prescription	1.13 (0.87–1.47)	1.06 (0.78–1.42)	0.94 (0.71–1.24)
Stratified by follow-up time			
3 mo	1.17 (0.90–1.52)	1.08 (0.80–1.45)	0.94 (0.71–1.24)
6 mo	1.17 (0.90–1.52)	1.08 (0.80–1.45)	0.94 (0.71–1.24)
Individuals with no known comorbidities	1.14 (0.80–1.61)	1.11 (0.76–1.63)	0.97 (0.69–1.37)
Adjusted for loop diuretics	1.21 (0.92–1.59)	1.11 (0.82–1.51)	0.85 (0.64–1.13)
Adjusted for β blockers	1.22 (0.93–1.59)	1.12 (0.83–1.52)	0.91 (0.69–1.20)
Adjusted for ACE inhibitors	1.16 (0.89–1.51)	1.09 (0.81–1.47)	0.94 (0.71–1.24)
Adjusted for statins	1.29 (0.99–1.68)	1.17 (0.87–1.58)	0.95 (0.72–1.26)
Using only patients with subclinical hypothyroidism confirmed in a second blood test	1.23 (0.92–1.65)	1.07 (0.76–1.50)	0.90 (0.65–1.24)
Adjusted for atrial fibrillation	1.43 (0.89–2.32)	1.17 (0.66–2.09)	0.56 (0.29–1.06)
Using only primary care patients	1.29 (0.98–1.69)	1.15 (0.85–1.57)	0.80 (0.58–1.09)

treatment was monitored, or how the response to the treatment (ie, whether patients became euthyroid or remained subclinical hypothyroid). We did not have access to clinical parameters such as blood pressure, body mass index, ejection fraction, smoking status, or the specific cause of thyroid dysfunction. Our findings could also be influenced by confounding by indication given that we do not have any background information as to what caused the physicians to prescribe levothyroxine treatment to some patients and not to others. For example, it could be an issue physicians could be more likely to prescribe levothyroxine to patients with milder heart disease, which potentially could conceal harmful effects of levothyroxine.

The present study has a median follow-up period of 5.6 years and it should be acknowledged that the outcomes studied might occur after even longer periods of thyroid disease and levothyroxine treatment.

Another limitation in the present study is the definition of the treated group. We considered patients as treated if they were prescribed levothyroxine at some point during the study. If patients initiate levothyroxine treatment a long time after their initial thyroid function test it could be because subsequent thyroid function tests demonstrated increasing levels of TSH or overt hypothyroidism causing the physician to prescribe levothyroxine. However, we performed sensitivity analyses using 3-, 9-, 6-, and 12-month run-in-periods from the date of the thyroid function test, which did not significantly change the main results.

Given that the study only included patients in the primary-care setting and hospital outpatients, extrapolation of these results to hospitalized patients should be done with caution. Likewise, extrapolation of the results to ethnic groups other than Caucasians should be done with care, given that the Danish population comprises mainly this group.

Conclusion

In conclusion, levothyroxine treatment in patients with subclinical hypothyroidism and concomitant heart disease seems not associated with a significant change in the risk of all-cause mortality, MACE or hospital admission in a real-world cohort study. Our findings support the idea that decisions regarding levothyroxine treatment in subclinical hypothyroid patients with concomitant heart disease should be patient based, given that treatment may have other health benefits such as change in cholesterol levels, symptom relief, weight loss, or quality of life in general, which in itself can be of significant importance for the patient.

Acknowledgments

Address all correspondence and requests for reprints to: Mette Nygaard Andersen, MD, Department of Cardiology, Gentofte University Hospital, Kildegaardsvej 28, 2900 Hellerup, Denmark. E-mail: mette.nygaard.andersen@gmail.com.

This work was supported by The Music publishers Agnes and Knut Mørks Foundation and FUKAP.

Disclosure Summary: The authors have nothing to disclose.

References

1. **Ross DS.** Serum thyroid-stimulating hormone measurement for assessment of thyroid function and disease. *Endocrinol Metab Clin North Am*. 2001;30(2):245–264, vii.
2. **Hollowell JG, Staehling NW, Flanders WD, et al.** Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*. 2002;87(2):489–499.
3. **Faber J, Selmer C.** Cardiovascular disease and thyroid function. *Front Horm Res*. 2014;43:45–56.
4. **Evered DC, Ormston BJ, Smith PA, Hall R, Bird T.** Grades of hypothyroidism. *Br Med J*. 1973;1(5854):657–662.
5. **Duntas LH.** Subclinical hypothyroidism: A misnomer in search of a new name. *Thyroid*. 2001;11(4):361–362.
6. **Kung AW, Pang RW, Janus ED.** Elevated serum lipoprotein(a) in subclinical hypothyroidism. *Clin Endocrinol (Oxf)*. 1995;43(4):445–449.
7. **Tanis BC, Westendorp GJ, Smelt HM.** Effect of thyroid substitution on hypercholesterolaemia in patients with subclinical hypothyroidism: A reanalysis of intervention studies. *Clin Endocrinol (Oxf)*. 1996;44(6):643–649.
8. **Rodondi N, den Elzen WP, Bauer DC, et al.** Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA*. 2010;304(12):1365–1374.
9. **Singh S, Duggal J, Molnar J, Maldonado F, Barsano CP, Arora R.** Impact of subclinical thyroid disorders on coronary heart disease, cardiovascular and all-cause mortality: A meta-analysis. *Int J Cardiol*. 2008;125(1):41–48.
10. **Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC.** Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: The Rotterdam Study. *Ann Intern Med*. 2000;132(4):270–278.
11. **Razvi S, Weaver JU, Vanderpump MP, Pearce SH.** The incidence of ischemic heart disease and mortality in people with subclinical hypothyroidism: Reanalysis of the Whickham Survey cohort. *J Clin Endocrinol Metab*. 2010;95(4):1734–1740.
12. **Walsh JP, Bremner AP, Bulsara MK, et al.** Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. *Arch Intern Med*. 2005;165(21):2467–2472.
13. **Imaizumi M, Akahoshi M, Ichimaru S, et al.** Risk for ischemic heart disease and all-cause mortality in subclinical hypothyroidism. *J Clin Endocrinol Metab*. 2004;89(7):3365–3370.
14. **Selmer C, Olesen JB, Hansen ML, et al.** Subclinical and overt thyroid dysfunction and risk of all-cause mortality and cardiovascular events: A large population study. *J Clin Endocrinol Metab*. 2014;jc20134184.
15. **Iervasi G, Molinaro S, Landi P, et al.** Association between increased mortality and mild thyroid dysfunction in cardiac patients. *Arch Intern Med*. 2007;167(14):1526–1532.
16. **Molinaro S, Iervasi G, Lorenzoni V, et al.** Persistence of mortality risk in patients with acute cardiac diseases and mild thyroid dysfunction. *Am J Med Sci*. 2012;343(1):65–70.

17. **Vanderpump M.** Subclinical hypothyroidism: The case against treatment. *Trends Endocrinol Metab*. 2003;14(6):262–266.
18. **Owen PJ, Lazarus JH.** Subclinical hypothyroidism: The case for treatment. *Trends Endocrinol Metab*. 2003;14(6):257–261.
19. **Stott DJ, Bauer DC, Ford I, et al.** The dilemma of treating subclinical hypothyroidism: Risk that current guidelines do more harm than good. *Eur Thyroid J*. 2014;3(2):137–138.
20. **Jabbar A, Ingoe L, Pearce S, Zaman A, Razvi S.** Thyroxine in acute myocardial infarction (ThyrAMI)—Levothyroxine in subclinical hypothyroidism post-acute myocardial infarction: Study protocol for a randomised controlled trial. *Trials*. 2015;16:115.
21. **Simon HS, Pearce GB, Leonidas H, et al.** 2013 ETA Guideline: Management of Subclinical Hypothyroidism. *Eur Thyroid Assoc*. 2013;2:14.
22. **Pedersen CB.** The Danish Civil Registration System. *Scand J Public Health*. 2011;39(7 Suppl):22–25.
23. **Lynge E, Sandegaard JL, Rebolj M.** The Danish National Patient Register. *Scand J Public Health*. 2011;39(7 Suppl):30–33.
24. **Helweg-Larsen K.** The Danish Register of Causes of Death. *Scand J Public Health*. 2011;39(7 Suppl):26–29.
25. **Kildemoes HW, Sorensen HT, Hallas J.** The Danish National Prescription Registry. *Scand J Public Health*. 2011;39(7 Suppl):38–41.
26. **Baadsgaard M, Quitzau J.** Danish registers on personal income and transfer payments. *Scand J Public Health*. 2011;39(7 Suppl): 103–105.
27. **Carstensen B.** Age-period-cohort models for the Lexis diagram. *Stat Med*. 2007;26(15):3018–3045.
28. **Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sorensen HT.** The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol*. 2011;11:83.
29. **Nuttall M, van der Meulen J, Emberton M.** Charlson scores based on ICD-10 administrative data were valid in assessing comorbidity in patients undergoing urological cancer surgery. *J Clin Epidemiol*. 2006;59(3):265–273.
30. **Gislason GH, Jacobsen S, Rasmussen JN, et al.** Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs after acute myocardial infarction. *Circulation*. 2006; 113(25):2906–2913.
31. **Fosbøl EL, Gislason GH, Jacobsen S, et al.** The pattern of use of non-steroidal anti-inflammatory drugs (NSAIDs) from 1997 to 2005: A nationwide study on 4.6 million people. *Pharmacoepidemiol Drug Saf*. 2008;17(8):822–833.
32. **Gerdes AM, Iervasi G.** Thyroid replacement therapy and heart failure. *Circulation*. 2010;122(4):385–393.
33. **Maia AL, Kim BW, Huang SA, Harney JW, Larsen PR.** Type 2 iodothyronine deiodinase is the major source of plasma T3 in euthyroid humans. *J Clin Invest*. 2005;115(9):2524–2533.
34. **Biondi B.** Mechanisms in endocrinology: Heart failure and thyroid dysfunction. *Eur J Endocrinol*. 2012;167(5):609–618.
35. **Holmager P, Schmidt U, Mark P, et al.** Long-term L-Triiodothyronine (T3) treatment in stable systolic heart failure patients: A randomised, double-blind, cross-over, placebo-controlled intervention study. *Clin Endocrinol (Oxf)*. 2015;83(6):931–937.
36. **Moruzzi P, Doria E, Agostoni PG, Capacchione V, Sganzerla P.** Usefulness of L-thyroxine to improve cardiac and exercise performance in idiopathic dilated cardiomyopathy. *Am J Cardiol*. 1994; 73(5):374–378.
37. **Shatynska-Mytsyk I, Rodrigo L, Cioccocioppo R, et al.** The impact of thyroid hormone replacement therapy on left ventricular diastolic function in patients with subclinical hypothyroidism. *J Endocrinol Invest*. 2016;39(6):709–713.
38. **Biondi B, Fazio S, Carella C, et al.** Cardiac effects of long term thyrotropin-suppressive therapy with levothyroxine. *J Clin Endocrinol Metab*. 1993;77(2):334–338.
39. **Razvi S, Weaver JU, Butler TJ, Pearce SH.** Levothyroxine treatment of subclinical hypothyroidism, fatal and nonfatal cardiovascular events, and mortality. *Arch Intern Med*. 2012;172(10):811–817.
40. **Somwaru LL, Rariy CM, Arnold AM, Cappola AR.** The natural history of subclinical hypothyroidism in the elderly: The cardiovascular health study. *J Clin Endocrinol Metab*. 2012;97(6): 1962–1969.