Subclinical Thyroid Dysfunction and the Risk of Heart Failure in Older Persons at High Cardiovascular Risk

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Context: Subclinical thyroid dysfunction is common in older people. However, its clinical importance is uncertain.

Objective: Our objective was to determine the extent to which subclinical hyperthyroidism and hypothyroidism influence the risk of heart failure and cardiovascular diseases in older people.

Setting and Design: The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) is an prospective cohort study.

Patients: Patients included men and women aged 70–82 yr (n = 5316) with known cardiovascular risk factors or previous cardiovascular disease.

Main Outcome Measures: Incidence rate of heart failure hospitalization, atrial fibrillation, and cardiovascular events and mortality according to baseline thyroid status were evaluated. Euthyroid participants (TSH =0.45–4.5 mIU/liter) were compared with those with subclinical hyperthyroidism (TSH <0.45 mIU/liter) and those with subclinical hypothyroidism (TSH ≥4.5 mIU/liter, both with normal free T_4).

Results: Subclinical hyperthyroidism was present in 71 participants and subclinical hypothyroidism in 199 participants. Over 3.2 yr follow-up, the rate of heart failure was higher for subclinical hyperthyroidism compared with euthyroidism [age- and sex-adjusted hazard ratio (HR) = 2.93, 95% confidence interval (CI) = 1.37–6.24, $P = 0.005$; multivariate-adjusted HR = 3.27, 95% CI = 1.52–7.02, $P = 0.002$). Subclinical hypothyroidism (only at threshold >10 mIU/liter) was associated with heart failure (age- and sex-adjusted HR = 3.01, 95% CI = 1.12–8.11, $P = 0.029$; multivariate HR = 2.28, 95% CI = 0.84–6.23). There were no strong evidence of an association between subclinical thyroid dysfunction and cardiovascular events or mortality, except in those with TSH below 0.1 or over 10 mIU/liter and not taking pravastatin.

Conclusion: Older people at high cardiovascular risk with low or very high TSH along with normal free T_4 appear at increased risk of incident heart failure. (***J Clin Endocrinol Metab* 97: 852–861, 2012**)

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2011-1978 Received July 7, 2011. Accepted December 6, 2011.
First Published Online January 11, 2012

Abbreviations: BMI, Body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; LDL, low-density lipoprotein; NYHA, New York Heart Association; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk.

Subclinical thyroid dysfunction is defined as a biochemical disorder including an abnormal TSH and normal free T_4 levels (1). The disorder has been proposed as a possible modifiable risk factor for cardiovascular disease (CVD) (1–3). Subclinical thyroid dysfunction increases with age (4). Because the prevalence is high, the cardiovascular consequences of thyroid dysfunction might have a large impact in an aging population, particularly in adults at high risk or with preexisting CVD (5). However, in older people, evidence from observational studies is rare and inconsistent, and therefore clinical relevance remains uncertain. For instance, subclinical hypothyroidism has been shown to be inversely related to mortality in the oldest old (6, 7), although this was not confirmed in a recent meta-analysis including younger adults (3).

Thyroid hormones have distinct effects on the heart and peripheral vasculature (8). Because of the significant hemodynamic changes driven by thyroid hormones, previous studies have reported altered cardiac function in subclinical thyroid dysfunction (8, 9), but very few have directly examined clinical cardiac events, such as heart failure or atrial fibrillation (10, 11).

Therefore, we examined the association between subclinical thyroid dysfunction with adjudicated cardiovascular events in a large prospective study of older people with cardiovascular risk factors or preexisting CVD, the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) (12).

Subjects and Methods

Study population

Participants were part of the PROSPER trial designed to examine the benefits of pravastatin *vs.* placebo in adults aged 70–82 yr old (12). Details of the design, data collection, and eligibility criteria have been previously described (12, 13). Briefly, 5804 individuals with a mean age of 75 yr (52% women), sufficiently mobile to attend visits at their general practitioner's office or the study center, were randomized to 40 mg pravastatin or placebo in The Netherlands, Scotland, and Ireland. Only participants with a history of vascular disease, defined as coronary, cerebral, or peripheral artery disease, or those with known cardiovascular risk factors, such as smoking, hypertension, or diabetes, were enrolled. Participants with congestive heart failure [New York Heart Association (NYHA) functional class III or IV] or electrocardiographic evidence of atrial fibrillation were excluded as well as those with poor cognitive function (Mini Mental State Examination score < 24). Adults with overt thyroid dysfunction (TSH levels >20 mIU/liter with any free T_4, or > 10 mIU/liter with low free T_4 levels) were also excluded. The Medical Ethics Committee of all centers approved the study, and informed consent was obtained from all participants. The present study represents a *post hoc* analysis (13).

From the original study sample of 5804 individuals, we excluded eight participants with unavailable TSH measurement at baseline and 297 with missing free T_4 measurement. We further excluded 146 patients with overt thyroid dysfunction based on free T_4 measurements, six participants taking antithyroid medication, and 27 participants taking amiodarone, because of its potential confounding effect because it affects both thyroid function and CVD (8). We additionally excluded four participants with atrial fibrillation at baseline, who in retrospect were protocol violators. Hence, the final sample of our study was 5316 participants for baseline analysis (Supplemental Fig. 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

Determinants

TSH levels and free T_4 were measured at baseline in all participants using state-of-the-art immunoassays for TSH (third-generation assays with functional sensitivity of 0.05 mIU/liter or less) and for free T_4 in respective laboratory centers (Cork, Ireland; Glasgow, Scotland; and Leiden, The Netherlands). Inter- and intraassay coefficients of variation were less than 5% for both analytes. To account for the differences of laboratory assays and to avoid the inclusion of participant with overt thyroid disease, the narrowest free T_4 reference range was used (between 12 and 18 pmol/liter). Thus, 105 older adults with free T_4 above 18 pmol/liter were excluded for overt hyperthyroidism and 41 with free T_4 values below 12 pmol/liter were excluded for overt hypothyroidism (Supplemental Fig. 1). In stored (-80 C) plasma drawn from participant at 6 months, we repeated measurement of TSH and free T_4 in all available samples stored at a single center (University of Glasgow), using the same electrochemiluminescence immunodetection method on a Roche Elecsys 2010 (Burgess Hill, UK). The limit of detection of TSH was below 0.005 mIU/liter. The limit of detection of free T_4 was 0.3 pmol/liter, with reference ranges of 12–22 pmol/liter.

We categorized patients into three groups according to TSH levels at study entry. At baseline, subclinical hyperthyroidism was defined as participants with TSH levels of less than 0.45 mIU/liter and normal free T_4 levels (1). Subclinical hypothyroidism was defined as participants with TSH of 4.5 mIU/liter or greater and normal free T_4 levels (1). Participants with TSH levels of 0.45 or greater but less than 4.5 were considered as euthyroid. To assess a possible dose-response effect of TSH, we further classified subclinical hyperthyroidism into two subgroups: TSH less than 0.1 mIU/liter and 0.1–0.44 mIU/liter (1). Subclinical hypothyroidism was further classified into two subgroups: TSH 4.5–10 mIU/liter and more than 10 mIU/liter (3). At 6 months, a similar classification was used to identify those with persistent subclinical hyperthyroidism, persistent euthyroidism and persistent subclinical hypothyroidism (Supplemental Fig. 1).

Heart failure, atrial fibrillation, and cardiovascular events and mortality

We examined combined and individual cardiovascular outcomes, as previously defined (12), including fatal and nonfatal coronary heart disease, and CVD, defined as fatal and nonfatal myocardial infarction, stroke, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, peripheral arterial surgery, or angioplasty. Incident heart failure hospitalizations were also recorded and all clinical endpoints were adjudicated by an expert committee blinded to randomized study medication and using predefined criteria (12). Incident heart failure hospitalizations were adjudicated using a panel of predefined

criteria including clinical symptoms, chest radiography, laboratory measurements, electrocardiograph, echocardiography, and hospital discharge reports. New-onset atrial fibrillation was diagnosed from an annual single-lead electrocardiograph or, if noted, on 12-lead electrocardiograph or telemetry performed as part of hospitalization or other clinical care (14). This general process of screening has been found to be very sensitive for identifying new cases in the Framingham study (15).

Potential confounders

Diabetes was defined as self-reported diagnosis or use of antidiabetic drugs or was defined as fasting blood glucose of 7.0 mmol/liter or greater or 11.1 mmol/liter or greater when fasting status was uncertain (16). Smoking was defined as never, current, or former. Baseline lipids, creatinine, blood pressure, heart rate, body mass index (BMI) measurements, education, alcohol intake, and medication use were assessed as previously reported (12, 13).

Statistical analyses

Baseline characteristics are reported in three subgroups according to thyroid dysfunction, as described above. Two-sample *t* tests and χ^2 tests were used for group comparisons. The association between subclinical thyroid dysfunction and the different endpoints were examined using age- and sex-adjusted and multivariate adjusted Cox proportional hazards models, with the euthyroidism group as the reference group. Events rates per 1000 person-years of follow-up were calculated and compared with log-rank tests. A Kaplan-Meier curve censored for death was used to represent the cumulative incidence of heart failure hospitalization. Potential confounders in the multivariate adjusted models were determined by biological plausibility for all endpoints: age, sex, education, history of CVD, diabetes, BMI, smoking status, systolic blood pressure, low-density lipoprotein (LDL) cholesterol, creatinine, use of β-blockers, and use of antiarrhythmic drugs. For each traditional cardiovascular risk factor and for the use of pravastatin and β-blockers, stratified analyses were conducted to better assess the presence of interaction or confounding. To account for potential change in thyroid status over time, we analyzed risks among older adults with persistent subclinical thyroid dysfunction at 6 months, after exclusion of deaths, those lost to follow-up, heart failure hospitalization, and atrial fibrillation events occurring during the first 6 months (Supplemental Fig. 1). We also run sensitivity analyses excluding 161 participants with thyroid replacement therapy to assess the effect of endogenous subclinical thyroid dysfunction only (1). Results are reported as hazard ratio (HR), with 95% confidence intervals (CI). All analyses were conducted using Stata version 11.0 (Stata Corp., College Station, TX), and $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

The mean age of the study population was 75 yr (SD 3.3 yr). Subclinical hyperthyroidism was present in 71 participants (1.3%) at baseline (Table 1). In line with expectation, more women than men had subclinical hyperthyroidism, and they had a lower weight and creatinine level than those with normal thyroid function. Five of them used thyroid hormone. Subclinical hypothyroidism was present in 199 participants (3.7%), and 66% were women. Prevalence of hypertension and LDL and total cholesterol levels were slightly elevated in the subclinical hypothyroidism group in comparison with those who were euthyroid, and nearly 15% used thyroid replacement therapy.

Incident heart failure hospitalization

During a 3.2-yr follow-up period, the incidence rate of hospitalization for heart failure was higher in older people with subclinical hyperthyroidism compared with the euthyroidism group, with 31 *vs.* 12 events per 1000 person-years ($P = 0.01$, Fig. 1) and age- and sex-adjusted HR of 2.93 (95% CI = 1.37–6.24, $P = 0.005$) (Table 2). This association persisted after further adjustment for education, history of CVD, diabetes, BMI, smoking status, systolic blood pressure, LDL cholesterol, creatinine, and use of β-blockers and antiarrhythmics (multivariate adjusted HR = 3.27, 95% CI = 1.52–7.02, $P = 0.002$). The association with heart failure was present in both subclinical hyperthyroidism subgroups, but mainly in those with a suppressed TSH below 0.1 mIU/liter (age- and sex-adjusted HR = 4.61, 95% CI = 1.71–12.47, $P = 0.003$, Table 2). In additional stratified analysis, the increased incidence rate of heart failure hospitalization in adults with subclinical hyperthyroidism did not differ by age, gender, history of CVD, β-blockers use (P for each interaction term > 0.05, Fig. 2). The incidence rate of heart failure within the subclinical hyperthyroidism group was lower in adults using pravastatin (age- and sex-adjusted HR = 2.44, 95% CI = 0.77–7.74) than in those using placebo (multivariate adjusted HR = 3.52, 95% CI = 1.29–9.61), but with a nonsignificant P for interaction term of 0.65 (Fig. 2).

There was no association between subclinical hypothyroidism defined with TSH levels equal or above 4.5 mIU/liter and incident heart failure hospitalization. However, in adults with TSH levels above 10 mIU/liter, the incident rate of heart failure was significantly higher in the age- and sex-adjusted model compared with euthyroid participants (HR = 3.01, 95% CI = 1.12–8.11, $P = 0.029$, Table 2).

Incident atrial fibrillation, cardiovascular events, and mortality

During the 3.2-yr follow-up, 497 (9.4%) had atrial fibrillation, 891 (16.8%) had fatal or nonfatal CVD, 585 participants (11.0%) had fatal or nonfatal myocardial infarction, and a total of 547 (10.3%) died. There were no differences in the incidence rate of atrial fibrillation, fatal or nonfatal coronary, cerebrovascular events, or total

TABLE 1. Baseline characteristics of the 5316 study participants by subclinical thyroid status

	Subclinical hyperthyroidism (n = 71); TSH <0.45 mIU/liter	Euthyroidism (n = 5046); TSH = 0.45–4.49 mIU/liter	Subclinical hypothyroidism (n = 199); TSH ≥4.5 mIU/liter
Thyroid measurements			
TSH (mIU/liter)	0.18 (0.13)[a]	1.95 (0.90)	7.84 (3.75)[a]
Free T_4 (pmol/liter)	16.0 (1.4)		14.9 (1.6)
Demographics			
Age (yr)	75.3 (3.1)	75.3 (3.4)	75.5 (3.2)
Female [n (%)]	54 (76.1)[a]	2497 (49.5)	132 (66.3)[a]
Education (yr)	15.2 (2.1)	15.1 (2.0)	15.0 (2.1)
Country [n (%)]			
Scotland	22 (31.0)	2186 (43.3)	25 (12.6)
Ireland	22 (31.0)	1912 (37.9)	96 (48.2)
The Netherlands	27 (38.3)	948 (18.8)	78 (39.2)
Smoking status [n (%)]			
Never	25 (35.2)	1673 (33.2)	83 (41.7)
Former	33 (46.5)	1985 (39.3)	71 (35.7)
Current	13 (18.3)	1388 (27.5)	45 (22.6)
Alcohol consumption (drinks/wk)	2.7 (5.6)[a]	5.4 (9.5)	4.4 (8.7)
Comorbidities			
Hypertension [n (%)]	41 (57.8)	3093 (61.3)	138 (69.3)[a]
Diabetes [n (%)]	10 (14.8)	534 (10.6)	28 (14.1)
History of vascular disease [n (%)][b]	30 (42.3)	2231 (44.2)	88 (44.2)
Objective measures			
Systolic blood pressure (mm Hg)	151.6 (20.9)	154.6 (21.9)	155.9 (22.0)
Diastolic blood pressure (mm Hg)	81.9 (11.3)	83.8 (11.5)	84.5 (11.1)
Heart rate (beat/min)[c]	65.6 (10.9)	66.3 (11.7)	65.7 (11.1)
Weight (kg)	69.1 (13.5)[a]	73.5 (13.2)	74.1 (13.7)
Height (cm)	162.9 (8.7)[a]	165.5 (9.5)	164.3 (8.4)
BMI (kg/m^2)	26.0 (4.4)	26.8 (4.1)	27.4 (4.5)
Total cholesterol (mmol/liter)	5.9 (0.9)	5.7 (0.9)	5.9 (0.9)[a]
LDL cholesterol (mmol/liter)	3.9 (0.8)	3.8 (0.8)	3.9 (0.8)[a]
HDL cholesterol (mmol/liter)	1.3 (0.4)	1.3 (0.3)	1.3 (0.4)
Triglycerides (mmol/liter)	1.6 (0.7)	1.5 (0.7)	1.6 (0.7)
Fasting glucose (mmol/liter)[d]	5.6 (1.8)	5.4 (1.4)	5.5 (1.7)
Creatinine (μmol/liter)	94.2 (17.5)[a]	101.1 (22.3)	97.7 (21.9)[a]
Medication use			
Thyroid hormone [n (%)]	5 (7.0)[a]	122 (2.4)	34 (17.1)[a]
Pravastatin [n (%)]	35 (49.3)	2530 (50.1)	95 (47.7)
Aspirin [n (%)]	24 (33.8)	1831 (36.3)	71 (35.7)
β-Blockers [n (%)]	17 (23.9)	1312 (26.0)	48 (24.1)
Antiarrhythmics [n (%)][e]	1 (1.4)	111 (2.2)	5 (2.5)

Data are given as mean (SD) unless otherwise indicated. HDL, High-density lipoprotein.

[a] $P < 0.05$ for comparison with the euthyroidism group.

[b] Vascular disease defined as history of coronary, cerebral, or peripheral vascular disease.

[c] Heart rate was available for 5204 participants (two missing in the subclinical hyperthyroidism group and seven missing in the subclinical hypothyroidism group).

[d] Fasting glucose was available for 5146 participants (three missing in the subclinical hyperthyroidism group and three missing in the subclinical hypothyroidism group).

[e] Other than amiodarone, because participants taking amiodarone were excluded from this study population.

CVD between the subclinical thyroid dysfunction groups and the euthyroidism group. In multivariate models, neither subclinical hyperthyroidism nor subclinical hypothyroidism was significantly associated with atrial fibrillation or cardiovascular-related events. However, when subclinical thyroid dysfunction was examined only in those without pravastatin, elevated TSH levels above 10 mIU/liter compared with euthyroidism were associated with an increased risk of cardiovascular events (age- and sex-adjusted HR = 2.15, 95% CI = 1.02–4.54, $P = 0.044$; multivariate adjusted HR = 2.03, 95% CI = 0.96–4.32, $P = 0.064$) and a nonsignificant increased cardiovascular mortality (age- and sex-adjusted HR = 2.14, 95% CI = 0.53–8.67).

Total and cardiovascular mortality rates were similar between the subclinical hyperthyroidism group, the eu-

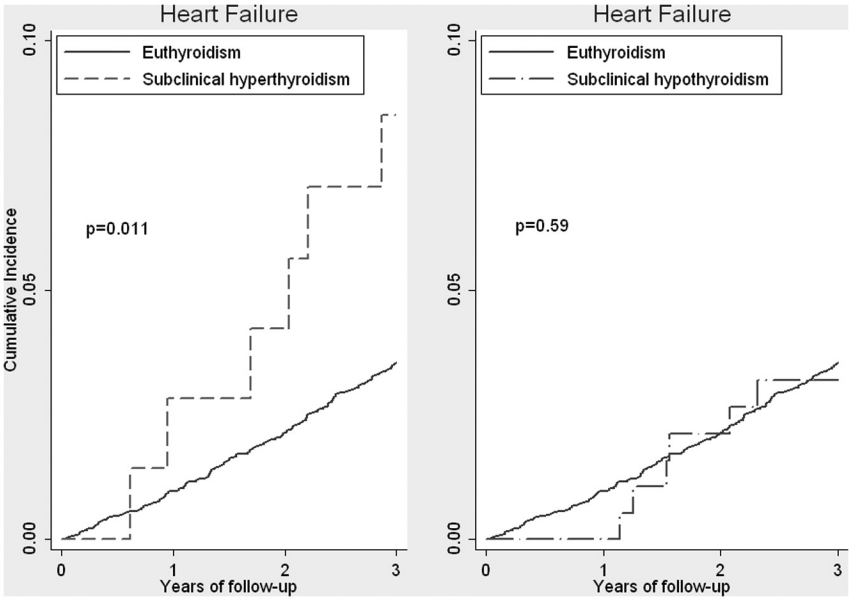

FIG. 1. Cumulative incidence of heart failure hospitalization, with respect to subclinical thyroid dysfunction. *P* values were based on log-rank tests for survival functions compared with the euthyroidism group.

thyroidism group, and the subclinical hypothyroidism group. In those with suppressed TSH levels below 0.1 mIU/liter, total and cardiovascular mortality estimates were above two in comparison with the euthyroidism group, but none of them reached statistical significance (Table 3). However, when subclinical hyperthyroidism was examined only in those without pravastatin, suppressed TSH levels below 0.1 mIU/liter were associated with significantly higher cardiovascular mortality (age- and sex-adjusted HR = 4.78, 95% CI = 1.17–19.5, $P = 0.029$; multivariate adjusted HR = 4.87, 95% CI = 1.18–20.0, $P = 0.028$) and higher total mortality (age- and sex-adjusted HR = 3.13, 95% CI = 1.00–9.83, $P = 0.05$; multivariate adjusted HR = 3.14, 95% CI = 1.00–9.90, $P = 0.051$) compared with euthyroidism.

Persistent subclinical thyroid dysfunction

Among the 71 participants with subclinical hyperthyroidism at baseline, two (3%) developed overt hyperthyroidism and 10 (14%) normalized both TSH and free T_4 at 6 months. Among the 199 participants with subclinical hypothyroidism at baseline, two died from CVD, one died

TABLE 2. Cardiovascular morbidities by subclinical thyroid status at baseline

	Subclinical hyperthyroidism				Subclinical hypothyroidism		
	TSH < 0.1 mIU/liter (n = 28)	TSH = 0.1–0.44 mIU/liter (n = 43)	Overall, TSH < 0.45 mIU/liter (n = 71)	Euthyroidism, TSH = 0.45–4.49 mIU/liter (n = 5046)	Overall, TSH ≥4.5 mIU/liter (n = 199)	TSH = 4.5–10 mIU/liter (n = 161)	TSH >10 mIU/liter (n = 38)
Heart failure hospitalization							
No. of events	4	3	7	194	6	2	4
Incidence rate[b]	45.7[a]	21.6	30.9[a]	12.1	9.7	4.0	32.9[a]
Age- and sex-adjusted HR (95% CI)	4.61[a] (1.71–12.47)	1.97 (0.63–6.17)	2.93[a] (1.37–6.24)	1.00	0.87 (0.38–1.96)	0.36 (0.09–1.44)	3.01[a] (1.12–8.11)
Multivariate adjusted HR (95% CI)[c]	4.78[a] (1.76–13.04)	2.29 (0.73–7.20)	3.27[a] (1.52–7.02)	1.00	0.80 (0.36–1.82)	0.35 (0.09–1.42)	2.28 (0.84–6.23)
Atrial fibrillation							
No. of events	1	2	3	478	16	11	5
Incidence rate[b]	11.6	14.2	13.2	30.5	26.1	22.3	41.0
Age- and sex-adjusted HR (95% CI)	0.46 (0.64–3.25)	0.51 (0.13–2.05)	0.49 (0.16–1.53)	1.00	0.93 (0.57–1.54)	0.80 (0.44–1.46)	1.47 (0.61–3.55)
Multivariate adjusted HR (95% CI)[c]	0.50 (0.07–3.55)	0.55 (0.14–2.20)	0.53 (0.17–1.65)	1.00	0.90 (0.55–1.48)	0.77 (0.42–1.41)	1.43 (0.59–3.46)
CVD[d]							
No. of events	3	4	7	852	32	23	9
Incidence rate[b]	34.0	29.3	31.1	55.8	54.9	48.8	80.9
Age- and sex-adjusted HR (95% CI)	0.71 (0.23–2.20)	0.58 (0.22–1.56)	0.63 (0.30–1.33)	1.00	1.06 (0.74–1.51)	0.94 (0.62–1.43)	1.56 (0.81–3.01)
Multivariate adjusted HR (95% CI)[c]	0.66 (0.21–2.06)	0.62 (0.23–1.66)	0.64 (0.30–1.34)	1.00	1.00 (0.71–1.43)	0.89 (0.59–1.35)	1.48 (0.78–2.87)
Coronary heart disease[e]							
No. of events	3	3	6	564	15	11	4
Incidence rate[b]	34.0	21.7	26.5	35.9	24.6	22.5	33.0
Age- and sex-adjusted HR (95% CI)	1.12 (0.36–3.48)	0.67 (0.22–2.09)	0.84 (0.37–1.88)	1.00	0.75 (0.45–1.25)	0.68 (0.38–1.24)	1.00 (0.38–2.68)
Multivariate adjusted HR (95% CI)[c]	1.10 (0.35–3.44)	0.72 (0.23–2.25)	0.87 (0.39–1.96)	1.00	0.70 (0.42–1.18)	0.66 (0.36–1.19)	0.89 (0.33–2.38)

The euthyroidism group was used as the reference group.

[a] $P < 0.05$ for comparison with the euthyroidism group.

[b] Per 1000 person-years.

[c] Adjusted for age, sex, education, history of CVD, diabetes, BMI, smoking status, systolic blood pressure, LDL cholesterol, creatinine, and β-blocker and antiarrhythmic use.

[d] CVD defined as fatal and nonfatal myocardial infarction or stroke, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or peripheral arterial surgery or angioplasty.

[e] Coronary heart disease defined as fatal and nonfatal myocardial infarction.

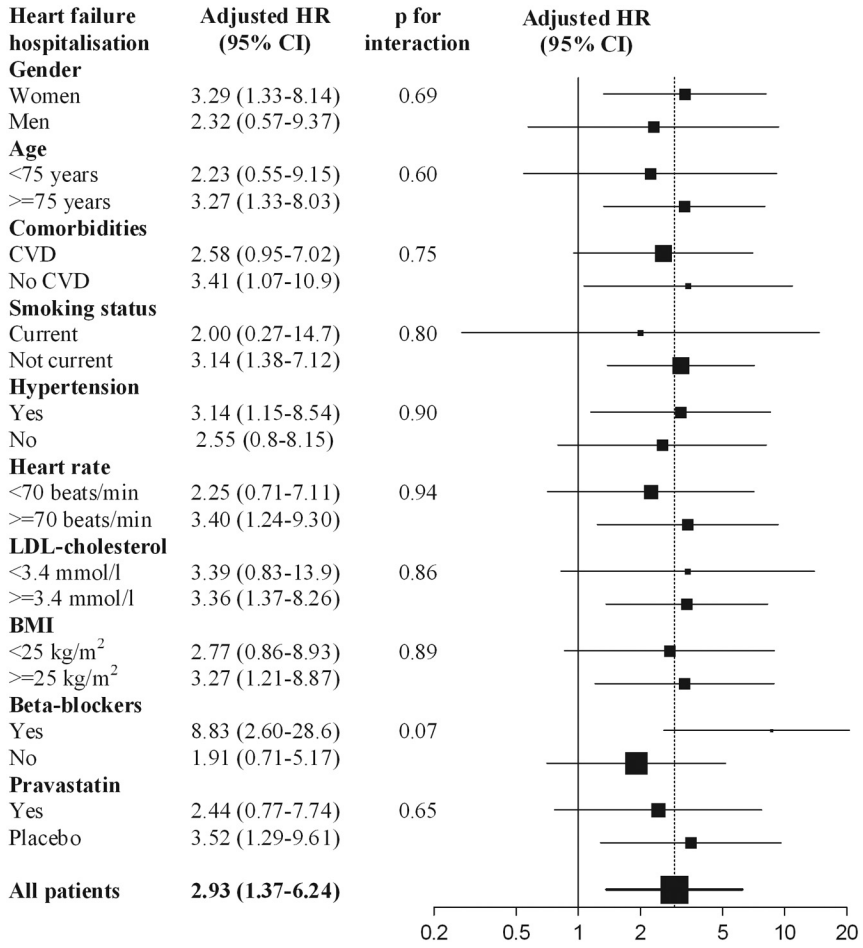

FIG. 2. Stratified analysis for the association of subclinical hyperthyroidism with the risk of heart failure hospitalization. The size of each *square* is proportional to the inverse variance of the HR. *Horizontal lines* represent 95% CI. HR are adjusted for age and sex.

from a nonvascular cause, one developed atrial fibrillation, 16 (8%) developed overt hypothyroidism, and 60 (30%) normalized both TSH and free T_4 (Supplemental Fig. 1). For heart failure hospitalization, point estimates of persistent subclinical hyperthyroidism compared with persistent euthyroidism were above two, but the association was not statistically significant (age- and sex-adjusted HR = 2.29, 95% CI = 0.73–7.21, Table 4). Persistent subclinical hypothyroidism with TSH above 10 mIU/liter remained associated with heart failure hospitalization compared with persistent euthyroidism with an age- and sex-adjusted HR of 4.99 (95% CI = 1.59–15.67, P = 0.006) and multivariate adjusted HR of 3.84 (95% CI = 1.20–12.29, P = 0.023) (Table 4).

Sensitivity analysis

The exclusion of 161 participants with thyroid replacement therapy yielded similar estimates for the association between subclinical hyperthyroidism (TSH <0.45 mIU/liter) and heart failure hospitalization, with a multivariate adjusted HR of 2.45 (95% CI = 1.00–6.01, P = 0.05) compared with euthyroidism. Similarly, after exclusion of thyroid replacement therapy, the association between subclinical hypothyroidism defined as TSH levels above 10 mIU/liter and incident heart failure persisted in both the age- and sex-adjusted model (HR = 3.87, 95% CI = 1.24–12.1, P = 0.02) and the multivariate adjusted model (HR = 3.25, 95% CI = 1.03–10.2, P = 0.045).

Discussion

In this large cohort of older people aged 70–82 yr old and at high risk of CVD, subclinical hyperthyroidism was independently associated with heart failure as estimated with hospital admissions. Only subclinical hypothyroidism at a threshold of TSH above 10 mIU/liter was associated with incident heart failure. The heart failure risk associated with low TSH or very high TSH values was maintained among those with persistent thyroid dysfunction at 6 months. There was no strong evidence of an association between subclinical thyroid dysfunction and atrial fibrillation or cardiovascular events and mortality, although TSH below 0.1 mIU/liter or above 10 mIU/liter seemed to confer a higher risk.

In a population-based study of older people, the Cardiovascular Health Study, no association was found between subclinical hyperthyroidism and heart failure (HR = 0.94, 95% CI = 0.48–1.83) (11). The prevalence of subclinical hyperthyroidism in that study (1.4%) was similar to ours but lower than the 6% previously reported in older people elsewhere (17). The Cardiovascular Health Study population was at lower CVD risk than our study population with lower prevalence of cardiovascular risk factors, such as age (72.6 yr in the Cardiovascular Health Study *vs.* 75.3 yr in PROSPER), current smoking (10.7 *vs.* 27.2%), hypertension (40.2 *vs.* 61.6%), or previous evidence of CVD (19.6 *vs.* 44.2%). We also found a lower BMI in participants with subclinical hyperthyroidism compared with the euthyroidism group, as might be expected (18). There are a number of mechanisms by which subclinical hyperthyroidism might influence cardiac output and increase the incidence of heart failure, including increased heart rate (19, 20), higher left ventricular mass, and impaired diastolic function with delayed relaxation (19), which in turn could cause or exacerbate heart failure.

TABLE 3. Cardiovascular and all-cause mortalities by subclinical thyroid status at baseline

	Subclinical hyperthyroidism			Euthyroidism, TSH = 0.45–4.49 mIU/liter (n = 5046)	Subclinical hypothyroidism		
	TSH <0.1 mIU/liter (n = 28)	TSH = 0.1–0.44 mIU/liter (n = 43)	Overall, TSH <0.45 mIU/liter (n = 71)		Overall, TSH ≥4.5 mIU/liter (n = 199)	TSH = 4.5–10 mIU/liter (n = 161)	TSH >10 mIU/liter (n = 38)
Cardiovascular mortality							
No. of events	3	1	4	250	10	8	2
Incidence rate[a]	33.9	7.0	17.3	15.4	16.0	16.0	16.0
Age- and sex-adjusted HR (95% CI)	2.79 (0.89–8.74)	0.52 (0.07–3.71)	1.33 (0.50–3.59)	1.00	1.16 (0.62–2.19)	1.16 (0.57–2.35)	1.17 (0.29–4.70)
Multivariate adjusted HR (95% CI)[b]	2.90 (0.92–9.13)	0.66 (0.09–4.73)	1.57 (0.58–4.24)	1.00	1.05 (0.56–1.99)	1.13 (0.55–2.28)	0.84 (0.21–3.41)
Total mortality							
No. of events	5	2	7	517	23	20	3
Incidence rate[a]	56.5	14.0	30.3	31.8	36.7	39.9	24.0
Age- and sex-adjusted HR (95% CI)	2.11 (0.87–5.09)	0.48 (0.12–1.94)	1.07 (0.51–2.27)	1.00	1.25 (0.82–1.90)	1.36 (0.87–2.13)	0.82 (0.26–2.55)
Multivariate adjusted HR (95% CI)[b]	2.01 (0.83–4.89)	0.57 (0.14–2.30)	1.17 (0.55–2.47)	1.00	1.23 (0.81–1.86)	1.39 (0.89–2.17)	0.69 (0.22–2.16)

The euthyroidism group was used as the reference group.

[a] Per 1000 person-years.

[b] Adjusted for age, sex, education, history of CVD, diabetes, BMI, smoking status, systolic blood pressure, LDL cholesterol, creatinine, and β-blocker and antiarrhythmic use.

Unlike the Cardiovascular Health Study, our study was not designed to evaluate cardiac dysfunction with longitudinal echocardiography, and we were not able to assess cardiac changes or differentiate between systolic and diastolic dysfunction. Indeed, there may be a reverse causal mechanism as there is limited evidence that cardiac resynchronization therapy may improve free T_4 and free T_3 levels (21). Thus, we cannot exclude the possibility that worsening cardiac function (leading to clinical heart failure) may impact on thyroid function. β-Blockers have been proposed as first-line agents in patient with overt hyperthyroidism to reduce symptoms, because heart rate might be in the causal pathway (8). In our subgroup analysis among adults using β-blockers, the number of events was too low to interpret with confidence point estimates. Thus, the potential effect of heart rate reduction to prevent incident heart failure in subclinical hyperthyroidism should be evaluated in a formal clinical trial.

TABLE 4. Persistent thyroid dysfunction at 6 months and cardiovascular morbidities and mortalities

	Persistent subclinical hyperthyroidism			Persistent euthyroidism, TSH = 0.45–4.49 mIU/liter (n = 4484)	Persistent subclinical hypothyroidism		
	TSH <0.1 mIU/liter (n = 16)	TSH = 0.1–0.44 mIU/liter (n = 30)	Overall, TSH <0.45 mIU/liter (n = 46)		Overall, TSH ≥4.5 mIU/liter (n = 110)	TSH = 4.5–10 mIU/liter (n = 89)	TSH >10 mIU/liter (n = 21)
Heart failure hospitalization							
No. of events	1	2	3	147	5	2	3
Incidence rate[b]	22.0	24.4	23.6	12.0	16.8	8.3	52.6[a]
Age- and sex-adjusted HR (95% CI)	2.29 (0.32–16.43)	2.29 (0.57–9.29)	2.29 (0.73–7.21)	1.00	1.46 (0.60–3.56)	0.71 (0.18–2.86)	4.99[a] (1.59–15.67)
Multivariate adjusted HR (95% CI)[c]	2.22 (0.31–16.08)	2.62 (0.64–10.67)	2.47 (0.78–7.83)	1.00	1.35 (0.55–3.31)	0.69 (0.17–2.79)	3.84[a] (1.20–12.29)
Atrial fibrillation							
No. of events	1	2	3	395	8	5	3
Incidence rate[b]	23.3	24.6	24.1	33.0	26.9	20.8	53.0
Age- and sex-adjusted HR (95% CI)	0.84 (0.12–5.98)	0.85 (0.21–3.42)	0.85 (0.27–2.64)	1.00	0.86 (0.43–1.73)	0.66 (0.27–1.59)	1.76 (0.56–5.48)
Multivariate adjusted HR (95% CI)[c]	0.96 (0.13–6.84)	0.89 (0.22–3.57)	0.91 (0.29–2.84)	1.00	0.82 (0.41–1.65)	0.63 (0.26–1.52)	1.68 (0.54–5.26)
CVD[d]							
No. of events	1	4	5	635	15	10	5
Incidence rate[b]	22.0	51.9	40.8	54.9	53.4	43.9	93.5
Age- and sex-adjusted HR (95% CI)	0.46 (0.07–3.29)	1.10 (0.41–2.94)	0.86 (0.36–2.08)	1.00	1.01 (0.61–1.69)	0.82 (0.44–1.54)	1.86 (0.77–4.49)
Multivariate adjusted HR (95% CI)[c]	0.40 (0.06–2.84)	1.12 (0.42–3.02)	0.82 (0.34–1.99)	1.00	0.91 (0.56–1.53)	0.75 (0.40–1.40)	1.62 (0.67–3.93)
Total mortality							
No. of events	2	2	4	386	9	7	2
Incidence rate[b]	44.0	24.0	31.1	31.2	29.8	28.7	34.1
Age- and sex-adjusted HR (95% CI)	1.72 (0.43–6.92)	0.90 (0.22–3.63)	1.18 (0.44–3.18)	1.00	1.02 (0.53–1.98)	0.97 (0.46–2.06)	1.23 (0.31–4.93)
Multivariate adjusted HR (95% CI)[c]	1.46 (0.36–5.92)	1.16 (0.29–4.69)	1.30 (0.48–3.49)	1.00	0.97 (0.50–1.88)	0.96 (0.46–2.04)	0.97 (0.24–3.94)

The euthyroidism group was used as the reference group.

[a] $P < 0.05$ for comparison with the euthyroidism group.

[b] Per 1000 person-years.

[c] Adjusted for age, sex, education, history of CVD, diabetes, BMI, smoking status, systolic blood pressure, LDL cholesterol, creatinine, and β-blocker and antiarrhythmic use.

[d] CVD defined as fatal and nonfatal myocardial infarction or stroke, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or peripheral arterial surgery or angioplasty.

The association between subclinical hypothyroidism and cardiovascular outcomes and mortality has been demonstrated mainly in adults with TSH values above 10 mIU/liter (3). Similar to our results, two previous studies reported an increased risk of incident heart failure in older adults particularly when TSH levels were above 10 mIU/liter (11, 22). However, the possible fluctuation of thyroid dysfunction over time might have contributed to the main negative findings of previous studies, because in many individuals, TSH normalizes over time (from 15–65% over follow-up periods going from 1–6 yr) (23, 24). Very few cohort studies have repeated TSH measurement within 3 or 6 months to exclude transient dysfunction (5, 17). In our study, we could demonstrate that the persistence of elevated TSH values above 10 mIU/liter over a 6-month period were still associated with incident heart failure hospitalizations and might even increase this risk, although the number of events was low.

Atrial fibrillation, a well-known consequence of overt hyperthyroidism (8, 25), might also predispose to the development of heart failure. However, we did not find any association between subclinical thyroid dysfunction and incident atrial fibrillation in our study, in contrast to previous reports (26–28). Thus, it seems unlikely that the increased incidence rate of heart failure that we have observed with subclinical hyperthyroidism and hypothyroidism was mediated by atrial fibrillation. The lack of effect on atrial fibrillation might be due to study selection criteria. In our population at high risk for vascular disease, subclinical thyroid dysfunction might not be a major factor in causing atrial fibrillation. In subgroup analyses, we found no association with atrial fibrillation in older adults with suppressed TSH below 0.1 mIU/liter. However, participants with free T_4 concentrations above 18 pmol/liter were excluded in our study (defined as overt thyrotoxicosis). Previous studies showing an association with atrial fibrillation have included participants with higher free T_4 concentrations, such as 20 pmol/liter (27) or 22 pmol/liter (10). These results might indicate that free T_4 concentrations may be more strongly associated with atrial fibrillation than TSH concentrations, as previously reported elsewhere (27).

Furthermore, we did not find an association between suppressed TSH below 0.1 mIU/liter or high TSH above 10 mIU/liter and cardiovascular events or mortality only in subgroups of older adults not using pravastatin over a 3.2-yr follow-up period. Previous studies with longer follow-up (10, 17, 29) or very old adults (6) have shown conflicting results, and meta-analyses found a modestly increased risk for cardiovascular mortality associated with subclinical hyperthyroidism (2, 30) and subclinical hypothyroidism (3). For subclinical hyperthyroidism, the highest cardiovascular mortality rates were found in studies with a convenience sample of hospitalized patients (5, 31), and a meta-analysis that included the two latter studies found a significant association between subclinical hyperthyroidism and all-cause mortality (32). In older adults or those with comorbidities, experts recommend treatment for TSH values lower than 0.1 mIU/liter and normal free T_4 (1). Our large study provides further evidence that subclinical thyroid dysfunction defined as suppressed TSH or high TSH values might be associated with first or recurrent cardiovascular events and cardiovascular mortality in ambulatory older adults at high-risk of CVD.

Our study has several limitations. Like most previous large cohort studies (6, 10, 29, 33), free T_3 was not measured, and thyroid dysfunction was diagnosed with TSH and free T_4 only. Free T_3 would have been important to diagnose older adults with overt hyperthyroidism and T_3 toxicosis, because they would have greater increase in free T_3 than free T_4. However, according to the protocol of the PROSPER study (13), participants with symptoms and signs of overt hyperthyroidism, including atrial fibrillation, shortness of breath, heart failure, hyperglycemia, and thyroid cancer were excluded at baseline. Moreover, we excluded patients with antithyroid drug therapy, which has been associated with discordance between free T_3 and T_4 levels (34). We additionally excluded participants with current use of amiodarone at baseline, but we were not able to assess previous use, because amiodarone can have long-lasting effects. Five older adults with subclinical hyperthyroidism and 34 (15%) with subclinical hypothyroidism used thyroid hormone. To examine the risks of endogenous subclinical thyroid dysfunction, we did a sensitivity analysis excluding those using thyroid hormone and found similar estimates. We were not able to adjust our estimates for NYHA classification, and residual confounding might have occurred. However, participants with existing heart failure (NYHA class III and IV) were excluded at baseline according to the study protocol (13). Finally, the study population was derived from a clinical trial among older people with cardiovascular risk factors or previous CVD, which might limit the external validity of our findings. However, with the rapid aging of the population, the prevalence of chronic cardiovascular conditions due to earlier CVD will increase. Consequently, our large cohort of high-risk older people with well-defined and adjudicated cardiovascular events can be viewed as a major opportunity to understand the future burden of aging disease.

In older adults at high risk of vascular disease, subclinical hyperthyroidism and subclinical hypothyroidism with TSH values above 10 mIU/liter were associated with increased incidence rate of heart failure hospitalization over a period of 3 yr. This effect was not mediated by the oc-

currence of atrial fibrillation. Heart failure is associated with a large morbidity and mortality in the aging population, and TSH is a potentially modifiable risk factor. Treatment of subclinical hyperthyroidism and subclinical hypothyroidism to prevent heart failure and cardiovascular disease in older people should be evaluated in large randomized clinical trials. Pending such future studies, current recommendations to consider therapy if TSH is above 10 mIU/liter or less than 0.1 mIU/liter seems appropriate.

Acknowledgments

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This research was supported by The Netherlands Genomics Initiative/Netherlands Organization for Scientific Research (NGI/NWO; 05040202 and 050-060-810 Netherlands Consortium for Healthy Aging to R.G.J.W. and A.J.M.d.C.). This research was also supported by Swiss National Science Foundation grants (PBLAP3-132943 to D.N. and SNSF 320030-138267 to N.R.), the SICPA Foundation and the Société Académique Vaudoise (to D.N.). The original PROSPER study was supported by an unrestricted, investigator-initiated grant from Bristol-Myers Squibb.

Disclosure Summary: The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

References

1. **Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ** 2004 Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 291:228–238
2. **Ochs N, Auer R, Bauer DC, Nanchen D, Gussekloo J, Cornuz J, Rodondi N** 2008 Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. Ann Intern Med 148:832–845
3. **Rodondi N, den Elzen WP, Bauer DC, Cappola AR, Razvi S, Walsh JP, Asvold BO, Iervasi G, Imaizumi M, Collet TH, Bremner A, Maisonneuve P, Sgarbi JA, Khaw KT, Vanderpump MP, Newman AB, Cornuz J, Franklyn JA, Westendorp RG, Vittinghoff E, Gussekloo J** 2010 Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA 304:1365–1374
4. **Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE** 2002 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 87:489–499
5. **Iervasi G, Molinaro S, Landi P, Taddei MC, Galli E, Mariani F, L'Abbate A, Pingitore A** 2007 Association between increased mortality and mild thyroid dysfunction in cardiac patients. Arch Intern Med 167:1526–1532
6. **Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frölich M, Westendorp RG** 2004 Thyroid status, disability and cognitive function, and survival in old age. JAMA 292:2591–2599
7. **Rozing MP, Westendorp RG, de Craen AJ, Frölich M, Heijmans BT, Beekman M, Wijsman C, Mooijaart SP, Blauw GJ, Slagboom PE, van Heemst D; Leiden Longevity Study (LLS) Group** 2010 Low serum free triiodothyronine levels mark familial longevity: the Leiden longevity study. J Gerontol A Biol Sci Med Sci 65:365–368
8. **Klein I, Danzi S** 2007 Thyroid disease and the heart. Circulation 116:1725–1735
9. **Biondi B, Palmieri EA, Lombardi G, Fazio S** 2002 Effects of subclinical thyroid dysfunction on the heart. Ann Intern Med 137:904–914
10. **Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL, Tracy RP, Ladenson PW** 2006 Thyroid status, cardiovascular risk, and mortality in older adults. JAMA 295:1033–1041
11. **Rodondi N, Bauer DC, Cappola AR, Cornuz J, Robbins J, Fried LP, Ladenson PW, Vittinghoff E, Gottdiener JS, Newman AB** 2008 Subclinical thyroid dysfunction, cardiac function, and the risk of heart failure. The Cardiovascular Health study. J Am Coll Cardiol 52:1152–1159
12. **Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG** 2002 Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 360:1623–1630
13. **Shepherd J, Blauw GJ, Murphy MB, Cobbe SM, Bollen EL, Buckley BM, Ford I, Jukema JW, Hyland M, Gaw A, Lagaay AM, Perry IJ, Macfarlane PW, Meinders AE, Sweeney BJ, Packard CJ, Westendorp RG, Twomey C, Stott DJ** 1999 The design of a prospective study of pravastatin in the elderly at risk (PROSPER). Am J Cardiol 84:1192–1197
14. **Macfarlane PW, Murray H, Sattar N, Stott DJ, Ford I, Buckley B, Jukema JW, Westendorp RG, Shepherd J** 2011 The incidence and risk factors for new onset atrial fibrillation in the PROSPER study. Europace 13:634–639
15. **Mozaffarian D, Psaty BM, Rimm EB, Lemaitre RN, Burke GL, Lyles MF, Lefkowitz D, Siscovick DS** 2004 Fish intake and risk of incident atrial fibrillation. Circulation 110:368–373
16. **Sattar N, McConnachie A, Shaper AG, Blauw GJ, Buckley BM, de Craen AJ, Ford I, Forouhi NG, Freeman DJ, Jukema JW, Lennon L, Macfarlane PW, Murphy MB, Packard CJ, Stott DJ, Westendorp RG, Whincup PH, Shepherd J, Wannamethee SG** 2008 Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies. Lancet 371:1927–1935
17. **Parle JV, Maisonneuve P, Sheppard MC, Boyle P, Franklyn JA** 2001 Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. Lancet 358:861–865
18. **Fox CS, Pencina MJ, D'Agostino RB, Murabito JM, Seely EW, Pearce EN, Vasan RS** 2008 Relations of thyroid function to body weight: cross-sectional and longitudinal observations in a community-based sample. Arch Intern Med 168:587–592
19. **Biondi B, Palmieri EA, Fazio S, Cosco C, Nocera M, Saccà L, Filetti S, Lombardi G, Perticone F** 2000 Endogenous subclinical hyperthyroidism affects quality of life and cardiac morphology and function in young and middle-aged patients. J Clin Endocrinol Metab 85:4701–4705
20. **Boutin JM, Matte R, D'Amour P, Gilbert F, Havrankova J, Belanger R, Chartrand R, Zakarija M** 1986 Characteristics of patients with normal T_3 and T_4 and a low TSH response to TRH. Clin Endocrinol (Oxf) 25:579–588
21. **Celikyurt U, Agacdiken A, Geyik B, Kozdag G, Vural A, Ural D**

2011 Effect of cardiac resynchronization therapy on thyroid function. Clin Cardiol 34:703–705
22. **Rodondi N, Newman AB, Vittinghoff E, de Rekeneire N, Satterfield S, Harris TB, Bauer DC** 2005 Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. Arch Intern Med 165:2460–2466
23. **Díez JJ, Iglesias P, Burman KD** 2005 Spontaneous normalization of thyrotropin concentrations in patients with subclinical hypothyroidism. J Clin Endocrinol Metab 90:4124–4127
24. **Meyerovitch J, Rotman-Pikielny P, Sherf M, Battat E, Levy Y, Surks MI** 2007 Serum thyrotropin measurements in the community: five-year follow-up in a large network of primary care physicians. Arch Intern Med 167:1533–1538
25. **Frost L, Vestergaard P, Mosekilde L** 2004 Hyperthyroidism and risk of atrial fibrillation or flutter: a population-based study. Arch Intern Med 164:1675–1678
26. **Auer J, Scheibner P, Mische T, Langsteger W, Eber O, Eber B** 2001 Subclinical hyperthyroidism as a risk factor for atrial fibrillation. Am Heart J 142:838–842
27. **Gammage MD, Parle JV, Holder RL, Roberts LM, Hobbs FD, Wilson S, Sheppard MC, Franklyn JA** 2007 Association between serum free thyroxine concentration and atrial fibrillation. Arch Intern Med 167:928–934
28. **Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P, Wilson PW, Benjamin EJ, D'Agostino RB** 1994 Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med 331:1249–1252
29. **Walsh JP, Bremner AP, Bulsara MK, O'Leary P, Leedman PJ, Feddema P, Michelangeli V** 2005 Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. Arch Intern Med 165:2467–2472
30. **Völzke H, Schwahn C, Wallaschofski H, Dörr M** 2007 The association of thyroid dysfunction with all-cause and circulatory mortality: is there a causal relationship? J Clin Endocrinol Metab 92:2421–2429
31. **Radácsi A, Kovács G, Bernard W, Feldkamp J, Horster FA, Szabolcs I** 2003 Mortality rate of chronically ill geriatric patients with subnormal serum thyrotropin concentration: a 2-yr follow-up study. Endocrine 21:133–136
32. **Haentjens P, Van Meerhaeghe A, Poppe K, Velkeniers B** 2008 Subclinical thyroid dysfunction and mortality: an estimate of relative and absolute excess all-cause mortality based on time-to-event data from cohort studies. Eur J Endocrinol 159:329–341
33. **Bauer DC, Rodondi N, Stone KL, Hillier TA** 2007 Thyroid hormone use, hyperthyroidism and mortality in older women. Am J Med 120:343–349
34. **Chen JJ, Ladenson PW** 1986 Discordant hypothyroxinemia and hypertriiodothyroninemia in treated patients with hyperthyroid Graves' disease. J Clin Endocrinol Metab 63:102–106