

Effects of Subclinical Thyroid Dysfunction on the Heart

Bernadette Biondi, MD; Emiliano A. Palmieri, MD; Gaetano Lombardi, MD; and Serafino Fazio, MD

Background: Mounting evidence indicates that subclinical thyroid dysfunction has important clinical effects and prognostic implications, supporting the view that it is not a compensated biochemical change *sensu strictu*.

Purpose: To review clinical information on the effects of subclinical thyroid dysfunction on the heart.

Data Sources: English-language articles identified from files and a MEDLINE search (1970–September 2001), references of relevant articles, textbooks, and meeting abstracts.

Study Selection: Reports on the effects of subclinical hypothyroidism and subclinical hyperthyroidism on the cardiovascular system in humans.

Data Extraction: Data on cardiac structure and performance, arrhythmias, and risk for coronary artery disease were independently assessed by all authors and summarized.

Data Synthesis: Subclinical hypothyroidism is associated with

impaired left ventricular diastolic function at rest, systolic dysfunction on effort, and enhanced risk for atherosclerosis and myocardial infarction. Subclinical hyperthyroidism is associated with increased heart rate, atrial arrhythmias, increased left ventricular mass with marginal concentric remodeling, impaired ventricular relaxation, reduced exercise performance, and increased risk for cardiovascular death. All abnormalities were reversed by restoration of euthyroidism (subclinical hypothyroidism) or were blunted by β -blockade and tailoring of the L-thyroxine dose (subclinical hyperthyroidism).

Conclusion: The heart responds to the minimal but persistent changes in circulating thyroid hormone levels typical of subclinical thyroid dysfunction. Thus, the condition is not a compensated biochemical change *sensu strictu*, and timely treatment should be considered in an attempt to avoid adverse cardiovascular effects.

Ann Intern Med. 2002;137:904-914.

www.annals.org

For author affiliations, see end of text.

The cardiovascular system is very sensitive to thyroid hormone, and a wide spectrum of cardiac changes has long been recognized in overt thyroid dysfunction (1–5). In contrast, cardiovascular impairment in patients with subclinical thyroid dysfunction has only recently been studied in detail (6–9). This condition, characterized by normal levels of circulating free thyroxine (FT₄) and free triiodothyronine (FT₃) and elevated (subclinical hypothyroidism) or below-normal (subclinical hyperthyroidism) thyroid-stimulating hormone (TSH) concentrations, is associated with changes in several cardiovascular measures. These changes support the view that subclinical thyroid dysfunction is not a compensated biochemical change *sensu strictu*. To clarify this process, we reviewed clinical studies of the consequences of subclinical thyroid dysfunction on the heart.

METHODS

Data sources were articles in our collection about the cardiovascular effects of subclinical thyroid dysfunction in humans published between 1970 and September 2001. We checked that articles had not been overlooked by searching the MEDLINE database (keywords were *thyroid hormone, heart, subclinical hypothyroidism, subclinical hyperthyroidism, and cardiovascular risk*), references of relevant articles, textbooks, and abstracts of presentations at international thyroid meetings. Given the relatively few studies on the effect of subclinical thyroid disease on the cardiovascular system, we are confident that we considered all English-language peer-reviewed reports. All authors assessed the reports and agreed about article content.

SUBCLINICAL HYPOTHYROIDISM

Subclinical hypothyroidism, defined as increased serum TSH concentrations associated with normal FT₄ and FT₃ concentrations, may be caused by exogenous (L-thyroxine under-replacement in hypothyroid patients; medication with lithium, cytokines, iodine, or antithyroid drugs; and iodine 131 therapy or thyroidectomy) or endogenous (Hashimoto thyroiditis and previous subacute or silent thyroiditis) factors (8). Its prevalence ranges from 1.3% to 17.5%, depending on age, sex, and iodine intake (10–14). A large cross-sectional study from Colorado reported a mean prevalence of 9% (15). People with thyroid antibodies caused by Hashimoto thyroiditis are prone to subclinical hypothyroidism. The incidence of subclinical hypothyroidism, derived from a review (14) of three longitudinal studies that included a total of 2956 patients (with 6-, 10-, and 20-year follow-up, respectively) (16–18), is 2.1% to 3.8% per year in thyroid antibody-positive patients and about 0.3% per year in thyroid antibody-negative patients. The annual risk for developing overt hypothyroidism after 20 years is 4.3% in women with increased TSH concentrations and thyroid antibodies and 2.6% in women with subclinical hypothyroidism without thyroid antibodies (18).

Cardiac Manifestations

Table 1 lists the cardiovascular abnormalities reported in subclinical hypothyroidism (19–33). Resting heart rate was normal in all patients in whom it was evaluated (21, 22, 25, 28–30, 33). Cardiac function, evaluated from systolic time intervals, was also normal in patients with subclinical hypothyroidism (19, 27). In contrast, the preejec-

Table 1. Cardiovascular Abnormalities in Subclinical Hypothyroidism*

Study, Year (Reference)	Patients, n	Mean TSH Concentration \pm SD, mU/L	Method	Heart Rate	LV Mass	LV Systolic Function	LV Diastolic Function	Exercise Performance
Bough et al., 1978 (19)	10	13.1 \pm 1.1	STI	-	-	\leftrightarrow PEP, \leftrightarrow LVET, \leftrightarrow PEP/LVET	-	-
Ridgway et al., 1981 (20)	20	28 \pm 6	STI	-	-	\uparrow PEP, \uparrow PEP/LVET, \uparrow QKd	-	-
Cooper et al., 1984 (21)	17	10.8 \pm 2.2	STI	\leftrightarrow	-	\uparrow PEP/LVET	-	-
Bell et al., 1985 (22)	18	17.9 \pm 2.4	RNV	\leftrightarrow	-	\leftrightarrow Ejection fraction	-	\downarrow Ejection fraction
Forfar et al., 1985 (23)	10	-	RNV	-	-	\leftrightarrow Ejection fraction	-	\downarrow Ejection fraction
Földes et al., 1987 (24)	17	10.31 \pm 1.54	STI, RNV	-	-	\leftrightarrow PEP, \downarrow ejection fraction, \leftrightarrow cardiac output, \leftrightarrow stroke index	-	\downarrow Ejection fraction
Nyström et al., 1988 (25)	17	7.7 \pm 0.9	STI	\leftrightarrow	-	\uparrow PEP, \uparrow PEP/LVET	-	-
Tseng et al., 1989 (26)	22	10.7 \pm 2.2	Echo	-	-	\leftrightarrow PEP, \leftrightarrow PEP/LVET	-	-
Staub et al., 1992 (27)	14	8.6 \pm 0.5	STI	-	-	\leftrightarrow PEP, \leftrightarrow PEP/LVET	-	-
Arem et al., 1996 (28)	8	14.8 \pm 3.3	Doppler echo	\leftrightarrow	-	\leftrightarrow Fractional shortening, \leftrightarrow ejection fraction	\leftrightarrow E/A, \downarrow LVEDD	\uparrow PEP
Biondi et al., 1999 (29)	26	8.6 \pm 0.9	Doppler echo	\leftrightarrow	\leftrightarrow	\leftrightarrow Fractional shortening, \leftrightarrow VCF, \downarrow aortic acceleration	\downarrow E/A, \uparrow IVRT	-
Di Bello et al., 2000 (30)	16	5.27 \pm 0.47	Doppler echo	\leftrightarrow	\leftrightarrow	\leftrightarrow Fractional shortening, \leftrightarrow cardiac output, \uparrow PEP, \uparrow PEP/LVET	\uparrow A, \leftrightarrow E/A, \uparrow IVRT	-
Kahaly, 2000 (31)	20	11.2 (6.3–19.5)	Doppler echo, CPEX	-	-	\leftrightarrow	-	\downarrow Stroke volume, \downarrow cardiac output, \uparrow PEP, \downarrow aortic flow velocity, \downarrow anaerobic threshold (Watt)
Brenta et al., 2000 (32)	10	11.0 \pm 1.4	RNV	-	-	-	\uparrow TPF	-
Monzani et al., 2001 (33)	20	\approx 5.1 \pm 0.6	Doppler echo	\leftrightarrow	\uparrow	\leftrightarrow Fractional shortening, \uparrow PEP, \uparrow PEP/LVET, \leftrightarrow cardiac output	\uparrow A, \uparrow IVRT	-

* \uparrow = increased; \downarrow = decreased; \leftrightarrow = unchanged; A = late transmitral peak flow velocity; CPEX = cardiopulmonary exercise testing; E/A = early to late transmitral peak flow velocity ratio; echo = echocardiography; IVRT = isovolumic relaxation time; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVET = left ventricular ejection time; PEP = preejection period; QKd = the interval from Q wave on the electrocardiogram to the pulse arrival time at the brachial artery; RNV = radionuclide ventriculography; STI = systolic time intervals; TPF = time to peak filling rate; TSH = thyroid-stimulating hormone; VCF = velocity of circumferential fiber shortening.

tion period and the interval from Q wave to pulse arrival at the brachial artery were prolonged, and the preejection period–left ventricular ejection time ratio was higher in 20 patients with subclinical hypothyroidism than in the same patients after L-thyroxine replacement therapy (20).

In the first double-blind study of the effects of 1 year of L-thyroxine therapy compared with placebo in 17 patients with subclinical hypothyroidism of different origins, the preejection period–left ventricular ejection time ratio was significantly decreased after L-thyroxine therapy, particularly in patients with the highest ratio (>0.390) (21). In 18 patients, L-thyroxine caused a small but significant increase in left ventricular ejection fraction (evaluated by radionuclide ventriculography) during maximal exercise but caused no change at rest or during moderate exercise (22).

In 10 patients evaluated before and after TSH concentrations were normalized with L-thyroxine, the treatment did not affect left ventricular ejection fraction at rest but did enhance the increase in ejection fraction during exercise (23). In the same study, sodium nitroprusside pro-

duced similar increases in cardiac output in patients with subclinical hypothyroidism and in euthyroid persons. However, in the former group, enhanced cardiac output was due to a large increase in heart rate and reduced stroke volume, whereas euthyroid persons had a smaller increase in heart rate and no change in stroke volume. Therefore, restoration of euthyroidism by L-thyroxine improves systolic function on effort in patients with subclinical hypothyroidism. This could have resulted from improved myocardial contractility and, perhaps, lusitropic function. The preejection period was prolonged in only 5 of 17 patients with subclinical hypothyroidism compared with 50 euthyroid controls, whereas the mean left ventricular ejection fraction was reduced both at rest and during isometric exercise (24).

In the first double-blind, crossover study of women with subclinical hypothyroidism due to Hashimoto thyroiditis, 20 randomly selected women with primary subclinical hypothyroidism received L-thyroxine and placebo for 6 months each (25). Left ventricular systolic function

was assessed from systolic time intervals before and after L-thyroxine. Heart rate–corrected preejection period and the preejection period–left ventricular ejection time ratio decreased significantly after treatment. In another study, left ventricular function, evaluated by echocardiography-derived systolic time intervals, was unchanged in 22 patients with subclinical hypothyroidism compared with normal controls (26).

In eight subclinical hypothyroid patients evaluated at rest and during bicycle-ergometer exercise testing before and after L-thyroxine treatment, Doppler-derived systolic time intervals showed a more prolonged preejection period and a higher preejection period–left ventricular ejection time ratio during pretreatment maximum exercise (28). Echocardiographic left ventricular end-diastolic dimension was slightly but significantly lower before L-thyroxine treatment.

Left ventricular structure and function at rest were evaluated by using Doppler echocardiography in 26 selected patients with stable subclinical hypothyroidism due to Hashimoto thyroiditis and in 30 normal controls (29). In 10 randomly selected patients, the evaluation was repeated after 6 months of L-thyroxine therapy (daily dose, 68 μg). No significant abnormality in left ventricular structure was seen, whereas Doppler-derived mean aortic acceleration, a reliable index of left ventricular systolic function, was significantly lower in patients than in controls. This acceleration normalized after L-thyroxine therapy. Furthermore, isovolumic relaxation time was prolonged, and the early–late ratio of Doppler-derived transmitral peak flow velocities was lower in patients than in controls. Both measures of diastolic function returned to normal after L-thyroxine replacement. Doppler echocardiography and ultrasonic myocardial textural analysis confirmed these findings in 16 patients with subclinical hypothyroidism (30). They had a significantly increased left ventricular mass and lower cyclic variation measures (percentage systolic/diastolic change in mean gray levels) in both the interventricular septum and the left ventricular posterior wall (30).

Radionuclide ventriculography revealed a longer time to peak filling rate in 10 patients with subclinical hypothyroidism than in 10 normal controls (32). This index of diastolic function normalized after L-thyroxine replacement. Using stress Doppler echocardiography and cardiopulmonary exercise testing, Kahaly (31) studied 20 patients with subclinical hypothyroidism before and after L-thyroxine therapy and 20 normal controls. At rest, the cardiac measures recorded in untreated patients approximated those obtained in controls and in euthyroid patients. However, patients had significantly lower stroke volume, cardiac index, and peak aortic flow velocity and significantly prolonged preejection period during exercise. All measures normalized after a euthyroid state was achieved. Furthermore, the oxygen pulse (oxygen uptake per heartbeat), an index of stroke volume, was significantly decreased both at

the anaerobic threshold and at maximal work capacity, and work rate was reduced at the anaerobic threshold in patients versus controls. These measures normalized after replacement therapy.

Finally, in a double-blind, placebo-controlled study of the effects of L-thyroxine replacement therapy on cardiac structure and function in subclinical hypothyroidism, cardiac measures, evaluated by Doppler echocardiography and videodensitometry, were almost normal after L-thyroxine therapy (33).

Coronary Artery Disease

Overt hypothyroidism increases serum cholesterol levels (15, 27, 34–36), but it is not known whether subclinical hypothyroidism affects serum lipid profiles. Serum cholesterol levels have been significantly higher in patients with subclinical hypothyroidism than in normal controls (31, 37–40). In other studies, levels were only marginally increased (41–43). In three studies, the prevalence of subclinical or overt hypothyroidism was higher in hypercholesterolemic patients (44–46), a finding not confirmed in a subsequent study (47). Other markers of atherosclerotic risk described in overt hypothyroidism (enhanced low-density lipoprotein oxidation, elevated lipoprotein(a) levels, and hyperhomocysteinemia) may also be responsible for an association between subclinical hypothyroidism and coronary artery disease (48–50). Of interest, a recent quantitative review of patients with subclinical hypothyroidism showed that restoration of euthyroidism by L-thyroxine reduced both total and low-density lipoprotein cholesterol levels. The reduction was more pronounced in patients with higher pretreatment cholesterol levels and TSH concentrations (51). Moreover, L-thyroxine significantly reduced lipoprotein(a) and homocysteine levels in patients with overt and subclinical hypothyroidism (52, 53).

Two studies have shown an association between subclinical hypothyroidism and coronary artery disease (54, 55), whereas others have either found no association or only a weak association between minor electrocardiographic changes and a minor degree of hypothyroidism in women (41, 56, 57). Striking evidence of a higher risk for atherosclerotic cardiovascular death in patients with subclinical hypothyroidism emerged from the Rotterdam study (58). This large epidemiologic study concluded that subclinical hypothyroidism is associated with a greater prevalence of aortic atherosclerosis and myocardial infarction in elderly women. Perk and O'Neill, using sequential coronary angiography, found that appropriate thyroid hormone replacement therapy prevented progression of angiographic coronary artery disease in hypothyroid patients (59).

Patients with subclinical hypothyroidism have abnormal vascular reactivity, which is identified by impaired flow-mediated, endothelium-dependent vasodilatation (31, 60, 61). The association between pathologic immune vascular damage due to thyroid autoimmunity and coronary artery disease is controversial (54–58, 62, 63). The two

largest epidemiologic studies that addressed this issue did not identify an association between autoimmune thyroid disease and mortality or development of coronary artery disease (58, 63). This finding weakens the hypothesis that pathologic immune vascular damage may be an important factor in the association of autoimmune thyroiditis with coronary artery disease, independently of whether the TSH concentration is normal or increased.

Commentary

The results of studies on the effects of subclinical hypothyroidism on left ventricular structure and function are controversial, particularly with regard to the effects on left ventricular systolic function at rest. Conflicting results might be related to a less than rigorous selection of patients (enrollment of patients with previous hyperthyroidism or with acute or unstable subclinical hypothyroidism) and to different diagnostic criteria for subclinical hypothyroidism (a wide range of TSH concentrations) (19–24, 26–28). Indeed, in many early studies, inclusion of patients with previous overt hyperthyroidism could have confounded the evaluation of left ventricular structure and function. In other studies, the cardiac measures obtained during the subclinical hypothyroid state were compared with those obtained in the same patients after L-thyroxine replacement therapy. However, thyroid hormone could itself affect the heart independently of the underlying thyroid disease. Nevertheless, studies have clearly shown that patients with subclinical hypothyroidism have impaired left ventricular diastolic function at rest and systolic dysfunction on effort, which may result in poor physical exercise capacity. Moreover, resting left ventricular diastolic dysfunction is often the first manifestation of heart disease, even preceding systolic dysfunction at rest (64, 65). Altered serum lipid levels and abnormal vascular reactivity in patients with subclinical hypothyroidism, particularly in elderly women, may confer a higher risk for cardiovascular disease. Therefore, subclinical hypothyroidism should be considered a mild form of thyroid failure *sensu strictu* that is associated with initial signs of cardiovascular hypothyroidism.

SUBCLINICAL HYPERTHYROIDISM

Subclinical hyperthyroidism, characterized by low or undetectable serum TSH concentrations and normal FT₄ and FT₃ concentrations, may be caused by exogenous and endogenous factors (9, 66). The major exogenous cause is the use of L-thyroxine to suppress TSH in patients with thyroid nodular disease or to prevent local or metastatic progression of differentiated thyroid carcinoma after surgery (9, 66). Overzealous hormone replacement therapy; misunderstandings about prescriptions; and changes in L-thyroxine requirement, absorption, and formulation are additional potential causes (9, 15, 66–68). Like overt hyperthyroidism, endogenous subclinical hyperthyroidism is due to Graves disease, multinodular goiter, or an autonomously functioning thyroid nodule (9, 66). The prevalence

of subclinical hyperthyroidism ranges from 0.6% to 16% (13, 14, 66), depending on the definition used (that is, TSH concentration lower than normal, <0.1 mU/L, or undetectable in a given assay), the sensitivity of the method used to measure TSH concentrations, and iodine intake in the study sample. The exogenous form of subclinical hyperthyroidism is the most prevalent (15); the endogenous form is frequent in geographic areas with iodine insufficiency (69, 70).

Low or undetectable TSH concentrations are generally temporary in patients with Graves disease. Conversely, multinodular goiter or autonomously functioning thyroid nodules are characterized by prolonged periods of subclinical hyperthyroidism (71–73). Overt thyrotoxicosis is often precipitated by increased iodine intake after administration of iodine-containing drugs or radiographic contrast agents (74). Iodine-induced thyrotoxicosis can be secondary to iodine prophylaxis in populations with endemic goiter (75–77). Prospective studies of patients with endogenous subclinical hyperthyroidism (1 to 4 years of follow-up) showed that TSH concentrations increased spontaneously in almost 50% of cases (although the normal reference range was not always reached) and remained unchanged in 35%, whereas overt hyperthyroidism developed in 10% of patients at a rate of 5% per year (78–82).

Cardiac Manifestations

Given the pathophysiologic differences between exogenous and endogenous subclinical hyperthyroidism, we review cardiac manifestations of the two disorders separately (Table 2) (26, 83–96).

Exogenous Subclinical Hyperthyroidism

Bell and colleagues (83) first demonstrated the cardiac effects of exogenous subclinical hyperthyroidism. They studied 7 normal persons by using 24-hour Holter electrocardiography at baseline and after L-thyroxine administration, when the plasma TSH response to TSH-releasing hormone was inhibited. The mean nocturnal and mean daytime heart rate increased after treatment, the former significantly so. The first evidence of mild but significant changes in myocardial function was reported in 1984 in hypothyroid patients receiving over-replacement therapy with L-thyroxine and showing minimally elevated serum FT₄ concentrations and suppressed TSH (84). Systolic time intervals within the thyrotoxic range alerted the physician to tissue thyrotoxicosis and to the need to reduce the L-thyroxine dose. The mean preejection period–left ventricular ejection time ratio was lower than normal in 15 patients receiving replacement L-thyroxine therapy and increased in 7 patients after reduction of the L-thyroxine dose (84). Results were similar in 18 patients with exogenous subclinical hyperthyroidism (86).

Concurrent aortic and mitral valve echocardiographic tracing has revealed a significantly shorter isovolumic contraction time and preejection period and lower preejection

Table 2. Cardiovascular Abnormalities in Subclinical Hyperthyroidism*

Study, Year (Reference)	Patients, n	Methods	Cause	Heart Rate	LV Mass	LV Systolic Function	LV Diastolic Function	Exercise Performance	Ventricular Arrhythmias	Supraventricular Arrhythmias
Bell et al., 1983 (83)	7	Holter ECG	Exogenous	↑	-	-	-	-	-	-
Jennings et al., 1984 (84)	15	STI	Exogenous	-	-	↓ PEP/LVET	-	-	-	-
Boutin et al., 1986 (85)	16	Pulse examination	Endogenous	↑	-	-	-	-	-	-
Banovac et al., 1989 (86)	18	STI	Exogenous	-	-	↓ PEP, ↓ PEP/LVET	-	-	-	-
Tseng et al., 1989 (26)	15	Echo	Exogenous	↔	-	↓ Isovolumic contraction time, ↓ PEP, ↓ PEP/LVET	-	-	-	-
Grund and Niewoehner, 1989 (87)	11	RNV	Exogenous	↑	-	↔ Ejection fraction	-	-	-	-
Biondi et al., 1993 (88)	20	Echo, Holter ECG	Exogenous	↑	↑	↑ VCF, ↑ fractional shortening	-	-	↔	↑
Fazio et al., 1995 (89)	25	Doppler echo	Exogenous	↑	↑	-	↑ IVRT, ↓ E/A	-	-	-
Biondi et al., 1996 (90)	10	RNV	Exogenous	↑	-	↔ Ejection fraction	↓ Peak filling rate	↓ Ejection fraction	-	-
Ching et al., 1996 (91)	11	Echo, Holter blood pressure	Exogenous	↔	↑	↔ Ejection fraction, ↔ fractional shortening	-	-	-	-
Shapiro et al., 1997 (92)	17	Doppler echo, Holter ECG	Exogenous	↔	↑	↔ Ejection fraction	↔ E/A	-	↔	↔
Biondi et al., 1999 (93)	60	Doppler echo, Holter ECG	Exogenous	↑	↑	↑ Fractional shortening, ↑ VCF	↑ IVRT, ↓ E/A	-	↔	↑
Mercuro et al., 2000 (94)	19	Doppler echo, CPEx	Exogenous	↔	↑	↔ Ejection fraction	↑ IVRT, ↔ E/A	↓ Peak Watt, ↓ VO ₂ max, ↓ VO ₂ anaerobic threshold	-	-
Biondi et al., 2000 (95)	23	Doppler echo, Holter ECG	Endogenous	↑	↑	↑ Fractional shortening, ↑ VCF, ↑ aortic acceleration	↑ IVRT, ↓ E/A	-	↔	↔
Sgarbi et al., 2000 (96)	10	Doppler echo, Holter ECG	Endogenous	↑	↑	↑ VCF	-	-	↑	↑

* ↑ = increased; ↓ = decreased; ↔ = unchanged; CPEx = cardiopulmonary exercise testing; E/A = early to late transmitral peak flow velocity ratio; ECG = electrocardiography; echo = echocardiography; IVRT = isovolumic relaxation time; LV = left ventricular; LVET = left ventricular ejection time; PEP = preejection period; RNV = radionuclide ventriculography; STI = systolic time intervals; VCF = velocity of circumferential fiber shortening; VO₂ = oxygen uptake.

period–left ventricular ejection time ratios in patients with exogenous subclinical hyperthyroidism (26). Eleven patients with an elevated FT₄ index and suppressed TSH due to L-thyroxine over-replacement therapy were evaluated by using resting radionuclide ventriculography at baseline and after the daily L-thyroxine dose was progressively reduced by 25 μg at 3-month intervals until normalization of the FT₄ index (87). Heart rate was significantly reduced by titration of the L-thyroxine dose, while left ventricular ejection fraction decreased nonsignificantly in 8 of 11 patients.

Echocardiography showed an increased left ventricular mass index in 20 patients with persistent exogenous subclinical hyperthyroidism (88). Left ventricular systolic function was also enhanced, as documented by the increase of fractional shortening and the rate-adjusted velocity of shortening. During a 24-hour period, the patients' heart rates, assessed by 24-hour Holter electrocardiography, were constantly higher than those of controls. Atrial premature beats were more frequent in patients than in controls: Two patients had atrial fibrillation. The prevalence of ventricu-

lar arrhythmias did not differ between groups (88). A subsequent study confirmed these results in a much larger group of patients (93).

The effects of 6-month β-blockade were evaluated in 11 patients with exogenous subclinical hyperthyroidism who were selected because of symptoms mimicking exaggerated β-adrenergic activity (97). This study showed a significant reduction in the average heart rate and the prevalence of atrial premature beats. After β-blockade, atrial fibrillation disappeared, left ventricular mass index was substantially reduced, and measures of left ventricular systolic function remained slightly enhanced.

Compared with normal controls, 25 patients receiving long-term TSH suppressive therapy evaluated with Doppler echocardiography had a significant increase in the left ventricular mass index accompanied by impaired indices of left ventricular diastolic function (prolonged isovolumic relaxation time and reduced ratio of early to late transmitral peak flow velocities) (89). Impaired left ventricular diastolic function was more evident in a subgroup of 10 pa-

tients who had greater adrenergic overactivity and higher left ventricular mass index values. In these 10 patients, 4 months of β -blockade significantly reduced cardiac hypertrophy, thereby improving left ventricular diastolic filling.

In 1996, Biondi and colleagues (90) investigated cardiac reserve and exercise capacity using radionuclide ventriculography in 10 patients receiving long-term L-thyroxine therapy who reported symptoms of adrenergic overactivity. Patients were evaluated before and after 4 months of β -blockade. Exercise capacity, assessed as peak workload and exercise duration, was markedly worse in patients than in controls. In addition, resting left ventricular diastolic filling was impaired and ejection fraction decreased during exercise. β -Adrenergic blockade reversed the decrease in ejection fraction and almost normalized resting diastolic function, which improved exercise tolerance.

Blood pressure, heart rate, left ventricular systolic function, autonomic function, forearm blood flow, and vascular resistance did not change in 11 patients with exogenous subclinical hyperthyroidism evaluated with 24-hour monitoring of pulse and blood pressure, echocardiography, forearm plethysmography, and autonomic function testing (91). However, patients had significantly higher left ventricular mass index values than did controls.

L-Thyroxine treatment did not affect left ventricular systolic and diastolic function in 17 patients with subclinical hyperthyroidism evaluated by using Doppler echocardiography and 24-hour Holter electrocardiography (92), but the mean left ventricular mass index was significantly higher in patients than in controls. Mean heart rate and the prevalence of atrial or ventricular premature contractions did not change. However, patients taking β -blocker drugs during L-thyroxine treatment were excluded from the evaluation.

Finally, Mercurio and colleagues (94) studied cardiac function and physical exercise capacity by using Doppler echocardiography and cardiopulmonary exercise testing in 19 patients receiving long-term TSH-suppressive treatment. The mean resting heart rate was marginally higher in patients than in controls. Doppler echocardiography showed significantly increased left ventricular mass in patients with subclinical hyperthyroidism accompanied by impaired left ventricular relaxation and preserved resting systolic function. Nine of the 19 patients had significantly reduced exercise performance, as shown by a significant reduction in peak workload, peak oxygen uptake, and anaerobic threshold. Of interest, noradrenaline concentrations at rest were significantly lower in TSH-suppressed patients when measured in both supine and standing positions. Individual tailoring of the TSH-suppressive L-thyroxine dose in 7 patients almost normalized all Doppler echocardiographic and cardiopulmonary exercise measures but did not alter noradrenaline concentrations. Reduced noradrenaline concentration in the patients with subclinical hyperthyroidism agrees with a report of lower noradrenaline levels in patients with overt thyrotoxicosis (98).

Endogenous Subclinical Hyperthyroidism

Only three studies have evaluated the effect of endogenous subclinical hyperthyroidism on the heart (85, 95, 96). In a pioneering investigation among participants with multinodular goiter, normal FT₃ and FT₄ concentrations, and a low TSH response to TSH-releasing hormone, Boutin and colleagues reported a higher pulse rate in patients than in controls (85). More recently, 23 patients with endogenous subclinical hyperthyroidism (15 affected by multinodular goiter and 8 by autonomously functioning thyroid nodule) were investigated by using 24-hour Holter electrocardiography and Doppler echocardiography (95). The average heart rate was significantly higher in patients than in normal persons. The prevalence of supraventricular and ventricular arrhythmias did not differ between the two groups. In the patients with subclinical hyperthyroidism, fractional shortening increased by about 14%, the heart rate–adjusted mean velocity of circumferential fiber shortening increased by about 7%, and peak aortic flow velocity increased by about 19%. Left ventricular mass was significantly higher in this group because of the increased thickness of both the interventricular septum and the posterior wall. These patients also had impaired diastolic function characterized by delayed relaxation.

Results were similar in 10 patients with endogenous subclinical hyperthyroidism (96). When these patients reached euthyroidism after 6 months of methimazole treatment, the mean 24-hour heart rate, atrial premature beats, and left ventricular mass had returned to normal.

Epidemiologic Evidence on Subclinical Hyperthyroidism and Atrial Fibrillation

Two longitudinal studies of older people have addressed atrial fibrillation in subclinical hyperthyroidism (82, 99). In 40 patients with subclinical hyperthyroidism (mean age, 65 years), Tenerz and colleagues (82) found 8 cases of atrial fibrillation, and 3 additional patients developed atrial fibrillation during the 2-year follow-up. The total rate of atrial fibrillation was 28% in patients compared with 10% in an age-matched group of euthyroid persons. In the Framingham study (99), 2007 participants 60 years of age or older with low TSH levels due to exogenous or endogenous factors had a threefold higher risk for atrial fibrillation. Studies of overt hyperthyroidism have shown that 10% to 15% of patients with atrial fibrillation may have an arterial embolic event (3, 6). Although there are no data on the incidence of arterial embolism due to atrial fibrillation in patients with subclinical hyperthyroidism, observations made in overt hyperthyroidism might apply to patients with subclinical hyperthyroidism.

Commentary

Exogenous and endogenous subclinical hyperthyroidism exert many relevant effects on the heart (82–97, 99). Results about resting heart rate in patients with subclinical hyperthyroidism are not consistent. Only four studies of exogenous subclinical hyperthyroidism (83, 88, 92, 93)

and two studies of the endogenous condition (95, 96) assessed heart rate by using 24-hour Holter electrocardiography. The mean 24-hour heart rate was increased, also during nocturnal hours, in all these studies except one (93); that study had excluded patients with subclinical hyperthyroidism who were taking β -blockers. Increased exercise heart rate was reported in two studies, and, at a comparable workload, patients with exogenous subclinical hyperthyroidism had a higher heart rate than normal controls (90, 94). The prevalence and incidence of atrial fibrillation were higher in patients with subclinical hyperthyroidism 60 years of age or older (82, 99), whereas atrial premature beats were increased in some younger patients (88, 93, 96).

There is no consensus about the effects of subclinical hyperthyroidism on left ventricular function at rest. Systolic function has been reported to be increased (26, 84, 86, 88, 93, 95, 96) and unchanged (91, 92, 94). However, impaired left ventricular performance on exercise and decreased effort tolerance were found in the only two studies that evaluated cardiac performance and exercise capacity in patients with subclinical hyperthyroidism (90, 94). All the studies of cardiac structure in patients with subclinical hyperthyroidism showed an increased left ventricular mass with a tendency toward left ventricular concentric remodeling (88–96). This was sometimes accompanied by impaired ventricular relaxation (89, 90, 93–95) and decreased exercise performance (90, 94). The favorable effect promoted by thyroid hormone on diastolic performance (100, 101) may be counteracted by the adverse effect of myocardial hypertrophy on diastolic function (64, 65). These abnormalities were improved by β -blockade or by tailoring the L-thyroxine dose in patients with exogenous subclinical hyperthyroidism and by methimazole in patients with endogenous subclinical hyperthyroidism (89, 90, 94, 96). The prognostic significance of increased left ventricular mass in exogenous and endogenous subclinical hyperthyroidism is unclear because of the scarcity of epidemiologic studies on cardiovascular risk in these patients (99, 102). Patients with endogenous subclinical hyperthyroidism have been reported to have a higher rate of death from all causes, but especially from circulatory disease, than people with normal thyroid function (103). The mechanisms by which subclinical hyperthyroidism may increase mortality from cardiovascular disease are unknown. Although left ventricular mass in patients with subclinical hyperthyroidism is not sufficiently high to be classified as “left ventricular hypertrophy,” an increase in left ventricular mass is more likely to be harmful than beneficial (104–106). Increased heart rate may also increase risk for cardiovascular and noncardiovascular death (107). Finally, because increased morbidity and mortality from thromboembolic events are associated with atrial fibrillation, subclinical hyperthyroidism in older patients may be considered a risk factor for thromboembolism.

GENERAL CONSIDERATIONS

Despite the high prevalence of subclinical thyroid dysfunction in the general population, treatment of this condition is controversial (66, 108–117). Our overview of the cardiovascular effects induced by subclinical hypothyroidism and subclinical hyperthyroidism shows that minimal but “persistent” changes in thyroid hormone levels, as occur in subclinical thyroid dysfunction, cause changes in the heart. Large epidemiologic studies have shown that, in elderly persons, subclinical hypothyroidism is associated with increased risk for atherosclerosis and coronary artery disease (58), whereas subclinical hyperthyroidism is associated with increased mortality from all causes, but especially from cardiovascular disease (103). Further research is needed to clarify better the intrinsic mechanisms by which subclinical thyroid dysfunction affects cardiovascular risk.

The data show that subclinical thyroid dysfunction is not a compensated biochemical state, and hence timely treatment could help to prevent cardiovascular involvement. An important observation to emerge from this review is that changes in cardiovascular measures can also be found in subclinical hypothyroid patients with TSH values less than 10 mU/L. According to the literature, “persistent” subclinical hypothyroidism with TSH values stably above 4.0 mU/L should be treated, particularly if associated with thyroid antibodies. The benefits of treatment are an improved lipid profile, possible reduced risk for atherosclerosis and coronary artery disease, prevention of cardiac morphologic and functional abnormalities and progression to overt hypothyroidism, a modest symptomatic benefit after L-thyroxine, and prevention of goiter in some patients. The L-thyroxine dose must be lower in patients with subclinical hypothyroidism than in those with overt disease (1.0 $\mu\text{g}/\text{kg}$ of body weight vs. 2.0 $\mu\text{g}/\text{kg}$), and patients must be monitored until the optimal replacement dose is achieved. Young and middle-aged patients may start with 25 μg of L-thyroxine, with progressive increases in the dose until the TSH level ranges from 1 to 2 mU/L. If TSH concentrations remain normal, values may be checked every 6 to 12 months. In elderly patients with subclinical hypothyroidism, it is prudent to begin with a low dose of L-thyroxine (12.5 to 25 μg) and then titrate the dose upward at 4- to 6-week intervals on the basis of serial TSH determinations and clinical evaluation. Cardiac conditions should be assessed before initiating therapy to avoid exacerbation of ischemic heart disease. The target dose of L-thyroxine is lower in elderly patients than in young and middle-aged patients because of decreased thyroxine metabolism in the former group.

Because the most common cause of subclinical thyroid dysfunction is L-thyroxine therapy (15), periodic evaluations of serum TSH levels seem justified to ensure that replacement therapy is not under- or over-prescribed. Appropriate replacement therapy to maintain TSH levels in the normal range is necessary in hypothyroid patients to

avoid the adverse cardiovascular effects of mild thyroid hormone excess or deficiency.

Given the increased mortality in patients with subclinical hyperthyroidism older than 60 years of age, subnormal TSH concentrations should be avoided in elderly patients (103, 117). Before surgery or iodine 131 therapy, elderly patients with subclinical hyperthyroidism should receive treatment with low doses of antithyroid drugs or β -blockers. However, the cardiovascular risk related to the increased left ventricular mass and to the deleterious effects of overt thyrotoxicosis in hearts previously exposed to prolonged subclinical hyperthyroidism should also be considered in younger patients (118).

L-thyroxine suppressive therapy must be carefully customized in patients with benign thyroid disease; TSH concentrations should be maintained at the low end of normal range, and treatment outcome should be assessed after 6 to 12 months of therapy. Long-term TSH suppressive therapy must be associated with periodic cardiovascular assessment. Cancer recurrence and mortality rate may be increased in patients with differentiated thyroid cancer who are inadequately treated with L-thyroxine (119). New guidelines for L-thyroxine therapy are needed for patients with the highest-risk tumors to maximize the benefit of therapy on thyroid cancer cell growth while avoiding the long-term adverse effects of TSH suppression. In the meantime, β -blockade may be considered in patients with adrenergic hyper-responsiveness to L-thyroxine, since it blunts the increase in heart rate, prevents the development of left ventricular hypertrophy, and effectively reduces the risk for supraventricular arrhythmias (89, 90, 93, 97).

From the University of Naples Federico II School of Medicine, Naples, Italy.

Acknowledgments: The authors thank Jean Ann Gilder for editing the text.

Grant Support: In part by Grant of Ministero dell'Università e della Ricerca Scientifica e Tecnologica (co-financed project, year 2000) (no. MM06263471-005).

Requests for Single Reprints: Bernadette Biondi, MD, Department of Clinical and Molecular Endocrinology and Oncology, University of Naples Federico II School of Medicine, via S. Pansini 5, 80131 Naples, Italy; e-mail, bebiondi@libero.it.

Current author addresses are available at www.annals.org.

References

1. Parry CH. Enlargement of thyroid gland in connection with enlargement or palpitation of the heart. Collection from the Unpublished Papers of the Late Caleb Hillier Parry. London: Wellcome Library for the History and Understanding of Medicine; 1825:111-25.
2. Amidi M, Leon DF, DeGroot WJ, Kroetz FW, Leonard JJ. Effect of the thyroid state on myocardial contractility and ventricular ejection rate in man. *Circulation*. 1968;38:229-39. [PMID: 5666839]
3. Polikar R, Burger AG, Scherrer U, Nicod P. The thyroid and the heart. *Circulation*. 1993;87:1435-41. [PMID: 8490997]

4. Fadel BM, Ellahham S, Ringel MD, Lindsay J Jr, Wartofsky L, Burman KD. Hyperthyroid heart disease. *Clin Cardiol*. 2000;23:402-8. [PMID: 10875028]
5. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. *N Engl J Med*. 2001;344:501-9. [PMID: 11172193]
6. Ladenson PW. Thyrotoxicosis and the heart: something old and something new [Editorial]. *J Clin Endocrinol Metab*. 1993;77:332-3. [PMID: 8345036]
7. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system: from theory to practice [Editorial]. *J Clin Endocrinol Metab*. 1994;78:1026-7. [PMID: 8175954]
8. Ross DS. Subclinical hypothyroidism. In: Braverman LE, Utiger RD, eds. *Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text*. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 1996:1010-5.
9. Ross DS. Subclinical thyrotoxicosis. In: Braverman LE, Utiger RD, eds. *Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text*. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 1996:1016-20.
10. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, et al. The spectrum of thyroid disease in a community: the Whickham survey. *Clin Endocrinol (Oxf)*. 1977;7:481-93. [PMID: 598014]
11. Sawin CT, Castelli WP, Hershman JM, McNamara P, Bacharach P. The aging thyroid. Thyroid deficiency in the Framingham Study. *Arch Intern Med*. 1985;145:1386-8. [PMID: 4026469]
12. Vanderpump MP, Tunbridge WM. The epidemiology of thyroid disease. In: Braverman LE, Utiger RD, eds. *Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text*. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 1996:474-82.
13. Wang C, Crapo LM. The epidemiology of thyroid disease and implications for screening. *Endocrinol Metab Clin North Am*. 1997;26:189-218. [PMID: 9074859]
14. Samuels MH. Subclinical thyroid disease in the elderly. *Thyroid*. 1998;8:803-13. [PMID: 9777754]
15. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med*. 2000;160:526-34. [PMID: 10695693]
16. Hawkins BR, Cheah PS, Dawkins RL, Whittingham S, Burger HG, Patel Y, et al. Diagnostic significance of thyroid microsomal antibodies in randomly selected population. *Lancet*. 1980;2:1057-9. [PMID: 6107681]
17. Geul KW, van Sluisveld IL, Grobbee DE, Docter R, de Bruyn AM, Hooykaas H, et al. The importance of thyroid microsomal antibodies in the development of elevated serum TSH in middle-aged women: associations with serum lipids. *Clin Endocrinol (Oxf)*. 1993;39:275-80. [PMID: 8222290]
18. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin Endocrinol (Oxf)*. 1995;43:55-68. [PMID: 7641412]
19. Bough EW, Crowley WF, Ridgway C, Walker H, Maloof F, Myers GS, et al. Myocardial function in hypothyroidism. Relation to disease severity and response to treatment. *Arch Intern Med*. 1978;138:1476-80. [PMID: 708167]
20. Ridgway EC, Cooper DS, Walker H, Rodbard D, Maloof F. Peripheral responses to thyroid hormone before and after L-thyroxine therapy in patients with subclinical hypothyroidism. *J Clin Endocrinol Metab*. 1981;53:1238-42. [PMID: 7298802]
21. Cooper DS, Halpern R, Wood LC, Levin AA, Ridgway EC. L-Thyroxine therapy in subclinical hypothyroidism. A double-blind, placebo-controlled trial. *Ann Intern Med*. 1984;101:18-24. [PMID: 6428290]
22. Bell GM, Todd WT, Forfar JC, Martyn C, Wathen CG, Gow S, et al. End-organ responses to thyroxine therapy in subclinical hypothyroidism. *Clin Endocrinol (Oxf)*. 1985;22:83-9. [PMID: 3978830]
23. Forfar JC, Wathen CG, Todd WT, Bell GM, Hannan WJ, Muir AL, et al. Left ventricular performance in subclinical hypothyroidism. *Q J Med*. 1985;57:857-65. [PMID: 4095255]
24. Földes J, Istvánfy M, Halmágyi M, Váradi A, Gara A, Pártos O. Hypothyroidism and the heart. Examination of left ventricular function in subclinical hypothyroidism. *Acta Med Hung*. 1987;44:337-47. [PMID: 3444711]
25. Nyström E, Caidahl K, Fager G, Wikkelso C, Lundberg PA, Lindstedt G. A double-blind cross-over 12-month study of L-thyroxine treatment of women with 'subclinical' hypothyroidism. *Clin Endocrinol (Oxf)*. 1988;29:63-75. [PMID: 3073880]

26. Tseng KH, Walfish PG, Persaud JA, Gilbert BW. Concurrent aortic and mitral valve echocardiography permits measurement of systolic time intervals as an index of peripheral tissue thyroid functional status. *J Clin Endocrinol Metab.* 1989;69:633-8. [PMID: 2760174]
27. Staub JJ, Althaus BU, Engler H, Ryff AS, Trabucco P, Marquardt K, et al. Spectrum of subclinical and overt hypothyroidism: effect on thyrotropin, prolactin, and thyroid reserve, and metabolic impact on peripheral target tissues. *Am J Med.* 1992;92:631-42. [PMID: 1605145]
28. Arem R, Rokey R, Kiefe C, Escalante DA, Rodriguez A. Cardiac systolic and diastolic function at rest and exercise in subclinical hypothyroidism: effect of thyroid hormone therapy. *Thyroid.* 1996;6:397-402. [PMID: 8936662]
29. Biondi B, Fazio S, Palmieri EA, Carella C, Panza N, Cittadini A, et al. Left ventricular diastolic dysfunction in patients with subclinical hypothyroidism. *J Clin Endocrinol Metab.* 1999;84:2064-7. [PMID: 10372711]
30. Di Bello V, Monzani F, Giorgi D, Bertini A, Caraccio N, Valenti G, et al. Ultrasonic myocardial textural analysis in subclinical hypothyroidism. *J Am Soc Echocardiogr.* 2000;13:832-40. [PMID: 10980086]
31. Kahaly GJ. Cardiovascular and atherogenic aspects of subclinical hypothyroidism. *Thyroid.* 2000;10:665-79. [PMID: 11014311]
32. Brenta G, Mutti LA, Schnitman M, Fretes O, Perrone A, Matute ML. Diastolic function in subclinical hypothyroidism before and after treatment with thyroid hormones [Abstract]. 12th International Thyroid Congress. Kyoto 2000. *Endocr J.* 2000;47(Suppl):221.
33. Monzani F, Di Bello V, Caraccio N, Bertini A, Giorgi D, Giusti C, et al. Effect of levothyroxine on cardiac function and structure in subclinical hypothyroidism: a double blind, placebo-controlled study. *J Clin Endocrinol Metab.* 2001;86:1110-5. [PMID: 11238494]
34. Klein I, Ojamaa K. The cardiovascular system in hypothyroidism. In: Braverman LE, Utiger RD, eds. *Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text.* 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2000:777-82.
35. Vanhaelst L, Neve P, Chailly P, Bastenie PA. Coronary-artery disease in hypothyroidism. Observations in clinical myxoedema. *Lancet.* 1967;2:800-2. [PMID: 4167274]
36. Steinberg AD. Myxedema and coronary artery disease—a comparative autopsy study. *Ann Intern Med.* 1968;68:338-44. [PMID: 5713917]
37. Althaus BU, Staub JJ, Ryff-De Lèche A, Oberhänsli A, Stähelin HB. LDL/HDL-changes in subclinical hypothyroidism: possible risk factors for coronary heart disease. *Clin Endocrinol (Oxf).* 1988;28:157-63. [PMID: 3168304]
38. Kung AW, Pang RW, Janus ED. Elevated serum lipoprotein(a) in subclinical hypothyroidism. *Clin Endocrinol (Oxf).* 1995;43:445-9. [PMID: 7586619]
39. Müller B, Zulewski H, Huber P, Ratcliffe JG, Staub JJ. Impaired action of thyroid hormone associated with smoking in women with hypothyroidism. *N Engl J Med.* 1995;333:964-9. [PMID: 7666915]
40. Bauer DC, Ettinger B, Browner WS. Thyroid functions and serum lipids in older women: a population-based study. *Am J Med.* 1998;104:546-51. [PMID: 9674717]
41. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, et al. Lipid profiles and cardiovascular disease in the Whickham area with particular reference to thyroid failure. *Clin Endocrinol (Oxf).* 1977;7:495-508. [PMID: 598015]
42. Geul KW, van Sluisveld IL, Grobbee DE, Docter R, de Bruyn AM, Hooykaas H, et al. The importance of thyroid microsomal antibodies in the development of elevated serum TSH in middle-aged women: associations with serum lipids. *Clin Endocrinol (Oxf).* 1993;39:275-80. [PMID: 8222290]
43. Parle JV, Franklyn JA, Cross KW, Jones SR, Sheppard MC. Circulating lipids and minor abnormalities of thyroid function. *Clin Endocrinol (Oxf).* 1992;37:411-4. [PMID: 1486690]
44. Oettgen P, Ginsburg GS, Horowitz GL, Pasternak RC. Frequency of hypothyroidism in adults with serum total cholesterol levels > 200 mg/dl. *Am J Cardiol.* 1994;73:955-7. [PMID: 8184852]
45. Ball MJ, Griffiths D, Thorogood M. Asymptomatic hypothyroidism and hypercholesterolaemia. *J R Soc Med.* 1991;84:527-9. [PMID: 1941853]
46. Series JJ, Biggart EM, O'Reilly DS, Packard CJ, Shepherd J. Thyroid dysfunction and hypercholesterolaemia in the general population of Glasgow, Scotland. *Clin Chim Acta.* 1988;172:217-21. [PMID: 3370836]
47. Pirich C, Müllner M, Sinzinger H. Prevalence and relevance of thyroid dysfunction in 1922 cholesterol screening participants. *J Clin Epidemiol.* 2000;53:623-9. [PMID: 10880781]
48. Diekmann T, Demacker PN, Kastelein JJ, Stalenhoef AF, Wiersinga WM. Increased oxidizability of low-density lipoproteins in hypothyroidism. *J Clin Endocrinol Metab.* 1998;83:1752-5. [PMID: 9589687]
49. Kung AW, Pang RW, Janus ED. Elevated serum lipoprotein(a) in subclinical hypothyroidism. *Clin Endocrinol (Oxf).* 1995;43:445-9. [PMID: 7586619]
50. Morris MS, Bostom AG, Jacques PF, Selhub J, Rosenberg IH. Hyperhomocysteinemia and hypercholesterolemia associated with hypothyroidism in the third US National Health and Nutrition Examination Survey. *Atherosclerosis.* 2001;155:195-200. [PMID: 11223442]
51. Danese MD, Ladenson PW, Meinert CL, Powe NR. Clinical review 115: effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature. *J Clin Endocrinol Metab.* 2000;85:2993-3001. [PMID: 10999775]
52. Tzotzas T, Krassas GE, Konstantinidis T, Bougoulia M. Changes in lipoprotein(a) levels in overt and subclinical hypothyroidism before and during treatment. *Thyroid.* 2000;10:803-8. [PMID: 11041458]
53. Hussein WI, Green R, Jacobsen DW, Faiman C. Normalization of hyperhomocysteinemia with L-thyroxine in hypothyroidism. *Ann Intern Med.* 1999;131:348-51. [PMID: 10475887]
54. Tièche M, Lupi GA, Gutzwiller F, Grob PJ, Studer H, Bürgi H. Borderline low thyroid function and thyroid autoimmunity. Risk factors for coronary heart disease? *Br Heart J.* 1981;46:202-6. [PMID: 7272132]
55. Dean JW, Fowler PB. Exaggerated responsiveness to thyrotropin releasing hormone: a risk factor in women with coronary artery disease. *Br Med J (Clin Res Ed).* 1985;290:1555-61. [PMID: 3924164]
56. Heinonen OP, Gordin A, Aho K, Punsar S, Pyörälä K, Puro K. Symptomless autoimmune thyroiditis in coronary heart-disease. *Lancet.* 1972;1:785-6. [PMID: 4111258]
57. Miura S, Itaka M, Suzuki S, Fukasawa N, Kitahama S, Kawakami Y, et al. Decrease in serum levels of thyroid hormone in patients with coronary heart disease. *Endocr J.* 1996;43:657-63. [PMID: 9075605]
58. 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;132:270-8. [PMID: 10681281]
59. Perk M, O'Neill BJ. The effect of thyroid hormone therapy on angiographic coronary artery disease progression. *Can J Cardiol.* 1997;13:273-6. [PMID: 9117915]
60. Lekakis J, Papamichael C, Alevizaki M, Pipingos G, Marafelia P, Mantzos J, et al. Flow-mediated, endothelium-dependent vasodilation is impaired in subjects with hypothyroidism, borderline hypothyroidism, and high-normal serum thyrotropin (TSH) values. *Thyroid.* 1997;7:411-4. [PMID: 9226212]
61. Caraccio N, Viridis A, Diadoni N, Taddei S, Monzani F. Subclinical hypothyroid patients are characterized by endothelial dysfunction caused by an impairment in the L-arginine-nitric oxide pathway [Abstract]. 12th International Thyroid Congress. Kyoto 2000. *Endocr J.* 2000;47(Suppl):225.
62. Bastenie PA, Vanhaelst L, Golstein J, Smets P. Asymptomatic autoimmune thyroiditis and coronary heart-disease. Cross-sectional and prospective studies. *Lancet.* 1977;2:155-8. [PMID: 69779]
63. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The development of ischemic heart disease in relation to autoimmune thyroid disease in a 20-year follow-up study of an English community. *Thyroid.* 1996;6:155-60. [PMID: 8837320]
64. Bonow RO, Udelson JE. Left ventricular diastolic dysfunction as a cause of congestive heart failure. Mechanisms and management. *Ann Intern Med.* 1992;117:502-10. [PMID: 1503353]
65. Cuocolo A, Sax FL, Brush JE, Maron BJ, Bacharach SL, Bonow RO. Left ventricular hypertrophy and impaired diastolic filling in essential hypertension. Diastolic mechanisms for systolic dysfunction during exercise. *Circulation.* 1990;81:978-86. [PMID: 2137735]
66. Marqusee E, Haden ST, Utiger RD. Subclinical thyrotoxicosis. *Endocrinol Metab Clin North Am.* 1998;27:37-49. [PMID: 9534026]
67. Hennessey JV, Evald JE, Tseng YC, Burman KD, Wartofsky L. L-thyroxine dosage: a reevaluation of therapy with contemporary preparations. *Ann Intern Med.* 1986;105:11-5. [PMID: 3087253]
68. Ross DS, Daniels GH, Gouveia D. The use and limitations of a chemilu-

- minescent thyrotropin assay as a single thyroid function test in an out-patient endocrine clinic. *J Clin Endocrinol Metab.* 1990;71:764-9. [PMID: 2394778]
69. Belfiore A, Sava L, Runello F, Tomaselli L, Vigneri R. Solitary autonomously functioning thyroid nodules and iodine deficiency. *J Clin Endocrinol Metab.* 1983;56:283-7. [PMID: 6822638]
70. Aghini-Lombardi F, Antonangeli L, Martino E, Vitti P, Maccherini D, Leoli F, et al. The spectrum of thyroid disorders in an iodine-deficient community: the Pescopagano survey. *J Clin Endocrinol Metab.* 1999;84:561-6. [PMID: 10022416]
71. Hamburger JI. Evolution of toxicity in solitary nontoxic autonomously functioning thyroid nodules. *J Clin Endocrinol Metab.* 1980;50:1089-93. [PMID: 7372787]
72. Sandrock D, Olbricht T, Emrich D, Benker G, Reinwein D. Long-term follow-up in patients with autonomous thyroid adenoma. *Acta Endocrinol (Copenh).* 1993;128:51-5. [PMID: 8447194]
73. Elte JW, Bussemaker JK, Haak A. The natural history of euthyroid multinodular goitre. *Postgrad Med J.* 1990;66:186-90. [PMID: 2114018]
74. Dunn JT, Semigran MJ, Delange F. The prevention and management of iodine-induced hyperthyroidism and its cardiac features. *Thyroid.* 1998;8:101-6. [PMID: 9492159]
75. Davies PH, Franklyn JA, Daykin J, Sheppard MC. The significance of TSH values measured in a sensitive assay in the follow-up of hyperthyroid patients treated with radioiodine. *J Clin Endocrinol Metab.* 1992;74:1189-94. [PMID: 1569166]
76. Stanbury JB, Ermans AE, Bourdoux P, Todd C, Oken E, Tonglet R, et al. Iodine-induced hyperthyroidism: occurrence and epidemiology. *Thyroid.* 1998;8:83-100. [PMID: 9492158]
77. Bourdoux PP, Ermans AM, Mukalay wa Mukalay A, Filetti S, Vigneri R. Iodine-induced thyrotoxicosis in Kivu, Zaire [Letter]. *Lancet.* 1996;347:552-3. [PMID: 8596306]
78. Stott DJ, McLellan AR, Finlayson J, Chu P, Alexander WD. Elderly patients with suppressed serum TSH but normal free thyroid hormone levels usually have mild thyroid overactivity and are at increased risk of developing overt hyperthyroidism. *Q J Med.* 1991;78:77-84. [PMID: 1670067]
79. Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC. Prevalence and follow-up of abnormal thyrotropin (TSH) concentrations in the elderly in the United Kingdom. *Clin Endocrinol (Oxf).* 1991;34:77-83. [PMID: 2004476]
80. Sawin CT, Geller A, Kaplan MM, Bacharach P, Wilson PW, Hershman JM. Low serum thyrotropin (thyroid-stimulating hormone) in older persons without hyperthyroidism. *Arch Intern Med.* 1991;151:165-8. [PMID: 1985591]
81. Sundbeck G, Jagenburg R, Johansson PM, Edén S, Lindstedt G. Clinical significance of low serum thyrotropin concentration by chemiluminometric assay in 85-year-old women and men. *Arch Intern Med.* 1991;151:549-56. [PMID: 1900411]
82. Tenerz A, Forberg R, Jansson R. Is a more active attitude warranted in patients with subclinical thyrotoxicosis? *J Intern Med.* 1990;228:229-33. [PMID: 2401873]
83. Bell GM, Sawers JS, Forfar JC, Doig A, Toft AD. The effect of minor increments in plasma thyroxine on heart rate and urinary sodium excretion. *Clin Endocrinol (Oxf).* 1983;18:511-6. [PMID: 6409460]
84. Jennings PE, O'Malley BP, Griffin KE, Northover B, Rosenthal FD. Relevance of increased serum thyroxine concentrations associated with normal serum triiodothyronine values in hypothyroid patients receiving thyroxine: a case for "tissue thyrotoxicosis." *Br Med J (Clin Res Ed).* 1984;289:1645-7. [PMID: 6439358]
85. Boutin JM, Matte R, D'Amour P, Gilbert F, Havrankova J, Bélanger R, et al. Characteristics of patients with normal T3 and T4 and a low TSH response to TRH. *Clin Endocrinol (Oxf).* 1986;25:579-88. [PMID: 2887310]
86. Banovac K, Papic M, Bilsker MS, Zakarija M, McKenzie JM. Evidence of hyperthyroidism in apparently euthyroid patients treated with levo-thyroxine. *Arch Intern Med.* 1989;149:809-12. [PMID: 2495780]
87. Grund FM, Niewoehner CB. Hyperthyroxinemia in patients receiving thyroid replacement therapy. *Arch Intern Med.* 1989;149:921-4. [PMID: 2705841]
88. Biondi B, Fazio S, Carella C, Amato G, Cittadini A, Lupoli G, et al. Cardiac effects of long term thyrotropin-suppressive therapy with levo-thyroxine. *J Clin Endocrinol Metab.* 1993;77:334-8. [PMID: 8345037]
89. Fazio S, Biondi B, Carella C, Sabatini D, Cittadini A, Panza N, et al. Diastolic dysfunction in patients on thyroid-stimulating hormone suppressive therapy with levo-thyroxine: beneficial effect of beta-blockade. *J Clin Endocrinol Metab.* 1995;80:2222-6. [PMID: 7608283]
90. Biondi B, Fazio S, Cuocolo A, Sabatini D, Nicolai E, Lombardi G, et al. Impaired cardiac reserve and exercise capacity in patients receiving long-term thyrotropin suppressive therapy with levo-thyroxine. *J Clin Endocrinol Metab.* 1996;81:4224-8. [PMID: 8954019]
91. Ching GW, Franklyn JA, Stallard TJ, Daykin J, Sheppard MC, Gammage MD. Cardiac hypertrophy as a result of long-term thyroxine therapy and thyrotoxicosis. *Heart.* 1996;75:363-8. [PMID: 8705762]
92. Shapiro LE, Sievert R, Ong L, Ocampo EL, Chance RA, Lee M, et al. Minimal cardiac effects in asymptomatic athyreotic patients chronically treated with thyrotropin-suppressive doses of L-thyroxine. *J Clin Endocrinol Metab.* 1997;82:2592-5. [PMID: 9253339]
93. Biondi B, Fazio S, Palmieri EA, Tremalaterra R, Angellotti G, Bonè F, et al. [Effects of chronic subclinical hyperthyroidism from levo-thyroxine on cardiac morphology and function]. *Cardiologia.* 1999;44:443-9. [PMID: 10389349]
94. Mercurio G, Panzuto MG, Bina A, Leo M, Cabula R, Petrini L, et al. Cardiac function, physical exercise capacity, and quality of life during long-term thyrotropin-suppressive therapy with levo-thyroxine: effect of individual dose tailoring. *J Clin Endocrinol Metab.* 2000;85:159-64. [PMID: 10634380]
95. Biondi B, Palmieri EA, Fazio S, Cosco C, Nocera M, Saccà L, et al. Endogenous subclinical hyperthyroidism affects quality of life and cardiac morphology and function in young and middle-aged patients. *J Clin Endocrinol Metab.* 2000;85:4701-5. [PMID: 11134131]
96. Sgarbi JA, Villaca F, Scanduzzi S, Motta K, Villar H, Tsuj H, et al. Improvement of cardiac effects of endogenous subclinical hyperthyroidism with methimazol treatment [Abstract]. 12th International Thyroid Congress. Kyoto 2000. *Endocr J.* 2000;47(Suppl):179.
97. Biondi B, Fazio S, Carella C, Sabatini D, Amato G, Cittadini A, et al. Control of adrenergic overactivity by beta-blockade improves the quality of life in patients receiving long term suppressive therapy with levo-thyroxine. *J Clin Endocrinol Metab.* 1994;78:1028-33. [PMID: 8175955]
98. Levey GS, Klein I. Catecholamine-thyroid hormone interactions and the cardiovascular manifestations of hyperthyroidism. *Am J Med.* 1990;88:642-6. [PMID: 2189309]
99. Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med.* 1994;331:1249-52. [PMID: 7935681]
100. Rohrer D, Dillmann WH. Thyroid hormone markedly increases the mRNA coding for sarcoplasmic reticulum Ca²⁺ -ATPase in the rat heart. *J Biol Chem.* 1988;263:6941-4. [PMID: 2966798]
101. Mintz G, Pizzarello R, Klein I. Enhanced left ventricular diastolic function in hyperthyroidism: noninvasive assessment and response to treatment. *J Clin Endocrinol Metab.* 1991;73:146-50. [PMID: 2045465]
102. Leese GP, Jung RT, Guthrie C, Waugh N, Browning MC. Morbidity in patients on L-thyroxine: a comparison of those with a normal TSH to those with a suppressed TSH. *Clin Endocrinol (Oxf).* 1992;37:500-3. [PMID: 1286519]
103. Parle JV, Maisonneuve P, Sheppard MC, Boyle P, Franklyn JA. Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. *Lancet.* 2001;358:861-5. [PMID: 11567699]
104. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med.* 1990;322:1561-6. [PMID: 2139921]
105. Padayatty S. Concerning minimal cardiac effects in asymptomatic athyreotic patients treated with thyrotropin-suppressive doses of L-thyroxine [Letter]. *J Clin Endocrinol Metab.* 1998;83:2607-8. [PMID: 9661656]
106. Haider AW, Larson MG, Benjamin EJ, Levy D. Increased left ventricular mass and hypertrophy are associated with increased risk for sudden death. *J Am Coll Cardiol.* 1998;32:1454-9. [PMID: 9809962]
107. Greenland P, Daviglus ML, Dyer AR, Liu K, Huang CF, Goldberger JJ, et al. Resting heart rate is a risk factor for cardiovascular and noncardiovascular mortality: the Chicago Heart Association Detection Project in Industry. *Am J Epidemiol.* 1999;149:853-62. [PMID: 10221322]
108. Mandel SJ, Brent GA, Larsen PR. Levothyroxine therapy in patients with thyroid disease. *Ann Intern Med.* 1993;119:492-502. [PMID: 8357116]

109. **Toft AD.** Thyroxine therapy. *N Engl J Med.* 1994;331:174-80. [PMID: 8008032]
110. **Surks MI, Ocampo E.** Subclinical thyroid disease. *Am J Med.* 1996;100:217-23. [PMID: 8629658]
111. **Helfand M, Redfern CC.** Clinical guideline, part 2. Screening for thyroid disease: an update. American College of Physicians. *Ann Intern Med.* 1998;129:144-58. [PMID: 9669977]
112. **Cooper DS.** Subclinical thyroid disease: a clinician's perspective [Editorial]. *Ann Intern Med.* 1998;129:135-8. [PMID: 9669974]
113. **Adlin V.** Subclinical hypothyroidism: deciding when to treat. *Am Fam Physician.* 1998;57:776-80. [PMID: 9491000]
114. **Ayala AR, Danese MD, Ladenson PW.** When to treat mild hypothyroidism. *Endocrinol Metab Clin North Am.* 2000;29:399-415. [PMID: 10874537]
115. **Cooper DS.** Clinical practice. Subclinical hypothyroidism. *N Engl J Med.* 2001;345:260-5. [PMID: 11474665]
116. **Toft AD.** Clinical practice. Subclinical hyperthyroidism. *N Engl J Med.* 2001;345:512-6. [PMID: 11519506]
117. **Fatourechchi V.** Adverse effects of subclinical hyperthyroidism. *Lancet.* 2001;358:856-7. [PMID: 11567696]
118. **Peters A, Ehlers M, Blank B, Exler D, Falk C, Kohlmann T, et al.** Excess triiodothyronine as a risk factor of coronary events. *Arch Intern Med.* 2000;160:1993-9. [PMID: 10888973]
119. **Cooper DS, Specker B, Ho M, Sperling M, Ladenson PW, Ross DS, et al.** Thyrotropin suppression and disease progression in patients with differentiated thyroid cancer: results from the National Thyroid Cancer Treatment Cooperative Registry. *Thyroid.* 1998;8:737-44. [PMID: 9777742]

Current Author Addresses: Drs. Biondi and Lombardi: Department of Clinical and Molecular Endocrinology and Oncology, University of Naples Federico II School of Medicine, 80131 Naples, Italy.

Drs. Palmieri and Fazio: Department of Clinical Medicine and Cardiovascular Sciences, University of Naples Federico II School of Medicine, 80131 Naples, Italy.