ORIGINAL INVESTIGATION

Association Between Increased Mortality and Mild Thyroid Dysfunction in Cardiac Patients

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Background: The effects of subclinical thyroid dysfunction on cardiac outcome are not well defined.

Methods: To assess the relationship between mild thyroid dysfunction and the incidence of death in cardiac patients, we evaluated 3121 cardiac patients. Cardiac and overall deaths were considered. Four groups were defined: euthyroidism, subclinical hypothyroidism (SCH), subclinical hyperthyroidism (SCT), and low triiodothyronine syndrome (low T_3).

Results: After mean follow-up of 32 months, there were 65 and 140 cardiac and overall deaths (3.4% and 7.3%), respectively, in euthyroidism, 15 and 27 (7.2% and 13.0%) in SCH, 8 and 9 (8.2% and 9.2%) in SCT, and 59 and 119 (6.5% and 13.1%) in low T_3. Survival rates for cardiac death were lower in SCH, SCT, and low T_3 than in euthyroidism (log-rank test; $\chi^2=19.46$; $P<.001$). Survival rates for overall death were lower in SCH and low T_3 than in euthyroidism (log-rank test; $\chi^2=26.67$; $P<.001$). After adjustment for several risk factors, hazard ratios (HRs) for cardiac death were higher in SCH (HR, 2.40; 95% confidence interval [CI], 1.36-4.21; $P=.02$), SCT (HR, 2.32; 95% CI, 1.11-4.85; $P=.02$), and low T_3 (HR, 1.63; 95% CI, 1.14-2.33; $P=.007$) than in euthyroidism; HRs for overall death were higher in SCH (HR, 2.01; 95% CI, 1.33-3.04; $P<.001$) and low T_3 (HR, 1.57; 95% CI, 1.22-2.01; $P<.001$) but not in SCT.

Conclusion: A mildly altered thyroid status is associated with an increased risk of mortality in patients with cardiac disease.

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CARDIOVASCULAR DISEASE IS the foremost cause of premature death in men and women in Western countries; these diseases also have a major impact on health care and can be a great economic burden, being the most common cause of hospital admission.[1] At the same time, the death rate for cardiovascular disease has been declining in the past few years. Strategies for reducing risk factors have unequivocally played an important role in reducing mortality and morbidity rates, especially in people with recognized cardiovascular disease.[1,2] Attention has particularly focused on discovering new, potentially important risk factors. In population-based studies,[3-9] the effects of mild thyroid dysfunction on cardiovascular outcome are increasingly emerging but are not yet well defined. A low triiodothyronine syndrome (low T_3) has been related to a poor outcome in different groups of cardiac patients.[10-12] Data on the prognostic impact of mild thyroid dysfunction in patients with cardiac disease are, however, limited and somewhat conflicting.[13-15] In this context, no increase in cardiovascular death has been reported by Rodondi et al[13] and Cappola et al.[14] An association between increased reverse triiodothyronine levels and mortality was found, on the contrary, after acute myocardial infarction.[15] This large prospective study tests the hypothesis that a mildly altered thyroid status is associated with an increased risk of mortality in patients with diagnosed ischemic or nonischemic cardiac disease.

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METHODS

STUDY POPULATION

A total of 4368 patients were admitted to the Cardiology Department of the National Research Council Institute of Clinical Physiology in Pisa, Italy, between January 1, 2000, and January 1, 2006. The study's exclusion criteria were as follows: (1) emergency admissions for acute coronary syndrome or pulmonary edema (563 patients); (2) severely ill patients, that is, with clinical evidence of sepsis or cachexia or the concomitant presence of any predominant severe systemic disease (50 patients); (3) in-hospital deaths (42 patients); (4) primary overt hypothyroidism (thyrotropin level >10 mIU/L and free thyroxine level <0.71 ng/dL [to convert to picomoles per liter, multiply by 12.871])

Table 1. Baseline Characteristics of the Study Population by Thyroid Status[a]

Characteristic	Euthyroidism (n = 1905)	Subclinical Hypothyroidism (n = 208)	Subclinical Hyperthyroidism (n = 98)	Low T_3 (n = 910)	Total (N = 3121)
Age, y	59.9 (59.3-60.4)	60.9 (59.1-62.7)	60.5 (58.6-62.4)	63.8 (63.1-64.6)[b]	61.1 (60.7-61.5)
Female sex, No. (%)	548 (28.8)	89 (42.8)	45 (45.9)[b]	336 (36.9)	**1018** (32.6)
Hypertension, No. (%)[c]	972 (51.0)	109 (52.4)	55 (56.1)	451 (49.6)	**1587** (50.8)
Smoke, No. (%)	857 (45.0)	87 (41.8)	48 (49.0)	308 (33.8)	**1300** (41.7)
Diabetes mellitus, No. (%)	363 (19.1)	51 (24.5)	21 (21.4)	206 (22.6)	**641** (20.5)
History of coronary artery disease, No. (%)	869 (45.6)	89 (42.8)	39 (39.8)	378 (41.5)	**1375** (44.1)
NYHA functional class III-IV, No. (%)	189 (9.9)	32 (15.4)[b]	5 (5.1)	119 (13.1)	**345** (11.1)
Obesity, No. (%)	1076 (56.5)	120 (57.7)	61 (62.2)	507 (55.7)[b]	**1764** (56.5)
Thyrotropin, mIU/L	1.67 (1.73-1.71)	6.7 (6.01-7.44)	0.15 (0.13-0.17)	1.66 (1.59-1.73)	1.96 (1.88-2.03)
Free triiodothyronine, pg/dL	252 (249-255)	231 (226-237)	266 (255-273)	183 (181-186)	231 (229-233)
Free thyroxine, ng/dL	1.17 (1.16-1.18)	1.10 (1.05-1.14)	1.39 (1.34-1.45)	1.23 (1.20-1.26)	1.19 (1.17-1.20)
Total cholesterol, mg/dL	190 (188-192)	194 (188-200)	185 (175-194)	182 (179-185	188 (186-190)
LDL cholesterol, mg/dL	121 (119-123)	122 (117-127)	116 (108-125)	116 (113-118)[b]	120 (118-121)
HDL cholesterol, mg/dL	43.8 (43.2-44.4)	47.4 (45.6-49.2)[b]	43 (40.1-45.9)	42.5 (41.6-43.4)	43.8 (43.4-44.3)
Triglycerides, mg/dL	126 (123-130)	120 (109-130)[b]	129 (106-152)	118 (111-124)[b]	124 (121-127)
Creatinine, mg/dL	1.07 (1.04-1.09)	1.10 (1.00-1.21)	1.08 (0.98-1.19)	1.14 (1.11-1.20)[b]	1.10 (1.07-1.11)
C-reactive protein, mg/L	0.90 (0.81-0.99)	0.98 (0.73-1.23)	0.89 (0.57-1.20)	1.52 (1.24-1.81)[b]	1.08 (0.98-1.18)
Ejection fraction, %	53 (52.7-53.7)	50 (48-52)	52 (50-54)	51 (50-52)	52 (52-53)
Ischemic heart disease, No. (%)	998 (52.4)	104 (50.0)	46 (46.9)	531 (58.4)[b]	**1679** (53.8)
Nonischemic dilated cardiomyopathy, No. (%)	229 (12.0)[b]	42 (20.2)	17 (17.3)	121 (13.3)	**409** (13.1)
Arrhythmias, No. (%)	513 (26.9)[b]	72 (34.6)	32 (32.7)	268 (29.5)	**885** (28.4)
Valvular heart disease, No. (%)	174 (9.1)[b]	34 (16.3)	9 (9.2)	113 (12.4)	**330** (10.6)
Others, No. (%)[d]	37 (1.9)	7 (3.4)	1 (1.0)	29 (3.2)	**74** (2.4)
ACE inhibitors, No. (%)	698 (36.6)	77 (37.0)	39 (39.8)	362 (39.8)	**1176** (37.7)
β-Blockers, No. (%)	829 (43.5)	86 (41.3)	33 (33.7)	426 (46.8)	**1374** (44.0)
Nitrates, No. (%)	839 (44.0)	76 (36.5)	40 (40.8)	433 (47.6)[b]	**1388** (44.5)
Calcium antagonists, No. (%)	278 (14.6)	24 (11.5)	16 (16.3)	126 (13.8)	**444** (14.2)
Diuretics, No. (%)	491 (25.8)	73 (35.1)	37 (37.8)[b]	312 (34.3)	**913** (29.3)

Abbreviations: ACE, angiotensin-converting enzyme; HDL, high-density lipoprotein; LDL, low-density lipoprotein; low T_3, low triiodothyronine syndrome; NYHA, New York Heart Association.

SI conversion factors: To convert cholesterol (HDL, LDL, and total) to millimoles per liter, multiply by 0.0259; C-reactive protein to nanomoles per liter, multiply by 9.524; creatinine to micromoles per liter, multiply by 88.4; free thyroxine to picomoles per liter, multiply by 12.871; free triiodothyronine to picomoles per liter, multiply by 0.0154; triglycerides to millimoles per liter, multiply by 0.0113.

[a] See the "Definition of Thyroid Status" subsection of the "Methods" section for thyroid category definitions. Data are given as mean (95% confidence interval), except where noted otherwise.

[b] $P \leq .05$ by χ^2 test or t test.

[c] Blood pressure was measured after the patient was as relaxed as possible for several minutes, not talking, and seated comfortably. The reported value is the mean of 2 measures in 2 minutes.

[d] Hypertrophic cardiomyopathy, myocarditis, pericarditis, and endocarditis.

(15 patients); (5) primary overt hyperthyroidism (free triiodothyronine level >420 pg/dL [to convert to picomoles per liter, multiply by 0.0154] or free thyroxine level >1.85 ng/dL, with an undetectable thyrotropin level) (31 patients); (6) concomitant treatment with synthetic thyroid hormones, antithyroid drugs, corticosteroids, dopamine, dobutamine, or amiodarone (262 patients); and (7) atypical thyroid status, in which the thyroid hormone pattern could not be clustered in any defined group after the first hormone evaluation (97 patients) or the thyroid hormone pattern modified at repeated thyroid function testing (187 patients) (see "Definition of Thyroid Status" subsection herein). Thus, the final population consisted of 3121 consecutive patients (32.6% female; mean age, 61 years) routinely admitted for evaluation and diagnosed as having heart disease. During hospitalization all the patients underwent conventional noninvasive and, if necessary, invasive diagnostic procedures for the characterization of heart disease and related risk factors according to international guidelines. Baseline data, including blood pressure and blood determinations, were collected at the time of hospitalization (**Table 1**). The diagnosis of cardiac disease was based on data collected during hospitalization; previous cardiac diseases were defined according to patients' documentation of their cardiac history. Blood pressure was measured twice at admittance according to a standardized protocol; Table 1 gives the mean value of the 2 measures. Hypertension was defined as systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg. Diabetes mellitus was defined as a fasting glucose level greater than 126 mg/dL (to convert to millimoles per liter, multiply by 0.0555) or the use of insulin or an oral hypoglycemic drug. Weight and height were measured in all the patients; obesity was defined as a body mass index (calculated as weight in kilograms divided by height in meters squared) greater than 30. The National Council of Research, Clinical Physiology Institute ethics review committee approved the study, and the investigation conformed to the principles of the Declaration of Helsinki.

THYROID HORMONE SAMPLING

The thyroid function profile was assessed in all the patients within 2 to 5 days of hospital admission.[11,12] After rapid centrifugation of a blood sample collected at 7 AM from an antecubital vein, free triiodothyronine, free thyroxine, and thyrotropin levels were measured immediately after the blood sample

Table 2. Survival Data for Cardiac and Overall Deaths by Thyroid Status[a]

Variable	Euthyroidism (n = 1905)	Subclinical Hypothyroidism (n = 208)	Subclinical Hyperthyroidism (n = 98)	Low T_3 (n = 910)	χ^2 Value[b]	*P* Value
Cardiac death						
Death by AMI, No.	36	9	5	37		
Sudden death, No.	12	3	2	18		
Other causes of death, No.	17	3	1	4	19.46	<.001
Subtotal, No. (%)	**65** (**3.4**)	**15** (**7.2**)	**8** (**8.2**)	**59** (**6.5**)		
Survival time, mean (95% CI), d	2278 (2254-2302)	1973 (1889-2058)	1940 (1873-2042)	2202 (2160-2243)		
Overall death						
Events, No. (%)	140 (7.3)	27 (13.0)	9 (9.2)	119 (13.1)	26.67	<.001
Survival time, mean (95% CI), d	2167 (2130-2204)	1853 (1750-1955)	1923 (1817-2029)	2047 (1992-2102)		

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; low T_3, low triiodothyronine syndrome.
[a] See the "Definition of Thyroid Status" subsection of the "Methods" section for thyroid category definitions.
[b] Determined using the log-rank test.

was collected using a completely automated AIA 600 system (Tosho Corp, Tokyo, Japan). The reference intervals were as follows: free triiodothyronine, 210 to 420 pg/dL; free thyroxine, 0.71 to 1.85 ng/dL; and thyrotropin, 0.30 to 4.5 mIU/L.

DEFINITION OF THYROID STATUS

Patients were divided into 4 groups: (1) euthyroid, with all circulating levels of free triiodothyronine, free thyroxine, and thyrotropin in the reference range; (2) subclinical primary hypothyroidism (SCH), with thyrotropin levels between 4.5 and 10 mIU/L and free triiodothyronine and free thyroxine levels in the reference range; (3) subclinical primary hyperthyroidism (SCT), with thyrotropin levels less than 0.3 mIU/L and free triiodothyronine and free thyroxine levels in the reference range; and (4) low T_3, with free triiodothyronine levels below the lower limit of the reference interval and free thyroxine and thyrotropin levels in the reference range.[7] Because of the multidisciplinary nature of the Clinical Physiology Institute, a team of cardiologists, internal medicine specialists, and endocrinologists strictly collaborate, taking care of patients during hospitalization and follow-up. All patients with an altered thyroid profile were evaluated by an endocrinologist. According to the guidelines for the diagnosis and management of subclinical thyroid disease, to exclude transient forms of thyroid dysfunction, thyroid function tests were repeated within 2 to 12 weeks.[7,16,17] The main criteria to determine the timing of repeated testing were (1) recovery of good general clinical conditions and (2) stable or normalized values of the main biohumoral/instrumental variables (in particular, blood cell count, electrolytes, indexes of renal and liver function, indexes of phlogosis, electrocardiogram, echocardiogram, and chest radiograph). To define the nature of thyroid disease, patients also underwent, when recommended for diagnostic purposes, ultrasound evaluation, thyroid scintigraphy, and thyroid autoantibody determination. All the initial and confirmatory thyroid testing data were available to the endocrinologists examining the patients and to the cardiologists caring for the patients at the time of hospitalization. Because the benefits of treatment have not yet been established for patients with subclinical thyroid dysfunction,[7,16,17] treatment was not recommended at the time of patient enrollment.

FOLLOW-UP

Follow-up started the day of thyroid hormone evaluation (mean duration, 32 months). Follow-up data were obtained semiannually from at least 1 of the following 4 sources: patient hospital records, the patient's physician, patient telephone interviews by trained personnel, and periodic examination of the patient in the outpatient setting.[11] Follow-up was censored at initiation of therapy with synthetic thyroid hormones or antithyroid drugs during follow-up.

The events considered were cardiac and overall deaths. Information about deaths was obtained from death certificates competed by a medical officer in 137 cases (90.1%) and by medical or autopsy reports in 15 cases (9.9%). Cardiac death required documentation of (1) arrhythmia or cardiac arrest, (2) death due to progressive heart failure, or (3) myocardial infarction in the absence of a precipitating factor. Sudden unexpected death was classified as a cardiac death when it occurred outside the hospital and was not followed by an autopsy. Overall deaths were considered all deaths from any natural cause. Deaths caused by accidents were excluded (follow-up censored at the time of death).

STATISTICAL ANALYSIS

Parametric and nonparametric data are given as mean±SD and percentage. Groups were compared using the χ^2 test (Yates correction) and the unpaired *t* test. All the tests were 2-sided, and $P<.05$ was considered statistically significant. Univariate Cox regression analysis was used to determine which variables (age, sex, New York Heart Association functional class, ejection fraction, ischemic heart disease, nonischemic dilated cardiomyopathy, arrhythmias, valvular heart disease, angiotensin-converting enzyme inhibitors, β-blockers, nitrates, calcium antagonists, diuretics, and levels of thyrotropin, free triiodothyronine, free thyroxine, total cholesterol, high- and low-density lipoprotein cholesterol, triglycerides, creatinine, and C-reactive protein) might have predicted cardiac-related death and overall death. To adjust for several risk factors, multivariate Cox analysis was performed, with all the variables found to be significant in univariate analysis entered in a single step (age, sex, ischemic and nonischemic cardiac disease, and thyroid status). During follow-up the risks of cardiac-related death and all causes of death were evaluated using Cox proportional hazards and the Kaplan-Meier model. The hazard ratios (HRs) related to the different thyroid statuses of patients were assessed, controlling for other prognostic risk factors. The Kaplan-Meier life-table method, estimating cardiac-related death and overall death, was used to summarize the follow-up experience in the patient population. Differences in survival curves were tested using the log-rank test (Mantel-Cox), adjusting for prognostic risk factors; $P<.05$ was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS

After initial hormone evaluation 3308 patients were divided into the following groups: euthyroid, 1905 patients; SCH, 218 patients; SCT, 138 patients; and low T_3, 1047 patients. Repeated thyroid function tests (mean time from first evaluation, 34 days; 95% confidence interval, 22.8-42.2 days) gave confirmatory results in 1905 euthyroid patients (100.0%), 208 SCH patients (95.4%), 98 SCT patients (71.0%), and 910 low T_3 patients (86.9%); the remaining patients (n=187) were excluded from the study. Clinical and hormonal data at baseline are reported in Table 1.

The cause of the SCH was atrophic thyroiditis in 81 patients (38.9%), Hashimoto thyroiditis in 74 (35.6%), and iatrogenic chronic hypothyroidism (ie, after partial thyroidectomy or after sodium iodide I 131 therapy) in 53 (25.5%). The cause of the SCT was multinodular goiter in 79 patients (80.6%), Graves disease in 15 (15.3%), and thyroid adenoma in 4 (4.1%).

CARDIAC AND OVERALL MORTALITY BY THYROID STATUS

There were 65 cardiac deaths in the euthyroid group, 15 in the SCH group, 8 in the SCT group, and 59 in the low T_3 group; the distribution of specific causes of cardiac death did not differ in the 4 groups (**Table 2**). There were 140 overall deaths in the euthyroid group, 27 in the SCH group, 9 in the SCT group, and 119 in the low T_3 group (Table 2). Regarding cardiac death, Kaplan-Meier mean survival time was significantly longer for the euthyroid group than for the other 3 groups (log-rank test; $\chi^2=19.46$; $P<.001$). Mean survival time was significantly shorter in SCH and low T_3 than in euthyroidism (log-rank test; $\chi^2=26.67$; $P<.001$) (Table 2 and the **Figure**). When the relationship between thyroid status and cardiac and overall deaths was assessed using Cox proportional hazards regression and modeling strategies in adjusted analyses, the HR of cardiac death was significantly higher in the last 3 groups than in the euthyroid group (**Table 3**). Compared with euthyroidism, the HR of overall death was significantly higher in SCH and low T_3 but not in SCT.

When patients were subdivided according to ischemic (n=1679) and nonischemic (n=1442) heart disease, the HR for cardiac death in patients with ischemic heart disease was significantly higher in SCT, SCH, and low T_3 than in euthyroidism (**Table 4**).

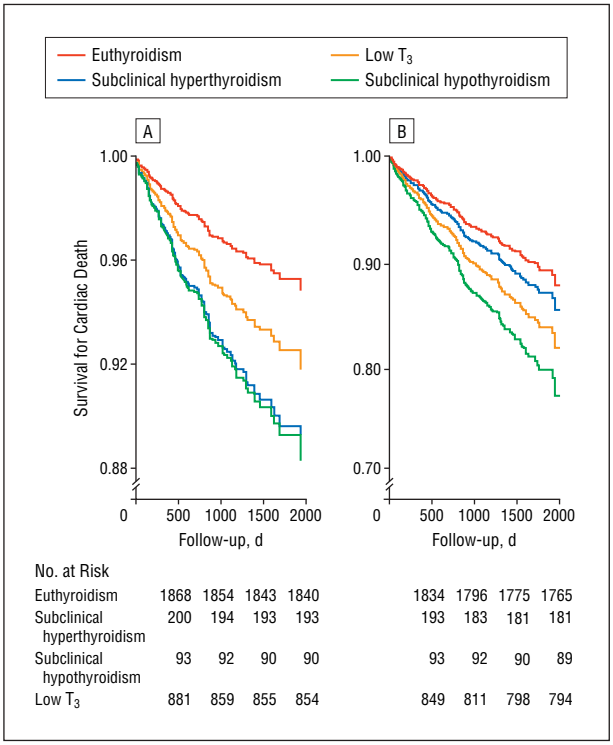

Figure. Kaplan-Meier survival curves for cardiac death (A) and overall death (B) by thyroid status. For cardiac death, $P<.001$ for euthyroidism vs the other 3 groups. For overall death, $P<.001$ for euthyroidism vs subclinical hypothyroidism and low triiodothyronine syndrome (low T_3).

COMMENT

The major finding of this large prospective observational study was that the concomitant presence of an unknown mild thyroid dysfunction is linked to an increased risk of mortality in patients with cardiac disease. Moreover, analysis of subgroups of patients (ie, ischemic and nonischemic patients) showed that mild thyroid dysfunction increased the risk of death particularly in ischemic heart disease. These results have been reached in a large population of patients with clinically stable cardiac disease. In this study the prevalence of SCH (6.6%), SCT (3.1%), and low T_3 (29.2%) was in close agreement with that reported in the literature regarding the general population without known thyroid disease,[7,11,13] thus confirming the suitability of the criteria used and the classification of thyroid status according to guidelines.[7] At the same time, note that the present data were obtained in a cohort of mainly male patients. Thus, because subclinical thyroid disease affects mostly women, we have to be very careful in giving direct applicability of the present results. Altogether, the results of this observational prospective study open the way to interesting pathophysiologic interpretations. The observed negative prognostic impact of any form of mild thyroid dysfunction in cardiac patients reinforces the hypothesis that a normal thyroid status is essential for maintaining systemic and cardiovascular homeostasis[5,6]; when a normal thyroid status is persistently lost, increased whole-body and cardiovascular vulnerability is observed.

MILD HYPOTHYROIDISM

In this study the Kaplan-Meier curves showed a statistically significant increase in the incidence of cardiac and overall deaths in patients with SCH compared with euthyroid patients. This finding is further reinforced at HR analysis, which showed that SCH is an independent predictor of death. Several pathophysiologic studies[18,19] have shown the presence of cardiovascular abnormali-

Table 3. Hazard Ratios for Cardiac and Overall Deaths by Thyroid Status[a]

Variable	Euthyroidism (n = 1905)	Subclinical Hypothyroidism (n = 208)	Subclinical Hyperthyroidism (n = 98)	Low T_3 (n = 910)
Cardiac deaths, No. (n = 147)	65	15	8	59
Hazard ratio (95% CI)	1 [Reference]	2.40 (1.36-4.21)	2.32 (1.11-4.85)	1.63 (1.14-2.33)
P value[b]		.02	.02	.007
Overall deaths, No. (n = 295)	140	27	9	119
Hazard ratio (95% CI)	1 [Reference]	2.01 (1.33-3.04)	1.22 (0.62-2.40)	1.57 (1.22-2.01)
P value		<.001	.56	<.001

Abbreviations: CI, confidence interval; low T_3, low triiodothyronine syndrome.
[a]See the "Definition of Thyroid Status" subsection of the "Methods" section for thyroid category definitions. Factors included in the multivariate model were age, sex, ischemic and nonischemic heart disease, and levels of thyrotropin, free thyroxine, and free triiodothyronine.
[b]Compared with euthyroidism.

Table 4. Hazard Ratios[a] for Cardiac Death by Thyroid Status[b] in Ischemic and Nonischemic Heart Disease

Variable	Euthyroidism (n = 1905)	Subclinical Hypothyroidism (n = 208)	Subclinical Hyperthyroidism (n = 98)	Low T_3 (n = 910)
Ischemic heart disease				
Patients, No.	999	101	46	565
Cardiac deaths, No.	43	12	7	9
Hazard ratio (95% CI)	1 [Reference]	3.1 (1.6-5.9)	3.5 (1.2-7.9)	1.6 (1.1-2.4)
P value[c]	. . .	.001	.002	.05
Nonischemic heart disease				
Patients, No.	906	107	52	345
Cardiac deaths, No.	22	3	1	20
Hazard ratio (95% CI)	1 [Reference]	1.2 (0.4-4.0)	0.6 (0.1-4.8)	1.8 (1.0-3.4)
P value[c]	. . .	.76[c]	.66	.05

Abbreviations: CI, confidence interval; low T_3, low triiodothyronine syndrome.
[a]Hazard ratios are corrected for age and sex.
[b]See the "Definition of Thyroid Status" subsection of the "Methods" section for thyroid category definitions.
[c]Compared with euthyroidism.

ties in patients with SCH. Moreover, some population-based studies[9,20,21] provided evidence that SCH affects serum cholesterol levels and increases atherosclerotic processes. Whether SCH per se contributes to worsening cardiovascular outcome is still a debated issue. In particular, 2 unresolved questions are whether SCH increases the risk of cardiovascular disease in the general population and whether it has a negative prognostic impact in cardiac patients. Only a few health survey population-based studies have attempted to answer the first question, and results are somewhat contradictory. Indeed, SCH was found to be associated with increased risk of myocardial infarction in elderly women,[15] increased overall death in men,[22] increased risk of heart failure in older adults,[23] and more cardiovascular events.[24] The negative prognostic impact of SCH has also been shown in a recent meta-analysis.[13] In contrast to the present results, Rodondi et al[23] and Cappola et al[14] did not find any association between SCH and cardiac mortality. One of the main differences with these studies was that whereas the present findings were obtained in a population of cardiac patients with a mean age of 61 years, their data were obtained in a population-based cohort of elderly (>65 years) people. Furthermore, in the present study the definition of groups as SCH, SCT, low T_3, and euthyroid was based on simultaneous measurement of free triiodothyronine, free thyroxine, and thyrotropin levels; this is at variance with all the previously mentioned studies, in which thyrotropin and, when available, free thyroxine were used for definition of the thyroid status. In the absence of triiodothyronine data, patients with low T_3 could have been included in the euthyroid group; this inclusion might have affected the cardiac end points owing to the strong negative prognostic impact of low T_3. The lack of triiodothyronine data would have been particularly relevant in studies in which elderly patients were enrolled[14] and in whom an altered thyroid hormone peripheral metabolism can be a common feature.

MILD HYPERTHYROIDISM

The main finding of this study was that although mild hyperthyroidism has no impact on overall mortality, it represents an independent predictor of cardiac death because the survival rate in SCT is significantly lower than that in euthyroidism. The few studies[14,24,25] that have attempted to assess the effects of SCT on cardiac outcome provided somewhat contrasting results. The present data are not comparable with those of previous studies for 2 main reasons: (1) as already observed for mild hypothyroidism, the cited studies were population-

based studies only, where individuals were free of any recognized cardiac disease,[14,24,25] and (2) the small number of individuals with mild hyperthyroidism enrolled in previous studies may have limited their ability to detect the effect of SCT on cardiovascular outcome.[14,25] In the present study the SCT prevalence (3.1%) was smaller than that of SCH (6.6%), as expected[7]; a lower power in these data are, however, unlikely because this study included almost 2 times more patients with SCT, with more cardiac deaths than each of the 2 cited population-based studies.[14,25]

From a pathophysiologic point of view, the present observation of a significant increase in cardiac mortality in cardiac patients with SCT should not be considered a surprising finding; SCT has relevant unfavorable effects on cardiac morphologic features and function, blood pressure, resting heart rate,[18] and the performance of left ventricular systolic function during exercise.

LOW TRIIODOTHYRONINE SYNDROME

It has already been reported that low T_3 is an independent predictor of death in cardiac patients.[10-12] The present results expand the previous findings and provide additional evidence regarding the association between low T_3 and mortality in cardiac patients; this was possible because of the large cohort of enrolled patients with low T_3, the number of registered events, and the length of follow-up of the present study. Overall, the biologically active thyroid hormone triiodothyronine is a critical determinant of cardiac function.[5,6] For this reason the progressive decrease in triiodothyronine levels, as observed in low T_3, may be part of the pathologic processes leading to a progressive disturbance of the cardiovascular system. Data in favor of this interpretation have been emerging in recent years; on the contrary, the alternative hypothesis of an adaptive and protective effect of decreased triiodothyronine levels, at least in cardiac patients, has become questionable.[26] Another possible interpretation is that low T_3 is a marker of poor health that is not causally related to cardiovascular disease. Indeed, cardiac and noncardiac deaths are similarly increased in patients with low T_3.

LIMITATIONS

The major limitation of the present study is the lack of information about follow-up thyroid function tests. However, the use of thyroid function tests obtained at a single point in time is a limitation of all major published studies examining the relationship between endogenous thyroid dysfunction and cardiovascular disease.[11,12,14,15,20-25] Nevertheless, of all patients with mild hypothyroidism, only 2% to 5% per year will progress to overt hypothyroidism. At the same time, it is well known that few patients with serum thyrotropin levels between 0.1 and 0.45 mIU/L and less than 2% per year of those with levels less than 0.1 mIU/L progress to overt hyperthyroidism.[7] Other limitations are the lack of nonfatal cardiovascular events, possible misclassification of causes of death based on death certificates, and lack of analysis by thyrotropin levels because of the small number of events.

In summary, a clear association between an increased risk of death and the presence of mild thyroid dysfunction has been documented in a large cohort of cardiac patients. The potential clinical impact of thyroid dysfunction on cardiac patients is important if one considers the high incidence of a mildly altered thyroid hormone pattern in the cardiac population (38.9% of total), as observed in this study.

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Correction

Error in Acknowledgments. In the Original Investigation by Jha et al titled "Concentration and Quality of Hospitals That Care for Elderly Black Patients," published in the June 11, 2007, issue of the *Archives* (2007;167[11]:1177-1182), the Funding/Support information paragraph in the acknowledgments section was missing and should have read as follows: "**Funding/Support:** This study was supported by the Robert Wood Johnson Foundation, Princeton, New Jersey." The online version of this article was corrected on June 11, 2007.