

Thyroid Status, Cardiovascular Risk, and Mortality in Older Adults

Anne R. Cappola, MD, ScM

Linda P. Fried, MD, MPH

Alice M. Arnold, PhD

Mark D. Danese, PhD

Lewis H. Kuller, MD, DrPH

Gregory L. Burke, MD, MS

Russell P. Tracy, PhD

Paul W. Ladenson, MD

CARDIOVASCULAR DISEASES (CVDs) are the most common cause of mortality, primarily affecting older adults. Heart disease causes nearly 700 000 deaths annually in the United States.¹ Although established risk factors explain most cardiac risks,² significant attention has been focused on alternative biochemical markers to assist in identifying those at risk of a clinical cardiac event.³ Previous studies have suggested that abnormal levels of thyroid-stimulating hormone (TSH) may represent a novel cardiac risk factor.⁴⁻⁸

Thyroid hormone excess and deficiency are common,^{9,10} as well as readily diagnosed and treated. Even mildly altered thyroid status reportedly affects serum cholesterol levels,¹¹ heart rhythm¹² and rate,¹³ ventricular function,^{14,15} risk of coronary artery disease,^{4,8,16} and cardiovascular mortality.⁵ However, the relationship between abnormal thyroid function and cardiovascular outcomes remains unclear, as prior studies reporting a relationship included individuals with overt thyroid disease¹²; included individuals taking thyroid hormone^{8,17}; inadequately adjusted for important confounders or initiation of thyroid

Context Previous studies have suggested that subclinical abnormalities in thyroid-stimulating hormone levels are associated with detrimental effects on the cardiovascular system.

Objective To determine the relationship between baseline thyroid status and incident atrial fibrillation, incident cardiovascular disease, and mortality in older men and women not taking thyroid medication.

Design, Setting, and Participants A total of 3233 US community-dwelling individuals aged 65 years or older with baseline serum thyroid-stimulating hormone levels were enrolled in 1989-1990 in the Cardiovascular Health Study, a large, prospective cohort study.

Main Outcome Measures Incident atrial fibrillation, coronary heart disease, cerebrovascular disease, cardiovascular death, and all-cause death assessed through June 2002. Analyses are reported for 4 groups defined according to thyroid function test results: subclinical hyperthyroidism, euthyroidism, subclinical hypothyroidism, and overt hypothyroidism.

Results Individuals with overt thyrotoxicosis (n = 4) were excluded because of small numbers. Eighty-two percent of participants (n = 2639) had normal thyroid function, 15% (n = 496) had subclinical hypothyroidism, 1.6% (n = 51) had overt hypothyroidism, and 1.5% (n = 47) had subclinical hyperthyroidism. After exclusion of those with prevalent atrial fibrillation, individuals with subclinical hyperthyroidism had a greater incidence of atrial fibrillation compared with those with normal thyroid function (67 events vs 31 events per 1000 person-years; adjusted hazard ratio, 1.98; 95% confidence interval, 1.29-3.03). No differences were seen between the subclinical hyperthyroidism group and euthyroidism group for incident coronary heart disease, cerebrovascular disease, cardiovascular death, or all-cause death. Likewise, there were no differences between the subclinical hypothyroidism or overt hypothyroidism groups and the euthyroidism group for cardiovascular outcomes or mortality. Specifically, individuals with subclinical hypothyroidism had an adjusted hazard ratio of 1.07 (95% confidence interval, 0.90-1.28) for incident coronary heart disease.

Conclusion Our data show an association between subclinical hyperthyroidism and development of atrial fibrillation but do not support the hypothesis that unrecognized subclinical hyperthyroidism or subclinical hypothyroidism is associated with other cardiovascular disorders or mortality.

JAMA. 2006;295:1033-1041

www.jama.com

Author Affiliations: Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, and Division of Epidemiology, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia (Dr Cappola); Division of Geriatric Medicine and Gerontology and Center on Aging and Health, Johns Hopkins Medical Institutions, Baltimore, Md (Dr Fried); Department of Biostatistics, University of Washington, Seattle (Dr Arnold); Outcomes Insights Inc, Newbury Park, Calif (Dr Danese); Department of Epidemiology, University of Pittsburgh Graduate School of Public Health,

Pittsburgh, Pa (Dr Kuller); Department of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC (Dr Burke); Departments of Pathology and Biochemistry, University of Vermont, Burlington (Dr Tracy); and Division of Endocrinology and Metabolism, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Md (Dr Ladenson).

Corresponding Author: Anne R. Cappola, MD, ScM, University of Pennsylvania School of Medicine, 718 Blockley Hall, 423 Guardian Dr, Philadelphia, PA 19104-6021 (acappola@ceeb.med.upenn.edu).

hormone therapy^{4,5,8,17}; or used poorly characterized cardiovascular end points.⁴ Furthermore, no clinical trials have been performed to examine whether correction of thyroid dysfunction results in improvement of cardiovascular outcomes. This lack of experimental evaluation has resulted in continued controversy, as detailed in recommendations by both an expert panel and the US Preventive Services Task Force.^{18,19}

Using data from a large cohort study representative of community-dwelling individuals aged 65 years or older, we have tested the hypothesis that abnormal thyroid status is associated with increased cardiovascular risk and mortality in individuals with unrecognized thyroid dysfunction.

METHODS

Study Population

These analyses are based on data in the Cardiovascular Health Study (CHS).²⁰ The CHS is a population-based, longitudinal study of risk factors for the development of CVD in 5888 adults aged 65 years or older. Enrollment of an original cohort of 5201 adults occurred between May 1989 and June 1990, and an additional cohort of 687, predominantly African Americans, was enrolled in 1992-1993. Eligible individuals were identified from an age- and sex-stratified random sample of the Medicare eligibility rosters in 4 US communities: Washington County, Maryland; Pittsburgh (Allegheny County), Pennsylvania; Sacramento County, California; and Forsyth County, North Carolina. To be eligible, individuals had to be noninstitutionalized; expecting to remain in the area for the following 3 years; not in active treatment for cancer; not wheelchair-bound in the home; not requiring a proxy respondent at entry; and capable of providing consent. Household members of the sampled individual were recruited, if eligible. The institutional review boards of all 4 sites and the coordinating center at the University of Washington in Seattle approved the study. All participants gave written informed consent.

At the initial visit, a detailed medical history (including medication history), physical examination, and health status assessment that included any evidence of vascular disease were performed. Blood was drawn after a 12-hour fast and serum was frozen in -70°C freezers for future investigations.

Thyroid Hormone Analyses

Thyroid function tests were performed at the Nuclear Medicine In Vitro Laboratory of the Johns Hopkins Hospital (Baltimore, Md) from 1991 through 1993 in a subsample of individuals from the original cohort, selected according to availability of stored serum for analysis. Serum TSH concentration was measured using a chemiluminescent immunometric assay (LumaTag hTSH, Nichols Institute, San Juan Capistrano, Calif) with a functional sensitivity of 0.008 mU/L. Of the 3699 samples tested, there was sufficient serum for analysis in 3678 (99%). Free thyroxine (FT_4) concentrations were measured in individuals with serum TSH levels of less than 0.10 mU/L or more than 4.50 mU/L for the 95% of samples with sufficient serum for this additional test, which was performed with a direct monoclonal antibody assay (Amerlex-MAB, Amersham International, Amersham, England) with a normal range of 0.7 to 1.7 ng/dL (9-22 pmol/L).

Participants from the CHS in whom thyroid function testing was performed were more likely to be female than those in the untested group. The mean ages of the tested and untested groups were not different, nor were there differences in race, income, thyroid medication use, or prevalent CVD.

Classification by Thyroid Status

Study participants were classified into 1 of the following 5 groups based on their thyroid function tests:

1. Overt thyrotoxicosis was defined as a TSH concentration of less than 0.10 mU/L with an elevated FT_4 level ($n=2$).
2. Subclinical hyperthyroidism was defined as a TSH concentration of 0.10-

0.44 mU/L ($n=40$) or less than 0.10 mU/L with a normal FT_4 concentration ($n=7$).

3. Euthyroidism was defined as a normal TSH concentration (0.45-4.50 mU/L) ($n=2639$).

4. Subclinical hypothyroidism was defined as a TSH concentration of more than 4.50 mU/L and less than 20 mU/L with a normal FT_4 concentration ($n=496$).

5. Overt hypothyroidism was defined as a TSH level of 20 mU/L or more ($n=33$) or a TSH concentration of more than 4.50 mU/L with an FT_4 concentration level below normal (<0.7 ng/dL [<9 pmol/L]) ($n=18$).

Because our primary study question pertained to unrecognized thyroid function testing abnormalities, participants taking thyroid hormone preparations at baseline were excluded from the above categorization ($n=339$), as were individuals taking other medications that could affect thyroid testing, including antithyroid drugs and corticosteroids ($n=78$). No patients were taking amiodarone at the baseline examination. One participant whose test result suggested nonthyroidal illness (low TSH and low FT_4 levels) was excluded. Those with definite ($n=2$) or possible ($n=2$) overt thyrotoxicosis were also excluded based on the small number in this category.

Ascertainment of Events

The events studied were atrial fibrillation, coronary heart disease, cerebrovascular disease, and death (cardiovascular and all-cause). Atrial fibrillation at baseline was self-reported or determined with a 12-lead resting electrocardiogram (ECG) or Holter monitor. Incident atrial fibrillation was determined from self-report, annual ECG, or *International Classification of Diseases, Ninth Revision* hospital discharge codes 427.3, 427.31, or 427.32. Coronary heart disease was defined by the occurrence of angina, myocardial infarction, coronary angioplasty, or coronary artery bypass graft surgery. Cerebrovascular disease was defined as

a cerebrovascular accident or a transient ischemic attack. Subclinical CVD, which has been shown to be an independent predictor of CVD in the CHS population,²¹ was defined as any 1 of the following: ankle-arm index of 0.9 or less, common or internal carotid wall thickness of more than the 80th percentile, carotid stenosis greater than 25%, major ECG abnormalities, Rose questionnaire claudication- or angina-positive, or abnormal ejection fraction or wall motion on echocardiogram in the absence of clinical CVD. Cardiovascular deaths were defined as those due to atherosclerosis (including peripheral vascular disease), coronary heart disease, cerebrovascular events, and other cardiovascular causes.

Participants were contacted semiannually regarding hospitalizations or new occurrences of cardiovascular events. The full details of the surveillance and ascertainment of events in the CHS have been published previously.²² Provisional diagnoses of coronary heart disease and cerebrovascular disease were reviewed and adjudicated at periodic meetings of the study's morbidity and mortality subcommittee, including investigators from each field center and the coordinating center. All outcomes were adjudicated except atrial fibrillation. Information about deaths was obtained from reviews of medical records, death certificates, autopsy reports, and coroners' reports. Ascertainment of mortality in the CHS was 100%. The incident events in this report occurred after baseline and through June 30, 2002, with a mean duration of follow-up of 12.5 years.

Assessment of Covariates

Thyroid and lipid-lowering medication use was assessed annually via medication bottle examination. Information on race was collected in the CHS to examine racial differences in CVD risk. Race was self-described as white, black, American Indian/Alaskan native, Asian/Pacific Islander, or other after reviewing a card that displayed these options. Fasting total cholesterol, high-density lipoprotein cholesterol, and tri-

glycerides were measured directly and standardized according to Centers for Disease Control and Prevention guidelines, with low-density lipoprotein cholesterol calculated according to the Friedewald equation.²³ Hypertension was defined as systolic blood pressure of 140 mm Hg or more, diastolic blood pressure of 90 mm Hg or more, or self-report of hypertension and antihypertensive medication use. Diabetes was defined as a fasting glucose level of 126 mg/dL (7.0 mmol/L) or more or use of insulin or an oral hypoglycemic medication. Impaired fasting glucose was defined as a fasting glucose level of 100 mg/dL (5.6 mmol/L) or more. C-reactive protein was measured using an enzyme-linked immunosorbent assay (CHS Blood Laboratory, Colchester, Vt).

Statistical Analysis

Study participants' baseline characteristics were summarized according to thyroid status and compared with those in the euthyroidism group using a *t* test or χ^2 test as appropriate. Incidence rates of cardiovascular and total mortality and first occurrence of coronary heart disease or cerebrovascular disease were calculated by dividing the total number of each event by person-years at risk among participants without clinical CVD or atrial fibrillation at baseline. Incidence rates of atrial fibrillation were calculated similarly, excluding only participants with atrial fibrillation at baseline from the risk set. Kaplan-Meier analysis was used to study the cumulative incidence of atrial fibrillation, cerebrovascular disease, coronary heart disease, and mortality by thyroid status across the 13 years of follow-up.

Multivariable Cox regression models were used to estimate the hazard ratio (HR) of each thyroid status group compared with the euthyroidism group, adjusting for other baseline risk factors or potential confounders and thyroid medication use during follow-up. Participants who died or were lost to follow-up before having an event were censored at the date of death or last contact. Both incident and recurrent coronary heart disease and cerebrovascular events

were considered, but only incident atrial fibrillation was modeled. Models were originally stratified by CVD status at baseline and by sex. Results were consistent across strata and, when combined, statistical tests for interactions between thyroid status group and sex or between thyroid status group and baseline CVD were not significant. Final models included men and women and participants with and without CVD at baseline. Models were done in stages, adjusting first for age, sex, disease status at baseline, and thyroid medication use during follow-up as a time-dependent covariate. For atrial fibrillation, the second and final stage of analysis added black race, left atrial size, systolic blood pressure, fasting glucose level, valvular disease history, and diuretics or β -adrenergic blocking agent use, factors that have previously been shown to predict atrial fibrillation in CHS.²⁴ For other outcomes, a second adjustment stage added black race, smoking status (never, former, or current), and diabetes. Cardiovascular risk factors that could have been mediated via thyroid dysfunction were added in the final adjustment stage, and included low-density lipoprotein cholesterol, lipid-lowering medications, hypertension, body mass index, and C-reactive protein. Results from the second and final models were compared to assess for overadjustment in the final model. Separate models that incorporated thyroid hormone use as a time-dependent covariate and that censored at the time of thyroid hormone use were examined, with similar results; the model incorporating the time-dependent covariate is shown. All analyses were conducted using SPSS for Windows, version 13 (SPSS Inc, Chicago, Ill) and STATA, version 9 (Stata Corp, College Station, Tex), and $P < .05$ was considered statistically significant for all analyses.

RESULTS

Baseline Characteristics

At study entry, 2639 individuals (82%) had euthyroidism. Subclinical hypothyroidism had the highest prevalence of any thyroid testing abnormality ($n = 496$;

Table 1. Baseline Characteristics by Thyroid Status in the Cardiovascular Health Study*

| Characteristics | Total (N = 3233) | Subclinical Hyperthyroidism (n = 47) | Euthyroidism (n = 2639) | Subclinical Hypothyroidism (n = 496) | Hypothyroidism (n = 51) |
|------------------------------------|---------------------|--|----------------------------|--|----------------------------|
| TSH, mU/L | 3.27 (4.26) | 0.25 (0.13) | 2.20 (0.99) | 6.67 (2.54) | 28.1 (15.7) |
| Free thyroxine, ng/dL | | 1.26 (0.24) | | 0.99 (0.16) | 0.63 (0.19) |
| Age, y | 72.7 (5.6) | 73.9 (6.8) | 72.6 (5.6) | 73.2 (5.6)† | 73.1 (6.0) |
| Female, No. (%) | 1926 (59.6) | 32 (68.1) | 1543 (58.5) | 321 (64.7)† | 30 (58.8) |
| White race, No. (%) | 3064 (94.8) | 45 (95.7) | 2495 (94.5) | 476 (96.0) | 48 (94.1) |
| BMI | 26.2 (4.4) | 27.5 (5.4)† | 26.2 (4.4) | 26.4 (4.8) | 27.0 (4.5) |
| Current or former smoking, No. (%) | 1661 (51.4) | 25 (53.2) | 1377 (52.2) | 235 (47.5) | 24 (47.1) |
| Cholesterol, mg/dL | | | | | |
| Total | 215 (39) | 203 (41)† | 215 (38) | 214 (41) | 228 (54)† |
| LDL | 133 (35) | 121 (30)† | 133 (35) | 132 (36) | 148 (53)† |
| HDL | 54 (16) | 52 (16) | 55 (16) | 54 (16) | 53 (13) |
| Lipid-lowering medication, No. (%) | 166 (5.1) | 2 (4.3) | 141 (5.3) | 15 (3.0)† | 8 (15.7)† |
| Hypertension, No. (%) | 1823 (56.6) | 32 (68.1) | 1496 (56.9) | 266 (53.7) | 29 (56.9) |
| Glucose status, No. (%) | | | | | |
| Normal | 1590 (49.2) | 25 (53.2) | 1274 (48.3) | 262 (52.8) | 29 (56.9) |
| IFG | 1188 (36.9) | 11 (23.4) | 1002 (38.0) | 161 (32.5) | 14 (27.5) |
| Diabetes | 454 (14.0) | 11 (23.4) | 362 (13.7) | 73 (14.7) | 8 (15.7) |
| Fasting glucose, mg/dL | 109 (33) | 111 (39) | 109 (33) | 108 (32) | 109 (30) |
| Fasting insulin, IU/mL‡ | 13.3 (24) | 16.1 (79)† | 13.3 (24) | 13.4 (16) | 12.8 (9) |
| Estrogen use (women only), No. (%) | 227 (11.8) | 4 (12.5) | 182 (11.8) | 40 (12.5) | 1 (3.3) |
| CRP, mg/L‡ | 1.80 (6.3) | 2.15 (7.8) | 1.77 (5.8) | 1.92 (7.1) | 2.10 (15.9) |
| Lp(a), mg/dL‡ | 31.1 (57) | 27.6 (50) | 31.0 (51) | 31.0 (82) | 37.1 (56) |

Abbreviations: BMI, body mass index, defined as weight in kilograms divided by the square of height in meters; CRP, C-reactive protein; HDL, high-density lipoprotein; IFG, impaired fasting glucose; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); TSH, thyroid-stimulating hormone.

SI conversions: To convert free thyroxine to pmol/L, multiply by 12.87; LDL, HDL, and total cholesterol to mmol/L, multiply by 0.0259; and glucose to mmol/L, multiply by 0.0555.

*See "Methods" section of text for thyroid category definitions. Data are presented as mean (SD) unless otherwise indicated.

†P<.05 for comparison with euthyroidism category.

‡Geometric mean.

Table 2. Prevalence of Cardiovascular Diseases by Thyroid Status*

| Prevalent Cardiovascular Diseases | Subclinical Hyperthyroidism (n = 47) | Euthyroidism (n = 2639) | Subclinical Hypothyroidism (n = 496) | Hypothyroidism (n = 51) |
|-------------------------------------|--|----------------------------|--|----------------------------|
| Atrial fibrillation | 4 (8.5) | 137 (5.2) | 24 (4.8) | 2 (3.9) |
| Coronary heart disease | 11 (23.4) | 489 (18.5) | 98 (19.8) | 12 (23.5) |
| Cerebrovascular disease | 2 (4.3) | 154 (5.8) | 25 (5.0) | 4 (7.8) |
| Subclinical cardiovascular disease† | 17 (36.2) | 949 (36.0) | 184 (38.1) | 14 (27.5) |

*See "Methods" section of text for thyroid category definitions. All data are expressed as No. (%).

†Without clinical cardiovascular disease.

15%), with fewer participants displaying results consistent with overt hypothyroidism (n=51; 1.6%) or subclinical hyperthyroidism (n=47; 1.5%). Ages were similar across all thyroid status categories in these elderly participants, with a mean age of 72.7 years (TABLE 1). Women were more likely to have subclinical thyroid dysfunction than men, achieving statistical significance for the comparison between the subclinical hypothyroidism and euthyroidism groups.

Examination of cardiovascular risk factors showed that study participants with subclinical hyperthyroidism had a higher body mass index than those with normal thyroid function, along with higher fasting insulin levels and a non-statistically significant higher prevalence of hypertension. Among those not using lipid-lowering medications, serum total low-density lipoprotein and total cholesterol levels were lowest in the subclinical hyperthyroid-

ism group and highest in the overt hypothyroidism group; furthermore, those with undetected overt hypothyroidism used lipid-lowering medication the most. However, lipid levels did not differ between the subclinical hypothyroidism and euthyroidism groups, and those with subclinical hypothyroidism had a slightly lower rate of lipid-lowering medication use.

Prevalent CVD by Thyroid Status

There was no difference in atrial fibrillation, coronary heart disease, cerebrovascular disease, or subclinical CVD at baseline between the euthyroidism group and any of the 3 thyroid dysfunction groups (TABLE 2).

Thyroid Medication Use During the Study

Thyroid medication use was available throughout follow-up. Seven participants in the subclinical hyperthy-

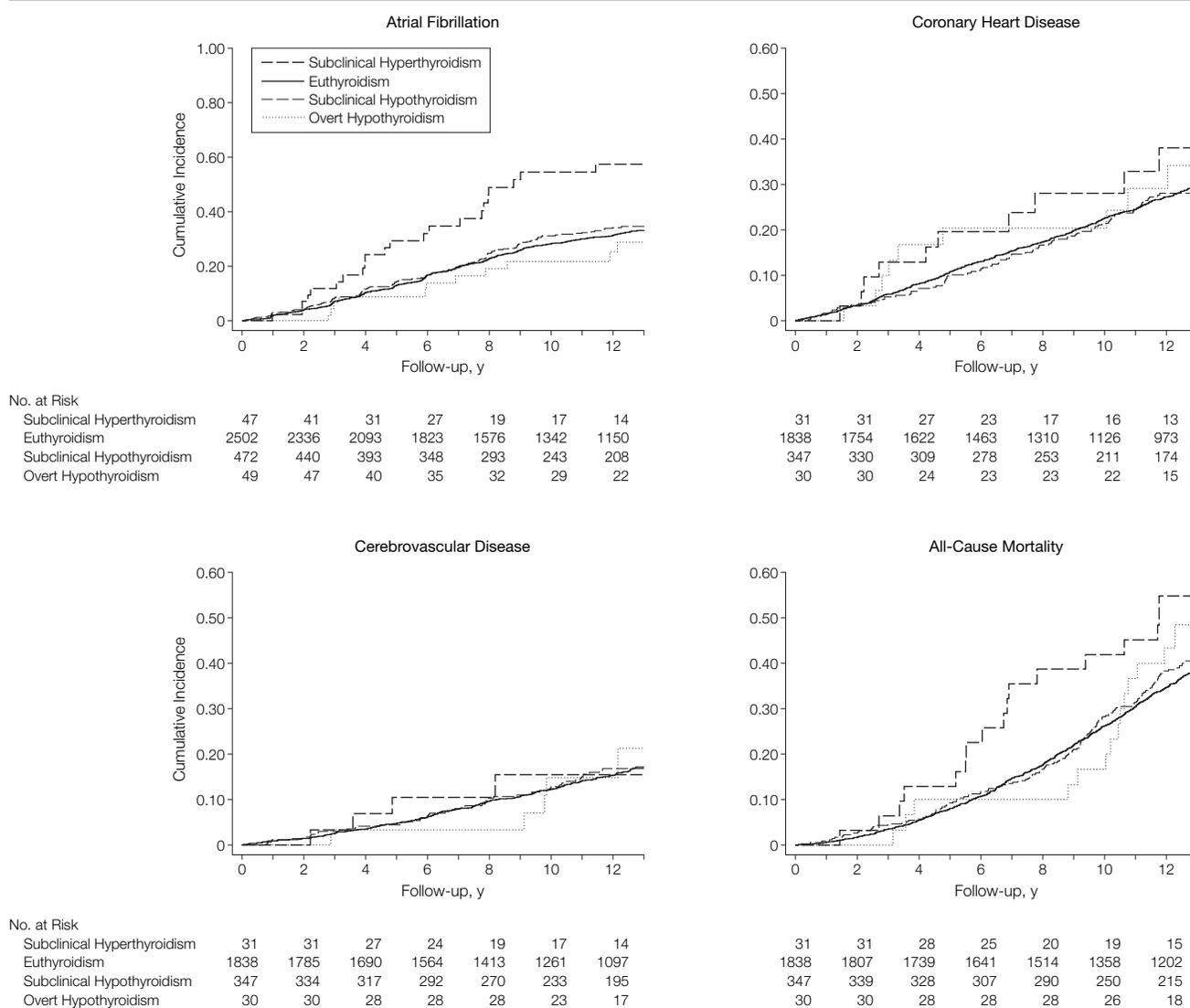
roidism group started thyroid hormone therapy during the follow-up period, 91 in the euthyroidism group, 142 in the subclinical hypothyroidism group, and 31 in the hypothyroidism group. Because of the potential effect of thyroid hormone initiation on subsequent cardiovascular risk, thyroid hormone medication use was included in all adjusted analyses.

Incident Atrial Fibrillation by Thyroid Status

After excluding those with prevalent atrial fibrillation, individuals with subclinical hyperthyroidism had a greater incidence of atrial fibrillation over the 13-year follow-up than the euthyroidism group, with 67 vs 31 events per 1000 person-years ($P<.001$) (FIGURE and TABLE 3). This effect persisted after sequential

adjustment for other risk factors for atrial fibrillation. As shown in Table 3, after adjustment for age, sex, clinical CVD at baseline, subsequent thyroid medication use, and other known risk factors for atrial fibrillation, participants with subclinical hyperthyroidism had nearly twice the risk of developing atrial fibrillation (HR, 1.98; 95% confidence interval [CI], 1.29-3.03).

Figure. Cumulative Incidence of Atrial Fibrillation, Coronary Heart Disease, Cerebrovascular Disease, and Death From All Causes Over 13 Years of Follow-up, by Thyroid Status



$P<.001$ for comparison of atrial fibrillation incidence between subclinical hyperthyroidism and euthyroidism groups; $P=.02$ for comparison of mortality between subclinical hyperthyroidism and euthyroidism groups. All other comparisons are not statistically significant.

We subsequently repeated these analyses, limiting it to those with a TSH level of 0.1 to 0.44 mU/L (n=40). The incidence rate in this subgroup was 59 per 1000 person-years (P=.007 compared with the euthyroidism group). After adjustment for age, sex, baseline clinical cardiovascular disease, and thyroid hormone use during follow-up, the HR was 1.85 (95% CI, 1.14-3.00).

Incident and Recurrent Cardiovascular Events by Thyroid Status

There were no differences in the incidence of coronary heart disease, cere-

brovascular disease, cardiovascular death, or all-cause death between the euthyroidism and subclinical or overt hypothyroidism groups (Figure and TABLE 4). There was a statistically significant increase in mortality in the subclinical hyperthyroidism group (58.1 vs 34.2 events per 1000 person-years; P=.02), which disappeared after adjustment for age and sex (P=.29). We subsequently evaluated the relationship between each thyroid status group and each cardiovascular outcome using various modeling strategies in adjusted analyses. No thyroid category was statistically sig-

nificantly different from the euthyroidism category; thus, only our crude and final models are displayed in TABLE 5. After adjustment, those with subclinical hypothyroidism had an HR of 1.07 (95% CI, 0.90-1.28) for coronary heart disease. All-cause death was not increased in subclinical hyperthyroidism (HR, 1.08; 95% CI, 0.72-1.62) or subclinical hypothyroidism (HR, 1.14; 95% CI, 0.98-1.32). Estimates for each of the covariates included in the final model for coronary heart disease validate increased risk associated with age, male sex, diabetes, low-density lipoprotein cholesterol level, hypertension, C-reactive protein level, and baseline CVD in our study population, while showing no appreciable increase in risk from any of the thyroid categories.

COMMENT

We report an independent association of subclinical hyperthyroidism with incident atrial fibrillation but not with other clinical cardiovascular conditions or mortality in a large, population-based cohort designed to examine cardiovascular risk factors in men and women aged 65 years or older. We also found no relationship between subclinical hypothyroidism or overt hypothyroidism and prevalent or incident atherosclerotic disease, cardiovascular mortality, or all-cause mortality, though relationships between traditional cardiovascular risk factors and CVD were confirmed in our models.

Prevalence of Endogenous Thyroid Dysfunction

Excluding those taking thyroid hormone preparations, the prevalence of subclinical hyperthyroidism in our cohort was 1.5%, a percentage that is lower than in 2 published reports on older people.^{12,25} The prevalence of subclinical hypothyroidism was 15%, which is comparable with estimates from several community-based cohorts²⁶⁻²⁸ and somewhat higher than others.^{4,25,29-31} The discrepancies seen in these prevalence rates likely reflect dif-

Table 3. Incidence of Atrial Fibrillation in Participants Without Atrial Fibrillation at Baseline, by Thyroid Status*

| | Subclinical Hyperthyroidism | Euthyroidism | Subclinical Hypothyroidism | Hypothyroidism |
|--|-----------------------------|------------------|----------------------------|------------------|
| No. at risk | 43 | 2502 | 472 | 49 |
| No. of events | 22 | 703 | 142 | 11 |
| Incidence (95% CI) per 1000 person-years | 67.0 (44-102)† | 31.0 (28.8-33.4) | 33.6 (28.5-39.6) | 25.2 (13.9-45.5) |
| Hazard ratio (95% CI) | | | | |
| Model 1‡ | 2.18 (1.42-3.33) | 1.0 | 1.11 (0.92-1.34) | 0.88 (0.48-1.63) |
| Model 2§ | 1.98 (1.29-3.03) | 1.0 | 1.13 (0.94-1.36) | 0.96 (0.52-1.79) |

Abbreviation: CI, confidence interval.
 *See "Methods" section of text for thyroid category definitions.
 †P<.001 for comparison with euthyroidism category; P = .001 after adjustment for age and sex.
 ‡Model 1 is adjusted for age, sex, clinical cardiovascular disease at baseline, and thyroid medication use during follow-up.
 §Model 2 is adjusted for the covariates listed for model 1 plus left atrial size, systolic blood pressure, fasting glucose, history of valvular disease, and use of diuretics or β-blockers.

Table 4. Incidence of Cardiovascular Events and Mortality in Participants Without Cardiovascular Disease at Baseline, by Thyroid Status*

| | Subclinical Hyperthyroidism | Euthyroidism | Subclinical Hypothyroidism | Hypothyroidism |
|--|-----------------------------|------------------|----------------------------|------------------|
| No. at risk | 31 | 1838 | 347 | 30 |
| Coronary heart disease | | | | |
| No. of events | 10 | 462 | 85 | 9 |
| Incidence (95% CI) per 1000 person-years | 37.4 (20.1-69.5) | 25.9 (23.6-28.3) | 25.1 (20.3-31.1) | 32.0 (16.6-61.5) |
| Cerebrovascular disease | | | | |
| No. of events | 4 | 261 | 50 | 5 |
| Incidence (95% CI) per 1000 person-years | 14.4 (5.4-38.3) | 13.8 (12.2-15.6) | 14.1 (10.7-18.6) | 15.6 (6.5-37.4) |
| Death due to cardiovascular causes | | | | |
| No. of deaths | 6 | 228 | 47 | 5 |
| Incidence (95% CI) per 1000 person-years | 20.5 (9.2-45.6) | 11.5 (10.1-13.1) | 12.7 (9.5-16.9) | 15.3 (6.4-36.8) |
| Death due to all causes | | | | |
| No. of deaths | 17 | 678 | 138 | 14 |
| Incidence (95% CI) per 1000 person-years | 58.1 (36.1-93.4)† | 34.2 (31.8-36.9) | 37.2 (31.5-43.9) | 42.9 (25.4-72.5) |

Abbreviation: CI, confidence interval.
 *See "Methods" section of text for thyroid category definitions.
 †P = .02 for comparison with euthyroidism category; P = .29 after adjustment for age and sex.

ferences in definitions of subclinical thyroid disease and the health status of participants among the cohorts.

Subclinical Hyperthyroidism

Our findings of increased risk of atrial fibrillation concur with a cross-sectional study³² and with prospective results from the Framingham Heart Study, in which individuals with TSH values of 0.1 mU/L or less who were not receiving thyroid hormone therapy had an adjusted relative risk of 3.8 (95% CI, 1.7-8.3) for developing atrial fibrillation and those with TSH values between 0.1 mU/L and 0.4 mU/L had an adjusted relative risk of 1.6 (95% CI, 1.0-2.5).¹² Individuals with elevated thyroxine levels, indicating overt hyperthyroidism, were included in their category of TSH values of less than 0.1 mU/L, which could have led to an overestimate of the effect of subclinical hyperthyroidism. Our results clearly show a relationship between low TSH levels and atrial fibrillation incidence in older individuals with endogenous subclinical hyperthyroidism, including those with TSH levels of 0.1 mU/L to 0.44 mU/L.

We found no relationship between subclinical hyperthyroidism and atherosclerotic CVD, cardiovascular mortality, or all-cause mortality between those with subclinical hyperthyroidism and euthyroidism. In contrast, Parle et al⁵ reported a higher cardiovascular mortality rate in those with TSH levels of less than 0.5 mU/L in comparison with the remainder of their cohort and the mortality rate from circulatory disease in England and Wales. However, their analyses are limited by a less rigorous definition of subclinical hyperthyroidism, so that those with other causes of low TSH level may have been included in their low TSH category and, by minimal adjustment for other covariates, associated with cardiovascular mortality, excepting age and sex.

Subclinical Hypothyroidism

We found no association between subclinical hypothyroidism and atherosclerotic disease, either prevalent or incident. Multiple prior studies have

Table 5. Hazard Ratios for Events and Death by Thyroid Status*

| | Subclinical Hyperthyroidism (n = 47) | Euthyroidism (n = 2639) | Subclinical Hypothyroidism (n = 496) | Hypothyroidism (n = 51) |
|------------------------------|--|----------------------------|--|----------------------------|
| Coronary heart disease | | | | |
| Model 1 | 1.18 (0.74-1.88) | 1.0 | 1.04 (0.87-1.23) | 0.97 (0.59-1.59) |
| Model 2 | 1.04 (0.64-1.69) | 1.0 | 1.07 (0.90-1.28) | 0.93 (0.57-1.53) |
| Cerebrovascular disease | | | | |
| Model 1 | 0.82 (0.39-1.73) | 1.0 | 0.99 (0.78-1.26) | 0.87 (0.42-1.78) |
| Model 2 | 0.70 (0.31-1.57) | 1.0 | 1.01 (0.79-1.29) | 0.86 (0.42-1.76) |
| Death due to vascular causes | | | | |
| Model 1 | 1.02 (0.53-1.98) | 1.0 | 1.14 (0.91-1.43) | 0.88 (0.44-1.73) |
| Model 2 | 0.94 (0.49-1.83) | 1.0 | 1.16 (0.92-1.46) | 0.97 (0.49-1.92) |
| Death due to all causes | | | | |
| Model 1 | 1.13 (0.76-1.70) | 1.0 | 1.10 (0.95-1.27) | 1.26 (0.84-1.89) |
| Model 2 | 1.08 (0.72-1.62) | 1.0 | 1.14 (0.98-1.32) | 1.43 (0.95-2.14) |

*All data are presented as hazard ratio (95% confidence interval). See "Methods" section of text for thyroid category definitions. Model 1 is adjusted for age, sex, clinical cardiovascular disease at baseline, atrial fibrillation at baseline, and thyroid medication use during follow-up. Model 2 is additionally adjusted for race, smoking status, diabetes, low-density lipoprotein cholesterol, use of lipid-lowering medications, hypertension, body mass index, and C-reactive protein.

examined the relationship of subclinical hypothyroidism and CVD. They have shown subclinical hypothyroidism to either increase^{4,6,8} or have no effect^{5,17,33} on CVD risk, though 1 has shown decreased cardiovascular and all-cause mortality,³⁴ and each has had serious design limitations not present in our study, fueling the controversy rather than providing evidence to resolve it.

Cross-sectional associations between subclinical hypothyroidism and CVD^{4,6,8} have held up longitudinally in only 1 study, the Busselton Health Study.⁸ Although the Busselton Health Study has 20 years of follow-up, data were not collected specifically on thyroid hormone therapy; cardiovascular events were collected by record linkage rather than prospective follow-up and adjudication; and low-density lipoprotein cholesterol concentrations were not available for adjusted analyses. Interestingly, the separation in CVD risk between the subclinical hypothyroidism and euthyroidism groups did not occur until 10 years of follow-up. Our study suggests an increase in all-cause mortality in the subclinical hypothyroidism group at 10 years, which is not paralleled in the atrial fibrillation, coronary heart disease, and cerebrovascular disease curves, which are nearly indistinguishable from the euthyroidism group over the entire study

follow-up. The late increase in all-cause mortality either reflects an increase in noncardiovascular causes or is simply due to chance.

Other studies that have shown no association between subclinical hypothyroidism and cardiovascular risk have been questioned because of shorter follow-up^{5,17} or inclusion of individuals who subsequently initiated thyroid hormone therapy, which theoretically could have attenuated their cardiovascular risk.³³ During the course of our study, 27% of those in the subclinical hypothyroidism group initiated thyroid hormone therapy. We saw no evidence of an effect on cardiovascular risk, and our thyroid hormone therapy covariate was not statistically significant for any of the outcomes studied, suggesting that thyroid hormone initiation has no effect on cardiovascular risk.

Thyroid Status and Atherosclerotic Risk Factors

Our results suggest a dose-response effect between TSH and serum total cholesterol levels, with the lowest levels of cholesterol present in those with subclinical hyperthyroidism and the highest in those with overt hypothyroidism, a previously reported effect.^{31,35} In our cohort, individuals with hypothyroidism had the highest levels of serum total and low-density lipoprotein cho-

lesterol and took lipid-lowering medications at 3 times the rate of the euthyroidism population. This finding highlights the need to investigate secondary causes of hypercholesterolemia before initiation of lipid-lowering medications, as recommended by the National Cholesterol Education Program.³⁶

Earlier observational studies examining the relationship between subclinical hypothyroidism and cholesterol levels yielded conflicting results.³⁷ In our study, serum cholesterol concentrations were similar between individuals with normal thyroid function and with untreated subclinical hypothyroidism. Similarly, there were no differences in lipoprotein(a), C-reactive protein, or fasting insulin and glucose concentrations between those with normal thyroid function and subclinical hypothyroidism.

Strengths and Weaknesses

A major strength of our study is the use of a large, population-based cohort of older men and women, designed to examine cardiovascular risk factors, with an average of 12.5 years of follow-up data for events. The prevalent and incident disease assignments were made using objective information collected during examination and review of hospital and physicians' records.²⁰ Laboratory assays were performed without knowledge of CVD status. Furthermore, we excluded individuals taking thyroid medication or with other conditions that could affect thyroid function testing at baseline, and we incorporated thyroid medication use over time as a time-dependent covariate to examine risk of endogenous thyroid dysfunction.

We performed analyses using multiple models: stratified by sex and prevalent CVD, adjusting for incident thyroid hormone use in several ways (none, censoring at the time of thyroid hormone initiation, or used as a time-dependent covariate), and adjusting for cardiovascular risk factors in a stepwise manner to avoid overadjustment. We showed an independent effect

of subclinical hyperthyroidism on incident atrial fibrillation and of traditional cardiovascular risk factors on incident CVD. The presence of these positive findings and the thoroughness of our modeling strategies suggest that it is unlikely that we failed to detect a cardiovascular risk factor of consequence in the remainder of our analyses. Post hoc calculations showed adequate power to detect meaningful differences between the subclinical hypothyroidism and euthyroidism groups for each outcome; specifically, our study had adequate power to detect an HR of 1.30 or higher for coronary heart disease and an HR of 1.26 or higher for all-cause death.

We are limited in looking at thyroid function testing abnormalities to a single point in time. Thus, we are unable to comment on the relationship between persistent thyroid abnormalities and CVD and mortality. In addition, the number of individuals with subclinical hyperthyroidism or overt hypothyroidism is small in our study, limiting our power to detect an effect of either of these types of thyroid dysfunction on CVD outcomes or mortality.

Clinical Implications

Thyroid testing abnormalities are quite common in older women and men without known thyroid dysfunction. While the US Preventive Services Task Force and an expert panel do not recommend generalized screening for thyroid disease,^{18,38} the American College of Physicians currently advises screening women older than 50 years for unsuspected but symptomatic thyroid disease,³⁹ and the American Thyroid Association recommends screening adults every 5 years beginning at age 35 years.⁴⁰ Our analyses do not support screening older individuals solely to prevent atrial fibrillation, with an estimated number needed to screen of 2500 older individuals to find 1 case of atrial fibrillation associated with subclinical hyperthyroidism. Our findings suggest that if endogenous subclinical hyperthyroidism is detected, older individuals may benefit from treatment to

prevent atrial fibrillation. An expert panel has recommended consideration of treatment for those with endogenous subclinical hyperthyroidism and TSH levels below 0.1 mU/L, with insufficient evidence to treat those with TSH levels between 0.1 mU/L and 0.45 mU/L.¹⁸ Our data support treatment of all older individuals with subclinical hyperthyroidism, even those with mild decreases in TSH level (0.1-0.44 mU/L). Our analyses do not support screening older individuals for thyroid disease to prevent CVD, and, although our data are observational, they do not support treatment of individuals with subclinical hypothyroidism to prevent cardiovascular events.

Author Contributions: Dr Arnold had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Cappola, Fried, Danese, Burke, Tracy, Ladenson.

Acquisition of data: Fried, Kuller, Burke, Tracy, Ladenson.

Analysis and interpretation of data: Cappola, Fried, Arnold, Danese, Kuller, Burke, Tracy, Ladenson.

Drafting of the manuscript: Cappola, Arnold.

Critical revision of the manuscript for important intellectual content: Cappola, Fried, Danese, Kuller, Burke, Tracy, Ladenson.

Statistical analysis: Arnold, Danese.

Obtained funding: Fried, Kuller, Burke, Tracy, Ladenson.

Administrative, technical, or material support: Cappola, Kuller, Tracy, Ladenson.

Study supervision: Cappola, Fried, Ladenson.

Financial Disclosures: None reported.

CHS Investigators: A complete list of participating CHS investigators and institutions can be found at <http://www.chs-nhlbi.org>.

Funding/Support: This study was supported by an American Heart Association Grant-in-Aid (to Dr Fried) with funding from July 1991 to June 1993. The research reported in this article was supported by contracts N01-HC-85079 through N01-HC-85086, N01-HC-35129, and N01-HC-15103 from the National Heart, Lung, and Blood Institute (NHLBI). Dr Cappola is supported by grant K23-AG19161 from the National Institute on Aging.

Role of the Sponsor: This study was funded through contracts with the NHLBI and included substantial NHLBI involvement in study design and oversight. A member of the NHLBI serves on the executive committee of the study, and NHLBI reviews all manuscripts prior to publication.

REFERENCES

1. Hoyert DL, Kung HC, Smith BL. Deaths: preliminary data for 2003. *Natl Vital Stat Rep*. 2005;53:1-48.
2. Magnus P, Beaglehole R. The real contribution of the major risk factors to the coronary epidemics: time to end the "only-50%" myth. *Arch Intern Med*. 2001; 161:2657-2660.
3. Pahor M, Elam MB, Garrison RJ, Kritchevsky SB, Applegate WB. Emerging noninvasive biochemical

measures to predict cardiovascular risk. *Arch Intern Med.* 1999;159:237-245.

4. 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;132:270-278.

5. 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;358:861-865.

6. Imaizumi M, Akahoshi M, Ichimaru S, et al. Risk for ischemic heart disease and all-cause mortality in subclinical hypothyroidism. *J Clin Endocrinol Metab.* 2004;89:3365-3370.

7. Kvetny J, Heldgaard PE, Bladbjerg EM, Gram J. Subclinical hypothyroidism is associated with a low-grade inflammation, increased triglyceride levels and predicts cardiovascular disease in males below 50 years. *Clin Endocrinol (Oxf).* 2004;61:232-238.

8. Walsh JP, Bremner AP, Bulsara MK, et al. Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. *Arch Intern Med.* 2005;165:2467-2472.

9. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab.* 2002;87:489-499.

10. Vanderpump MP, Tunbridge WM, French JM, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Wickham Survey. *Clin Endocrinol (Oxf).* 1995;43:55-68.

11. 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.

12. Sawin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med.* 1994;331:1249-1252.

13. 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;18:511-516.

14. Biondi B, Palmieri EA, Fazio S, 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;85:4701-4705.

15. Biondi B, Fazio S, Palmieri EA, et al. Left ventricular diastolic dysfunction in patients with subclinical hypothyroidism. *J Clin Endocrinol Metab.* 1999;84:2064-2067.

16. Cappola AR, Ladenson PW. Hypothyroidism and atherosclerosis. *J Clin Endocrinol Metab.* 2003;88:2438-2444.

17. Rodondi N, Newman AB, Vittinghoff E, et al. Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. *Arch Intern Med.* 2005;165:2460-2466.

18. Surks MI, Ortiz E, Daniels GH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA.* 2004;291:228-238.

19. Helfand M. Screening for subclinical thyroid dysfunction in nonpregnant adults: a summary of the evidence for the US Preventive Services Task Force. *Ann Intern Med.* 2004;140:128-141.

20. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol.* 1991;1:263-276.

21. Kuller LH, Shemanski L, Psaty BM, et al. Subclinical disease as an independent risk factor for cardiovascular disease. *Circulation.* 1995;92:720-726.

22. Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events: the Cardiovascular Health Study. *Ann Epidemiol.* 1995;5:278-285.

23. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem.* 1972;18:499-502.

24. Psaty BM, Manolio TA, Kuller LH, et al. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation.* 1997;96:2455-2461.

25. 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.

26. Lindeman RD, Schade DS, LaRue A, et al. Subclinical hypothyroidism in a biethnic, urban community. *J Am Geriatr Soc.* 1999;47:703-709.

27. Rosenthal MJ, Hunt WC, Garry PJ, Goodwin JS. Thyroid failure in the elderly: microsomal antibodies as discriminant for therapy. *JAMA.* 1987;258:209-213.

28. Sawin CT, Chopra D, Azizi F, Mannix JE, Bachar-

ach P. The aging thyroid: increased prevalence of elevated serum thyrotropin levels in the elderly. *JAMA.* 1979;242:247-250.

29. Tunbridge WM, Evered DC, Hall R, et al. The spectrum of thyroid disease in a community: the Wickham survey. *Clin Endocrinol (Oxf).* 1977;7:481-493.

30. Bagchi N, Brown TR, Parish RF. Thyroid dysfunction in adults over age 55 years: a study in an urban US community. *Arch Intern Med.* 1990;150:785-787.

31. Kanaya AM, Harris F, Volpato S, Perez-Stable EJ, Harris T, Bauer DC. Association between thyroid dysfunction and total cholesterol level in an older biracial population: the health, aging and body composition study. *Arch Intern Med.* 2002;162:773-779.

32. Auer J, Scheibner P, Mische T, Langsteger W, Eber O, Eber B. Subclinical hyperthyroidism as a risk factor for atrial fibrillation. *Am Heart J.* 2001;142:838-842.

33. Vanderpump MP, Tunbridge WM, French JM, 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;6:155-160.

34. Gussekloo J, Van EE, de Craen AJ, Meinders AE, Frolich M, Westendorp RG. Thyroid status, disability and cognitive function, and survival in old age. *JAMA.* 2004;292:2591-2599.

35. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med.* 2000;160:526-534.

36. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486-2497.

37. Chu JW, Crapo LM. The treatment of subclinical hypothyroidism is seldom necessary. *J Clin Endocrinol Metab.* 2001;86:4591-4599.

38. US Preventive Services Task Force. Screening for thyroid disease: recommendation statement. *Ann Intern Med.* 2004;140:125-127.

39. American College of Physicians. Clinical guideline, part 1: screening for thyroid disease. *Ann Intern Med.* 1998;129:141-143.

40. Ladenson PW, Singer PA, Ain KB, et al. American Thyroid Association guidelines for detection of thyroid dysfunction. *Arch Intern Med.* 2000;160:1573-1575.