Levothyroxine Treatment of Subclinical Hypothyroidism, Fatal and Nonfatal Cardiovascular Events, and Mortality

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Background: Subclinical hypothyroidism (SCH) has been associated with ischemic heart disease (IHD); however, it is unknown whether treatment of SCH with levothyroxine sodium will reduce the risk of IHD. The aim of this study was to investigate the association between levothyroxine treatment of SCH with IHD morbidity and mortality.

Methods: We used the United Kingdom General Practitioner Research Database to identify individuals with new SCH (serum thyrotropin levels of 5.01-10.0 mIU/L and normal free thyroxine levels) recorded during 2001 with outcomes analyzed until March 2009. All analyses were performed separately for younger (40-70 years) and older (>70 years) individuals. Hazard ratios (HRs) for IHD events (fatal and nonfatal) were calculated after adjustment for conventional IHD risk factors, baseline serum thyrotropin levels, and initiation of levothyroxine treatment as a time-dependent covariate.

Results: Subclinical hypothyroidism was identified in 3093 younger and 1642 older individuals. For a median follow-up period of 7.6 years, 52.8% and 49.9% of younger and older patients with SCH were treated with levothyroxine, respectively. There were 68 incident IHD events in 1634 younger patients treated with levothyroxine (4.2%) vs 97 IHD events in 1459 untreated individuals (6.6%) (multivariate-adjusted HR, 0.61; 95% CI, 0.39-0.95). In contrast, in the older group there were 104 events in 819 treated patients (12.7%) vs 88 events in 823 untreated individuals (10.7%) (HR, 0.99; 95% CI, 0.59-1.33).

Conclusions: Treatment of SCH with levothyroxine was associated with fewer IHD events in younger individuals, but this was not evident in older people. An appropriately powered randomized controlled trial of levothyroxine in SCH examining vascular outcomes is now warranted.

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Subclinical hypothyroidism (SCH) is defined as an elevated serum thyrotropin level in the presence of normal thyroid hormone concentrations. Subclinical hypothyroidism is frequently asymptomatic and is relatively common, being found in up to 10% of the adult population.[1] It has been argued for 4 decades that SCH predisposes individuals to cardiovascular disease.[2,3] Recent meta-analyses[4,5] have confirmed that SCH is associated with increased cardiovascular events and mortality, particularly in young to middle-aged adults. However, these epidemiologic associations do not prove that treatment of SCH would be efficacious. Indeed, SCH in elderly individuals may not have any adverse effects; one population-based cohort study[6] of people 85 years old showed that SCH was associated with improved survival compared with euthyroid individuals. Thus, only adequately powered randomized controlled intervention trials will be able to demonstrate whether treatment of SCH is worthwhile in terms of improvement in both cardiovascular disease risk and symptoms. However, such a trial has not been performed to date and no such trials are ongoing.[7]

See also page 799

Despite this, a high proportion of individuals with SCH are treated with levothyroxine sodium for its subjective effect on hypothyroid symptoms and for perceived amelioration of cardiovascular risk factors, such as dyslipidemia. Nevertheless, several studies[8] show that approximately 40% of patients who are treated with levothyroxine have subsequent serum thyrotropin concentrations outside the reference range, suggesting that a decision to treat may frequently not lead to ideal biochemical control of their thy-

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roid state. Empirical observation of real-life outcome may provide information to guide future practice. We have examined the United Kingdom General Practitioner Research Database (GPRD), a large primary care database, which provided a unique opportunity to ascertain cardiovascular morbidity and mortality in patients with SCH stratified by subsequent levothyroxine treatment.

METHODS

GPRD DATABASE

We examined case records from the GPRD, which is the world's largest primary care database, for which detailed characteristics have been described elsewhere.[9] In brief, the GPRD is a database of anonymous longitudinal records containing medical information on a population of more than 10 million patients (approximately 16% of the UK population) who participate via contributing family physician practices. The GPRD population broadly reflects the demographics of the UK population. Information collected includes demographic characteristics, lifestyle factors, medical symptoms and diagnoses, laboratory test results, medication prescriptions with dose instructions, referrals to specialists, and hospital discharge reports. Quality control of data entry and consistency with medical records are checked regularly.[10] The reliability of data concerning vascular events has previously been shown to be more than 90%.[11]

STUDY DESIGN

We identified a group of patients with SCH within the GPRD cohort and analyzed outcomes according to subsequent treatment with levothyroxine. In calendar year 2001, serum thyrotropin was measured 322 291 times in patients from 314 GPRD-contributing practices. After exclusion of individuals treated with thyroid hormones (n=2279) and antithyroid drugs (n=165), individuals aged 40 years or older with first-ever increased serum thyrotropin levels of 5.01 to 10.00 mIU/L and normal serum free thyroxine (FT_4) levels (0.7-1.9 ng/dL [to convert to picomoles per liter, multiply by 12.871]) were identified (n=8351). We excluded individuals with a history of ischemic heart disease (n=583) or cerebrovascular disease (n=214) and those individuals who were registered with practices that did not fulfill at least 12 months of predefined data quality criteria leading up to their index elevated thyrotropin level (n=1647). Poor-quality records as judged by lack of continuous follow-up or with incomplete or inaccurate data recording were excluded. In addition, individuals treated at any time before their index elevated thyrotropin level with amiodarone hydrochloride or lithium carbonate or for up to 365 days with an oral corticosteroid were excluded (n=1172). Moreover, information regarding baseline (within 180 days of the index elevated serum thyrotropin level) cardiovascular risk factors, including body mass index (BMI), blood pressure, total cholesterol levels, history of diabetes mellitus (present or absent), smoking status (current, former, or nonsmoker), and locality social and economic deprivation index (obtained from practice postcode–based socioeconomic status using the Index of Multiple Deprivation 2007)[12] were also noted. Information concerning prescription of levothyroxine and measurements of serum thyrotropin were ascertained throughout the follow-up period after the index abnormal thyrotropin measurement. All patients were followed up until the date of ischemic heart disease (IHD) event, stroke, death, end of registration with the practice, or end of the study period (March 31, 2009), whichever occurred first. Causes of death were ascertained from death certificates obtained from the UK Office of National Statistics according to the *International Statistical Classification of Diseases, 10th Revision (ICD-10)*. Ethical and scientific approval for the study was obtained from the Independent Scientific Advisory Committee of the GPRD.

OUTCOMES

A priori, the planned primary outcome was a composite of incident fatal and nonfatal first-recorded diagnosis of IHD identified by the relevant *ICD-10* codes (I20-I25) or Read/Oxford Medical Information System (Read/OXMIS) codes (eAppendix 1; http://www.archinternmed.com), respectively. Secondary outcomes of first fatal and nonfatal cerebrovascular disease (ischemic, hemorrhagic, or nonspecified stroke, including transient ischemic attack) identified by means of the relevant *ICD-10* codes (I60-I69) or Read/OXMIS diagnostic codes (eAppendix 2) and all-cause and cause-specific mortality during the study period were identified. New-onset atrial fibrillation was identified from the relevant Read/OXMIS codes (eAppendix 3). Levothyroxine use was identified through individual GPRD prescribing records.

STATISTICAL ANALYSIS

At the outset, the analyses were performed separately for individuals aged 40 to 70 years (younger group) and those older than 70 years (older group) at baseline based on cohort data showing that the upper limit of the serum thyrotropin reference range exceeds 5.00 mIU/L after the age of 70 years.[13] To validate this a priori categorization, we performed a test for interaction using Cox proportional hazards between younger and older age groups and levothyroxine treatment status to confirm whether there was a significant difference in the primary outcome of fatal and nonfatal IHD events between the 2 age groups. The result of the test for interaction was positive (P=.004). Therefore, all analyses were performed separately for younger and older SCH individuals. Similarly, we also tested for the interaction between levothyroxine treatment and the primary outcome in men and women and found no significant difference (P for interaction=.66); hence, both sexes were analyzed together. Outcome hazard ratios (HRs) were calculated using Cox proportional analysis in the levothyroxine–treated vs the untreated groups, with the primary analysis adjusting for the following baseline cardiovascular risk factors: age, sex, BMI, socioeconomic deprivation score, total cholesterol level, index serum thyrotropin level, smoking status, history of diabetes mellitus, systolic and diastolic blood pressure, and use of levothyroxine therapy as a time-dependent covariate so that participants switched stratum when levothyroxine therapy was initiated. The assumption of proportional hazards was tested and met by plotting scaled Schoenfeld residuals against time for each covariate. A secondary analysis of HR was also performed adjusting for baseline age and sex alone because mild hypothyroidism may adversely influence some cardiovascular risk factors.[14-17] For individuals in whom baseline cardiovascular risk factors were not available within 180 days of their index elevated serum thyrotropin level (21% of the total cohort), the last available reading was carried forward. Further analysis was performed to calculate HRs for the primary outcome using length of exposure to levothyroxine (in months) as a continuous variable (untreated individuals would have a value of zero) to detect any temporal effects of treatment of SCH. Data in relation to baseline characteristics and variables were compared using the t test or χ^2 test for continuous and categorical data, respectively. Variables that were not normally dis-

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Table 1. Baseline Characteristics of Individuals With Subclinical Hypothyroidism in 2001 Stratified by Younger (40-70 Years) and Older (>70 Years) Age Groups

Characteristic	Age 40-70 y			Age >70 y		
	Not Treated (n = 1459)	Treated (n = 1634)	*P* Value	Not Treated (n = 823)	Treated (n = 819)	*P* Value
Age, mean (SD), y	55.9 (8.34)	55.9 (8.4)	.75	79.89 (6.45)	79.37 (6.22)	.12
Female sex, No. (%)	1204 (82.5)	1428 (87.4)	<.001	622 (75.6)	693 (84.6)	<.001
BMI mean (SD)	27.83 (5.94)	28.12 (6.24)	.20	25.35 (4.63)	26.33 (5.11)	<.001
Systolic BP, mean (SD), mm Hg	136.45 (20.0)	135.23 (19.28)	.09	149.37 (23.5)	149.37 (22.0)	.99
Diastolic BP, mean (SD), mm Hg	80.97 (11.28)	80.91 (10.91)	.88	81.1 (11.64)	81.56 (11.03)	.39
Thyrotropin level, mean (SD), mIU/L	6.32 (1.25)	6.74 (1.36)	<.001	6.32 (1.22)	6.77 (1.38)	<.001
FT_4 level, mean (SD), ng/dL	1.04 (0.34)	1.00 (0.23)	.001	1.13 (0.34)	1.08 (0.27)	.003
Total cholesterol level, mean (SD), mg/dL	226 (52)	225 (47)	.14	229 (53)	230 (48)	.79
Diabetes mellitus, No. (%)	263 (18.0)	295 (18.1)	.98	221 (26.9)	218 (26.6)	.91
Smoking, No. (%)						
Current	262 (18.3)	288 (17.9)		85 (10.9)	76 (10.1)	
Former	286 (20)	341 (21.2)	.70	181 (23.1)	157 (20.8)	.42
Nonsmoker	882 (61.7)	977 (60.8)		516 (66.0)	521 (69.1)	
Index of deprivation[a]	22.88 (17.5)	22.14 (16.75)	.24	21.36 (15.86)	22.66 (16.58)	.10

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; FT_4, free thyroxine.
SI conversion factors: To convert FT_4 to picomoles per liter, multiply by 12.871; to convert total cholesterol to millimoles per liter, multiply by 0.0259.
[a] Index of deprivation is provided to give information on practice postcode–based socioeconomic status using the Index of Multiple Deprivation. This score is calculated differently for each of the 4 countries of the United Kingdom. A high score indicates the most deprived, whereas a low score indicates the least deprived on a scale of 1 to 80.

tributed were log-transformed before analyses. Annualized contact with health professionals during the follow-up period and before primary outcome (total number of visits to general physicians divided by length of follow-up in years) was also compared in the treated and untreated groups. All *P* values reported are 2-sided. The statistical software program SPSS version 15.0 (SPSS Inc) was used for performing analyses.

RESULTS

BASELINE FEATURES AND TREATMENT

Baseline characteristics of the younger (n=3093) and older (n=1642) groups with SCH are given in **Table 1**. Overall, during the follow-up period, 52.8% and 49.9% of individuals were treated with levothyroxine in the younger and older groups, respectively. The median levothyroxine sodium dosage was 75 µg/d (range, 12.5-175 µg/d). In the individuals with SCH who were not treated during the follow-up, 58.2% were still in an SCH state, 38.4% had reverted to euthyroidism, 2.5% were in the subclinical hyperthyroid state (thyrotropin level <0.4 mIU/L and normal FT_4 levels), and 1.3% had progressed to overt hypothyroidism (thyrotropin level >10 mIU/L and/or FT_4 level <0.7 ng/dL). In the levothyroxine–treated group with SCH, 12.2% began treatment after progression to overt hypothyroidism, and 6.4% of individuals had discontinued treatment during the follow-up period (**Figure 1**).

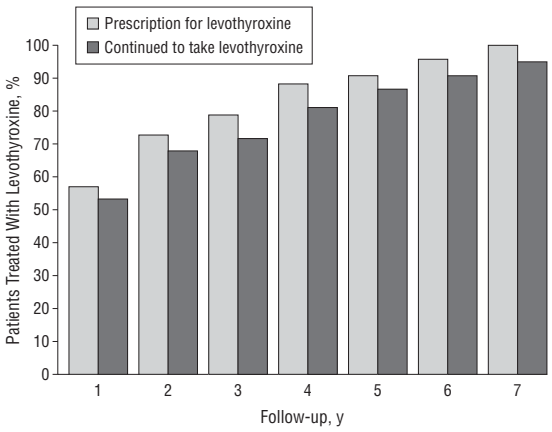

Figure 1. Percentage of patients in the treated group who commenced and continued levothyroxine sodium treatment in each year of follow-up. During the 7.6-year follow-up period, 93.6% of patients prescribed levothyroxine continued to take it.

OUTCOME OF SCH IN THOSE 40 TO 70 YEARS OF AGE

During the follow-up period (median, 7.6 years; range, 0-8 years), IHD events (both fatal and nonfatal) occurred in 165 individuals (5.3%) from the younger group. After adjustment for baseline cardiovascular risk factors, age, sex, baseline serum thyrotropin levels, and levothyroxine use as a time-dependent covariate, the number of incident IHD events was lower in the levothyroxine–treated group (adjusted HR, 0.61; 95% CI, 0.39-0.95) (**Table 2** and **Figure 2**). Adjustment only for baseline age and sex did not change the result (Table 2). All-cause mortality was lower in the levothyroxine–treated younger group (multivariate-adjusted HR, 0.36; 95% CI, 0.19-0.66), mostly because of a reduction in circulatory and cancer-related deaths (Table 2). Incident cerebrovascular disease events were unchanged (Table 2). In the temporal analysis, for each month of exposure to levothyroxine the adjusted HR for IHD events was 0.989 (95% CI, 0.986-0.993). Incident atrial fibrillation was not related to levothyroxine exposure (multivariate-adjusted

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Table 2. Outcomes in Relation to Treatment of Subclinical Hypothyroidism by Age Group

	Age 40-70 y (n = 3093)				Age >70 y (n = 1642)			
	No. (%) of Patients		HR (95% CI)		No. (%) of Patients		HR (95% CI)	
Outcome	Untreated (n = 1459)	Treated (n = 1634)	Multivariate Adjusted[a]	Age and Sex Adjusted	Untreated (n = 823)	Treated (n = 819)	Multivariate Adjusted[a]	Age and Sex Adjusted
Fatal and nonfatal IHD events	97 (6.6)	68 (4.2)	0.61 (0.39-0.95)	0.64 (0.41-0.89)	88 (10.7)	104 (12.7)	0.99 (0.59-1.33)	1.03 (0.98-1.83)
All-cause mortality	94 (6.4)	55 (3.4)	0.36 (0.19-0.66)	0.43 (0.30-0.78)	333 (40.5)	288 (35.2)	0.71 (0.56-1.08)	0.91 (0.65-1.14)
Death due to circulatory[b] diseases (I00-I99)	38 (2.4)	23 (1.4)	0.54 (0.37-0.92)	0.61 (0.37-0.91)	116 (18.3)	134 (17.1)	0.91(0.56-1.46)	0.87 (0.43-1.37)
Death due to IHD events (I20-I25)	27 (1.7)	17 (1.0)	0.43 (0.19-2.05)	0.55 (0.38-1.19)	70(6.3)	56 (5.5)	1.04 (0.56-1.93)	1.12 (0.66-2.05)
Death due to malignant neoplasms (C00-C97)	35 (2.2)	21 (1.2)	0.59 (0.21-0.88)	0.61 (0.36-0.95)	73 (6.5)	49 (4.6)	0.51 (0.24-1.09)	0.73 (0.34-1.16)
Fatal and nonfatal CVA	44 (3.0)	55 (3.4)	1.03 (0.51-2.13)	1.09 (0.75-1.89)	147 (17.9)	145 (17.7)	0.81 (0.31-2.12)	1.11 (0.45-2.01)
Atrial fibrillation	36 (2.3)	35 (2.0)	0.76 (0.26-1.73)	0.87 (0.59-1.44)	87 (7.7)	86 (8.1)	0.98 (0.54-1.76)	1.23 (0.69-1.58)

Abbreviations: CVA, cerebrovascular disease; HR, hazard ratio; IHD, ischemic heart disease.

[a] Adjusted for age, sex, body mass index, socioeconomic deprivation score, total cholesterol level, index serum thyrotropin level, smoking status, history of diabetes mellitus, systolic and diastolic blood pressure, and levothyroxine sodium use as a time-dependent covariate so that patients switched stratum at the time of treatment initiation.

[b] Circulatory events include IHD, CVA, and peripheral vascular disease. *International Statistical Classification of Diseases, 10th Revision (ICD-10)* codes are presented in parentheses.

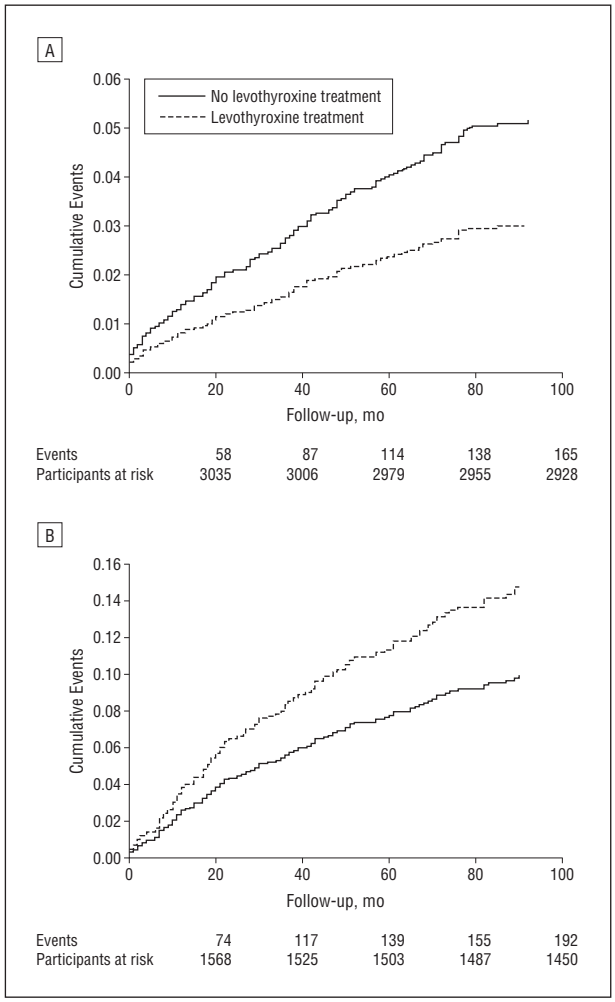

Figure 2. Multivariate-adjusted cumulative event plots for levothyroxine sodium–treated and untreated individuals with subclinical hypothyroidism for fatal and nonfatal ischemic heart disease. A, Younger patients ($P = .02$). B, Older patients ($P = .56$). Multivariate analysis shown is adjusted for age, sex, body mass index, socioeconomic deprivation score, total cholesterol level, index serum thyrotropin level, smoking status, systolic and diastolic blood pressure, history of diabetes mellitus, and levothyroxine use as a time-dependent covariate.

HR for each month of exposure, 0.998; 95% CI, 0.995-1.001).

OUTCOME OF SCH IN THOSE OLDER THAN 70 YEARS

During the follow-up period (median, 5.2 years; range, 0-8 years), IHD events occurred in 192 individuals (11.7%) in the older SCH group. After adjustment for baseline cardiovascular risk factors, age, sex, baseline serum thyrotropin levels, and levothyroxine use as a time-dependent covariate, incident IHD events were not different in the levothyroxine–treated group (adjusted HR, 0.99; 95% CI, 0.59-1.33) (Table 2 and Figure 2). Adjustment for only baseline age and sex did not change the result (Table 2). All-cause mortality was similar in the levothyroxine–treated older group (multivariate-adjusted HR, 0.71; 95% CI, 0.56-1.08). Cause-specific mortality and incident cerebrovascular events were also comparable in the treated older group (Table 2). For each month of exposure to levothyroxine, the risk of IHD events was unchanged (HR, 1.001; 95% CI, 0.998-1.004) after multivariate adjustment. Incident atrial fibrillation was not associated with exposure to levothyroxine (HR adjusted for each month of exposure, 1.000; 95% CI, 0.999-1.001).

SENSITIVITY ANALYSES

Use of cardioprotective medication, contact with health professionals, and medication prescription during the follow-up period in the cohort are given in **Table 3**. The multivariate-adjusted HRs for incident fatal and nonfatal IHD events in the treated vs untreated SCH individuals by age, in decades, are given in **Table 4**. Further analysis of the primary outcome performed after censoring individuals' follow-up on the date when they received levothyroxine therapy showed that during a median follow-up of 4.3 and 3.8 years, respectively, treated vs untreated younger and older individuals had similar risks of incident IHD events (HR, 0.87; 95% CI, 0.59-1.23; and

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Table 3. Cardioprotective and Overall Medication Prescribing and Health Professional Contact During the Study

Variable	Age 40-70 y		Age >70 y	
	Untreated (n = 1459)	Treated (n = 1634)	Untreated (n = 823)	Treated (n = 819)
Aspirin, No. (%)	268 (18.4)	305 (18.7)	430 (52.3)	443 (54.1)
Statins, No. (%)		413 (25.3)	528 (64.2)	548 (66.9)[a]
ACE inhibitors or ARBs, No. (%)	298 (20.4)	322 (19.7)	483 (58.7)	486 (59.3)
Prescribed medications per year,[b] median (range)	4.6 (1-12)	5.1 (1-14)	8.1 (1-17)	7.6 (1-21)
Contact with health professionals per year per participant, median (range)	1.2 (0-6)	1.3 (0-8)	2.3 (1-12)	2.4 (1-14)

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers.
[a] $P = .04$; none of the other parameters assessed in this table were significantly different.
[b] Excluding levothyroxine sodium.

Table 4. Fatal and Nonfatal Ischemic Heart Disease Events by Age Deciles in Levothyroxine Sodium–Treated and Untreated Individuals With Subclinical Hypothyroidism

Age Group, y	Patients, No. (%)		Events, No. (%)		HR[a] (95% CI)
	Treated	Untreated	Treated	Untreated	
40-50	433	384	8 (1.8)	9 (2.3)	0.86 (0.09-18.92)
51-60	642	576	24 (3.7)	29 (5.0)	0.43 (0.16-1.15)
61-70	560	498	22 (3.9)	43 (8.6)	0.41 (0.17-0.97)
71-80	504	454	48 (9.5)	29 (6.4)	1.06 (0.62-1.70)
81-90	268	296	35 (13.1)	28 (9.5)	1.36 (0.57-3.20)
91-107	51	66	4 (7.8)	5 (7.6)	1.67 (0.09-31.4)

Abbreviation: HR, hazard ratio.
[a] Data were adjusted for sex, body mass index, socioeconomic deprivation score, total cholesterol level, index serum thyrotropin level, smoking status, systolic and diastolic blood pressure, history of diabetes mellitus, and levothyroxine use as a time-dependent covariate. Untreated group is the referent (HR = 1).

HR, 1.12; 95% CI, 0.90-1.46; respectively). The HRs for IHD events were also analyzed after excluding individuals who had an IHD event within 6 months of starting levothyroxine therapy (n = 16), and HRs for IHD events remained similar in both age groups (data not shown). Also, we investigated the primary outcome by only including individuals who had persistent SCH during the full follow-up period in the untreated group and by further excluding individuals who commenced treatment with levothyroxine after progression to overt hypothyroidism. This approach demonstrated that the HR for IHD events (99 events in 2367 individuals) was 0.63 (95% CI, 0.42-0.94) in the 40 to 70–year-old group and 1.06 (95% CI, 0.91-1.74) in the older than 70–years age group (n = 106 events in 1079 people). Finally, to look for a biologically plausible gradation of the levothyroxine effect, we analyzed outcomes in relation to median baseline serum thyrotropin levels (6.6 mIU/L). This approach revealed that, in the 40 to 70–years group, compared with untreated individuals with SCH (referent HR of 1.0), treatment with levothyroxine reduced the risk of IHD events (HR, 0.62; 95% CI, 0.39-0.96; in those with thyrotropin levels <6.6 mIU/L; and HR, 0.48; 95% CI, 0.26-0.88; in those with thyrotropin levels ≥6.6 mIU/L; $P = .007$ for trend). In comparison, in the group older than 70 years, treated individuals with SCH who had a thyrotropin level less than 6.6 mIU/L at baseline had an HR of 1.02 (95% CI, 0.66-1.82), and those with a thyrotropin level of 6.6 mIU/L or higher had an HR of 1.19 (95% CI, 0.74-1.8) (P for trend = .08).

COMMENT

Currently, the optimum management of SCH with serum thyrotropin levels of 5 to 10 mIU/L is unclear.[18] The evidence for improvement of symptoms after levothyroxine treatment is equivocal, and the evidence for improvement in vascular outcomes is nonexistent.[19] This analysis of a large cohort of individuals from the UK GPRD has shown that treatment of SCH with levothyroxine in a real-life situation is associated with better outcomes in younger (<70 years) people with respect to incident fatal and nonfatal IHD events and mortality. On the other hand, treatment of older people with SCH was not associated with similar benefits.

A number of cross-sectional and longitudinal epidemiologic studies[2,6,20-27] have assessed the relationship between SCH and IHD, with conflicting results. A recent meta-analysis[28] with individual data showed that the risk of incident IHD was increased in patients with SCH, particularly in those with a thyrotropin level above 10.0 mIU/L. In addition, other meta-analyses[4,5] have shown that the risk of developing IHD was higher only in younger individuals with SCH. Furthermore, SCH was associated with better survival in a study of 85-year-olds.[6] However, most cohort studies and the meta-analyses obtained thereof did not account for subsequent treatment with thyroid hormones; therefore, their results may have missed an important confounder.

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The mechanisms that underlie the results of our study, particularly the important differences in IHD outcomes between younger and older individuals, require explanation. Randomized trials of levothyroxine treatment of SCH have generally shown a beneficial effect on surrogate cardiovascular risk factors, for instance, reduction in low-density lipoprotein cholesterol levels.[14] In addition, improvement in endothelial function, carotid intima media thickness, and left ventricular diastolic function has been shown with treatment in some intervention studies.[15-17] However, in the absence of randomized controlled trial data concerning improved clinical outcomes, current guidelines have not advocated treatment of SCH unless the serum thyrotropin level is greater than 10 mIU/L.[1] In support of this, data are emerging to indicate that the serum thyrotropin reference range may extend upward in healthy older individuals as far as 7.0 mIU/L.[13] Hence, treating older individuals with a high serum thyrotropin level as judged by a reference interval derived from younger individuals may not be expected to improve outcome. It also remains possible that the benefits of treatment of SCH in older persons may be offset by an increased risk of levothyroxine–precipitating adverse cardiovascular events, such as atrial fibrillation, although we provide data, for the first time to our knowledge, that suggest no excess of atrial fibrillation in this group. One unpredicted finding was of lower malignant tumor–related deaths in the younger patients with SCH who were treated with levothyroxine. Although several possible mechanisms might explain this observation,[29,30] this finding could represent a stochastic effect and should be interpreted with caution, particularly because this was not the primary outcome of our analysis.

This study has several strengths. It has ascertained vascular events from a reliable source[9-11] in a large number of individuals with SCH during more than 7 years. The study provides evidence, for the first time to our knowledge, regarding the potential benefits of treatment of SCH on "hard" clinical outcomes, including a composite of fatal and nonfatal vascular events, all-cause morality, and fatal circulatory disease. Given that prospective randomized controlled trials of levothyroxine therapy have yet to commence, this investigation and other studies that examine the outcome of real-life practice may provide the best evidence about the management of SCH for some time. Our data suggest that physicians can be reassured that levothyroxine treatment of SCH in patients aged 40 to 70 years is not harmful and may be associated with modestly improved medium-term health outcomes. Indeed, this design is representative of real practice because it is impossible for a clinician to know how good subsequent biochemical control will be at the time of the decision to commence levothyroxine therapy in patients with SCH. We can also use these data to estimate that a well-powered randomized controlled trial of levothyroxine intervention in 40 to 70–year-old people with SCH would require approximately 1450 individuals to be recruited.

This analysis also has a number of weaknesses. This is a retrospective study and therefore has limitations with regard to unrecorded differences in the reason treatment may have been started between the groups. We have included all available cardiovascular risk factors, biochemical data, and medication use as variables in our analysis, but there may be unsuspected or unmeasured differences, such as a healthy user bias, between the groups. Nevertheless, physician contact with patients, overall medication use, and cardioprotective medication use were not different between the levothyroxine–treated and untreated groups, suggesting that concurrent illness did not substantially bias treatment decisions. Finally, we used serum values for thyrotropin and FT_4 uniformly in classifying individuals with SCH from many hundreds of contributing practices, whereas a number of different biochemical assays with slightly different reference ranges were used to record the data. The conservative definition of SCH used in this analysis makes it unlikely that we will have misclassified individuals with SCH. Also, adjustment for baseline thyrotropin level was included as a variable in our analyses to try to overcome this potential limitation.

In conclusion, treatment with levothyroxine was associated with fewer IHD events and reduced all-cause mortality during an 8-year period of observation in 40 to 70–year-old individuals with SCH but not in those who were older. A prospective randomized controlled trial is required to confirm these findings.

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Online-Only Material: The eAppendixes are available at http://www.archinternmed.com.

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