Thyroid Function and Mortality in Patients Treated for Hyperthyroidism

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Context Hyperthyroidism has been reported to cause excess all-cause and circulatory mortality. Whether this can be reversed is unknown, as is the influence of mild persisting thyroid dysfunction and treatment-induced hypothyroidism.

Objectives To determine whether radioiodine treatment is associated with increased mortality and to determine the influences of mild thyroid dysfunction and the development of overt hypothyroidism treated with thyroxine (T_4).

Design, Setting, and Participants A population-based study of 2668 individuals aged 40 years or older treated for overt hyperthyroidism with radioiodine in the West Midlands region of England from 1984-2002.

Main Outcome Measures Cause of death compared with age- and period-specific mortality in England and Wales and assessment of the influence of T_4 therapy for radioiodine-induced hypothyroidism and subclinical thyroid dysfunction on mortality.

Results In 15 968 person-years of follow-up, 554 died vs 487 expected deaths (standardized mortality ratio [SMR], 1.14; 95% confidence interval [CI], 1.04-1.24, *P*=.002). Increased risks of all-cause and circulatory deaths vs age- and period-specific mortality were observed in follow-up in those not requiring, or prior to, T_4 therapy. These increased risks were not observed during follow-up on T_4 therapy (circulatory disease SMR prior to T_4, 1.33; 95% CI, 1.14-1.53 vs SMR, 0.91; 95% CI, 0.70-1.17 during T_4). Patients receiving T_4 had decreased risk of mortality vs risk in the period not requiring, or prior to, T_4 therapy (all-cause mortality hazard ratio [HR], 0.65; 95% CI, 0.54-0.79; circulatory mortality HR, 0.65; 95% CI, 0.48-0.87). Increased all-cause mortality vs the background population was observed in the period prior to T_4 therapy in follow-up associated with low, normal, and high serum thyrotropin. The SMR for ischemic heart disease increased slightly when analyzed by serum thyrotropin, high serum thyrotropin being the highest SMR (low thyrotropin SMR, 1.06; 95% CI, 0.75-1.45; normal thyrotropin SMR, 1.17; 95% CI, 0.76-1.71; high thyrotropin SMR, 1.48; 95% CI, 0.86-2.37). Comparison within the cohort showed that mild hypothyroidism prior to T_4 therapy was associated with increased risk of mortality from ischemic heart disease vs biochemical euthyroidism (HR, 2.08; 95% CI, 1.04-4.19).

Conclusions Patients treated with radioiodine for hyperthyroidism had increased mortality vs age- and period-specific mortality in England and Wales, a finding no longer evident during T_4 therapy. This supports treating hyperthyroidism with doses of radioiodine sufficient to induce overt hypothyroidism. The association within the cohort of mortality from ischemic heart disease with subclinical hypothyroidism suggests T_4 replacement should be considered should this biochemical abnormality develop after radioiodine therapy.

JAMA. 2005;294:71-80 www.jama.com

HYPERTHYROIDISM IS A COMmon disorder affecting approximately 2% of women and 0.2% of men.[1] It exerts a major influence on the circulatory system with cardiovascular symptoms and signs being prominent.[2] The development of atrial fibrillation is one of the most significant manifestations of hyperthyroidism, being reported in 5% to 15% of those who have it. Increasing evidence suggests that mortality, especially from circulatory disease, is also increased in hyperthyroidism.

We previously reported increased all-cause and circulatory mortality in a cohort of 7209 individuals with overt hyperthyroidism treated with radioiodine from 1950 through 1989.[3] In that study, we concluded that increased mortality may have reflected a direct effect of thyroid hormone excess, a specific influence of radioiodine treatment, or (since hypothyroidism is a frequent complication of radioiodine therapy) an influence of hypothyroidism, its subsequent treatment with thyroxine (T_4), or both. In the present study, in which we have prospectively collected data on thyroid status after radioiodine treatment, we now address the influence of hypothyroidism and its treatment with T_4.

In contrast to hyperthyroidism, little is known about the effect of hypothyroidism (or its treatment with thyroid hormone) on mortality. Overt hypothyroidism has been reported to be associated with cardiovascular disease although evidence for an association is largely confined to older literature reporting findings from relatively small numbers.[4,5] Such an association is, however, plausible given the hypercholes-

See also Patient Page.

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terolemia, diastolic hypertension, and left ventricular dysfunction found in overt hypothyroidism.[6] Evidence is so far lacking that effective treatment of hypothyroidism with T_4 (indicated by restoration of serum thyrotropin to normal levels) is associated with reduction in any vascular risk due to hypothyroidism although it has been reported anecdotally that symptoms of ischemic heart disease may improve after initiation of T_4 treatment.[7]

Subclinical or mild thyroid disease is a common disorder, especially in those treated for overt thyroid dysfunction. *Subclinical hypothyroidism*, defined as high serum thyrotropin with normal serum free T_4, is found in up to 10% of the screened community-based cohorts, with increasing prevalence with age while *subclinical hyperthyroidism*, defined as low serum thyrotropin with normal serum free T_4, is found in approximately 2%.[8,9] Treatment of overt hyperthyroidism with radioiodine is often followed by a period of subclinical hyperthyroidism and also results in eventual subclinical or overt hypothyroidism in at least 50%.[10] Debate surrounds the question of whether *subclinical thyroid dysfunction*, defined biochemically as high or low serum thyrotropin concentrations with normal free T_4, is itself associated with clinically significant morbidity and mortality. There is evidence to support an association of serum thyrotropin values greater than 10 mIU/L with elevation in serum cholesterol levels, as well as evidence supporting an association of low serum thyrotropin with risk of development of atrial fibrillation and with circulatory mortality.[11] Overall, data supporting associations of subclinical thyroid disease with symptoms, adverse clinical outcomes, or benefits of treatment are few[11] although there is considerable ongoing debate about the management of subclinical thyroid dysfunction.[12]

In the present study, we have investigated mortality in a cohort of individuals treated with radioiodine for hyperthyroidism and examined the effect of T_4 treatment for radioiodine-induced overt hypothyroidism on mortality. In view of uncertainty about the effect of subclinical thyroid dysfunction on circulatory mortality risk, we also examined the influence of subclinical hypothyroidism and subclinical hyperthyroidism after radioiodine treatment.

METHODS

Participants and Data Recorded

The study participants were all patients who had been treated for hyperthyroidism in the West Midlands region of England during the years 1984 through 2002 and for whom serum thyrotropin and free T_4 concentrations had been recorded since 1988 (when measurement of serum thyrotropin using a sensitive assay was introduced). Participants treated as recently as 2002 were included in view of our previous finding of increased all-cause and circulatory mortality within the first year after treatment.[3] A start date of 1984 was chosen because serial measurements of free T_4 and thyrotropin were recorded routinely from that time; there was overlap of 542 patients between this cohort and another cohort investigated previously for mortality.[3]

Demographic data and information regarding the date, dose, and number of radioiodine treatments, serial measurements of serum free T_4 and thyrotropin, and date of initiation of T_4 therapy were recorded in the Birmingham Thyroid Follow-up Register, which was established in the 1950s to ensure regular biochemical testing of patients treated with radioiodine and detection of hypothyroidism after treatment. The register has been described elsewhere.[10,13] Patients were registered at the time of receiving their first radioiodine dose; they were discharged from clinic review and transferred to follow-up via the computerized register approximately 12 months after restoration of *euthyroidism*, defined as normal serum free T_4 and free triiodothyronine (T_3) and not receiving antithyroid drug therapy. The first recorded thyrotropin measurement was at this time. Patients were subsequently tested at maximum intervals of 14 months and T_4 therapy initiated when biochemical testing showed overt hypothyroidism (high serum thyrotropin [>5.0 mIU/L] and low free T_4 [0.69 ng/dL {<9.0 pmol/L}]). The findings of subclinical hyperthyroidism (serum thyrotropin <0.5 mIU/L with normal free T_4 and free T_3 levels) and subclinical hypothyroidism (serum thyrotropin >5.0 mIU/L with normal free T_4 levels) during follow-up did not prompt change in patient management. Other data, including risk factors for vascular disease, were not recorded on the Thyroid Follow-up Register and have not been analyzed in the present study.

The initial cohort comprised 3350 patients. Four were excluded because date of birth was unknown, 10 because date of first thyrotropin treatment was unknown, and 53 were recorded as emigrated or not traced by the Office for National Statistics. Those younger than 40 years (n = 615) were excluded to minimize potential confounding due to age and because they represented a group at low-risk of mortality during follow-up (4 deaths only observed vs expected 3.85). Those in the cohort for whom a biochemical test result was recorded during 2003 were deemed alive. For the remainder of the final group of 2668 patients, demographic data were sent to the UK Office for National Statistics for tracing in the National Health Service Central Register to determine vital status on December 31, 2003. For those who had died before that date, death certificates were obtained and underlying cause of death coded by Office for National Statistics according to the 9th or 10th revision of the *International Classification of Diseases* (*ICD-9* or *ICD-10*). The study was approved by the South Birmingham Research Ethics Committee.

Statistical Analysis

Comparison of Mortality With Background Population. The cause of death for each patient who had died was compared with age-, sex-, and year-specific mortality data from England

and Wales, recorded in the World Health Organization data bank. The number of person-years at risk, contibuted by each patient in the study, was calculated from the date of first serum thyrotropin measurement recorded on the register (approximately 12 months after euthyroidism was restored after radioiodine treatment) to the census date of December 31, 2003, or until the date of death.

The expected number of deaths was calculated by multiplying the number of person-years in each stratum defined according to age, sex, and calendar year by the corresponding mortality rate for that age, sex, and period in England and Wales. The standardized mortality ratio (SMR, the ratio of observed to expected deaths) was used to estimate the relative risk. The 95% confidence intervals (CIs) for the SMR were calculated on the assumption that the observed number of deaths followed a Poisson distribution. Similarly, we calculated the expected number of deaths during the period prior to or not requiring T_4 treatment, and during the period receiving T_4 treatment, based on the number of person-years accumulated not receiving and receiving T_4 treatment and calculated SMRs as described above.

Age-specific mortality rates for all causes of death were calculated for both sexes during follow-up prior to, or not requiring, T_4 treatment or during the period of T_4 treatment, and compared them with mortality rates for the background population. A similar method to that described above was used to calculate SMRs during the period of follow-up prior to T_4 therapy specifically associated with *mild hypothyroidism*, defined as increased serum thyrotropin levels); *euthyroidism*, normal serum thyrotropin levels; or *mild hyperthyroidism*, low serum thyrotropin.

Comparison of Mortality Within the Cohort. A time-dependent Cox proportional hazards-regression model was used to evaluate the prognostic influence of T_4 therapy and of serum thyrotropin measurements on survival.[14] The date of the first recorded thyrotropin value on the register was considered time 0 and recording of T_4 treatment (taking or not taking) was considered as a time-dependent covariable. We also investigated differences in risk associated with subclinical thyroid dysfunction recorded during follow-up before initiation of T_4 therapy for overt hypothyroidism. For this, we considered both the first recorded thyrotropin measurement as a single time-constant categorical variable (low, normal, or high serum thyrotropin levels), as well as repeated measures of serum thyrotropin considered as time-dependent categorical variables. These models were adjusted for patient age at entry (in 5-year age groups), sex, and interval between radioiodine treatment and date of first serum thyrotropin measurement. Before presenting results from the Cox models, we tested the proportional hazard assumption by introducing constructed time-dependent variables for all covariates and tested for their significance.

The hazard ratios with 95% CIs were used to estimate the adjusted relative risk of dying for patients requiring T_4 therapy for overt hypothyroidism and for those with subclinical thyroid dysfunction (low or high serum thyrotropin with normal free T_4 levels) during follow-up prior to T_4 therapy. Kaplan-Meier curves were constructed for survival from ischemic heart disease during the period of follow-up prior to T_4 therapy and predicted by the first recorded serum thyrotropin measurement (low, normal, or high).

Data were analyzed using SAS version 8.02 statistical software (SAS Institute Inc, Cary, NC). All *P* values were 2-sided. $P<.05$ was considered statistically significant.

RESULTS

Characteristics of the 2668 patients in the study are shown in TABLE 1. Their median age at first measurement of serum thyrotropin was 62 years (range, 40-96 years) and 84.3% had received only 1 dose of radioiodine, in accordance with the local treatment protocol of administration of fixed doses of 185 or 370 MBq.[10,13] Of the 2668, 1212 (45.4%) of the participants had commenced T_4 therapy by the end of the period of follow-up with similar rates of overt hypothyroidism regardless of the cumulative dose of radioiodine (<220 MBq, 43%; 221-480 MBq, 47%; >480 MBq, 45%). The baseline characteristics of men and women were similar (Table 1).

Mortality From All Causes

Of the 2668 patients, 554 died before the end of the study. The expected number of deaths for the total number of person-years at risk (15 968 years) was 487, leading to a relative risk of 1.14 for mortality from all causes (95% CI, 1.04-1.24; *P*=.002; TABLE 2). The risks of death due to endocrine and metabolic disorders and circulatory diseases were significantly greater than what they were in the general population and together accounted for 47 of the 67 excess deaths observed. The risk of death from other major causes, including cancer and respiratory diseases, were not increased significantly (Table 2).

Excess deaths from circulatory diseases were confined to cardiovascular deaths (SMR, 1.18; 95% CI, 1.00-1.38, *P*=.02), the highest relative risk being attributed to the *ICD* category "diseases of the pulmonary circulation and other heart disease." Of 43 deaths in this category, 30 were ascribed to dysrhythmias or cardiac failure. There were also small and nonsignificant increases in the number of deaths from ischemic heart disease and cerebrovascular disease. When mortality among men and women was considered separately, the increase in all-cause, circulatory, and cardiovascular risk was confined to women; in men an increase in deaths from respiratory diseases was apparent (Table 2). Repeat analysis confining the cohort to those treated with radioiodine since 1990 (n=2126; ie, excluding the 546 patients included in a cohort investigated previously[3]) showed an identical pattern of results, both in terms of

mortality from circulatory diseases (observed deaths, 143; expected, 119; SMR, 1.21; 95% CI, 1.02-1.42; *P*=.02) and other causes of death.

Mortality Compared Prior to T_4 Therapy and During T_4 Therapy

Mortality was compared during follow-up specifically associated with no T_4 therapy (ie, in those never overtly hypothyroid and requiring T_4 or prior to development of overt hypothyroidism) with follow-up specifically during treatment with T_4 for overt hypothyroidism. All-cause mortality was increased in the cohort compared with the background population of England and Wales when not taking, or before commencement of, T_4 therapy. This excess mortality was no longer evident when risk of death for the cohort (compared with the background population) was considered for the period of follow-up during T_4 therapy (TABLE 3). This difference largely reflected a difference in risk of death from circulatory diseases, and specifically from death due to cardiovascular diseases, especially the subcategory that included deaths from dysrhythmias and heart failure, as well as cerebrovascular diseases (Table 3). A similar pattern was observed when mortality was examined in men and women (Table 3) and when the cohort was stratified according to age (data available on request). Age-specific mortality rates for all causes of death and for both sexes, compared with the background population of England and Wales, for the period of follow-up prior to, or not requiring, T_4 and follow-up associated with T_4 therapy are shown in FIGURE 1. This illus-

Table 1. Demographic and Treatment Characteristics of the Participants With Hyperthyroidism Treated With Radioiodine From 1984-2002*

Characteristics	Whole Cohort	Men	Women
All participants	2668	505	2163
Median age, y	62	61	63
Age, y, No. (%)			
40-49	554 (20.8)	108 (21.3)	446 (20.6)
50-54	330 (12.4)	69 (13.6)	261 (12.1)
55-59	275 (10.3)	57 (11.3)	218 (10.1)
60-64	291 (10.9)	62 (12.3)	229 (10.6)
65-69	315 (11.8)	73 (14.5)	242 (11.2)
70-74	339 (14.9)	57 (11.3)	282 (13.0)
75-79	282 (10.6)	43 (8.5)	239 (11.0)
>80	282 (10.6)	36 (7.1)	246 (11.4)
Cumulative radioiodine dose, MBq, No. (%)†			
<220	669 (25.1)	104 (20.6)	565 (26.2)
221-480	1179 (44.3)	229 (45.5)	950 (44.0)
>480	812 (30.5)	170 (33.8)	642 (29.7)
Total No. of radioiodine doses, No. (%)			
1	2251 (84.3)	408 (81.0)	1843 (85.2)
2	350 (13.1)	85 (16.8)	265 (12.3)
3	67 (2.5)	12 (2.3)	55 (2.5)
Thyroxine replacement, No. (%)			
No	1456 (54.6)	256 (50.7)	1200 (55.5)
Yes	1212 (45.4)	249 (49.3)	963 (44.5)
Median duration of follow-up, y	5.6	5.5	5.6
Person-years of follow-up			
Overall	15 968	2949	13 019
Not taking or before T_4 replacement	9695	1658	8037
During T_4 replacement	6273	1291	4982

*Percentages may not sum to 100 due to rounding.
†Information on cumulative radioiodine dose was missing for 8 patients.

Table 2. Observed and Expected Numbers of Deaths and Standardized Mortality Ratios for Major Causes of Deaths

		Both Sexes (N = 2668)			Men (n = 505)			Women (n = 2163)		
Primary Cause of Death	*ICD-9* Code	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)
All causes		554	487	1.14 (1.04-1.24)	98	92.9	1.05 (0.86-1.29)	456	394	1.16 (1.05-1.27)
Malignant neoplasms	140-208	110	111	0.99 (0.82-1.20)	22	25.5	0.86 (0.54-1.31)	88	85.4	1.03 (0.83-1.27)
Endocrine and metabolic	240-279	13	6.9	1.90 (1.01-3.24)	2	1.2	1.65 (0.20-5.97)	11	5.6	1.95 (0.97-3.48)
Circulatory diseases	390-459	249	209	1.19 (1.05-1.35)	35	40.1	0.87 (0.61-1.21)	214	169	1.27 (1.10-1.45)
Cardiovascular diseases	390-429	159	135	1.18 (1.00-1.38)	25	28.8	0.87 (0.56-1.28)	134	106	1.27 (1.06-1.50)
Rheumatic or hypertensive	390-409	5	5	1.00 (0.32-2.33)	0	0.7	0.00 (0.00-5.43)	5	4.3	1.15 (0.37-2.70)
Ischemic heart disease	410-414	111	104	1.06 (0.88-1.28)	18	24.6	0.73 (0.43-1.16)	93	79.7	1.17 (0.94-1.43)
Diseases of pulmonary circulation and other heart disease	415-429	43	25.3	1.70 (1.23-2.29)	7	3.5	1.98 (0.79-4.07)	36	21.7	1.66 (1.16-2.30)
Cerebrovascular diseases	430-438	69	59.5	1.16 (0.90-1.47)	9	7.9	1.14 (0.52-2.16)	60	51.6	1.16 (0.89-1.50)
Other circulatory diseases	440-459	21	15	1.40 (0.87-2.14)	1	3.4	0.30 (0.01-1.66)	20	11.6	1.72 (1.06-2.66)
Respiratory diseases	460-519	94	83.8	1.12 (0.91-1.37)	24	15.3	1.57 (1.00-2.33)	70	68.5	1.02 (0.80-1.29)
Other causes		88	76.4	1.15 (0.92-1.42)	15	10.8	1.39 (0.78-2.29)	73	65.6	1.11 (0.87-1.40)

Abbreviations: CI, confidence interval; *ICD-9*, *International Classification of Diseases, Ninth Revision*; SMR, standardized mortality ratio.

trates an increase in all-cause mortality associated with follow-up prior to T_4, not evident during follow-up associated with T_4 therapy.

The absence of increased risk of death from all causes or from vascular diseases in the cohort when taking T_4 therapy was sustained, being evident both in the first 5 years after starting T_4 (circulatory disease SMR, 0.85; 95% CI, 0.59-1.18; *P*=.18) and the period 5 years or more after starting T_4 therapy (circulatory disease SMR, 1.02; 95% CI, 0.67-1.49; *P*=.46).

The results were similar when comparison within the cohort was performed using a multivariable Cox proportional hazards regression model including T_4 therapy as a time-dependent covariable (**TABLE 4**). All-cause mortality was decreased during fol-

Table 3. Observed and Expected Numbers of Deaths and Standardized Mortality Ratios for Selected Causes of Death Defined in the Cohort While Not Taking or Before Taking T_4 Therapy and During T_4 Therapy

	Not Taking or Before Taking T_4 Therapy			During T_4 Therapy		
Primary Cause of Death	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)
All causes						
All	408	324	1.26 (1.14-1.38)	146	162	0.90 (0.76-1.06)
Men	64	52.3	1.22 (0.94-1.56)	34	40.6	0.84 (0.58-1.17)
Women	344	272	1.26 (1.13-1.40)	112	122	0.92 (0.76-1.11)
Malignant neoplasms						
All	73	71.2	1.03 (0.80-1.29)	37	39.7	0.93 (0.66-1.28)
Men	13	14.4	0.90 (0.48-1.54)	9	11.0	0.82 (0.37-1.55)
Women	60	56.8	1.06 (0.81-1.36)	28	28.7	0.98 (0.65-1.41)
Endocrine and metabolic						
All	10	4.60	2.17 (1.04-4.00)	3	2.3	1.33 (0.27-3.88)
Circulatory diseases						
All	187	141	1.33 (1.14-1.53)	62	67.7	0.91 (0.70-1.17)
Men	23	22.7	1.01 (0.64-1.52)	12	17.4	0.69 (0.36-1.20)
Women	164	119	1.38 (1.18-1.61)	50	50.3	0.99 (0.74-1.31)
Cardiovascular diseases						
All	118	90.3	1.31 (1.08-1.56)	41	44.2	0.93 (0.67-1.26)
Men	18	16.3	1.10 (0.65-1.75)	7	12.5	0.56 (0.22-1.15)
Women	100	74.0	1.35 (1.10-1.64)	34	31.7	1.07 (0.74-1.50)
Rheumatic or hypertensive*						
All	4	3.4	1.19 (0.32-3.04)	1	1.6	0.61 (0.02-3.42)
Ischemic heart disease						
All	81	69.8	1.16 (0.92-1.44)	30	34.5	0.87 (0.59-1.24)
Men	12	14.0	0.86 (0.44-1.50)	6	10.6	0.57 (0.21-1.23)
Women	69	55.8	1.24 (0.96-1.56)	24	23.9	1.00 (0.64-1.49)
Diseases of pulmonary circulation or other heart diseases						
All	33	17.1	1.92 (1.33-2.71)	10	8.1	1.23 (0.59-2.27)
Men	6	2	3.06 (1.12-6.66)	1	1.6	0.64 (0.02-3.55)
Women	27	15.2	1.78 (1.17-2.58)	9	6.5	1.38 (0.63-2.61)
Cerebrovascular diseases						
All	52	40.9	1.27 (0.95-1.67)	17	18.6	0.91 (0.53-1.46)
Men	4	4.5	0.90 (0.24-2.30)	5	3.5	1.44 (0.47-3.36)
Women	48	36.5	1.32 (0.97-1.74)	12	15.1	0.79 (0.41-1.39)
Other circulatory diseases†						
All	17	10	1.70 (0.99-2.72)	4	4.9	0.81 (0.21-2.08)
Men	1	1.9	0.53 (0.01-2.93)	0	1.5	0.00 (0.00-2.52)
Women	16	8.1	1.97 (1.12-3.20)	4	3.5	1.15 (0.31-2.95)
Respiratory diseases						
All	70	56.1	1.25 (0.97-1.58)	24	27.7	0.87 (0.55-1.29)
Men	18	8.48	2.12 (1.26-3.35)	6	6.8	0.88 (0.32-1.92)
Women	52	47.6	1.09 (0.82-1.43)	18	20.9	0.86 (0.51-1.36)
Other causes of death						
All	68	51.7	1.32 (1.02-1.67)	20	24.8	0.81 (0.49-1.25)
Men	9	6.04	1.49 (0.68-2.83)	6	4.9	1.23 (0.45-2.68)
Women	59	45.6	1.29 (0.98-1.67)	14	20	0.70 (0.38-1.17)

Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.
*Diseases of the arteries, arterioles, capillaries, veins, lymphatic vessels, lymph nodes, and other and unspecified disorders of the circulatory system.
†Sex-specific estimates are not presented when based on fewer than 10 observed deaths.

low-up of patients receiving T_4 therapy compared with risk during follow-up when not taking T_4 therapy (hazard ratio, 0.65; 95% CI, 0.54-0.79; $P<.001$). This was largely accounted for by reduced risk of death from circulatory disorders while taking T_4 (hazards ratio, 0.65; 95% CI, 0.48-0.87; $P=.004$) and specifically by reduced risk of death from cardiovascular diseases. Significant differences in mortality from respiratory causes and causes of death other than due to cancer, circulatory, or respiratory diseases were also observed. Reductions in all-cause and circulatory mortality during T_4 therapy compared with no T_4, or before, T_4 therapy were observed in both men and women when analyzed separately (Table 4).

Influence of Subclinical Thyroid Dysfunction on Mortality

Mortality was compared with the background population during follow-up prior to, or not requiring, T_4 therapy (ie, the period when all-cause and circulatory mortality was increased) but specifically subdivided into follow-up also associated with low serum thyrotropin (<0.5 mIU/L), normal serum thyrotropin (0.5-5.0 mIU/L), or high thyrotropin (>5.0 mIU/L). All-cause mortality (as predicted from the overall SMR of 1.26 for this period of follow-up) was increased in the subgroups defined by serum thyrotropin measurements (all-cause SMRs during follow-up associated with thyrotropin at low [SMR, 1.19; 95% CI, 1.03-1.37], normal [SMR, 1.40; 95% CI, 1.18-1.65], and high [SMR, 1.19; 95% CI, 0.91-1.52] levels). Circulatory disease mortality followed a similar pattern, being significantly increased compared with the background population for follow-up associated with normal serum thyrotropin (circulatory disease SMRs associated with low [SMR, 1.18; 95% CI, 0.9-1.46], normal [SMR, 1.53; 95% CI, 1.20-1.94], and high [SMR, 1.37; 95% CI, 0.93-1.95] thyrotropin levels). Ischemic heart disease mortality was nonsignificantly increased in all thyrotropin subgroups, the highest SMR being associated with high serum thyrotropin (ischemic heart disease SMRs associated with low [SMR, 1.06; 95% CI, 0.75-1.45], normal [1.17, 95% CI, 0.76-1.71], and high [SMR, 1.48; 95% CI, 0.86-2.37] serum thyrotropin).

Comparison according to serum thyrotropin was also performed within the cohort during follow-up when not re-

Figure 1. Age-Specific Mortality Rates for All Causes

Represents 2163 women and 505 men during follow-up before or not requiring thyroxine (T_4) therapy or during T_4 therapy compared with the rates for the background population of England and Wales.

Table 4. Effect of Thyroxine Therapy for Overt Hypothyroidism

Cause of Death	*ICD-9* Code	Both Sexes		Men		Women	
		HR (95%CI)*	*P* Value	HR (95%CI)*	*P* Value	HR (95%CI)*	*P* Value
All causes		0.65 (0.54-0.79)	<.001	0.54 (0.35-0.85)	.008	0.67 (0.54-0.84)	<.001
Malignant neoplasms	140-208	0.80 (0.53-1.20)	.28	0.67 (0.28-1.61)	.37	0.82 (0.52-1.30)	.40
Endocrine and metabolic	240-279	0.58 (0.16-2.14)	.41	8.47 (0.25-290)	.24	0.44 (0.09-2.04)	.29
Circulatory diseases	390-459	0.65 (0.48-0.87)	.004	0.52 (0.24-1.11)	.09	0.67 (0.49-0.93)	.01
Cardiovascular diseases	390-429	0.68 (0.47-0.97)	.03	0.41 (0.17-1.03)	.06	0.78 (0.52-1.15)	.21
Rheumatic or hypertensive	390-409	0.63 (0.07-6.07)	.69	. . .		0.63 (0.07-6.07)	.69
Ischemic heart disease	410-414	0.69 (0.45-1.06)	.09	0.52 (0.19-1.41)	.20	0.76 (0.47-1.22)	.25
Diseases of pulmonary circulation and other heart disease	415-429	0.64 (0.31-1.32)	.22	0.14 (0.01-1.59)	.11	0.84 (0.39-1.83)	.66
Cerebrovascular disease	430-438	0.66 (0.38-1.17)	.15	1.34 (0.28-6.32)	.72	0.55 (0.29-1.05)	.07
Other circulatory diseases	440-459	0.42 (0.14-1.27)	.12	. . .		0.44 (0.14-1.33)	.15
Respiratory diseases	460-519	0.62 (0.38-1.00)	.05	0.31 (0.11-0.88)	.03	0.71 (0.41-1.22)	.26
Other causes of death		0.52 (0.31-0.88)	.01	0.58 (0.19-1.76)	.33	0.52 (0.29-0.94)	.03

Abbreviation: *ICD-9*, *International Classification of Diseases, Ninth Revision*; ellipses, no deaths observed.
*Hazard ratios (HRs) and 95% confidence intervals (CIs) for the effect of T_4 replacement on the risk of dying for selected causes of death obtained from a multivariate Cox proportional hazards regression model adjusted for age, sex, and interval between radioiodine treatment and date of first thyrotropin measurement.

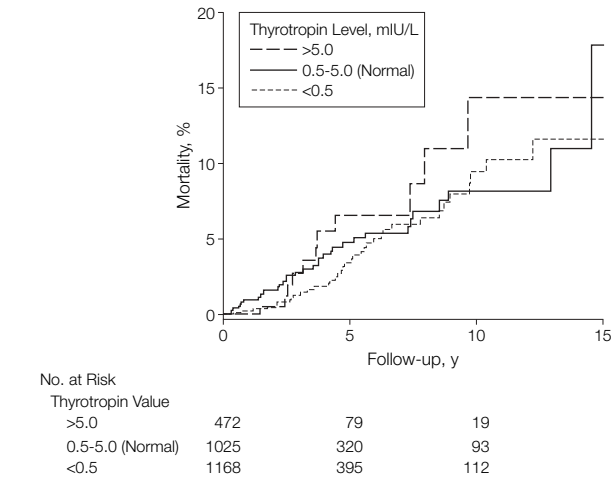
Table 5. Prognostic Influence of Initial and Repeated Thyrotropin Measurements on Mortality During Follow-up Not Requiring or Before Thyroxine Therapy

Cause of Death	*ICD-9* Code	1st Recorded Thyrotropin Measurement After Radioiodine Treatment, mIU/L			Using Repeated Thyrotropin Measures, mIU/L		
			HR (95% CI)*			HR (95% CI)*	
		Normal (0.5-5.0)	Low (<0.5)	High (>5.0)	Normal (0.5-5.0)	Low (<0.5)	High (>5.0)
All causes		1.00	0.95 (0.77-1.17)	0.95 (0.65-1.39)	1.00	0.86 (0.70-1.07)	1.08 (0.78-1.50)
Malignant neoplasms	140-208	1.00	0.95 (0.58-1.55)	0.75 (0.29-1.98)	1.00	0.75 (0.45-1.26)	0.82 (0.36-1.84)
Endocrine and metabolic	240-279	1.00	0.66 (0.17-2.61)	0.97 (0.11-8.72)	1.00	1.08 (0.28-4.12)	1.04 (0.12-9.15)
Circulatory diseases	390-459	1.00	0.86 (0.63-1.17)	1.14 (0.67-1.94)	1.00	0.78 (0.57-1.08)	1.33 (0.85-2.10)
Cardiovascular diseases	390-429	1.00	1.00 (0.60-1.48)	1.44 (0.76-2.75)	1.00	0.89 (0.60-1.34)	1.66 (0.96-2.87)
Rheumatic or hypertensive	390-409	1.00	1.57 (0.14-18.2)	3.63 (0.21-62.3)	1.00	1.06 (0.07-17.2)	7.80 (0.67-90.4)
Ischemic heart disease	410-414	1.00	1.06 (0.66-1.71)	2.08 (1.04-4.19)	1.00	0.97 (0.59-1.57)	1.93 (1.02-3.66)
Diseases of pulmonary circulation and other heart disease	415-429	1.00	0.86 (0.43-1.74)	. . .	1.00	0.75 (0.36-1.58)	0.63 (0.14-2.72)
Cerebrovascular disease	430-438	1.00	0.76 (0.42-1.36)	0.88 (0.30-2.57)	1.00	0.63 (0.34-1.17)	0.86 (0.33-2.25)
Other circulatory diseases	440-459	1.00	0.47 (0.16-1.33)	0.44 (0.06-3.56)	1.00	0.66 (0.22-1.95)	0.99 (0.21-4.63)
Respiratory diseases	460-519	1.00	0.98 (0.59-1.62)	1.00 (0.41-2.45)	1.00	0.82 (0.49-1.38)	1.07 (0.49-2.32)
Other causes		1.00	1.22 (0.74-2.02)	0.57 (0.17-1.89)	1.00	1.28 (0.78-2.11)	0.67 (0.24-1.92)

Abbreviation: *ICD-9*, *International Classification of Diseases, Ninth Revision*; ellipses, no deaths observed.
*Hazard ratio (HRs) and 95% confidence intervals (CIs) for the effect of thyrotropin category on the risk of dying for selected causes of death obtained from a multivariate Cox proportional hazards regression model adjusted for age, sex, and interval between radioiodine treatment and date of first serum thyrotropin measurement.

quiring or before T_4 therapy. Outcome was considered in relation to both first recorded measurement of serum thyrotropin during long-term follow-up and in relation to repeated measures of serum thyrotropin (TABLE 5). During this period, the presence of high serum thyrotropin was not associated with significant differences in all-cause or circulatory mortality overall compared with normal thyrotropin values. However, an increased risk of death from ischemic heart disease was found, both when high thyrotropin was considered as a single measure (first recorded measurement on the register; FIGURE 2) or as a repeated finding recorded during follow-up (Table 5). In contrast, subclinical hyperthyroidism (serum thyrotropin <0.5 mIU/L) was not associated with a difference in risk of mortality compared with normal thyrotropin levels. No relationship was evident when mortality was investigated according to recorded serum free T_4 concentrations (data available on request).

Figure 2. Kaplan-Meier Survival Curves



Relationship between survival from ischemic heart disease and first recorded serum thyrotropin measurement.

COMMENT

Mortality in Whole Cohort

We have found an increased risk of all-cause and circulatory mortality in a cohort of patients treated with radioiodine from 1984 through 2002. These findings were similar to those reported previously from our follow-up of a cohort treated with radioiodine from 1950 through 1989,[3] our results indicating that despite perception of earlier or better diagnosis and treatment for overt hyperthyroidism, increased risk of death persists in this disorder in a contemporary cohort. Our present findings of a 14% increase in mortality compared with the background population agrees not only with our previous study[3] but also with 2 other cohort studies in the United States[15] and Sweden[16] that reported similar findings 10 to 15 years ago. We found significant increases in the risk of death attributed to endocrine disorders, especially thyroid disease, as expected, and all forms of cardiovascular disease (especially deaths due to

dysrhythmias and cardiac failure), without significant effects on other major causes of mortality, such as cancer, again in agreement with previous results. A significant excess of deaths due to respiratory disease was confined to men, a finding reported previously in Sweden.[16]

Effect of Development of Overt Hypothyroidism

Because hypothyroidism frequently develops during long-term follow-up of patients treated for hyperthyroidism with radioiodine,[10] we wished to determine whether treatment of overt hypothyroidism with T_4 might affect the adverse influence of hyperthyroidism on mortality seen in this and previous studies. One study of 710 women with idiopathic hypothyroidism described increased mortality from all causes,[15] which may have reflected hyperlipidemia, diastolic hypertension, or diastolic left ventricular dysfunction known to be associated with overt hypothyroidism.[6]

In the present study, we found that cardiovascular risk was increased compared with the background population in those who received treatment for hyperthyroidism and survived hyperthyroidism. During follow-up of individuals not taking T_4 therapy, the increased risk of mortality persisted compared with the background population. This increase in risk compared with the background population was no longer evident during follow-up of individuals taking T_4 replacement. These findings may reflect the fact that development of overt hypothyroidism requiring T_4 therapy after radioiodine is the best indicator of effective cure of hyperthyroidism and is thus associated with the greatest likelihood of amelioration of the adverse effects of thyroid hormone excess on the vascular system. Atrial fibrillation is considered one of the major risk factors for morbidity and mortality associated with hyperthyroidism.[2] Interestingly, older literature refers to the specific role of radioiodine in the treatment of overt hyperthyroidism in those with heart disease, including atrial fibrillation, and reports striking improvement in cardiac status.[17] It is notable that an increased rate of reversion to sinus rhythm has been described in those with atrial fibrillation and hyperthyroidism who subsequently develop hypothyroidism as a consequence of their treatment.[18] It is also possible that improved prognosis associated with T_4 therapy in the present study reflects survival of a "healthier" group within the cohort who have survived both overt hyperthyroidism and development of overt hypothyroidism. Prescription of T_4 might also prompt increased medical contact.

Influence of Subclinical Hypothyroidism and Hyperthyroidism

In view of the uncertainty about the effect of subclinical thyroid dysfunction on significant clinical end points, especially mortality,[11] we investigated the influence of subclinical hyperthyroidism and hypothyroidism, as indicated by low or increased serum thyrotropin concentrations, respectively (with normal free T_4), during follow-up. Because subclinical hyperthyroidism may persist for a variable period after treatment of overt hyperthyroidism with radioiodine and because eventual development of hypothyroidism is typically a gradual process in those treated with radioiodine, overt hypothyroidism being preceded by a variable period of subclinical hypothyroidism, we examined the association between mortality and subclinical thyroid dysfunction during the period prior to T_4 therapy when all-cause and circulatory mortality was increased for the cohort as a whole compared with the control population of England and Wales.

We found an increased risk of all-cause mortality compared with the background population in patients who were being followed up prior to, or not requiring, T_4 therapy when their follow-up was subdivided according to the presence of low, normal, or high serum thyrotropin concentration. All-cause mortality was elevated even in those with normal serum thyrotropin levels, a similar result being evident for mortality from circulatory diseases. Ischemic heart disease mortality was not significantly increased compared with the background population when follow-up was subdivided according to serum thyrotropin measurements although the highest SMR for ischemic heart disease was observed during follow-up associated with high serum thyrotropin. It is likely that these findings reflect an ongoing adverse influence of overt hyperthyroidism in patients not experiencing the beneficial influence of complete reversal of overt hyperthyroidism as indicated by the surrogate marker of development of overt hypothyroidism and hence requirement for T_4 therapy. However, the lack of association of mortality with low serum thyrotropin argues against a specific adverse influence of persisting mild thyroid hormone excess during this period of follow-up prior to T_4 therapy.

Comparison within the cohort demonstrated that high serum thyrotropin concentrations, considered both as a single measure at the start of long-term follow-up and as a serial finding, was not associated with increased circulatory mortality overall. High serum thyrotropin was, however, independently associated with doubling of risk of mortality from ischemic heart disease compared with risk associated with normal serum thyrotropin concentration, broadly in accord with the SMR analysis for ischemic heart disease described above. This association between mild hypothyroidism and ischemic heart disease is plausible given the documented, albeit relatively minor, association between subclinical hypothyroidism and hyperlipidemia.[19] This finding is also in accord with a recent study of 235 subjects with subclinical hypothyroidism identified by screening a selected group of atomic bomb survivors from Nagasaki who were found to have increased risk of ischemic heart disease in a cross-sectional analysis (odds ratio [OR], 2.5; 95% CI, 1.1-5.4), and in whom increased mortality (cause not deter-

mined) was evident from years 3 to 6 of follow-up, albeit confined to men.[20]

The present finding is also supported by the results of follow-up of a subgroup of a Rotterdam cohort in whom those with subclinical hypothyroidism had a higher age-adjusted prevalence of aortic calcification (OR, 1.7; 95% CI, 1.1-2.6) and myocardial infarction (OR, 2.3; 95% CI, 1.3-4.0) on cross-sectional analysis compared with those with normal thyrotropin concentrations.[21] Other studies have, however, failed to demonstrate an increase in vascular morbidity or mortality associated with subclinical hypothyroidism, including the Cardiovascular Health Study involving 3768 participants,[6] a 20-year follow-up of 2779 participants in the Whickham cohort in the United Kingdom,[22] and a recent study of 599 participants older than 85 years.[23]

We also investigated the association of subclinical hyperthyroidism (defined as serum thyrotropin <0.5 mIU/L with normal serum free T_4) with mortality within the cohort during follow-up prior to T_4 therapy. Compared with an outcome associated with normal serum thyrotropin concentrations, we found no increase in all-cause or circulatory mortality specifically associated with low serum thyrotropin, either considered as a single measure at the start of long-term follow-up or as a serial finding during follow-up. This lack of specific association of mortality with low serum thyrotropin levels, which is in accordance with the SMR data mentioned above, argues against the assertion that the overall excess circulatory mortality observed during this period of follow-up prior to T_4 therapy reflects on-going subclinical hyperthyroidism. It is thus more likely that the observed excess mortality reflects ongoing adverse effects of the previous overt hyperthyroidism, perhaps exacerbated by development of subclinical hypothyroidism as described above. The present finding of a lack of association of mortality with low serum thyrotropin concentration is in agreement with a study from Scotland, which found no difference in hospital admission rates for ischemic heart disease in those receiving long-term T_4 treatment when comparing those with normal and low serum thyrotropin (<0.05 mIU/L).[24]

The present findings add to the current debate about the cardiovascular consequences of subclinical hyperthyroidism—which was prompted by the finding of a 3-fold increased incidence of atrial fibrillation during a 10-year follow-up of those with low serum thyrotropin levels identified among those older than 60 years in the Framingham population (low serum thyrotropin reflecting a variety of causes including T_4 therapy).[25] These findings were supported by another cross-sectional study revealing a 5-fold increased likelihood of atrial fibrillation in those with serum thyrotropin levels lower than 0.4 mIU/L that were identified from within a large and heterogeneous group of 23 638 participants in whom thyroid function tests were measured.[26] The present finding of lack of association of increased risk with low serum thyrotropin concentration, either as a single measure at the start of long-term follow-up or as a serial measure, also appears to conflict with our own population-based study of those older than 60 years (which importantly excluded those taking T_4 or taking antithyroid treatment for thyrotoxicosis) in whom increased all-cause and vascular mortality during follow-up of more than 10 years was predicted by a single low measurement of serum thyrotropin at recruitment.[27] This difference may reflect the fact that the participants reported about herein all had a diagnosis of thyrotoxicosis and were younger than those previously screened in the community and followed up. It may also reflect shorter duration of the biochemical abnormality in the present study.

Limitations of the Study

We did not have recorded information about other risk factors for circulatory mortality, particularly smoking history, family history, hypertension, or lipid profile in the cohort, nor did we have information about medications other than that of T_4 replacement. In the future, we propose to investigate a subset of the cohort with regard to this information to determine interaction between thyroid status and other such risk factors or confounders. The cohort was confined to individuals with overt hyperthyroidism treated with radioiodine. Findings cannot therefore be extrapolated to those with hyperthyroidism who are treated with other modalities, such as thionamides alone or thyroid surgery. It is possible that patient selection, especially a history of underlying vascular disease, prompted management with radioiodine.

Conclusion and Clinical Implications

We have demonstrated increased all-cause and circulatory mortality in those treated for hyperthyroidism with radioiodine between 1984 and 2002. We demonstrated that this association was no longer evident during follow-up while receiving T_4 therapy for radioiodine-induced hypothyroidism. We found that subclinical hypothyroidism during follow-up before T_4 therapy was itself independently associated with risk of ischemic heart disease death, which may reflect adverse influences of even mild thyroid failure on cardiovascular risk factors, particularly lipid profile or blood pressure.[6] It is reassuring that development of overt hypothyroidism and its treatment with T_4 following radioiodine treatment of hyperthyroidism is associated with risk of all-cause and circulatory death similar to that of the background population. The finding of increased risk confined to follow-up in those not requiring or before T_4 therapy argues for definitive treatment of hyperthyroidism with doses of radioiodine sufficient to induce overt hypothyroidism, however, the association within the cohort of mortality from ischemic heart disease predicted by either a single or serial high measures of serum thyrotropin emphasizes the potential importance of prompt treatment of subclini-

cal hypothyroidism when this develops after radioiodine therapy.

Author Contributions: Dr Franklyn 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: Franklyn, Sheppard, Maisonneuve.
Acquisition of data: Franklyn, Sheppard.
Analysis and interpretation of data: Franklyn, Sheppard, Maisonneuve.
Drafting of the manuscript: Franklyn, Sheppard, Maisonneuve.
Critical revision of the manuscript for important intellectual content: Franklyn, Sheppard, Maisonneuve.
Statistical analysis: Franklyn, Maisonneuve.
Obtained funding: Franklyn, Sheppard, Maisonneuve.
Administrative, technical, or material support: Franklyn.
Study supervision: Franklyn, Sheppard.

Financial Disclosures: None reported.
Funding/Support: Contributions were received from the BUPA Foundation, the Research Committee of the former West Midlands Regional Health Authority, and the Research Committee of the UHB Charities (Drs Franklyn and Sheppard) and from the Italian Association for Cancer Research (Dr Maisonneuve).
Role of the Sponsor: These sponsors had no role in design and conduct of the study or data collection/analysis, nor role in preparation or approval of the manuscript.

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