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CLINICAL RESEARCH

Thyroid-Stimulating Hormone and Clinical Outcomes

The CORONA Trial (Controlled Rosuvastatin Multinational Study in Heart Failure)

Ana Cristina Perez, MD,* Pardeep S. Jhund, MB, PHD,* David J. Stott, MD,† Lars Gullestad, MD, PHD,‡ John G. F. Cleland, MD,§ Dirk J. van Veldhuisen, MD, PHD,‖ John Wikstrand, MD, PHD,¶ John Kjekshus, MD, PHD,‡ John J. V. McMurray, MD*

Glasgow, Scotland; Oslo, Norway; Kingston-Upon-Hull, United Kingdom; Groningen, the Netherlands; and Gothenburg, Sweden

Objectives This study sought to examine the association between thyroid status and clinical outcomes in patients in the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) study.

Background Hypo- and hyperthyroidism were associated with worse clinical outcomes in the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial).

Methods In CORONA, 4,987 patients underwent baseline thyroid-stimulating hormone (TSH) measurement, 237 of which (4.8%) were receiving thyroid replacement therapy (TRT). Patients were classified as euthyroid (TSH: 0.3 to 5.0 μU/ml, and no TRT), hyperthyroid (<0.3 μU/ml and no TRT), or hypothyroid (>5.0 μU/ml and no TRT). The outcome composites of cardiovascular (CV) death or hospitalization for heart failure (HF), the components of this composite, and all-cause death were compared among hyperthyroid, hypothyroid, and euthyroid states, using multivariable models adjusting for previously reported prognostic variables.

Results A total of 91.3% of patients were euthyroid, 5.0% were hypothyroid, and 3.7% were hyperthyroid. Compared with euthyroid patients, hypothyroid patients were more likely to have a history of stroke, had worse renal function and higher N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, were more likely to be treated with an antiarrhythmic drug (or have an implantable cardioverter defibrillator), and were less likely to smoke or be treated with a beta-blocker or angiotensin-converting enzyme inhibitor/angiotensin receptor blocker. In univariate analyses, hypothyroidism was associated with an increased risk of the composite outcome of CV death or HF hospitalization (hazard ratio: 1.29; 95% confidence interval: 1.07 to 1.57; $p = 0.008$), as well as all-cause death (HR: 1.36; 95% confidence interval: 1.03 to 1.76; $p = 0.004$). However, after adjustment for other known predictors of outcome, the associations were weakened, and when NT-proBNP was added to the models, the association between hypothyroidism and all outcomes was eliminated.

Conclusions Thyroid status is not an independent predictor of outcome in heart failure with reduced ejection fraction. (Controlled Rosuvastatin Multinational Study in Heart Failure [CORONA]; NCT00206310) (J Am Coll Cardiol HF 2014;2:35–40)
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Although both hypothyroidism and hyperthyroidism are associated with an increased risk of developing heart failure (HF), the relationship between thyroid dysfunction and clinical outcomes in patients with established HF is uncertain (1–3). Because thyroid hormone affects the function of all tissues, including the heart, it is plausible that disturbance of thyroid function might influence outcome in patients with HF although this possibility had not been studied in a large patient sample until recently in

From the *BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, Scotland; †Department of Academic Geriatric Medicine, Walton Building, Glasgow Royal Infirmary, Glasgow, Scotland; ‡Department of Cardiology, Oslo University Hospital, Rikshospitalet, and K. G. Jebsen Cardiac Research Centre and Centre for Heart Failure Research, Faculty of Medicine, University of Oslo, Oslo, Norway; §Hull York Medical School, Kingston-Upon-Hull, United Kingdom; ‖University Medical Centre, Groningen, the Netherlands; and the ¶Wallenberg Laboratory for Cardiovascular Research, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden. Dr. Perez was supported by Consejo Nacional de Ciencia y Tecnologia (CONACYT), Mexico, scholarship no. 31306, scholar no. 215001. Dr. Stott's research of subclinical hypothyroidism is funded through the European Commission 7th Framework Programme on Research. Dr. Cleland has received honoraria for the steering committee of CORONA from AstraZeneca. Dr. van Veldhuisen has received fees for board membership with Amgen, BG Medicine, Biocontrol, Johnson & Johnson, Novartis, Sorbent, St. Jude, and Vifor. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Abbreviations and Acronyms

CV = cardiovascular

HF = heart failure

HF-REF = heart failure with reduced ejection fraction

ICD = implantable cardioverter defibrillator

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

TRT = thyroid replacement therapy

TSH = thyroid-stimulating hormone

SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) (1–3). The SCD-HeFT investigators reported that both elevated and suppressed thyroid-stimulating hormone (TSH) levels were associated with an increased risk of death, even after adjusting for other prognostic variables (4). We have now examined the same question in the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) (5).

Methods

CORONA enrolled 5,011 patients who were at least 60 years of age with symptomatic (New York Heart Association [NYHA] class II to IV), ischemic, systolic (left ventricular ejection fraction [LVEF]: ≤40%) HF (no more than 35% in patients in NYHA class II). The exclusion criteria included uncontrolled hypothyroidism, as indicated by a TSH level >2 times the upper limit of normal at enrollment visit 2, and concomitant conditions of clinical significance, including systemic disease (e.g., uncorrected hyperthyroidism or amyloidosis). Patients were randomized to receive 10 mg of rosuvastatin or matching placebo once daily (5). The ethics committee at each of the participating hospitals approved the trial, and patients provided written informed consent. The primary composite outcome was death from cardiovascular (CV) causes, nonfatal myocardial infarction, or nonfatal stroke. The median follow-up was 32.8 months. Rosuvastatin therapy did not reduce the primary outcome or death from any cause.

A total of 4,987 patients (99.5%) had a TSH measurement available at baseline, 237 of which (4.8%) were not considered because of baseline thyroid replacement therapy (TRT). As in the SCD-HeFT analysis, patients were classified as euthyroid if their TSH values were in the range of 0.3 to 5.0 μU/ml and they were not taking TRT, hyperthyroid if their TSH levels were <0.3 μU/ml and they were not taking TRT, or hypothyroid if they had TSH levels of >5.0 μU/ml (and no TRT); 4,750 patients were included in the final analyses.

We carried out a number of additional analyses including: 1) examination of the TSH categories listed above, without accounting for TRT; 2) use of a TSH threshold of >3.6 μU/ml to define hypothyroidism (6); 3) exclusion from analysis of those patients who were taking amiodarone; and 4) use of TSH as a continuous variable.

Statistical analysis. Baseline characteristics of euthyroid patients were compared with those of hypothyroid patients; comparisons between euthyroid and hyperthyroid patients were made using analysis of variance (ANOVA) tests for continuous variables and chi-square tests for categorical variables.

The association between thyroid states and composite outcome of CV death or hospitalization due to worsening HF was tested using time-to-event regression analyses on the basis of Cox proportional hazard models. Other outcomes analyzed were the components of the composite (CV death and HF hospitalization individually) and all-cause death. Hyperthyroid and hypothyroid states were tested simultaneously with indicators for each in a multivariable model relative to those of the euthyroid state. The covariates used were on the basis of previously reported predictive models (see the footnote to Table 3; baseline antiarrhythmic treatment was included as a covariate) (7).

Cumulative event curves are presented by thyroid state, estimated using the Kaplan-Meier method and compared with log-rank tests.

All p values are 2-sided, and a p value of <0.05 was considered significant. All statistical analyses were performed using Stata version 12 software (Stata Corp., College Station, Texas).

Results

Of the 4,750 patients with a TSH measurement and not taking TRT who were available for analysis, 91.3% of patients were euthyroid, 5.0% were hypothyroid, and 3.7% were hyperthyroid (Table 1, Fig. 1).

Patient characteristics. Compared with euthyroid patients, those with a hypothyroid TSH level were more likely to have a history of stroke and to have an implanted cardioverter defibrillator (ICD) or to be taking an antiarrhythmic drug; they were less likely to smoke or to be taking a beta-blocker, angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker. Hypothyroid patients also had worse renal function and higher N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels (Table 1). Hyperthyroid patients had a higher heart rate and were more likely to have an ICD, to be taking an ACE inhibitor, and to smoke (Table 1).

Unadjusted outcomes. Patients with hypothyroid TSH levels had significantly higher all-cause and CV mortality rates and showed a trend toward higher risk for hospitalization with worsening HF; hypothyroid TSH level was associated with a significantly higher risk of the composite outcome of CV death or HF hospitalization (Table 2, Fig. 2). There was no association between a hyperthyroid TSH level and risk of death or HF hospitalization (Table 2, Fig. 2).

Adjusted outcomes. Adjustment for other variables (excluding NT-proBNP) associated with worse clinical outcomes greatly weakened the relationship between hypothyroidism and death and the composite outcome (Table 3). Addition of NT-proBNP to these multivariable models eliminated the association between hypothyroidism and outcomes.

The additional analyses using a TSH cut-off point of 3.6 μU/ml, excluding patients treated with amiodarone, not excluding patients taking TRT and using TSH as a continuous variable, yielded similar results (see the Online Appendix).

Discussion

Although we were able to confirm and extend the findings of the SCD-HeFT investigators regarding the association between abnormal thyroid function and clinical outcomes in the

Table 1 Clinical Characteristics According to Baseline Thyroid Status Based Upon TSH Level

Variable	Euthyroid (n = 4,338)	Hypothyroid (n = 237)	Hyperthyroid (n = 175)	p Value
Age, yrs	72.6 ± 7.1	73.0 ± 6.8	72.9 ± 6.2	0.55
Age ≥70 yrs	64.5% (2,796)	67.1% (159)	72.0% (126)	0.08
Female	953 (22.0%)	55 (23.2%)	53 (30.3%)	0.03
Racial distribution				
Caucasian	4,279 (98.6%)	234 (98.7%)	172 (98.3%)	0.66
Black	12 (0.3%)	1 (0.4%)	0 (0%)	
Asian	30 (0.7%)	2 (0.8%)	1 (0.6%)	
Other	17 (0.4%)	0 (0.0%)	2 (1.1%)	
NYHA functional class III/IV	2,722 (62.8%)	151 (63.7%)	111 (63.4%)	0.94
LVEF ×100	30.9 ± 6.5	30.5 ± 6.7	31.3 ± 6.5	0.38
Systolic BP, mm Hg	129.3 ± 16.5	128.3 ± 16.4	130.3 ± 15.5	0.45
Heart rate, beats/min	71.6 ± 11.1	70.7 ± 11.1	73.8 ± 12.1	0.02
BMI, kg/m^2	27.2 ± 4.5	26.9 ± 4.2	27.3 ± 4.3	0.57
BMI >median (26.7 kg/m^2)	2,203 (50.8%)	110 (46.4%)	89 (50.9%)	0.94
Current smoker	382 (8.8%)	11 (4.7%)	23 (13.1%)	0.01
Medical history				
MI	2,612 (60.2%)	147 (62.0%)	91 (52.0%)	0.08
Angina pectoris	3,154 (72.7%)	158 (66.7%)	124 (70.9%)	0.12
CABG/PCI	1,113 (25.7%)	58 (24.5%)	54 (30.9%)	0.27
Hypertension	2,741 (63.2%)	157 (66.2%)	112 (64.0%)	0.63
Diabetes mellitus	1,283 (29.6%)	60 (25.3%)	56 (32.0%)	0.28
Baseline AF/F	1,021 (23.5%)	69 (29.1%)	45 (25.7%)	0.12
Stroke	529 (12.2%)	48 (20.3%)	14 (8.0%)	<0.001
Pacemaker	467 (10.8%)	25 (10.6%)	23 (13.1%)	0.61
ICD	98 (2.3%)	13 (5.5%)	8 (4.6%)	0.002
Laboratory measurements				
Cholesterol, mmol/l	5.35 ± 1.08	5.40 ± 1.17	5.28 ± 1.13	0.57
ApoB:ApoA-1 ratio	0.87 ± 0.25	0.91 ± 0.26	0.88 ± 0.25	0.07
Triglycerides, mmol/l	2.01 ± 1.29	1.99 ± 1.40	1.82 ± 0.85	0.18
Serum creatinine, mmol/l	114.7 ± 27.5	123.2 ± 27.3	113.4 ± 31.4	<0.001
Estimated GFR, ml/min/1.73 m^2	56.8 ± 15.0	51.8 ± 13.6	57.5 ± 16.9	<0.001
NT-proBNP, pmol/l	167.44 (69.74–362.73)	190.28 (103.1–433.3)	190.69 (92.54–309.75)	0.01
hs-CRP, mg/l	3.4 (1.5–7.3)	4.5 (1.8–9)	3.9 (1.7–7.0)	0.39
TSH, μU/ml	1.82 ± 1.01	9.65 ± 15.71	0.14 ± 0.10	<0.001
Median (IQR)	1.6 (1.0–2.4)	6.4 (5.6–8.0)	0.14 (0.02–0.24)	
Medication				
Loop diuretic	3,265 (75.3%)	189 (79.8%)	133 (76.0%)	0.29
Loop or thiazide diuretic	3,809 (87.8%)	214 (90.3%)	156 (89.1%)	0.46
ACE inhibitor	3,477 (80.2%)	179 (75.5%)	155 (88.6%)	0.004
ACE inhibitor or ARB	3,983 (91.8%)	209 (88.2%)	166 (94.9%)	0.04
Beta-blocker	3,273 (75.5%)	160 (67.5%)	142 (81.1%)	0.004
Digitalis glycoside	1,428 (32.9%)	78 (32.9%)	63 (36.0%)	0.70
Antiarrhythmic therapy	476 (11.0%)	82 (34.6%)	25 (14.3%)	<0.001
Antiplatelet therapy	2,603 (60.0%)	135 (57.0%)	95 (54.3%)	0.22
Anticoagulant therapy	1,507 (34.7%)	94 (39.7%)	65 (37.1%)	0.26
Antiplatelet or anticoagulant therapy	3,926 (90.5%)	218 (92.0%)	152 (86.9%)	0.20

Values are mean ± SD, % (n), or n (%).

ACE = angiotensin-converting enzyme; AF/F = atrial fibrillation/flutter; ApoA = apolipoprotein; ApoB = apolipoprotein B; ARB = angiotensin receptor blocker; BMI = body mass index; bpm = beats per minute; CABG = coronary artery bypass graft; GFR = glomerular filtration rate; hs-CRP = high-sensitivity C-reactive protein; ICD = implanted cardioverter defibrillator; IQR = interquartile range; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NT pro BNP = N-terminal pro B type natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; SD = standard deviation; TSH = thyroid-stimulating hormone.

CORONA study in unadjusted and partially adjusted analyses, the relationship between TSH and prognosis was eliminated when NT-proBNP was included in our multivariable models.

In CORONA, as in SCD-HeFT (n = 2,225), most patients were euthyroid (91.3% and 87%, respectively), although a slightly higher proportion in CORONA (5.0%

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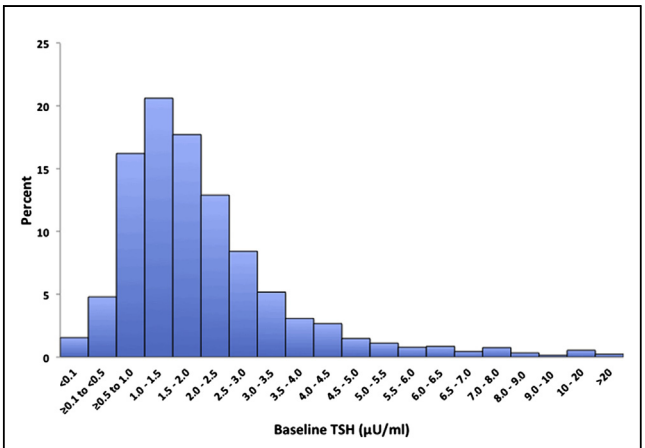

Figure 1 **Distribution of Baseline TSH Values**

Distribution of TSH levels (μU/ml) at baseline in CORONA patients with a left ventricular ejection fraction of 35% or less. Intervals on the right of the graph include a wider range of values due to the sparseness of data. TSH = thyroid-stimulating hormone.

vs. 1%, respectively) was hyperthyroid, and a lower proportion were hypothyroid (3.5% vs. 12%, respectively). In CORONA, only hypothyroid TSH values (and not hyperthyroid levels) were associated with increased mortality (all-cause and CV mortality). In univariate analyses, hypothyroid TSH level also tended to be associated with HF hospitalization, an outcome not considered in SCD-HeFT. Consequently, there was a strong, statistically significant association between hypothyroid TSH levels and the composite outcome of CV death or HF hospitalization (patients with hypothyroidism were 29% more likely to experience this outcome than those who were euthyroid). However, when these analyses were adjusted for other known predictors of outcome (excluding NT-proBNP) using previously constructed multivariable models (7), the associations were greatly weakened (only CV death remained close to statistically significant). When NT-proBNP was added to these models, the association between hypothyroidism and all outcomes was completely eliminated. NT-proBNP was not measured in SCD-HeFT and, therefore, could not be used in the multivariable model used to adjust for other predictors of death in that trial.

Unlike SCD-HeFT, the present study did not find a significant association between hyperthyroid TSH levels at baseline and outcomes in CORONA, although the numbers of patients with such levels was small in both trials (20 in SCD-HeFT and 175 in CORONA), and the findings in SCD-HeFT may have been due to chance. The only other study we know of that has examined the relationship between thyroid status and outcomes in patients with HF is the INH (Interdisciplinary Network Heart Failure) study (3). Of the 758 patients analyzed (all with an LVEF of ≤40%), 641 (85%) had normal TSH levels, 77 (10%) had suppressed TSH levels (<0.3 μU/ml), and 40 (5%) had elevated TSH levels (>4.0 μU/ml). In univariate analysis, there was a trend toward higher mortality in patients with a hyperthyroid TSH level (which was eliminated after adjustment for age) but no association between an elevated TSH and death.

Study limitations. One limitation of the CORONA, SCD-HeFT, and INH studies is that each was a randomized trial with specific inclusion and exclusion criteria. However, collectively, they enrolled a broad spectrum of patients with HF and reduced LVEF, including many elderly patients. Although the INH study did not have specific thyroid exclusion criteria, CORONA did (and likely SCD-HeFT did, although it was not reported in trial publications). Furthermore, clinical trials always recruit healthier patients with less comorbidity and exclude the very elderly. For all these reasons, a greater proportion of "real-world" patients with HF are likely to have clearly defined hypo- and hyperthyroidism, and these states could be predictive of clinical outcomes, unlike the mainly mild or subclinical thyroid dysfunction investigated in the 3 trials discussed. No study has looked at the prognostic importance of thyroid dysfunction in patients with HF and preserved EF.

Another limitation of this report (and that of the SCD-HeFT analysis) is the impossibility of teasing out cause and effect. In other words, the issue of whether hypothyroid patients have indicators of poorer clinical status because underactivity of the thyroid gland in some way worsens the HF syndrome or because having worse HF leads to an underactive thyroid is not clear. Alternatively, and in our view most likely, is the question: Are certain clinical features more common in both those likely to have an underactive thyroid gland and worse HF status? There were key differences between hypothyroid and euthyroid patients, including

Table 2 **Clinical Outcomes According to Baseline Thyroid Status Based Upon TSH Level**

Variable	Euthyroid (n = 4,338)	Hypothyroid (n = 237)	Hyperthyroid (n = 175)	HR (95% CI) Versus Euthyroid			
				Hypothyroid	p Value	Hyperthyroid	p Value
CV deaths or HF hospitalizations	1,668 (38.5)	111 (48.8)	62 (35.4)	1.29 (1.07–1.57)	0.008	0.93 (0.72–1.20)	0.591
CV deaths	997 (23.0)	76 (32.1)	31 (17.7)	1.46 (1.16–1.84)	0.002	0.77 (0.53–1.09)	0.143
HF hospitalizations	1096 (25.3)	69 (29.1)	45 (25.7)	1.23 (0.96–1.56)	0.102	1.03 (0.77–1.39)	0.823
All-cause deaths	1,266 (29.2)	90 (38.0)	46 (26.3)	1.36 (1.03–1.76)	0.004	0.89 (0.67–1.20)	0.457

Values are n (%).

CV = cardiovascular; HF = heart failure; TSH = thyroid-stimulating hormone.

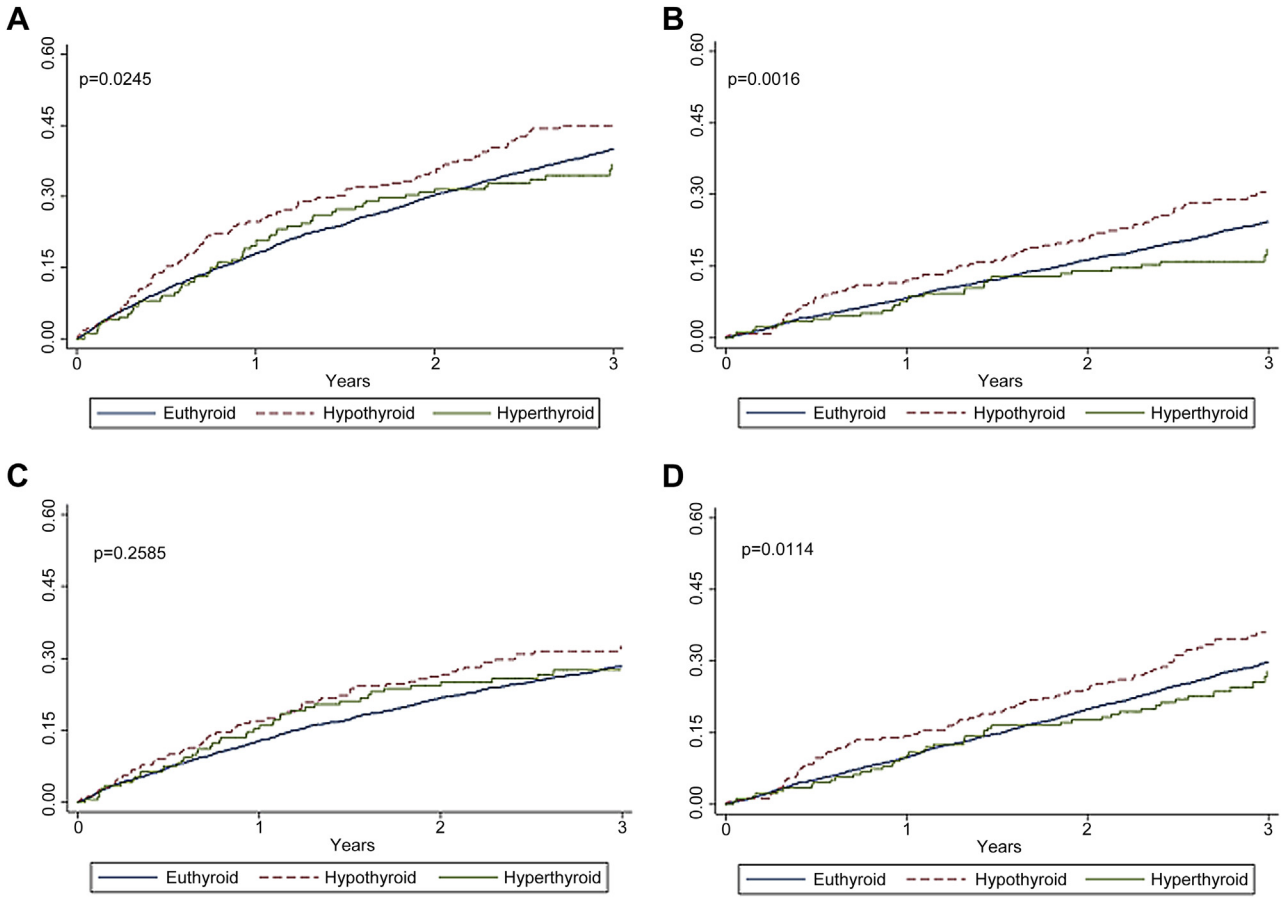

Figure 2 Clinical Outcomes According to Thyroid Status (Euthyroid, Hypothyroid, or Hyperthyroid) by Using Kaplan-Meier Curves

(A) Composite of CV death or HF hospitalization. **(B)** Cardiovascular death. **(C)** Heart failure hospitalization. **(D)** All-cause death. Y-axis = proportion of patients; X-axis = time (years); p values were derived from univariate log-rank tests.

more renal dysfunction and higher NT-proBNP, which are also more likely between patients with worse and those with better HF status. In patients without HF, it is hyperthyroidism and not hypothyroidism, which is associated with higher natriuretic peptide levels, suggesting that the higher natriuretic peptide levels in our hypothyroid patients were because they were sicker and not directly due to reduced thyroid hormone level (8). An additional confounding variable was the use of antiarrhythmic treatment (mainly amiodarone), which is known to cause disturbances of thyroid function and is a marker of worse clinical status (in that it is prescribed for atrial and ventricular arrhythmias),

Table 3 Risk of Clinical Outcomes According to Thyroid Status After Adjustment for Other Prognostic Variables

	Adjusted Outcome Excluding NT-proBNP*				Adjusted Outcome Including log (NT-proBNP)*			
	Hypothyroid		Hyperthyroid		Hypothyroid		Hyperthyroid	
Variable	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
CV deaths or HF hospitalizations	1.17 (0.96–1.44)	0.13	0.91 (0.70–1.19)	0.48	1.02 (0.79–1.32)	0.18	1.01 (0.74–1.38)	0.93
CV deaths	1.27 (0.99–1.63)	0.06	0.81 (0.56–1.18)	0.27	1.11 (0.82–1.52)	0.50	0.90 (0.59–1.39)	0.64
HF hospitalizations	1.13 (0.88–1.47)	0.34	0.93 (0.68–1.29)	0.68	1.00 (0.73–1.37)	0.99	1.15 (0.81–1.64)	0.43
All-cause deaths	1.17 (0.93–1.48)	0.17	0.85 (0.62–1.17)	0.32	1.02 (0.76–1.36)	0.89	0.96 (0.67–1.39)	0.83

*Adjusted for: age, sex, New York Heart Association class, left ventricular ejection fraction, body mass index (kg/m^2), systolic blood pressure, heart rate, smoking, myocardial infarction, angina pectoris, coronary artery bypass graft, percutaneous coronary intervention, aortic aneurysm, hypertension, diabetes, baseline atrial fibrillation/flutter, stroke, intermittent claudication, pacemaker, implanted cardioversion defibrillator, apolipoprotein A-1 and -B, creatinine, alanine aminotransferase, creatinine kinase, triglyceride level, C-reactive protein, and antiarrhythmic treatment.

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

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although our findings were unchanged after exclusion of these patients. Another limitation is our inability to study the "low T3 syndrome," which, although characterized by a normal TSH, may cause functional hypothyroidism (9,10).

Conclusions

Our results show that hypothyroidism, as identified by an elevated TSH level, is uncommon in patients with HF and is not an independent predictor of adverse clinical outcomes.

Reprint requests and correspondence: Prof. John J. V. McMurray, Institute of Cardiovascular and Medical Sciences, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow G12 8TA, Scotland, United Kingdom. E-mail: john.mcmurray@glasgow.ac.uk.

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Key Words: clinical outcome ▪ hyperthyroidism ▪ hypothyroidism.

APPENDIX

For supplemental tables, please see the online version of this article.