

# Clinical outcomes of patients with hypothyroidism undergoing percutaneous coronary intervention

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## Aims

The aim of this study was to investigate the association between hypothyroidism and major adverse cardiovascular and cerebral events (MACCE) in patients undergoing percutaneous coronary intervention (PCI).

## Methods and results

Two thousand four hundred and thirty patients who underwent PCI were included. Subjects were divided into two groups: hypothyroidism ( $n = 686$ ) defined either as a history of hypothyroidism or thyroid-stimulating hormone (TSH)  $\geq 5.0$  mU/mL, and euthyroidism ( $n = 1744$ ) defined as no history of hypothyroidism and/or  $0.3$  mU/mL  $\leq$  TSH  $< 5.0$  mU/mL. Patients with hypothyroidism were further categorized as untreated ( $n = 193$ ), or those taking thyroid replacement therapy (TRT) with adequate replacement ( $0.3$  mU/mL  $\leq$  TSH  $< 5.0$  mU/mL,  $n = 175$ ) or inadequate replacement (TSH  $\geq 5.0$  mU/mL,  $n = 318$ ). Adjusted hazard ratios (HRs) were calculated using Cox proportional hazards models. Median follow-up was 3.0 years (interquartile range, 0.5–7.0). After adjustment for covariates, the risk of MACCE and its constituent parts was higher in patients with hypothyroidism compared with those with euthyroidism (MACCE: HR: 1.28,  $P = 0.0001$ ; myocardial infarction (MI): HR: 1.25,  $P = 0.037$ ; heart failure: HR: 1.46,  $P = 0.004$ ; revascularization: HR: 1.26,  $P = 0.0008$ ; stroke: HR: 1.62,  $P = 0.04$ ). Compared with untreated patients or those with inadequate replacement, adequately treated hypothyroid patients had a lower risk of MACCE (HR: 0.69,  $P = 0.005$ ; HR: 0.78,  $P = 0.045$ ), cardiac death (HR: 0.43,  $P = 0.008$ ), MI (HR: 0.50,  $P = 0.0004$ ; HR: 0.60,  $P = 0.02$ ), and heart failure (HR: 0.50,  $P = 0.02$ ; HR: 0.52,  $P = 0.017$ ).

## Conclusion

Hypothyroidism is associated with a higher incidence of MACCE compared with euthyroidism in patients undergoing PCI. Maintaining adequate control on TRT is beneficial in preventing MACCE.

## Keywords

Hypothyroidism • Major adverse cardiovascular and cerebral events • Percutaneous coronary intervention

## Introduction

Thyroid hormone affects every cell, tissue, and organ in the body.<sup>1</sup> Minor changes in thyroid hormone levels may adversely affect the cardiovascular system.<sup>2</sup> The prevalence of hypothyroidism continues to be debated,<sup>3</sup> and the lack of consistency in results across studies may be due to varying definitions of hypothyroidism.<sup>4</sup> Most studies report a higher prevalence of hypothyroidism in elderly women,<sup>5,6</sup> with estimates as high as 24% in women  $> 60$  years of age. Up to 60% of those with hypothyroidism are unaware of their condition, yet the frequency of medical professionals prescribing thyroid medication has

increased dramatically over time in the USA, from an estimated 49.8 million prescriptions in 2006 to 70.5 million in 2010.<sup>7</sup>

Abnormal thyroid function has important public health consequences.<sup>8</sup> Patients with hypothyroidism have an increased risk of functional cardiovascular abnormalities, as well as accelerated atherosclerosis and an increased risk of coronary artery disease (CAD).<sup>9</sup> However, whether subclinical hypothyroidism (SCH) or overt hypothyroidism is independent risk factor for cardiovascular events or mortality remains uncertain.<sup>10</sup>

Evaluating risk and medically optimizing patients prior to percutaneous coronary intervention (PCI) is essential to limiting

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complications and improving prognosis.<sup>11</sup> To date, no clinical trial has been undertaken to examine the relationship between hypothyroidism and cardiovascular events in patients undergoing PCI. The purpose of the present study was to examine the association between hypothyroidism and major adverse cardiovascular and cerebral events (MACCE) in patients undergoing PCI.

## Methods

### Study population and design

All patients who undergo PCI at Mayo Clinic have information relating to demographic, clinical, procedural, and angiographic data entered into a prospective database. A clinical research nurse contacts all patients after 6 and 12 months and annually thereafter to ascertain relevant follow-up information. Records from outside hospitals relating to

adverse events are also collected. The supervisor for data integrity randomly audits 10% of all records to ensure data are collected accurately. Approval for this study was obtained from the Institutional Review Board of the Mayo Foundation. Figures 1 and 2 show the patient selection process.

### Definitions of hypothyroidism and subgroup classification

Patients were divided into subgroups as part of three separate analyses, as follows.

#### Clinical classification of hypothyroidism vs. euthyroidism

Hypothyroidism was defined as a documented history of hypothyroidism or SCH in the patients' clinical record or a thyroid-stimulating hormone (TSH) level  $\geq 5.0$  mU/mL at the time of the index PCI,  $n = 686$ . Euthyroidism was defined as no documented history of hypothyroidism

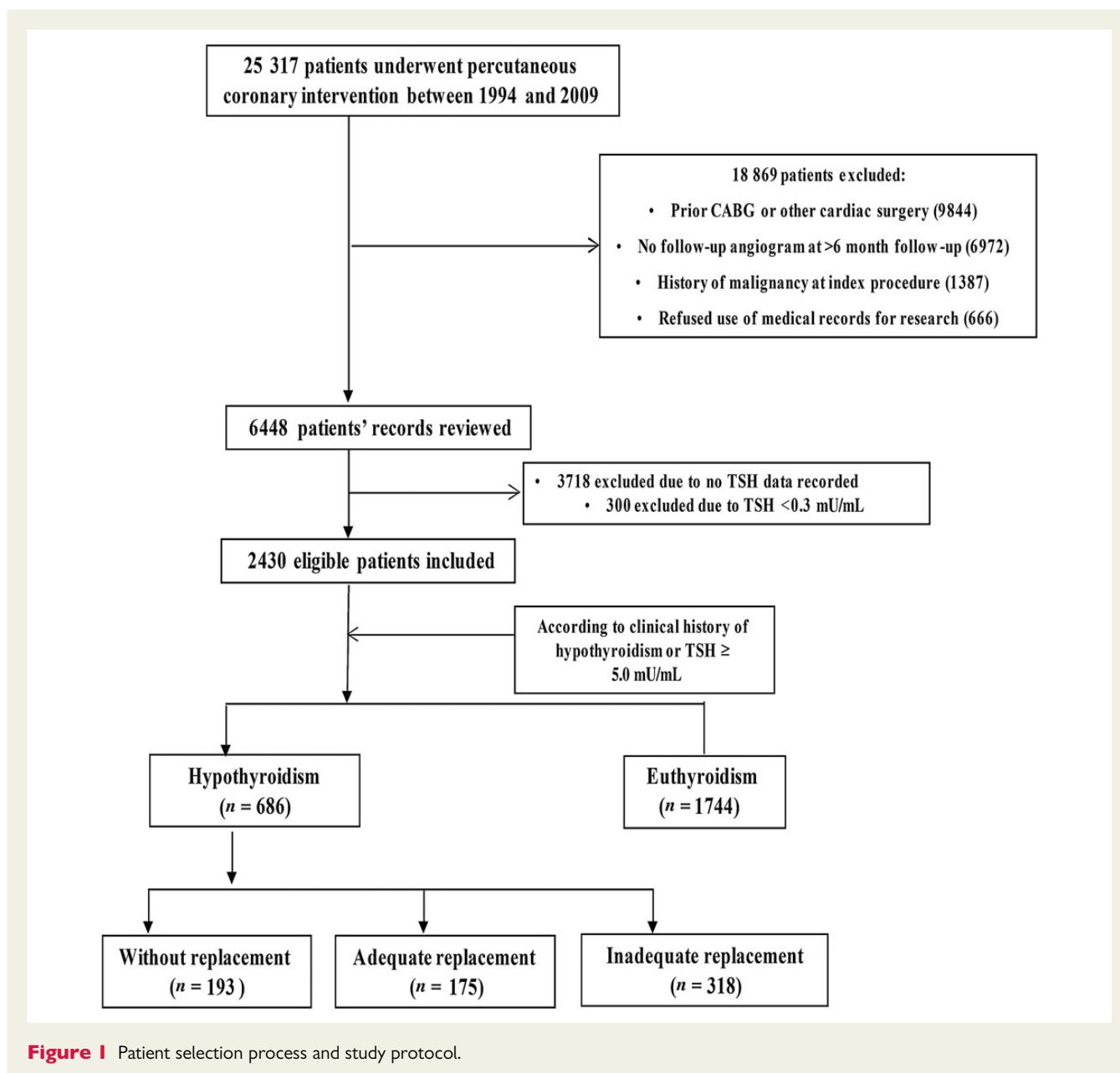
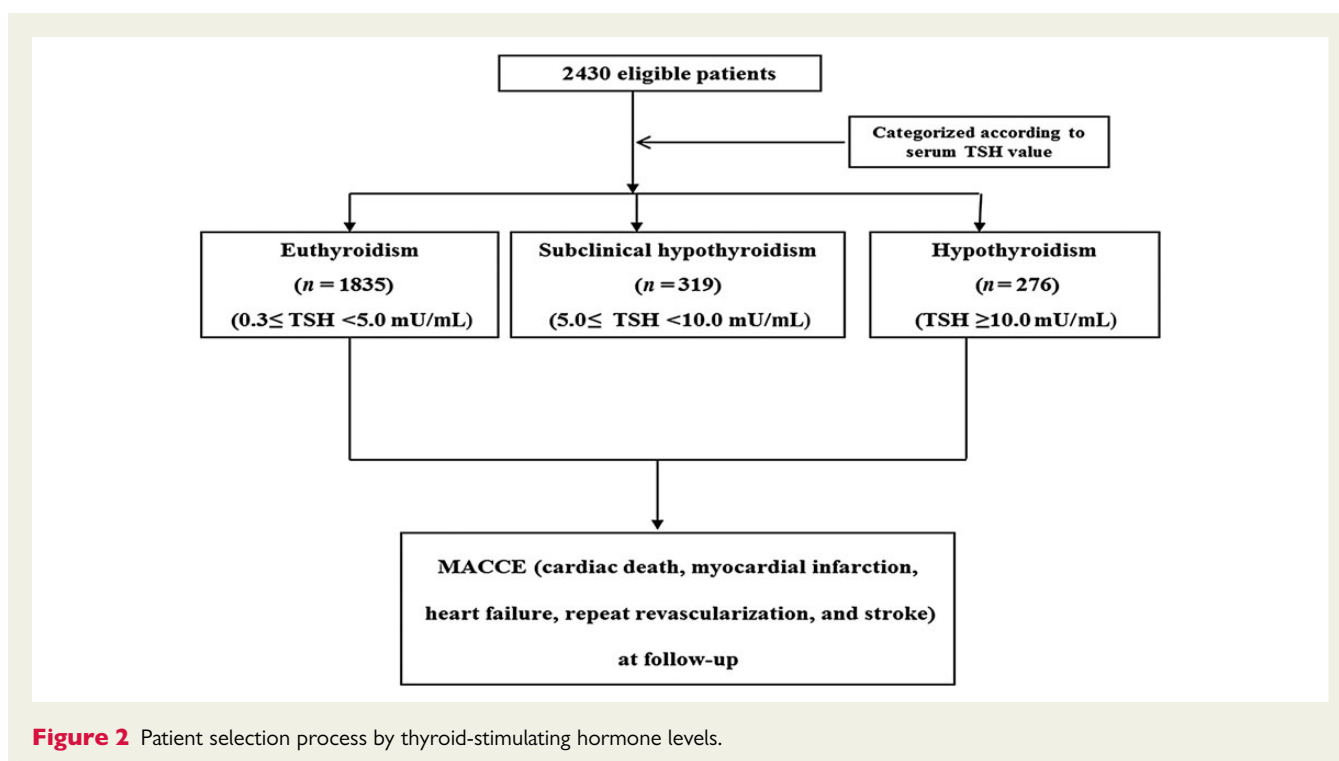


Figure 1 Patient selection process and study protocol.



**Figure 2** Patient selection process by thyroid-stimulating hormone levels.

in the patients' clinical record and/or  $0.3 \text{ mU/mL} \leq \text{TSH} < 5.0 \text{ mU/mL}$  at the time of the index PCI (Figure 1).

### Use of thyroid replacement therapy

Patients with a clinical diagnosis of hypothyroidism were further stratified according to those receiving no thyroid replacement therapy (TRT),  $n = 193$ ; patients who had inadequate replacement on TRT ( $\text{TSH} < 0.3$  or  $\text{TSH} \geq 5.0 \text{ mU/mL}$  at follow-up),  $n = 318$ , and patients with adequate replacement on TRT ( $0.3 \leq \text{TSH} < 5.0 \text{ mU/mL}$  at follow-up),  $n = 175$  (Figure 1).

### Biochemical classification of hypothyroidism vs. subclinical hypothyroidism vs. euthyroidism

Patients were separately categorized based on TSH levels only, as follows: euthyroidism,  $0.3 \text{ mU/mL} \leq \text{TSH} < 5.0 \text{ mU/mL}$ ,  $n = 1835$ ; SCH,  $5.0 \text{ mU/mL} \leq \text{TSH} < 10.0 \text{ mU/mL}$ ,  $n = 319$ ; and overt hypothyroidism,  $\text{TSH} \geq 10.0 \text{ mU/mL}$ ,  $n = 276$  (Figure 2).<sup>12</sup>

### Data collection and clinical follow-up

Information on patient demographics, conventional cardiovascular risk factors, laboratory data, and angiographic characteristics, as well as TSH values, history of hypothyroidism, and whether or not patients were prescribed TRT was abstracted from patients' electronic medical records by a single investigator (M.Z.) blinded to PCI data. Information on adverse cardiovascular events was collected prospectively as part of the Mayo Clinic PCI registry described above. Major adverse cardiovascular and cerebral event was defined as cardiac death, myocardial infarction (MI), target-vessel revascularization (TVR), stroke, and heart failure.

### Follow-up angiogram

To compare coronary disease progression between patients with hypothyroidism and euthyroidism, we randomly selected 102 patients from the hypothyroid group and 306 patients from the euthyroid group (to

maintain a 1:3 ratio between the two groups). Both baseline and follow-up coronary angiograms were analysed with quantitative coronary angiography (QCA) by a single trained investigator (M.Z.) blinded to each patient's hypothyroid status using QAngio XA software (Version 7.3, Medis Medical Imaging System BV, Leiden, The Netherlands). We examined disease progression in both the target lesion and in the segment downstream to the target lesion. Disease progression was defined as any of the following: (i) 30% luminal diameter reduction of a pre-existing stenosis of  $< 50\%$ , (ii) progression of any lesion to total occlusion, and (iii) 'new' lesions with a 30% luminal diameter reduction in a segment that was normal at the first angiogram.<sup>13</sup>

### Statistical analysis

Continuous variables are expressed as mean  $\pm$  SD or median (25th, 75th percentile) and were compared across groups using Student's *t*-test or the Wilcoxon rank-sum test as appropriate. Categorical variables are presented as counts and percentages and were compared across groups using the  $\chi^2$  test or Fisher's exact test as appropriate. Kaplan–Meier survival curves were generated and the log-rank test was used to assess for differences between the curves. Multivariate Cox proportional hazards models were developed to determine the hazards ratios for MACCE and its constituent parts in patients with hypothyroidism compared with those with euthyroidism, after adjusting for the following variables: age, gender, diabetes, hypertension, dyslipidaemia, family of CAD, renal failure, current smoking, heart failure, history of MI, number of diseased vessels, stent type used, and discharge medications, including aspirin,  $\beta$ -blockers, angiotensin-converting enzyme (ACE) inhibitors, or statins. These variables were selected from Table 1 due to the following: the variable is known to be related to both thyroid disease status and the risk of adverse cardiovascular events and thus may act as a potential confounder, including age and gender; the variable is strongly associated with the risk of adverse cardiovascular events and is therefore clinically important, including discharge medication or the variable differed significantly between the hypothyroid and

**Table 1** Baseline patient characteristics

Variable	All (n = 2430)	Euthyroidism (n = 1744)	Hypothyroidism (n = 686)	P-value
<b>Clinical characteristics</b>				
Age	64.6 ± 11.6	63.9 ± 11	66.4 ± 12.4	<0.0001
Female, n (%)	870 (36)	499 (29)	371 (54)	<0.0001
Body mass index (kg/m <sup>2</sup> )	30.2 ± 6.0	30.1 ± 5.7	30.4 ± 6.4	0.27
Diabetes mellitus, n (%)	640 (27)	418 (24.1)	222 (33)	<0.0001
Hypertension, n (%)	1658 (769)	1161 (68)	497 (74)	0.003
Current smoking, n (%)	324 (15)	241 (16)	83 (14)	0.24
Hyperlipidaemia, n (%)	1656 (81)	1207 (82)	450 (79)	0.08
Myocardial infarction, n (%)	933 (39)	643 (37)	290 (43)	0.02
F/H CAD, n (%)	678 (36)	490 (36)	188 (36.2)	0.99
Peripheral arterial disease, n (%)	201 (8.4)	136 (8)	65 (9.6)	0.2
Chronic lung disease, n (%)	239 (10)	174 (10)	65 (10)	0.77
EF_≤40, n (%)	155 (6)	116 (6.7)	39 (5.7)	0.37
Chronic heart failure, n (%)	249 (10.6)	160 (9.5)	89 (13.5)	0.005
Renal failure, n (%)	168 (7)	128 (7)	40 (6)	0.2
TSH, median (Q1, Q3)	2.5 (1.5, 4.7)	2 (1.3, 2.8)	7.8 (5.5, 13.5)	<0.0001
FT4, median (Q1, Q3)	1.1 (0.9, 1.3)	1.15 (1, 1.3)	1.1 (0.9, 1.3)	0.0009
Primary hypothyroidism	465 (19)	NA	465 (93)	NA
<b>Laboratory characteristics</b>				
White blood cells, median (Q1, Q3)	7.5 (6.2, 9.4)	7.5 (6.1, 9.3)	7.5 (6.3, 10)	0.3
Haemoglobin (g/dL), median (Q1, Q3)	13 (11.8, 14.1)	13.2 (12, 14.2)	12.6 (11.3, 13.6)	<0.0001
Platelet (g/L), median (Q1, Q3)	211 (176, 252)	210 (176, 249)	215 (177, 256)	0.08
Random glucose (mg/dL), median (Q1, Q3)	107 (96, 130)	106 (96, 127)	109 (97, 135)	0.008
Creatinine (mg/dL), median (Q1, Q3)	1.1 (1, 1.3)	1.1 (1, 1.3)	1.1 (0.9, 1.3)	0.67
Total cholesterol (mg/dL), median (Q1, Q3)	185 (158, 219)	184 (158, 218)	190 (160, 223)	0.03
Triglyceride (mg/dL), median (Q1, Q3)	145 (101, 206)	144 (100, 205)	149 (103, 209)	0.32
LDL (mg/dL), median (Q1, Q3)	109 (85, 137)	108 (84, 137)	111 (87, 138)	0.09
HDL (mg/dL), median (Q1, Q3)	43 (36, 52)	42 (35, 51)	44 (37, 55)	<0.0001
<b>Medications at discharge</b>				
Aspirin, n (%)	2216 (92)	1578 (91)	638 (94)	0.05
Clopidogrel, n (%)	1187 (49)	849 (49)	338 (50)	0.84
β-Blockers, n (%)	1811 (75)	1310 (76)	501 (73)	0.24
ACEI/ARBs, n (%)	1169 (49)	812 (50)	357 (52)	0.02
Calcium channel antagonist, n (%)	684 (28)	477 (28)	207 (30)	0.18
Nitrates, n (%)	1247 (52)	873 (51)	374 (55)	0.05
Statins, n (%)	1822 (76)	1289 (75)	533 (78)	0.06
Amiodarone, n (%)	39 (1.6)	19 (1)	20 (3)	0.002
<b>PCI characteristics</b>				
Diseased vessels, n (%)				<0.0001
1-vessel	557 (23)	353 (20)	204 (30)	
2-vessel	1076 (58)	813 (47)	263 (38)	
3-vessel	797 (42)	577 (33)	220 (32)	
Left main disease, n (%)	46 (2.0)	33 (1.9)	13 (1.9)	0.99
Status of procedure				0.05
Selective	1030 (42)	753 (43)	277 (40)	
Urgent	1102 (45)	794 (46)	308 (45)	
Emergent	297 (12)	195 (12)	102 (15)	
Drug-eluting stent	620 (26)	431 (25)	189 (28)	0.16
Stent number, median (Q1, Q3)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.10

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; TSH, thyroid-stimulating hormone; ACEI/ARBs, ACE inhibitors/angiotensin receptor blockers.

euthyroid groups at a Type 1 error rate of 0.05. In addition, to ensure stability of our models, variables associated with a high degree of collinearity were excluded from our final model. All variables selected from Table 1 were entered into an adjusted model with backward selection, and those covariates associated with a variance inflation factor of  $\geq 10$  were excluded from final model.

Prior to reporting hazard ratios, the proportional hazards assumption was verified in each model graphically by plotting the log hazard vs. time by levels of the covariates separately for hypothyroidism and euthyroidism. Each set of plotted lines was then visually assessed to ensure that the same vertical distance was maintained over time.

To ensure we did not violate the assumption of independent observations of Cox models, disease progression, when related to target-lesion or distal-to-target-lesion disease progression, was categorized as a binary event for each individual patient regardless of the number of coronary vessels affected. All tests were two tailed with a Type 1 error rate of 0.05. All analyses were undertaken using SAS 9.2 (SAS Institute, Cary, NC, USA).

## Results

### Baseline characteristics

Two thousand four hundred and thirty patients met the inclusion criteria for this study, of which 686 individuals (28%) with hypothyroidism. The median (Q1, Q3) follow-up for all patients was 3.0 years (0.5, 7.0). Baseline clinical, laboratory, and angiographic characteristics of the study groups are presented in Table 1. Compared with the euthyroid group, patients with hypothyroidism were significantly older and more likely to be female. The prevalence of hypertension (74.0 vs. 68.0%,  $P = 0.003$ ), diabetes mellitus (33.0 vs. 24.0%,  $P < 0.001$ ), previous MI (43.0 vs. 37.0%,  $P = 0.02$ ), and heart failure (13.5 vs. 9.5%,  $P = 0.001$ ) were significantly higher in patients with hypothyroidism. Levels of random glucose and high-density lipoprotein cholesterol were significantly higher, and levels of haemoglobin were significantly lower, in patients with hypothyroidism. Patients with hypothyroidism were also more likely to be taking nitrates, ACE inhibitors/angiotensin receptor blockers, and amiodarone.

### Cardiovascular events and hypothyroidism

The frequency of in-hospital MACCE and its constituent components are shown in Table 2. The incidence of heart failure was significantly higher in patients with hypothyroidism; however, the

frequency of MI, cardiac death, and TVR did not differ significantly between groups.

The relationship between hypothyroidism and MACCE at follow-up was evaluated using the Kaplan–Meier method. In patients with hypothyroidism, unadjusted Kaplan–Meier estimates for MACCE (86.5 vs. 78.3%, log-rank  $P < 0.0001$ ), cardiac death (11.9 vs. 6.4%, log-rank  $P = 0.0002$ ), MI (33.5 vs. 25.8%, log-rank  $P = 0.001$ ), TVR (75.0 vs. 69.6%, Log-rank  $P = 0.021$ ), and heart failure (26.6 vs. 16.3%, log-rank  $P < 0.0001$ ) at 10-year follow-up were significantly higher than for patients with euthyroidism (Figure 3). After adjusting for covariates, the risk of MACCE (HR: 1.28,  $P = 0.0001$ ), MI (HR: 1.25,  $P = 0.037$ ), heart failure (HR: 1.46,  $P = 0.004$ ), TVR (HR: 1.26,  $P = 0.0008$ ), and stroke (HR: 1.62,  $P = 0.04$ ) was higher in the hypothyroid group compared with the euthyroid group (Table 3).

### Thyroid status by thyroid-stimulating hormone levels and cardiovascular outcomes

To further evaluate the effect of thyroid status on MACCE, all patients were separately divided into three groups according only to their TSH level at the time of the index procedure as follows: euthyroidism, SCH, and hypothyroidism. At 10-year follow-up, the unadjusted Kaplan–Meier estimates for MACCE (86.1 vs. 78.1%,  $P = 0.0008$ ; 90.7 vs. 78.1%,  $P < 0.0001$ ), cardiac death (11.8 vs. 6.7%,  $P = 0.014$ ; 11.7 vs. 6.7%,  $P = 0.014$ ), MI (38.3 vs. 25.6%,  $P < 0.0001$ ; 32.1 vs. 25.6%,  $P = 0.14$ ), heart failure (21.1 vs. 16.4%,  $P = 0.003$ ; 33.0 vs. 16.4%,  $P < 0.0001$ ), and TVR (74.6 vs. 69.6%,  $P < 0.0001$ ; 77.0 vs. 69.6%,  $P < 0.0001$ ) were significantly higher in the SCH and hypothyroidism groups, respectively, compared with the euthyroid group (Figure 4). After adjusting for covariates, the risk of MACCE (HR<sub>SCH</sub>: 1.19,  $P = 0.033$  and HR<sub>hypothyroidism</sub>: 1.38,  $P = 0.0004$ ), MI (HR<sub>SCH</sub>: 1.43,  $P = 0.006$ ), heart failure (HR<sub>hypothyroidism</sub>: 1.60,  $P = 0.0007$ ), and TVR (HR<sub>SCH</sub>: 1.34,  $P = 0.003$ ) were higher in the SCH and hypothyroid groups compared with the euthyroid group. However, there were no significant differences between SCH and overt hypothyroidism with respect to any outcome (Figure 5).

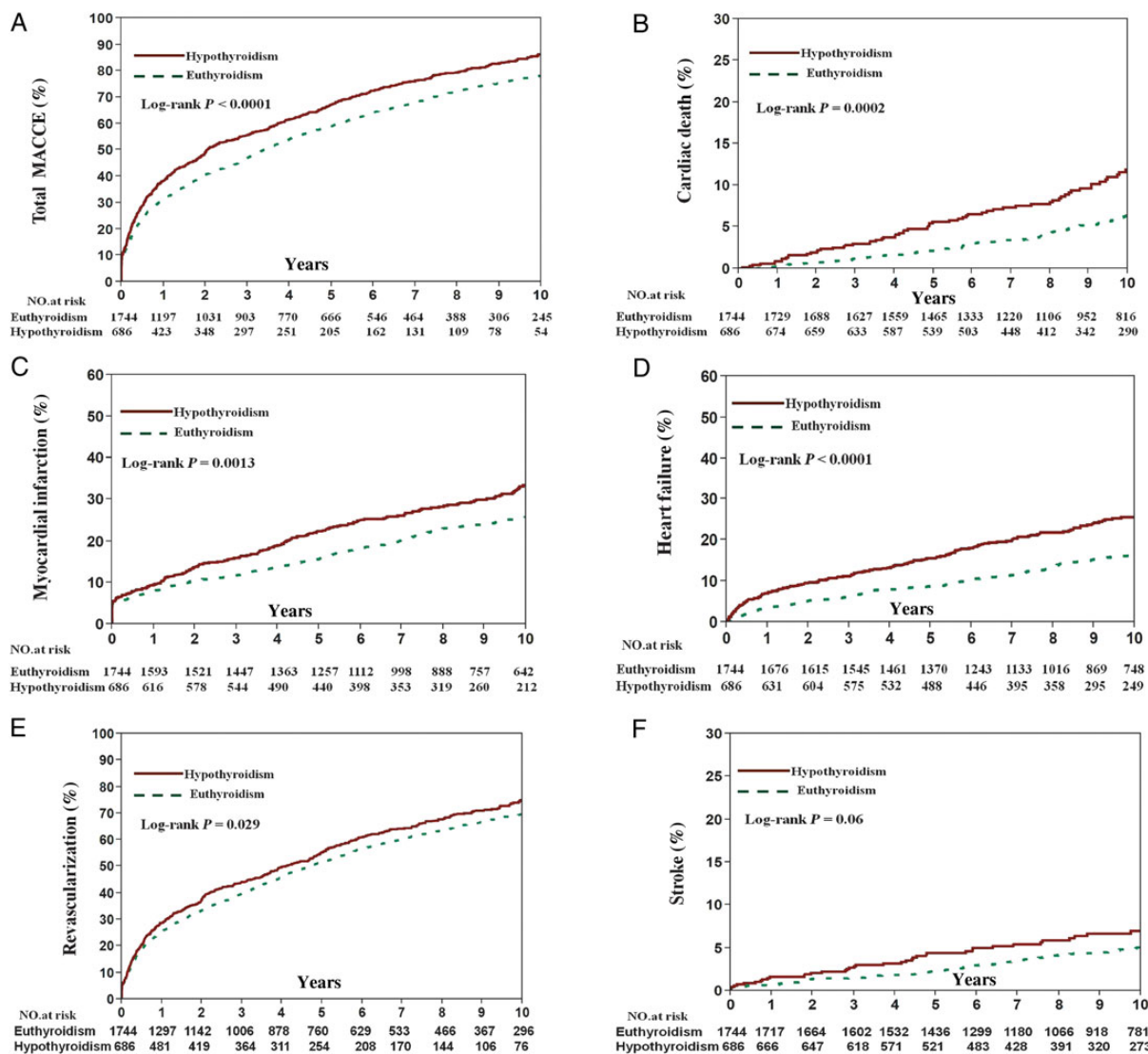
### Thyroid replacement therapy and cardiovascular outcomes

For patients on adequate replacement with TRT, the unadjusted Kaplan–Meier estimates at 10-year follow-up for MACCE

**Table 2** Frequency of in-hospital clinical outcomes in patients undergoing percutaneous coronary intervention

Variable	Euthyroidism (n = 1744)	Hypothyroidism (n = 686)	P-value
Myocardial infarction	85 (4.9)	36 (5.2)	0.71
Heart failure	160 (9.5)	89 (13.5)	0.005
Revascularization with PCI	69 (4)	25 (3.6)	0.71
Revascularization target vessel with PCI	21 (1.2)	13 (1.9)	0.2
Cardiac death	0 (0)	0 (0)	NA
Revascularization with CABG	13 (0.8)	8 (0.9)	0.33

NA, no statistical testing undertaken as no events recorded; CABG, coronary artery bypass grafting.



**Figure 3** Frequency of adverse cardiovascular events at follow-up in patients with hypothyroidism and euthyroidism. Unadjusted Kaplan–Meier curves during 10-year follow-up for (A) major adverse cardiovascular and cerebral events, (B) cardiac death, (C) myocardial infarction, (D) heart failure, (E) target-vessel revascularization, and (F) stroke.

(78.8 vs. 90.4%,  $P = 0.001$ ; 78.8 vs. 87.5%,  $P = 0.002$ ), cardiac death (5.5 vs. 16.3%,  $P = 0.002$ ; 5.5 vs. 12.1%,  $P = 0.003$ ), MI (19.7 vs. 43.8%,  $P < 0.0001$ ; 19.7 vs. 33.5%,  $P = 0.004$ ), heart failure (16.6 vs. 27.1%,  $P = 0.009$ ; 16.6 vs. 28.6%,  $P = 0.001$ ), TVR (70.6 vs. 78.0%,  $P = 0.04$ ; 70.6 vs. 75.6%,  $P = 0.12$ ), and stroke (6.5 vs. 2.6%,  $P = 0.009$ ; 6.5 vs. 4.9%,  $P = 0.68$ ) were lower compared with patients taking no TRT and patients with inadequate replacement on TRT, respectively (Figure 6). After adjusting for covariates, patients with adequate replacement on TRT had a lower risk of MACCE (HR: 0.69,  $P = 0.005$ ; HR: 0.78,  $P = 0.045$ ), cardiac death (HR: 0.43,  $P = 0.008$ ), MI (HR: 0.50,  $P = 0.0004$ ; HR: 0.60,  $P = 0.02$ ), and heart failure (HR: 0.50,  $P = 0.02$ ; HR: 0.52,  $P = 0.017$ ) compared with patients not taking TRT and patients with inadequate replacement on TRT, respectively. When comparing patients prescribed no TRT to patients with inadequate replacement on

TRT, there were no differences with respect to any outcome except stroke (HR: 2.81,  $P = 0.005$ ) (Figure 7).

### Coronary disease progression

Four hundred and eight patients were analysed for CAD progression. The Kaplan–Meier-estimated frequency of cumulative target-lesion disease progression at 10-year follow-up was higher for patients with hypothyroidism compared with those with euthyroidism (79.9 vs. 52.6%, log-rank  $P = 0.001$ ) (Figure 8A). After adjusting for covariates, hypothyroidism was associated with a higher risk of target-lesion disease progression compared with euthyroidism (HR: 1.43,  $P = 0.044$ ) (Table 4).

Thirty-one (7.6%) had total conduit occlusion at follow-up, and were therefore excluded from the downstream disease progression analysis. The Kaplan–Meier-estimated frequency of cumulative



**Table 3** Hazard ratios for major adverse cardiovascular and cerebral events in patients with hypothyroidism vs. euthyroidism

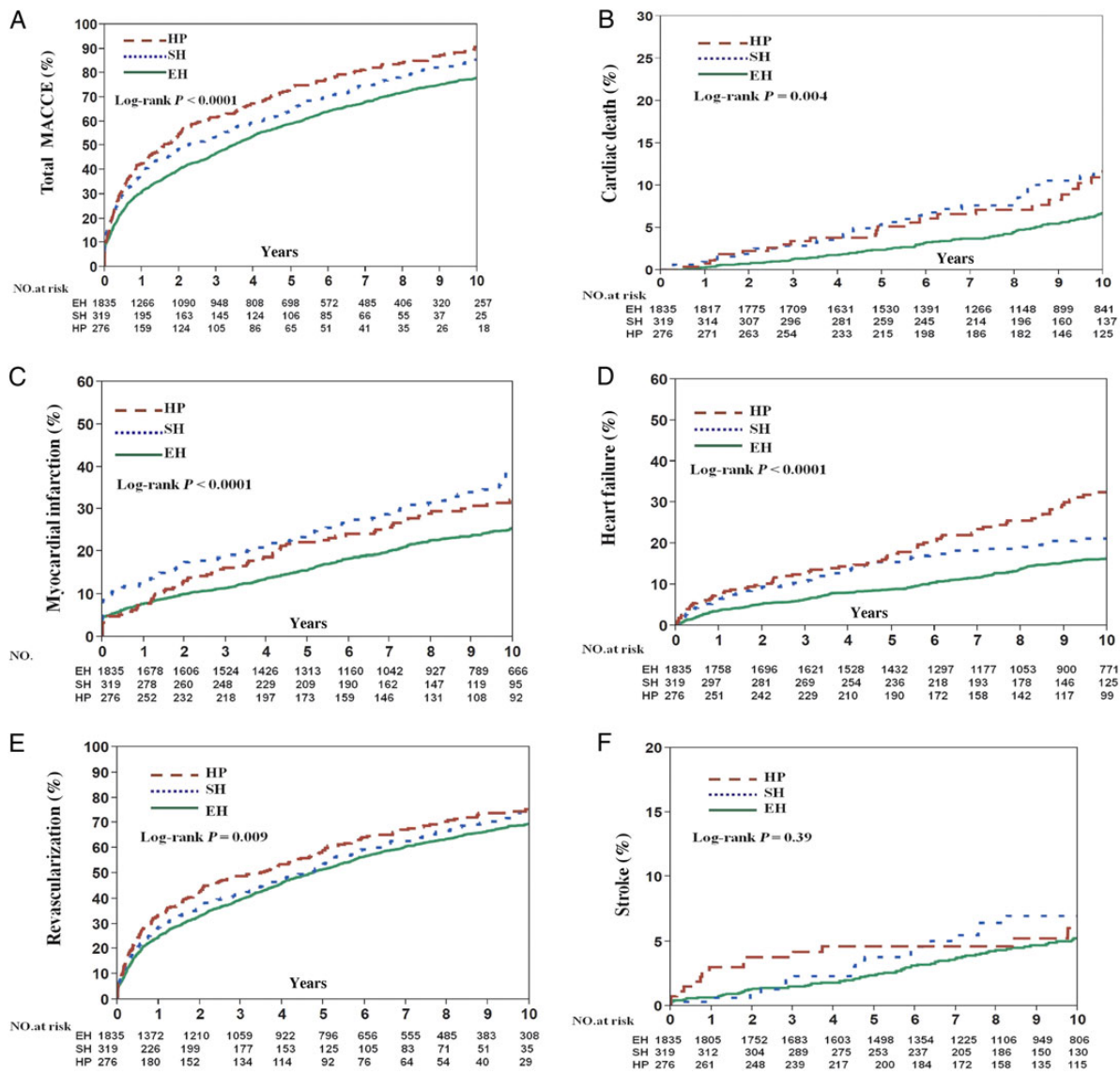
Variable	Adjusted HR <sup>a</sup>	95% CI	P-value
MACCE	1.28	1.13–1.45	0.0001
Cardiac death	1.14	0.75–1.69	0.54
Myocardial infarction	1.25	1.01–1.53	0.037
Heart failure	1.46	1.13–1.88	0.004
Revascularization	1.26	1.10–1.43	0.0008
Stroke	1.62	1.04–2.49	0.04

<sup>a</sup>Adjusted for age, gender, diabetes, hypertension, dyslipidaemia, family of CAD, renal failure, current smoking, heart failure, history of MI, number of diseased vessels, stent type, aspirin, β-blockers, ACE inhibitors, and statins.

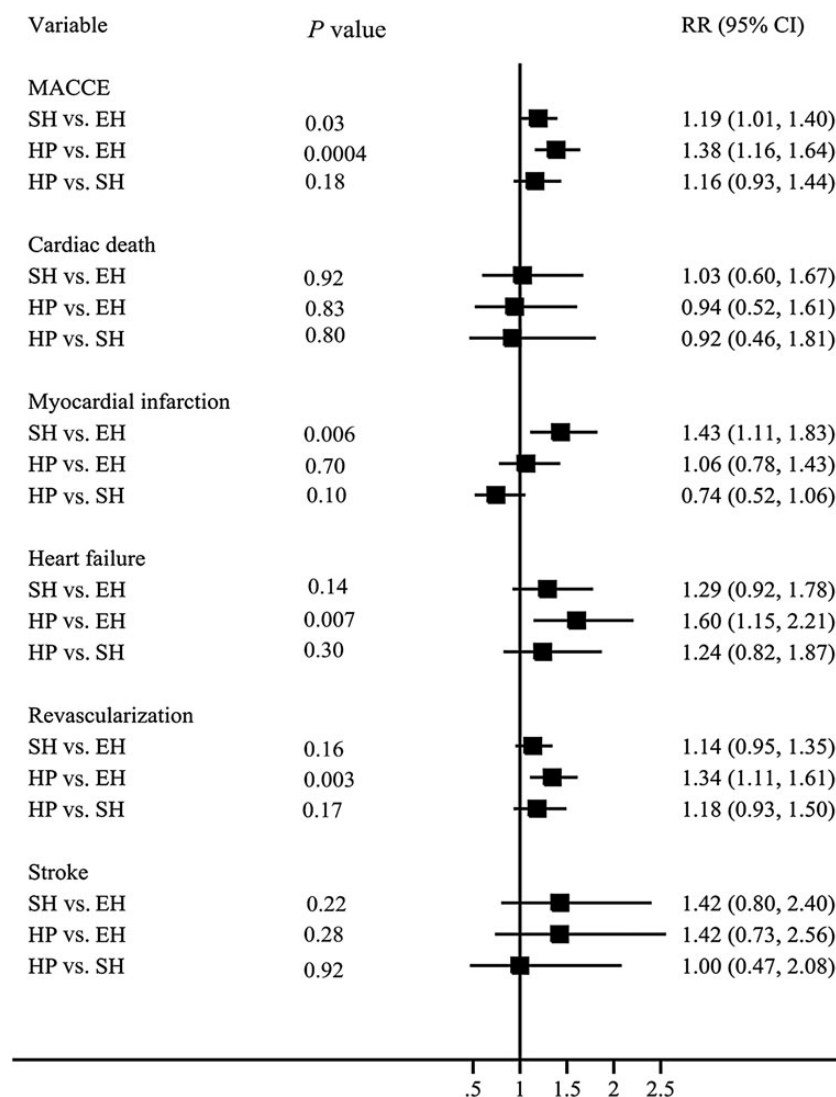
downstream disease progression at 10-year follow-up was significantly higher in patients with hypothyroidism (79.5 vs. 43.2%, log-rank  $P < 0.001$ ) (Figure 8B). After adjusting for covariates, hypothyroidism was associated with a higher risk for downstream disease progression compared with euthyroidism (HR: 1.90,  $P = 0.006$ ) (Table 4).

## Discussion

The present study demonstrates that patients with a clinical history of hypothyroidism have a higher risk of MACCE, cardiac death, MI, heart failure, and TVR following PCI compared with euthyroid patients. Hypothyroidism is also associated with a higher incidence of coronary target-lesion and downstream disease progression. In addition, our findings suggest that adequate replacement with



**Figure 4** Frequency of adverse cardiovascular events at follow-up in patients with hypothyroidism, subclinical hypothyroidism, and euthyroidism according to serum thyroid-stimulating hormone levels. Unadjusted Kaplan–Meier curves during 10-year follow-up for (A) major adverse cardiovascular and cerebral events, (B) cardiac death, (C) myocardial infarction, (D) heart failure, (E) revascularization, and (F) stroke. EH, euthyroidism; SH, subclinical hypothyroidism; HP, hypothyroidism.



**Figure 5** Hazard ratios for major adverse cardiovascular and cerebral events in patients with hypothyroidism, subclinical hypothyroidism, and euthyroidism.

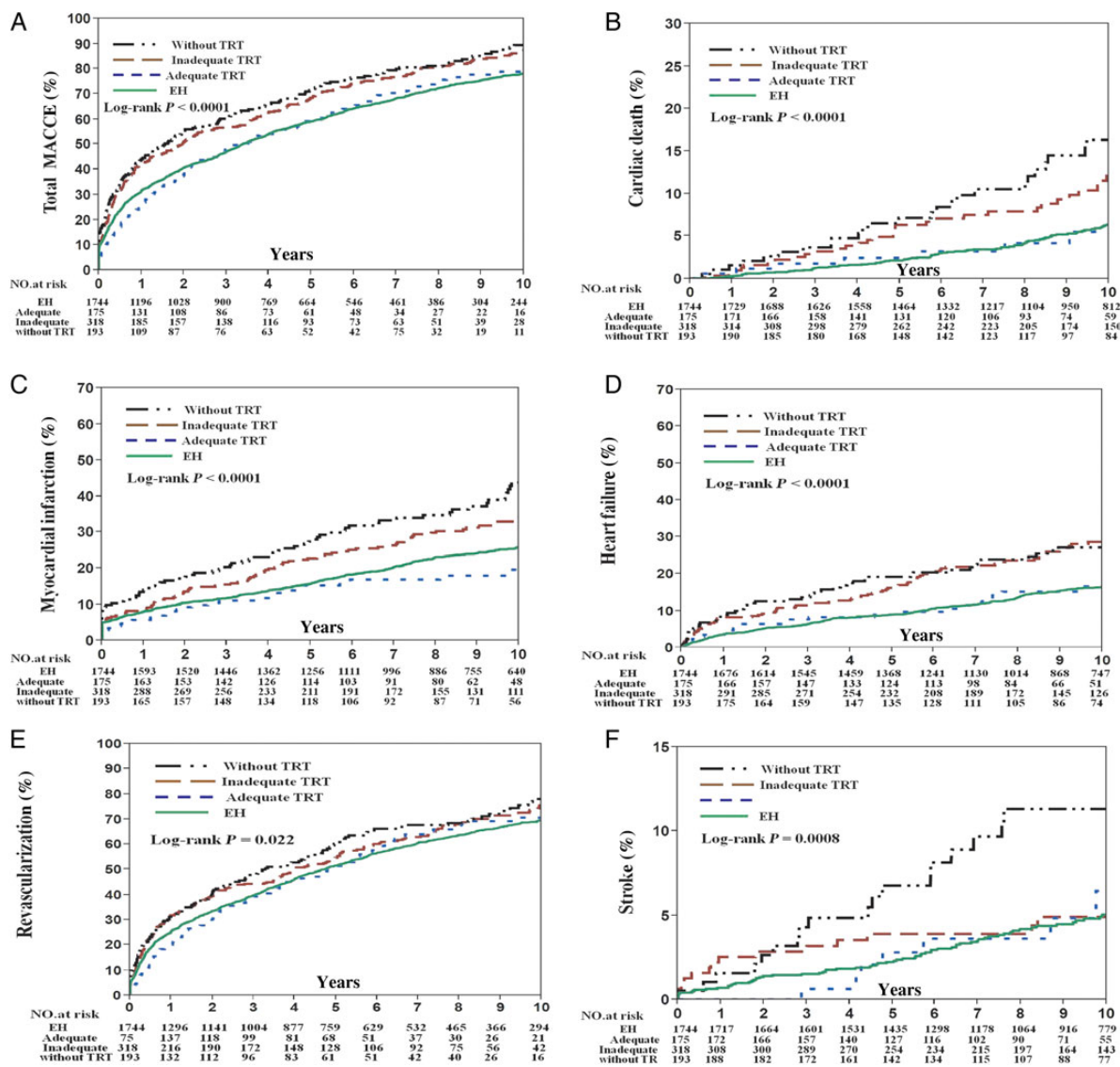
TRT among patients with a clinical history of hypothyroidism significantly reduces the risk of MACCE compared with patients with inadequate replacement or no TRT. The latter finding highlights the importance of monitoring TSH levels and maintaining a biochemically euthyroid state and supports a role for the routine testing of TSH levels in hypothyroid patients presenting for PCI as part of standard laboratory testing.

### Hypothyroidism and major adverse cardiovascular and cerebral events

Previous studies have linked hypothyroidism with accelerated atherosclerosis and an increased risk of CAD,<sup>9</sup> congestive heart failure,<sup>14</sup> and diabetes mellitus.<sup>15</sup> The present study extends these findings by also demonstrating a higher prevalence of hypertension, diabetes mellitus, previous MI, and heart failure in patients with hypothyroidism.

The most important finding of our study was that hypothyroidism was associated with an increased risk of MACCE at follow-up in patients who underwent PCI. This may in part be attributable to the higher prevalence of conventional cardiovascular risk factors in the hypothyroid cohort compared with the euthyroid cohort, particularly with respect to an atherogenic lipid profile.<sup>16</sup> However, the association between hypothyroidism and MACCE remained even after adjusting for cardiovascular risk factors, suggesting that other factors may be involved. In this study, we showed that patients with hypothyroidism have a higher risk of target-lesion and downstream disease progression compared with patients with euthyroidism, which could partly explain hypothyroidism's association with a higher incidence of MACCE. The mechanism of this accelerated disease progression may relate to other factors such as endothelial dysfunction<sup>17</sup> and low-grade systemic inflammation,<sup>18</sup> both of which are associated with atherosclerosis. Endothelial dysfunction is an





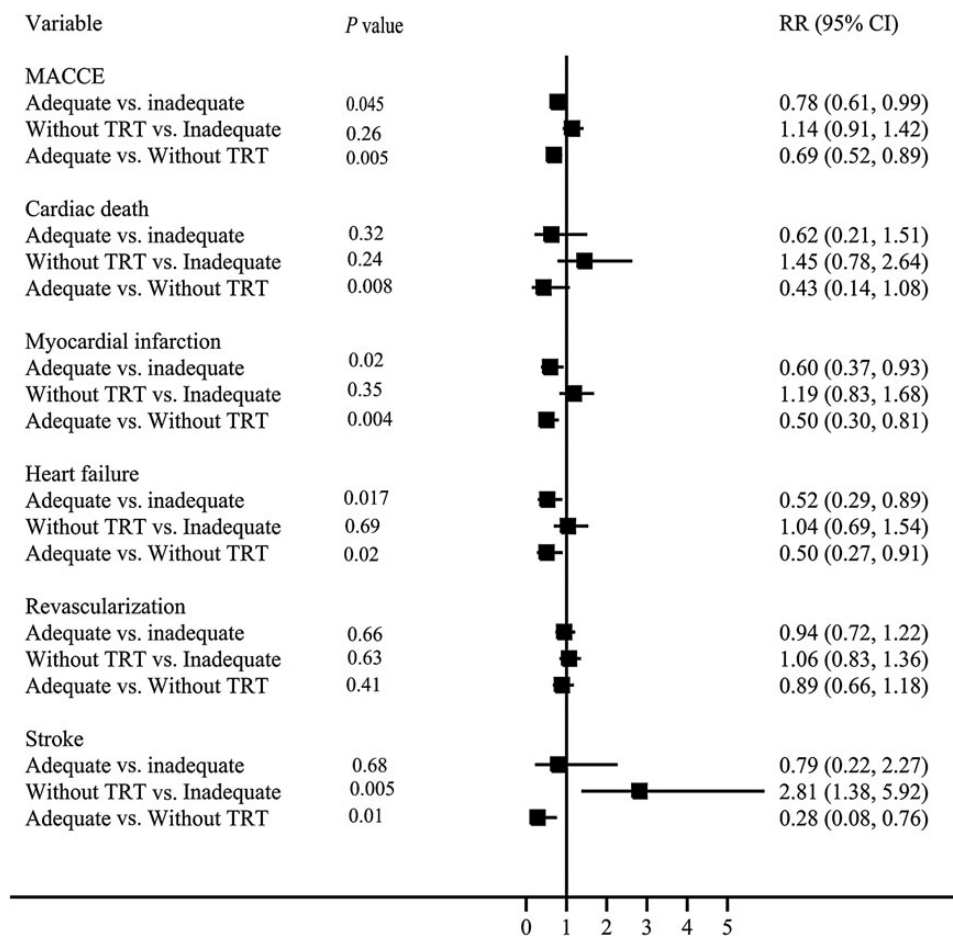
**Figure 6** Frequency of adverse cardiovascular events at follow-up between patients not taking thyroid replacement therapy and those taking thyroid replacement therapy with and without adequate replacement. Unadjusted Kaplan–Meier curves during 10-year follow-up for (A) major adverse cardiovascular and cerebral events, (B) cardiac death, (C) myocardial infarction, (D) heart failure, (E) target-vessel revascularization, and (F) stroke.

early marker of atherosclerosis<sup>19</sup> and arises in part due to the impaired bioavailability of nitric oxide and increased platelet adherence and smooth muscle cell migration and proliferation, both of which are implicated in the pathogenesis of atherosclerosis.<sup>20</sup> In addition, endothelial dysfunction is associated with coronary plaque progression and necrotic plaque, which are vulnerable to rupture and is also linked to an increased risk of adverse cardiovascular events. Recent studies have suggested that hypothyroidism may have adverse effects on endothelial function independent of other well-known atherosclerotic risk factors.<sup>17,21</sup> We recently showed that hypothyroidism is associated with microvascular endothelial dysfunction in women with non-obstructive CAD.<sup>22</sup> It has also been shown that the TSH receptor is expressed on vascular

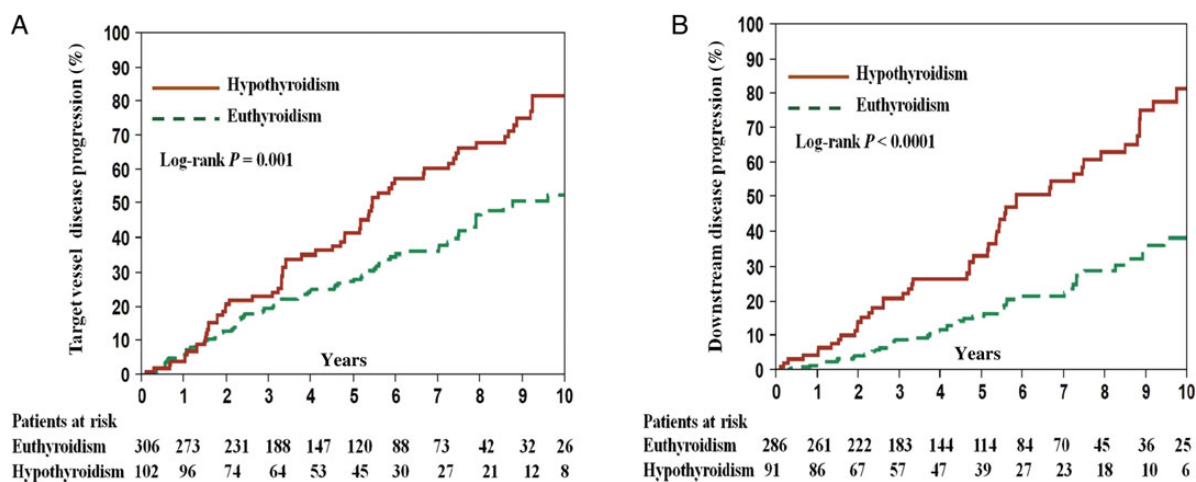
endothelial cells and elevated TSH can promote endothelial dysfunction by altering gene expression.<sup>23</sup> Thus, hypothyroidism may lead to an increased risk of adverse cardiovascular events through endothelial dysfunction; however, the precise mechanisms require further clarification.

### Thyroid status by thyroid-stimulating hormone and major adverse cardiovascular and cerebral events

We carried out a separate analysis evaluating the relationship between hypothyroidism, SCH and euthyroidism, and MACCE. Our results showed that patients with overt hypothyroidism and SCH



**Figure 7** Hazard ratios for major adverse cardiovascular and cerebral events in patients taking thyroid replacement therapy with adequate replacement vs. inadequate replacement and no replacement therapy.



**Figure 8** Kaplan–Meier-estimated cumulative target and downstream disease progression frequencies during 10-year follow-up. (A) Target-lesion disease progression and (B) downstream disease progression.

**Table 4 Hazard ratios for coronary disease progression in patients with hypothyroidism vs. euthyroidism**

Variable	Adjusted HR <sup>a</sup>	95% CI	P-value
Target lesion	1.43	1.01–1.99	0.04
Downstream lesion	1.90	1.21–2.95	0.006
Target-lesion total occlusion	1.25	0.57–2.59	0.57

<sup>a</sup>Adjusted for age, gender, diabetes, hypertension, dyslipidaemia, family of CAD, renal failure, current smoking, heart failure, history of MI, number of diseased vessels, stent type, aspirin,  $\beta$ -blockers, ACE inhibitors, and statins.

were at increased risk of MACCE at follow-up compared with patients with euthyroidism. Although some studies do not support the routine screening of individuals for thyroid disease,<sup>6</sup> these results suggest that routinely screening patients using TSH as a simple biomarker may be beneficial in identifying subjects with SCH or undiagnosed overt hypothyroidism who are at increased risk of cardiovascular events. This is particularly important as these patients may benefit from TRT to reduce the risk of adverse health outcomes<sup>24</sup> as well as cardiovascular disease.<sup>25</sup> Though there is controversy as to whether or not SCH merits treatment, our findings support previous lines of evidence that suggest that SCH is indeed a clinically important entity that requires identification and management, as its risk is comparable with that of overt hypothyroidism. However, given that other studies have found no differences in risk between patients with SCH and euthyroidism,<sup>10</sup> the clinical implications of SCH require further investigation.

### Thyroid replacement therapy

Among 686 participants with hypothyroidism, 493 were prescribed TRT at the time of index PCI. It remains unclear as to whether treatment with TRT can offset the increased risk of cardiovascular disease in patients with hypothyroidism. Some studies suggest that TRT reverses this risk<sup>25</sup> and improves the symptoms of patients with hypothyroidism while also improving the health status of patients with SCH.<sup>24</sup> Other studies, however, do not support the treatment of individuals with SCH to prevent cardiovascular events.<sup>10,26</sup> The aim of treating hypothyroidism is to achieve euthyroidism, and TRT is considered safe providing there is close monitoring of serum TSH levels.<sup>27</sup> However, despite frequent monitoring and dose adjustment, inadequate thyroid hormone replacement remained a problem in over a third of levothyroxine users in this population.<sup>28</sup> In our study, among the 72% of patients with hypothyroidism taking TRT, 65% had TSH levels outside the target range at follow-up. Other studies have reported that up to 40% of patients taking TRT have abnormal TSH levels.<sup>29</sup> We found that the risk of MACCE was significantly lower in patients with adequate replacement on TRT. However, the risk of MACCE was not significantly different between patients with inadequate replacement on TRT and those not taking TRT, further underscoring the importance of maintaining the euthyroid state. Our findings highlight the need to

evaluate the adequacy of treatment with TRT among patients with hypothyroidism by the routine monitoring of serum TSH levels.

### Study limitations

First, the present study was a prospective cohort study and our results may be influenced by confounding variables not accounted for in our analyses. There may also be a selection bias as patients must have had TSH levels drawn at the time of the index PCI to be eligible for this study. Second, most subjects who had documented TSH levels had no FT4 levels available, limiting the assessment of thyroid status to a single TSH value, which may result in a misclassification bias, particularly when diagnosing SCH. Thyroid-stimulating hormone levels are also known to fluctuate with time adding to this problem. Third, this study is limited by its observational design and its relatively modest sample size, thus further studies evaluating a larger sample size in the context of a randomized clinical trial are required. Nevertheless, the present study is, to our knowledge, the only prospective cohort study to have evaluated the relationship between hypothyroidism and adverse cardiovascular events in patients undergoing PCI and, despite the modest sample size, was still able to demonstrate a significant difference in the incidence of MACCE in patients with hypothyroidism compared with those with euthyroidism. Finally, when collecting our data, we were not able to identify other non-cardiac causes of death such as malignancy, which may be competing risks against cardiovascular death, and should also be considered.

### Conclusions

Hypothyroidism is associated with a higher incidence of MACCE compared with euthyroidism in patients undergoing PCI. Maintaining adequate control on TRT is beneficial in preventing cardiovascular events.

### Authors' contributions

M.Z., J.D.S.S., Y.M., H.G., M.R.B., R.G., L.O.L., and A.L. performed statistical analysis. A.L. handled funding and supervision. M.Z. and A.L. acquired the data. M.Z., J.D.S.S., Y.M., H.G., M.R.B., R.G., L.O.L., and A.L. conceived and designed the research. M.Z. and A.L. drafted the manuscript. M.Z. and A.L. made critical revision of the manuscript for key intellectual content.

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### References

- Kahaly GJ, Dillmann WH. Thyroid hormone action in the heart. *Endocr Rev* 2005;**26**: 704–728.
- Polikar R, Burger AG, Scherrer U, Nicod P. The thyroid and the heart. *Circulation* 1993;**87**:1435–1441.
- Baumgartner C, Blum MR, Rodondi N. Subclinical hypothyroidism: summary of evidence in 2014. *Swiss Med Wkly* 2014;**144**:w14058.

4. Ruge JB, Bougatso C, Chou R. Screening and treatment of thyroid dysfunction: an evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2015; **162**:35–45.
5. Boelaert K. Thyroid dysfunction in the elderly. *Nat Rev Endocrinol* 2013; **9**:194–204.
6. Tabatabaie V, Surks MI. The aging thyroid. *Curr Opin Endocrinol Diabetes Obes* 2013; **20**:455–459.
7. ATA. Prevalence and impact of thyroid disease. <http://www.thyroid.org/> (29 September 2014). 2014.
8. Taylor PN, Iqbal A, Minassian C, Sayers A, Draman MS, Greenwood R, Hamilton W, Okosieme O, Panicker V, Thomas SL, Dayan C. Falling threshold for treatment of borderline elevated thyrotropin levels—balancing benefits and risks: evidence from a large community-based study. *JAMA Intern Med* 2014; **174**:32–39.
9. Grais IM, Sowers JR. Thyroid and the heart. *Am J Med* 2014; **127**:691–698.
10. Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL, Tracy RP, Ladenson PW. Thyroid status, cardiovascular risk, and mortality in older adults. *JAMA* 2006; **295**:1033–1041.
11. Silber S, Albertsson P, Avilés FF, Camici PG, Colombo A, Hamm C, Jørgensen E, Marco J, Nordrehaug JE, Ruzyllo W, Urban P, Stone GW, Wijns W, Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J* 2005; **26**:804–847.
12. McQuade C, Skugor M, Brennan DM, Hoar B, Stevenson C, Hoogwerf BJ. Hypothyroidism and moderate subclinical hypothyroidism are associated with increased all-cause mortality independent of coronary heart disease risk factors: a PreCIS database study. *Thyroid* 2011; **21**:837–843.
13. Zouridakis EG, Schwartzman R, Garcia-Moll X, Cox ID, Fredericks S, Holt DW, Kaski JC. Increased plasma endothelin levels in angina patients with rapid coronary artery disease progression. *Eur Heart J* 2001; **22**:1578–1584.
14. Biondi B. Mechanisms in endocrinology: heart failure and thyroid dysfunction. *Eur J Endocrinol* 2012; **167**:609–618.
15. Radaideh AR, Nusier MK, Amari FL, Bateiha AE, El-Khateeb MS, Naser AS, Ajlouni KM. Thyroid dysfunction in patients with type 2 diabetes mellitus in Jordan. *Saudi Med J* 2004; **25**:1046–1050.
16. Ichiki T. Thyroid hormone and atherosclerosis. *Vascul Pharmacol* 2010; **52**:151–156.
17. Papaioannou GI, Lagasse M, Mather JF, Thompson PD. Treating hypothyroidism improves endothelial function. *Metabolism* 2004; **53**:278–279.
18. Taddei S, Caraccio N, Virdis A, Dardano A, Versari D, Ghiadoni L, Ferrannini E, Salvetti A, Monzani F. Low-grade systemic inflammation causes endothelial dysfunction in patients with Hashimoto's thyroiditis. *J Clin Endocrinol Metab* 2006; **91**:5076–5082.
19. Elesber AA, Solomon H, Lennon RJ, Mathew V, Prasad A, Pumper G, Nelson RE, McConnell JP, Lerman LO, Lerman A. Coronary endothelial dysfunction is associated with erectile dysfunction and elevated asymmetric dimethylarginine in patients with early atherosclerosis. *Eur Heart J* 2006; **27**:824–831.
20. Lüscher TF, Barton M. Biology of the endothelium. *Clin Cardiol* 1997; **20**:II-3–II-10.
21. Völzke H, Robinson DM, Spielhagen T, Nauck M, Obst A, Ewert R, Wolff B, Wallaschofski H, Felix SB, Dörr M. Are serum thyrotropin levels within the reference range associated with endothelial function? *Eur Heart J* 2009; **30**:217–224.
22. Sara JD, Zhang M, Gharib H, Lerman LO, Lerman A. Hypothyroidism is associated with coronary endothelial dysfunction in women. *J Am Heart Assoc* 2015; **4**:e002225.
23. Tian L, Zhang L, Liu J, Guo T, Gao C, Ni J. Effects of TSH on the function of human umbilical vein endothelial cells. *J Mol Endocrinol* 2014; **52**:215–222.
24. McDermott MT, Ridgway EC. Subclinical hypothyroidism is mild thyroid failure and should be treated. *J Clin Endocrinol Metab* 2001; **86**:4585–4590.
25. Razvi S, Ingole L, Keeka G, Oates C, McMillan C, Weaver JU. The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function, and quality of life in subclinical hypothyroidism: randomized, crossover trial. *J Clin Endocrinol Metab* 2007; **92**:1715–1723.
26. Chu JW, Crapo LM. The treatment of subclinical hypothyroidism is seldom necessary. *J Clin Endocrinol Metab* 2001; **86**:4591–4599.
27. Thvilum M, Brandt F, Brix TH, Hegedüs L. A review of the evidence for and against increased mortality in hypothyroidism. *Nat Rev Endocrinol* 2012; **8**:417–424.
28. Okosieme OE, Belludi G, Spittle K, Kadiyala R, Richards J. Adequacy of thyroid hormone replacement in a general population. *QJM* 2011; **104**:395–401.
29. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med* 2000; **160**:526–534.