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Prognostic value of thyroid-stimulating hormone within reference range in patients with coronary artery disease

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ABSTRACT

Background. Thyroid-stimulating hormone (TSH) in the upper part of reference range is associated with cardio-metabolic disorders. The association of TSH within reference range with prognosis of patients with coronary artery disease (CAD) after percutaneous coronary intervention (PCI) remains poorly investigated.

Methods. The study included 8010 consecutive patients with CAD who were treated with PCI. All patients had a TSH level within reference range (0.3 to 4.0 mU/L). The primary outcome was 3-year all-cause mortality.

Results. TSH tertiles were: 1st tertile (0.3 mU/L to <1.02 mU/L; n = 2694), 2nd tertile (1.02 mU/L to <1.67 mU/L; n = 2654) and 3rd tertile (1.67 mU/L to 4.00 mU/L; n = 2662). The primary outcome (3-year mortality) occurred in 753 patients: 240 deaths in the 1st, 227 deaths in the 2nd and 286 deaths in the 3rd TSH tertile (Kaplan–Meier estimates of mortality 10.2%, 9.8% and 12.3%; adjusted hazard ratio [HR] = 1.31, 95% confidence interval [CI] 1.04–1.66 for each tertile increase). TSH level was associated with 30-day mortality (mortality estimates, 1.6% in the 1st, 1.6% in the 2nd and 3.5% in the 3rd TSH tertile; adjusted HR = 2.30 [1.33–3.97] for each tertile increase) but not with 30-day to 3-year mortality (mortality estimates, 8.6% in the 1st, 8.2% in the 2nd and 8.8% in the 3rd TSH tertile; P = 0.603). The incidence of cardiogenic shock or peri-PCI bleeding was increased in patients in the upper TSH tertile.

Conclusion. In patients with CAD undergoing PCI, TSH level in the upper part of reference range was associated with increased risk of mortality after PCI.

1. Introduction

Thyroid function exerts major effects on the cardiovascular system. The association between overt hypothyroidism or hyperthyroidism and cardiovascular disease is well known [1]. Several prior studies have shown that subclinical hypothyroidism – defined as elevated serum thyroid-stimulating hormone (TSH) level with normal thyroxine concentrations –

Abbreviations: AUC, Area under the curve; CAD, Coronary artery disease; IDI, Integrated discrimination improvement; PCI, Percutaneous coronary intervention; ROC, Receiver operating characteristic; TSH, Thyroid-stimulating hormone.

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is associated with increased risk of coronary artery disease (CAD) and mortality [2–4]. Meta-analyses of population-based studies further confirm the existence of an association between subclinical hypothyroidism and CAD [5,6] or cardiovascular mortality particularly among patients <65 years of age [5,7]. Evidence available also suggests that TSH levels in the upper part of reference range are associated with worse cardiovascular risk profile including endothelial dysfunction [8], reduced glomerular filtration rate [9], systolic and diastolic blood pressure [10], arterial stiffness [11], body mass index [12], metabolic syndrome [13,14], less favorable lipid levels [15], coronary [16] or carotid [17] atherosclerosis and myocardial infarction [18]. Nevertheless the association between TSH level in the upper part of reference range and mortality remains debatable [19–21]. To date no study has investigated the association between TSH within reference range and prognosis in patients with CAD after percutaneous coronary intervention (PCI). We undertook this study to investigate whether there is an association between TSH within reference range and prognosis of patients with CAD after PCI.

2. Methods

2.1. Patients

The study included 8010 consecutive patients >18 years of age with CAD who underwent diagnostic angiography and PCI between January 2000 and January 2011 in 2 tertiary hospitals. By design, the study represents a retrospective analysis of prospectively collected data. To be included in the study, patients had to have angiographic CAD (coronary stenosis with ≥50% lumen obstruction in ≥ one of the major coronary arteries) and a TSH level within reference range (0.3 mU/L to 4.0 mU/L) [22]. Patients with prior or current thyroid gland disease (including prior history, surgery or drug therapy for thyroid gland disease) and those with acute infections, advanced renal disease (serum creatinine level ≥2 mg/dL), known malignancies or those receiving dopamine or dopamine agonists on admission were excluded. All patients gave written informed consent for PCI and the use of the data on anonymous basis. The study was carried out in accordance with the Declaration of Helsinki.

2.2. Cardiovascular Risk Factors

Cardiovascular risk factors were defined as follows: arterial hypertension — active treatment with antihypertensive agents or a documented systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg on ≥2 separate occasions; hypercholesterolemia — documented total cholesterol value ≥220 mg/dL or being on active treatment with cholesterol-lowering drugs; type 2 diabetes — active treatment with insulin or oral hypoglycemic agents, or the documentation of elevated fasting plasma glucose (glucose level ≥126 mg/dl or ≥7.0 mmol/dl) or a blood glucose >200 mg/dl (>11.1 mmol/dl) at any time or an abnormal 2-h glucose load test (post-load plasma glucose ≥200 mg/dl or 11.1 mmol/l) according to the World Health Organization criteria; current smoking — the use of any type or amount of tobacco in the prior six months. Body mass index was calculated using the patients' weight and height measured during the hospital stay. The creatinine clearance was estimated using the Cockcroft–Gault formula [23].

2.3. Angiographic Evaluation and PCI

Diagnostic angiography and PCI were performed as per standard practice. Coronary stents were implanted in all patients. Digital angiograms were analyzed offline in the core angiographic laboratory. CAD was diagnosed in the presence of coronary stenosis with ≥50% lumen obstruction in ≥1 of the major coronary arteries. The complexity of lesions was defined according to the modified American College of Cardiology/American Heart Association criteria [24]. Class B2 and C lesions were considered complex. Angiographic left ventricular ejection fraction was calculated with the area–length method. Pre-procedural antiplatelet therapy consisted of clopidogrel (300 or 600 mg as a loading dose) and aspirin (325 to 500 mg). Post-procedural therapy consisted of aspirin (80–325 mg/day indefinitely) and clopidogrel (75 mg/day for ≥1 month in patients with bare-metal stents or ≥6 months in patients with drug-eluting stents). Other medications were prescribed at the discretion of the patient's physician.

2.4. Biochemical Measurements

Blood samples were obtained on admission with patients in stable condition. TSH was measured quantitatively in plasma by an electrochemiluminescence immunoassay using the cobas e411 analyzer (Roche Diagnostics). The lower detection limit (representing the lowest analyte level that can be distinguished from zero) of this assay is 0.005 mU/L; the functional sensitivity (the lowest analyte concentration that can be reproducibly measured with an imprecision of 20%) is 0.014 mU/L. Current performance measures show a coefficient of variation of 3.32% at a TSH concentration of 1.57 mU/L. Creatinine was measured using a kinetic colorimetric assay based on the compensated Jaffe method. Other biochemical parameters were measured using the standard laboratory methods. Laboratory personnel who performed the measurements were unaware of clinical or outcome data of the patients.

2.5. Outcomes and Follow-up

The primary outcome analysis was 3-year all-cause mortality. Cardiovascular deaths, non-fatal myocardial infarction, stent thrombosis, bleeding (within 30 days of PCI) and stroke were also assessed. Data on mortality were obtained from hospital records, death certificates or phone contact with the referring physician(s), relatives of the patient, insurance companies or registration of address office. Myocardial infarction was diagnosed using electrocardiographic (development of new abnormal Q waves in ≥2 contiguous precordial leads or ≥2 adjacent limb leads) or enzymatic (an elevation of creatine kinase—myocardial band >2 times [>3 times for the 48 h after PCI] the upper limit of normal) criteria. Cardiovascular deaths and definite stent thrombosis were defined according to the Academic Research Consortium criteria [25]. All neurologic