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EDITORIAL

Should we screen for hypothyroidism in patients with cardiovascular disease?

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This editorial refers to 'Clinical outcomes of patients with hypothyroidism undergoing primary percutaneous coronary intervention'†, by A. Lerman *et al.*, on page 2055.

In contrast to overt dysfunction, the screening and treatment of subclinical hypothyroidism has been controversial for >20 years.[1] Subclinical hypothyroidism is defined as a thyroid-stimulating hormone (TSH) level above the upper limit of the reference ranges with normal free thyroxine (T_4) concentrations.[2] The prevalence of subclinical hypothyroidism increases with ageing, reaching up to 10% in the elderly.[3] The evidence on the cardiovascular risks of subclinical hypothyroidism has been recently investigated in several individual participant data (IPD) analyses of prospective cohorts.[4–6] The Thyroid Studies Collaboration pooled IPD of 50 953 patients with euthyroidism and 3348 with subclinical hypothyroidism from seven countries and 10 cohorts, and found a significant increase in coronary heart disease (CHD) mortality, especially in those with high levels of TSH ≥10.0 mIU/L (*Figure 1*).[4] The same observations were found for CHD events, including non-fatal and fatal myocardial infarction (MI) events and heart failure (HF) events (*Figure 1*).[4,6] These associations persisted after adjustment for traditional cardiovascular risk factors and after excluding those with thyroid medications or previous cardiovascular disease. IPD analysis is the most robust method to summarize data across observational studies, as it allows the analysis of reduced heterogeneity and the analysis of subgroups without ecological bias.

Lerman *et al.* from the Mayo Clinic reported in a cohort of 2430 patients undergoing percutaneous coronary intervention (PCI) an association between hypothyroidism and incidence of major adverse cardiovascular and cerebral events (MACCE) with a median follow-up time of 3 years.[7] After adjustment for traditional covariates, the risk of MACCE was higher in patients with hypothyroidism compared with euthyroidism [hazard ratio (HR) 1.27, 95% confidence interval (CI) 1.12–1.42, $P = 0.0001$], including for HF events (HR 1.42, 95% CI 1.12–1.79, $P = 0.004$), MI (HR 1.23, 1.01–1.50, $P = 0.039$), and revascularization events (HR 1.23, 95% CI 1.09–1.39, $P = 0.001$). Although the measurement of free T_4 was not available for all patients to distinguish overt from subclinical hypothyroidism, the risk of MACCE was higher in patients with subclinical hypothyroidism (HR 1.24, 95% CI 1.07–1.44, $P = 0.005$) and with overt hypothyroidism (HR 1.42, 95% CI 1.20–1.67, $P < 0.0001$) compared with euthyroidism. Hypothyroidism was also associated with progression of CHD as assessed by angiography in target lesions (HR 1.43, 95% CI 1.01–1.99, $P = 0.04$), as well as in downstream lesions (HR 1.90, 95% CI 1.21–2.95, $P = 0.006$).

The presented data are important given the large sample size, the quality of follow-up, and the interesting finding on the impact of thyroid replacement therapy. Screening for subclinical thyroid dysfunction in patients undergoing PCI might be an adequate setting to detect modifiable and treatable cardiovascular risk factors, especially in this group of patients with high risk. However, the study has some limitations. First, TSH was measured during hospitalization for PCI, including indications, such as acute coronary syndromes or possibly in patients with HF; as these acute conditions could modify TSH levels, non-thyroidal illness syndrome cannot be excluded and may have had an impact on the results. Another limitation is the absence of a second measurement of TSH to confirm persisting thyroid dysfunction, which would rather bias the results towards an absence of association. Thirdly, as free T_4 was not available in most patients, distinguishing overt (low T_4 levels) from subclinical hypothyroidism (normal T_4 levels) was not feasible.

One of the strengths of this study is the analysis according to the adequacy of thyroid replacement therapy and normalization of TSH levels. In the current study, patients with adequate thyroid replacement therapy (defined as normalization of TSH) had a significantly lower incidence rate of MACCE compared with untreated patients (HR 0.69, 95% CI 0.53–0.89, $P = 0.004$) or inadequately treated patients with hypothyroidism (HR 0.78, 95% CI 0.61–0.98, $P = 0.036$). Similarly, Razvi *et al.* reported in the United Kingdom General

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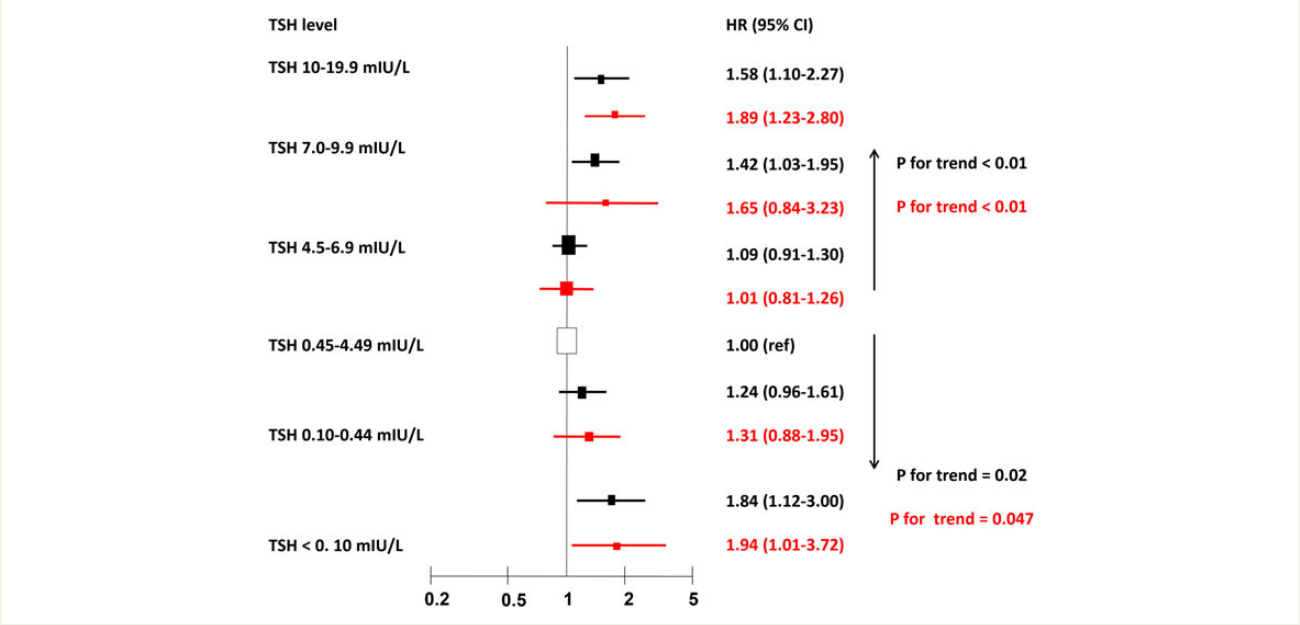

Figure 1 Hazard ratios (HRs) for coronary heart disease mortality (black) and heart failure event (red) according to thyroid-stimulating hormone (TSH) levels.[4–6] Age- and sex-adjusted HRs and their 95% confidence intervals (CIs) are represented by squares. Squares to the right of the solid lines indicate increased risk of heart failure events. The sizes of data markers are proportional to the inverse of the variance of the HRs. Figure reprinted with kind permission from EHJ CardioPulse article entitled 'Should we screen cardiovascular patients for thyroid dysfunction?'

Practitioner Research Database among 3093 patients aged between 40 and 70 years old with subclinical hypothyroidism an association between thyroid replacement therapy and lower incidence of CHD events (adjusted HR 0.61, 95% CI 0.39–0.95).[8] In contrast, in the elderly with subclinical hypothyroidism (>70 years old), no association was found between thyroid replacement therapy and lower risk of CHD events (HR 0.99, 95% CI 0.59–1.33).[8] However, the 2015 US Preventive Services Task Force for screening for thyroid dysfunction concluded that the current evidence was insufficient to assess the balance of benefits and harms of screening and treatment for thyroid dysfunction in asymptomatic adults, mainly due to the absence of large randomized controlled studies with clinical endpoints.[1]

Thyroid hormones have an important role in cardiovascular homeostasis, such as cardiac output, cardiac contractility, vascular resistance, and blood pressure. Subclinical hypothyroidism has been associated with left ventricular diastolic dysfunction at rest and during exertion, as well as with impaired left ventricular systolic function on exercise.[2] Higher TSH values in patients with subclinical hypothyroidism have been correlated with a decrease in left ventricular stroke volume, a decrease in cardiac index, and an increase in systemic vascular resistance.[9] In addition, abnormalities in the diastolic function parameters have been reported in patients with subclinical hypothyroidism and might explain the associated risk of clinical HF events observed for higher TSH values.[10,11] However, only a few trials with limited sample size (ranging between 10 and 56 patients) suggest that thyroid replacement therapy might be associated with normalization of echocardiographic diastolic parameters.[12] Biological abnormalities including elevated cholesterol levels, inflammatory markers, raised homocysteine, increased oxidative stress, insulin resistance, increased systemic vascular resistance, arterial stiffness, altered endothelial function, and activation of thrombosis and hypercoagulability have all been reported to be associated with subclinical hypothyroidism. Similar to clinical trials using echocardiographic outcomes, some small interventional studies (with a sample size of 45 patients with subclinical hypothyroidism) suggested that normalization of thyroid dysfunction was associated with a decrease in LDL-cholesterol and a regression of subclinical atherosclerosis, as measured by carotid intima media thickness.[13] Although a growing amount of data from observational studies reported that subclinical hypothyroidism has been associated with worse clinically relevant cardiovascular outcomes, evidence for screening and treating subclinical hypothyroidism remains limited by the lack of adequately powered randomized controlled trials. The TRUST ('Thyroid hormone Replacement for Untreated older adults with Subclinical Hypothyroidism a randomized placebo-controlled Trial among older adults', supported by FP-7 EU funding, Specific Program 'Cooperation'-Theme 'Health', Proposal No: 278148-2, NCT01660126) will assess the impact of thyroid replacement therapy on quality of life, potential symptoms, cardiovascular risk factors, and biomarkers.

What are the clinical and research implications of the current data? Recognizing modifiable and potentially treatable risk factors for CHD and HF, such as TSH, is recommended by the European Thyroid Association and European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic HF.[14,15] Data from large observational studies suggest that a threshold for TSH of 10 mU/L might be useful to consider thyroid medication. However, levels of evidence based only on non-randomized studies (Level B) are not adequately strong for clinical decisions. The European

Society of Cardiology guidelines for the management of acute coronary syndrome or stable CHD did not mention in their recommendations the issues for the screening of thyroid dysfunction with TSH measurement, probably as more trials are needed to strengthen the evidence.

The threshold TSH to define and treat subclinical hypothyroidism remains controversial. A strong argument for therapy at low TSH thresholds is to prevent progression to overt hypothyroidism. For CHD patients, a potential benefit of adequate thyroid replacement therapy could be associated with lower incidence of recurrence as well as the progression of HF events. Counterarguments are the lifelong daily therapy in asymptomatic individuals with potential overtreatment and side effects, such as bone fractures or atrial fibrillation.[5,16] Also, most importantly, there is a lack of evidence showing a benefit on clinical outcomes in an adequately powered randomized controlled trial. Until the results of a large trial on clinical cardiovascular outcomes, which are unlikely to appear in the next few years, clinicians must rely on existing observational data. The threshold for cardiovascular risk seems to be a TSH at least $\geq$7.0 mU/L and with clearer data for an increased risk when TSH values are $>$10.0 mU/L.[4,6]

Conflict of interest: N.R. has received funding for a randomized controlled trial on subclinical hypothyroidism (Thyroid hormone Replacement for Untreated older adults with Subclinical hypothyroidism; a randomised placebo-controlled, TRUST Study) from the European Commission FP7-HEALTH-2011, Specific Programme 'Cooperation'-Theme 'Health' Investigator-driven clinical trials for therapeutic interventions in elderly populations (Proposal No: 278148-2). B.G. has no conflicts to declare.

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