Zhang et al. (1) carried out a large prospective naturalistic study on patients who underwent percutaneous coronary intervention (PCI) evaluating the role of thyroid hypofunction on major clinical outcomes from in-hospital stay up to 10 years of follow up with a median observation of 3 years. The enrolled population was representative of adult patients (mean age of the whole cohort 64.6 years) with several traditional risk factors (previous cardiovascular events or coronary artery disease, hypertension, diabetes mellitus, obesity, dyslipidemia and smoking status), which accounted for high risk of cardiovascular events. The diagnosis of hypothyroidism, only defined by the presence of serum TSH level above 5 mIU/L at PCI time-point, was associated with underlying clinical features at baseline [age, female gender, history of myocardial infarction (MI), diabetes mellitus, heart failure (HF), hypertension, hyperlipidemia, arteriopathy as well as ACE/ARB and amiodarone administration] and a worse clinical composite outcome during follow up [cardiac death, MI, HF events, repeat vascularization (TRV) and stroke]. The risk of composite endpoint in hypothyroid patients remained significantly higher even after adjusting for several potential confounding factors, and accounted for about 30% of the increased risk. In detail, the greatest correlation between hypothyroidism and single endpoints was observed for MI, HF, TRV and stroke. By stratifying hypothyroid patients on the basis of serum TSH level above 5 mIU/L at PCI time-point, was associated with underlying clinical features at baseline [age, female gender, history of myocardial infarction (MI), diabetes mellitus, heart failure (HF), hypertension, hyperlipidemia, arteriopathy as well as ACE/ARB and amiodarone administration] and a worse clinical composite outcome during follow up [cardiac death, MI, HF events, repeat vascularization (TRV) and stroke]. The risk of composite endpoint in hypothyroid patients remained significantly higher even after adjusting for several potential confounding factors, and accounted for about 30% of the increased risk. In detail, the greatest correlation between hypothyroidism and single endpoints was observed for MI, HF, TRV and stroke. By stratifying hypothyroid patients on the basis of serum TSH value (≥5<10 mIU/L and ≥10 mIU/L), the authors demonstrated that even a mild increase of serum TSH (≥5<10 mIU/L) was significantly associated to the composite endpoint and the occurrence of MI, although to a lesser extent as compared to patients with TSH ≥10 mIU/L, while the statistical significance was not reached for the other single endpoints. On the other hand, patients with a marked increase of serum TSH (≥10 mIU/L, defined as affected by overt hypothyroidism independently from analyzing the level of serum free thyroxin) presented a greater risk of either the composite endpoint or all the single endpoints as compared to euthyroid patients. It is noteworthy that patients receiving adequate L-thyroxin replacement therapy (TRT) showed a significant reduction of composite or single endpoints while, those with inadequate TSH target value (≥5 mIU/L) maintained a risk profile similar to hypothyroid patients not receiving any TRT. Finally, in a nested group of patients randomly selected with a ratio of 1/3 from the two cohorts (euthyroid and hypothyroid patients at baseline) and evaluated in single blind by coronary angiogram at follow-up, the authors documented a significant worsening of target vessel diseases in hypothyroid as compared to euthyroid patients.

Although the study had some limitations mainly represented by the study design (observational), the definition of hypothyroidism (only based on a single TSH measurement without taking into account the level of serum free thyroxin) and the lack of age specific serum TSH reference ranges, the results are robust and consistent with previous experiences confirming the important role of thyroid function on the cardiovascular system especially in adult population younger than 65–70 years (2,3). In this regard, the link between thyroid function and cardiovascular risk factors is widely recognized and some meta-analyses documented an increased risk for CV events and mortality only in young adult population (≤65 years). At molecular level, thyroid hormones (TH) play a determinant role in the circulatory system, from heart structure and function...
to vessels and blood flow regulation (2-5). Moreover, as stated by Zhang et al. (1) and previously documented by our group both in experimental and human models (6,7), mild thyroid failure is associated to endothelial dysfunction (reduced NO induced vasodilatation) and a certain degree of systemic inflammation (6,7). These findings along with the effects of thyroid failure on intermediate metabolism (8) could at least in part explain the increased CV risk of hypothyroid individuals also in the presence of mild dysfunction as observed in subclinical hypothyroidism (SCH) (9-11). In this regard, the study by Zhang et al. showed a link between hypothyroidism and HF events both at baseline and during follow up, but only in individuals with serum TSH >10 mU/L, suggesting that heart function may be affected mainly by the extent of thyroid dysfunction, in agreement with the results of the largest pooled meta-analysis (12). Moreover, a recent meta-analysis, which analyzed data on 47,573 adults, documented a trend for risk of stroke only in subject younger than 65 years, which increases with increasing TSH value (13). Similarly, another meta-analysis documented an increased risk of cognitive alterations only in individuals younger than 75 years, more evident in those with higher serum TSH values (14). On the other hand, a recent systematic review and meta-analysis showed that either subclinical or overt hypothyroidism are independent predictors of hospitalization and mortality in HF patients, but only in those older than 65 years (15). Interestingly, data from our laboratory either in humans or animal models, showed that, apart from the extent of serum TSH increase, both endothelial and mitochondrial dysfunction were affected by the duration of the exposure of tissues and organs to the mild TH deficit of SCH (16,17). In this setting, a recent Editorial to the European Thyroid Association guidance for treating subclinical thyroid dysfunctions suggested to consider thyroid dysfunction as a cardiovascular risk factor that acts in continuum, depending from the patient’s age, the extent of thyroid dysfunction and the duration of the disease, similarly to other conventional cardiovascular risk factors such as hyperlipidemia, systemic hypertension, diabetes mellitus etc. (18).

SCH is a common feature in clinical practice, its prevalence is higher in women and increases with increasing age (5). In order to obtain an accurate diagnosis of SCH in the elderly, we have to consider the observed shift of serum TSH level toward upper values during age (19). In this setting, data from scientific literature obtained in disease free, oldest old population (>80–85 years) suggested that well ageing is characterized by a certain degree of down regulation of the hypothalamus-pituitary-thyroid peripheral axis, and this finding might lead to the idea that a mild decline of thyroid activity at the tissue level has favourable effect (2,20). However, sharing this interpretation with older people at all should be done with caution since a mild elevation of serum TSH may occur by either the aging process itself or an actual thyroid disease. Indeed, we should also consider that the prevalence of circulating anti-thyroid autoantibody levels increases with ageing (21), suggesting actual subclinical thyroid impairment as the cause of TSH raise in the elderly. Therefore, a correct diagnosis of SCH is challenging in the oldest old population (i.e., elevated serum TSH according to age related reference ranges and documented thyroid disease) but crucial in avoiding significant misclassification of patients with abnormal TSH value, who may or may not have an actual thyroid failure and may receive unnecessary or even harmful therapy (2,3,22,23). Keeping in mind these considerations, the fundamental clinical question regarding older persons with slightly elevated serum TSH value is how they have to be dealt with and, in the case of confirmed thyroid failure, whether they need hormone replacement therapy (2,19,23). The study by Zhang et al. demonstrated in an indirect way that an adequate L-thyroxin replacement may reverse the CV risk of SCH, however this is not easily to obtain in clinical practice since in a certain number of cases (mainly older women) the treatment could be detrimental if an excess of therapy is administered and a strict monitoring of serum TSH value is warranted (1,24).

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Footnote

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