

## Low Triiodothyronine and Cardiovascular Disease

To the Editor:

Iervasi et al<sup>1</sup> report a strong correlation between low free biologically active triiodothyronine (fT3), a thyroid hormone, and all-cause and cardiovascular mortality in 573 consecutive patients with heart disease. The observations in this study are stimulating and may be of major clinical interest. However, the following points deserve to be clarified for better appreciating the implications of this study.

(1) Neither creatinine nor other markers of renal function were considered as potential confounders of the relationship between fT3 and the outcomes. This is an important omission because fT3 is frequently reduced in patients with renal failure.<sup>2</sup> Because it is likely that some patients with heart disease included in the Iervasi et al<sup>1</sup> study had some degree of renal insufficiency, fT3 may be just a proxy of renal dysfunction.

(2) Cox survival analysis and logistic regression analysis do not seem to provide coherent results. In fact, the fT3 hazard ratio of 3.582 (see Cox regression model in Table 3 of Iervasi et al<sup>1</sup>) implies that an increase of 1 pmol/L in fT3 is associated with a 258% excess risk for all-cause mortality. In contrast, in the multivariate logistic regression analysis (Table 4<sup>1</sup>), the authors report a fT3 hazard ratio of 0.395, implying that an increase of 1 pmol/L in fT3 is associated with a 60.5% risk reduction in the hazard ratio of all-cause mortality.

Finally, with just 19 cardiac deaths during the follow-up, only 2 covariates can be entered into the Cox model (ie, 1 covariate every 10 events),<sup>3</sup> whereas data reported in Table 3<sup>1</sup> apparently include 4 covariates. This model is overfitted, and, therefore, the independence of the fT3–cardiovascular outcomes link requires confirmation in a more powerful study, or requires testing in more parsimonious statistical models.

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To the Editor:

Iervasi and colleagues,<sup>1</sup> in assessing the role of thyroid hormones in the prognosis of patients with heart disease, showed that the free triiodothyronine (fT3) level was the highest independent predictor of death during the 1-year follow-up period. The authors stated that clinical and experimental knowledge of the fundamental actions of thyroid hormones, in particular of T3, on both the heart and vessels favors the hypothesis of a direct relationship between low-T3 syndrome and mortality in patients with heart disease.

Overt hypothyroidism, with its accompanying hypercholesterolemia and hypertension, may be associated with cardiovascular disease.<sup>2</sup> Moreover, subclinical hypothyroidism is a strong indicator of risk for atherosclerosis and myocardial infarction in elderly women.<sup>3</sup> We recently performed a cross-sectional study of patients referred for coronary angiography to investigate whether variation of thyroid function within the statistical normal range may influence the presence and severity of coronary

atherosclerosis.<sup>4</sup> Coronary artery disease (CAD) severity was scored as 0 for those with smooth normal epicardial coronary arteries; 0.5 for plaquing (<50% diameter stenosis); and 1, 2, or 3 for those with single-, double-, or triple-vessel epicardial coronary artery stenosis of >50%, respectively. Serum fT3 was  $2.99 \pm 0.33$  pg/mL in patients with a CAD severity score of 0 to 1 and  $2.74 \pm 0.49$  pg/mL in patients with a CAD severity score of 2 and 3 ( $P < 0.01$ ). When grouped into subsets according to their serum fT3 levels, the prevalence of CAD score 2 and 3 was significantly higher in patients with low serum fT3 compared with patients with medium or high fT3 concentrations ( $P$  for trend  $< 0.05$ ). In this study,<sup>4</sup> HDL, LDL, and total homocysteine levels provided no pathophysiologic explanation for the association of thyroid hormone concentrations and severity of CAD. Thus, these data suggest that variation of thyroid function may influence the presence and severity of coronary atherosclerosis. The underlying mechanisms possibly involved in the association between variation of thyroid function and cardiovascular disease may include effects on endothelial function, relaxation of smooth muscle cells, hypercoagulability, and inhibition of collagen-induced platelet aggregation.<sup>5</sup>

Considering that a large proportion of the total study population investigated by Iervasi and colleagues<sup>1</sup> had CAD or documented myocardial ischemia, more advanced coronary atherosclerosis associated with low fT3 may contribute to the poor prognosis in this subgroup of cardiac patients.

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## Response

It is well known that—common to other severe nonthyroidal illnesses—a severe impairment in renal function is associated per se with a decrease in serum triiodothyronine (T3). As stated in the Methods of our paper,<sup>1</sup> every disease with systemic involvement (including severe renal failure) represented the main initial exclusion criterion utilized in the study protocol; on the basis of this criterion, 277 patients (26.2% of the total initial population) were not enrolled in the final studied population. Moreover, cardiac patients prone to develop severe renal failure, ie, with more compromised left ventricular ejection fraction (LVEF, <35%) represented only a small fraction (18.7%) of the population studied. Also, among all deceased patients ( $n=37$ ), the creatinine values measured in those with low T3 ( $n=25$ ,  $136.4 \pm 97$   $\mu\text{mol/L}$ , mean  $\pm$  SD; normal range 53 to 106  $\mu\text{mol/L}$ )

and in those with normal T3 ( $n=12$ ,  $114.4 \pm 26.4$   $\mu\text{mol/L}$ ) were not statistically different. Thus, given the considerations above, the hypothesis of free T3 (fT3) as “just a proxy of renal dysfunction” as suggested by Tripepi and Zoccali does not seem justified.

When considering the Cox and logistic regression, the differences between hazard ratios (HR) reported in Tables 2 to 4 of our paper<sup>1</sup> for fT3 and LVEF are only apparent and not substantial. According to the cited and conventionally accepted statistical approach used for the Cox regression,<sup>2,3</sup> the continuous “protective” covariates—as is the case for fT3 and LVEF—were inserted as the difference between the maximum measured value and their effective values. This way, the corresponding HR is forced to be  $>1$ . In other words, a HR  $>1$  for fT3 implies that when the fT3 decreases from the maximum measured value of 6.0 pmol/L, the mortality risk increases. Analogously, the positive HR value for LVEF implies an increased risk for a decrease of LVEF from the maximum possible value conventionally considered as 100%.

Finally, as stated in our paper<sup>1</sup> (see Discussion) and in accordance with the recent literature cited,<sup>4</sup> only cumulative mortality may represent a primary end point in clinical investigation. The cumulative deaths we observed ( $n=37$ ) were consistent with the number of covariates used ( $n=4$ ) and in agreement with the suggestions of the more accepted statistical guidelines.<sup>5</sup> Cardiac events represent only a secondary end point in our study, while we maintained the same number of covariates simply to guarantee as much homogeneity as possible in the analysis process. Obviously, future data based on a larger patient popu-

lation will be welcome, because it would allow better assessment of the effective weight of a single covariate in predicting cardiac and cumulative death.

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