

The Reply

Dr. Modarressi suggests in his letter that our interpretation of the TRUST study¹ needs caution because patients who had a thyroid-stimulating hormone (TSH) level between 4.6 and 6.9 mIU/L could be physiologically euthyroid. We disagree and provide 3 specific points in response.

When we designed the TRUST trial, we chose to set a TSH target of 0.40-4.59 mIU/L with levothyroxine treatment, which was the range used to define euthyroidism in the Thyroid Studies Collaboration² and contemporary guidelines,³ despite the current discussion of using an age-specific reference.⁴

We enrolled only participants who had persistent elevated TSH levels (4.60-19.99 mIU/L).^{1,5} The TSH value was required to be within the eligibility window on at least 2 occasions that were 3 months to 3 years apart. In the TRUST trial, among the 2647 older adults screened for eligibility, 1645 did meet inclusion criteria because of a reversion of TSH level.⁵ The TSH levels among participants randomized in the placebo group remained elevated over the study period (5.29 mIU/L in average).¹ Therefore, we can assume that participants who were truly euthyroid were not studied in the TRUST trial.

The proportion of older participants with TSH ≥ 7 mIU/L in our study (23.8%) was representative, as the prevalence of such abnormality at this age category accounts for about 10% of the elderly population.⁴ In our study, prespecified stratification according to baseline TSH levels (4.6-6.9, 7.0- 9.9, ≥ 10 mIU/L) yielded similar results without statistical interactions.¹ These findings were replicated in another trial of patients with subclinical hypothyroidism where levothyroxine compared with placebo had no impact on cardiac function.⁶ Because the vast majority of patients treated for subclinical hypothyroidism in practice have a TSH value between 4.6 and 6.9 mIU/L,⁴ the inclusion of those participants enabled us to evaluate the treatment effect of levothyroxine in this key subgroup.

Although we agree that age-specific reference for the diagnosis of subclinical hypothyroidism in the elderly needs to be re-discussed,⁴ current findings found no benefits of levothyroxine on cardiac function among older adults with subclinical hypothyroidism, including among those with TSH ≥ 7 mIU/L.^{1,6}

Baris Gencer, MD^a Douglas C. Bauer, MD^b Nicolas Rodondi, MD, MAS^{c,d}

^aService of Cardiology, University Hospitals of Geneva, University of Geneva, Switzerland

^bUniversity of San Francisco, California

^cInstitute of Primary Health Care (BIHAM), University of Bern, Switzerland

^dDepartment of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland

References

1. Gencer B, Moutzouri E, Blum MR, et al. The impact of levothyroxine on cardiac function in older adults with mild subclinical hypothyroidism: a randomized clinical trial. *Am J Med* 2020;133(7):848–856.e5.
2. Rodondi N, den Elzen WP, Bauer DC, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA* 2010;304(12):1365–74.
3. Pearce SH, Brabant G, Duntas LH, et al. 2013 ETA guideline: management of subclinical hypothyroidism. *Eur Thyroid J* 2013;2(4):215–28.
4. Surks MI, Hollowell JG. Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. *J Clin Endocrinol Metab* 2007;92(12):4575–82.
5. Stott DJ, Rodondi N, Kearney PM, et al. Thyroid hormone therapy for older adults with subclinical hypothyroidism. *N Engl J Med* 2017;376 (26):2534–44.
6. Jabbar A, Ingøe L, Junejo S, et al. Effect of levothyroxine on left ventricular ejection fraction in patients with subclinical hypothyroidism and acute myocardial infarction: a randomized clinical trial. *JAMA* 2020;324(3):249–58.

Funding: None.

Conflict of Interest: NR's research was supported by grants from the Swiss National Science Foundation (SNSF 320030-150025 and 320030-172676), and investigator-driven grants from the Velux Stiftung (974a, to NR) and the Swiss Heart Foundation (to NR). The TRUST Trial was supported by a research grant (grant agreement number 278148) from the European Union FP7-HEALTH-2011 program). No disclosures for other authors.

Authorship: All authors have participated in the preparation of the manuscript.

Requests for reprints should be addressed to Nicolas Rodondi, MD, MAS, Head of Ambulatory Care, Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Bern 3010, Switzerland.

E-mail address: nicolas.rodondi@insel.ch