Cardiac Safety and Efficacy of Combination LT4 and LT3 in patients with Athyreotic Hypothyroidism: Reassuring Initial Data but More is Needed.

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Thyroid hormones (TH) play an important role in regulating the development and function of almost all tissues including the cardiovascular system (1). Levothyroxine (LT4), a synthetic L form of tetraiodothyronine, has been the mainstay of treatment for hypothyroidism since the 1970s when it superseded thyroid extract (2). While LT4 therapy normalizes serum TSH levels in the majority of patients with primary hypothyroidism, several metabolic parameters remain abnormal suggesting that tissue euthyroidism hasn't been fully achieved (3). Furthermore. some patients treated with LT4 monotherapy display evidence of impaired psychological well-being and this led to trials of combination therapy with both LT4 and liothyronine (LT3, the synthetic form of triiodothyronine or T3) (4).

Fourteen randomized trials have evaluated the effect of combination LT4 and LT3 to date on various parameters including symptoms, quality of life and cardiovascular signs (5). A major concern of clinicians with regards to combination therapy with LT4 and LT3 is the potential for adverse effects with the long-term use of the active and more potent T3 on heart rate, risk of supraventricular arrhythmias and high-output heart failure. A *real-world* observational study from Scotland suggested that long-term LT3 use was not associated with increased observed risk of atrial fibrillation or cardiovascular disease (6). Results from previous randomized controlled trials have shown variable results. Resting heart rate was increased in the combination therapy group in two trials, decreased in another two trials, and no change was observed in the remaining trials in which it was assessed (5). In a randomized cross-over trial of 8 women with near-total thyroidectomy for Graves' disease, combination therapy with LT4 and LT3 for 5 weeks was suggestive of an improvement in diastolic function on echocardiographic assessment (7). A meta-analysis of 18 trials assessing combined LT4 and LT3 therapy versus LT4 monotherapy concluded that similar proportion of participants reported adverse events and reactions in both groups (8). The lack of long-term outcome data, in addition to inconsistent proof of benefit, has led the American and European Thyroid Associations to recommend that LT4 and LT3 combination therapy should not be used routinely or only to be used as an experimental therapy in some selected patients with close clinical and biochemical monitoring (9, 10).

In this issue of *Thyroid*, Biondi and colleagues report the results of a randomized double-blind placebo-controlled trial of combination LT4 and LT3 therapy compared to LT4 and placebo (11). The primary objective of this trial was to assess the cardiac effects of combination therapy using electrocardiography and echocardiography. Thirty-eight participants with hypothyroidism due to previous thyroidectomy for low-risk thyroid cancer were recruited and, of these, twenty-four participants had assessments at baseline after 6 and 12 months. An additional control arm of fifty euthyroid volunteers were also studied once. The LT3 and placebo was provided by a pharmaceutical company in the form of identical oral drops and participants were instructed to be consumed in the morning and after 12 hours. All participants continued their pre-existing LT4 therapy one-hour before breakfast. Thyroid function and metabolic parameters were assessed at baseline, 3, 8 and 12 months of therapy. The main investigator was aware of thyroid function test results and adjusted the dose of the LT4 to achieve an LT4:LT3 ratio of 17:1. Subsequently, doses of both LT4 and LT3 were further adjusted at 3 and 6 months to aim for a serum TSH level within the reference range and FT4 and FT3 concentrations in the middle of their respective reference ranges. The electrocardiographic and echocardiographic examinations were

performed by two cardiologists who were unaware of participants' allocated treatment group.

Participants allocated to the combined LT4 and LT3 group demonstrated a significant increase in serum FT3 levels and diastolic function at 12 months, as evaluated by a reduction in E/e' ratio on Doppler echocardiography. The improved E/e' ratio after 12 months of LT4 and LT3 therapy was similar to the ratio observed in the euthyroid control group. There were no significant differences observed in body weight, systolic and diastolic blood pressure values, total and LDL-cholesterol or heart rate between the combination therapy or LT4 and placebo group after 12 months. Furthermore, no serious adverse events including arrhythmias were reported during the duration of the trial.

Does this trial allay concerns about the safety of combination LT4 and LT3 therapy in patients with hypothyroidism? Before this question is answered, it is important to highlight the strengths and limitations of this trial. It was rigorously conducted and is the first trial to have assessed effect of combined LT4 and LT3 on cardiac parameters over 12 months. In addition, the doses of both LT4 and LT3 were adjusted at regular intervals to aim for thyroid function within the reference range. Also, a group of matched euthyroid volunteers provided control data against which cardiac and metabolic parameters could be compared against. However, this trial has several limitations with the most important being the lack of *a priori* sample size estimation. The number of participants providing data at both baseline and at 12 months was relatively small (14 in the combination and 10 in the LT4 and placebo groups, respectively), predominantly due to recruitment difficulties as a consequence of the COVID-19 pandemic. The other limitation is that this trial was conducted in a highly selected group: young to middle-aged (18-55 years) and relatively healthy (on no other medication except LT4) athyreotic patients due to previous thyroid surgery. Therefore, the results obtained may not be generalizable to the majority of patients with hypothyroidism. Finally, the clinical relevance of a statistical improvement in E/e' ratio is unclear. An E/e' ratio of <8 is considered to be normal, a ratio >15 is considered to be indicative of increased left ventricular filling pressure (diastolic dysfunction) and values between 8 and 15 may indicate possible diastolic dysfunction. Furthermore, using the E/e' ratio alone may not provide a complete assessment of diastolic function (12). This trial provides data regarding safety of combination therapy that supports other trials of T3 alone in high-risk cardiac patients (13).

Should the results of this trial change clinical practice? This trial mainly provides reassurance that combination therapy with LT4 and LT3 is safe over 12 months in younger patients without increased cardiovascular risk. This trial also provides preliminary evidence that combination therapy could improve some echocardiographic markers of diastolic function. Trials in larger group of patients with diverse characteristics including older patients, those with hypothyroidism due to other causes, those with comorbidities, and patients with known diastolic dysfunction are needed to confirm these findings. Until this time clinicians managing patients on combination LT4 and LT3 should continue to monitor for any adverse clinical effects.

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