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## The impact of levothyroxine on cardiac function in older adults with subclinical hypothyroidism: a randomized clinical trial

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**Importance:** Subclinical hypothyroidism has been associated with heart failure, but no conclusive clinical trial assessed whether treating subclinical hypothyroidism with levothyroxine has an impact on cardiac function.

**Objective:** To assess the impact of levothyroxine treatment on cardiac function in subclinical hypothyroidism.

**Design:** This is a randomized, double-blind placebo-controlled, multicenter Swiss substudy within the TRUST trial.

**Participants:** Participants aged  $\geq 65$  years with subclinical hypothyroidism.

**Intervention:** Levothyroxine to achieve TSH normalization, or placebo including mock titrations.

**Main outcome measures:** Primary outcomes, assessed by echocardiography at the end of the trial were the left ventricular ejection fraction (LVEF, normal defined as  $> 50\%$ ) for systolic function and the ratio between mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e') (E/e' ratio) for diastolic function. Secondary outcomes included transmitral E and A waves, e' lateral/septal, left atrial (LA) volume index and systolic pulmonary artery pressure.

**Results:** Of 217 randomized Swiss participants of the TRUST trial, 185

(mean age 74.1 years, 47% women, mean TSH at baseline  $6.35 \pm \text{SD } 1.95$  mIU/L) underwent echocardiography. After a median treatment duration of 18.4 months, the mean TSH among participants randomized to levothyroxine (n=95) decreased to 3.55 mIU/L, whereas it remained elevated in the placebo group (n=89; 5.29 mIU/L). The mean LVEF was similar in both arms (adjusted between-group difference 0.4%, 95% CI  $-1.8\%$  to  $2.5\%$ ,  $P=0.72$ ) and no significant differences were found for the E/e' ratio (adjusted between-group difference 0.4, 95% CI  $-0.7$  to  $1.4$ ,  $P=0.47$ ). In intention-to-treat and per-protocol analyses, no clinically significant differences were found for secondary diastolic function parameters: e' lateral 8 vs. 8 cm/s,  $P=0.54$ ; e' septal 6 vs. 6 cm/s,  $P=0.75$ ; LA volume index 34 vs. 33 ml/m<sup>2</sup>,  $P=0.57$ ; E/A ratio 0.8 vs. 0.8,  $P=0.94$ ; E deceleration time 225 vs. 216 ms,  $P=0.27$ , except for systolic pulmonary artery pressure (37 mm Hg in the levothyroxine group vs. 33 mm Hg in the placebo group,  $P=0.02$  intention-to-treat and  $P=0.06$  per protocol)

**Conclusion:** Treatment of subclinical hypothyroidism with levothyroxine was not associated with benefits regarding systolic and diastolic heart function in older adults with subclinical hypothyroidism.