Key Clinical Points

Subclinical Hypothyroidism

- Subclinical hypothyroidism is defined as an elevated thyrotropin level with a normal free thyroxine (T_4) level. To confirm the diagnosis, a transient increase in thyrotropin should be ruled out by a repeat measurement of thyrotropin and free T_4 after 2 to 3 months.
- In up to 46% of patients with subclinical hypothyroidism who have a thyrotropin level of less than 7 mIU per liter, the thyrotropin level normalizes within 2 years.
- Subclinical hypothyroidism, particularly when the thyrotropin level is more than 10 mIU per liter, is associated with an increased risk of hypothyroid symptoms and cardiovascular events.
- There are few data from randomized, controlled trials of levothyroxine therapy for subclinical hypothyroidism to inform the effects of treatment on cardiovascular outcomes.
- Treatment is generally recommended for persons 70 years of age or younger who have thyrotropin levels of at least 10 mIU per liter, although long-term benefits have not been shown.
- Among patients who have thyrotropin levels of less than 10 mIU per liter or who are older than 70 years of age, treatment decisions are based on individual patient factors (e.g., symptoms of hypothyroidism, a positive test for antibodies to thyroid peroxidase, or cardiac risk factors).

Table 1. Causes of Elevated Thyrotropin Levels, Unrelated to Chronic Mild Thyroid Failure.*

Causes of a transient increase in the thyrotropin level combined with a normal free T_4 level
Recovery from nonthyroidal illness
Recovery phase of various types of thyroiditis
Medication, such as amiodarone and lithium
Lack of adherence to treatment with levothyroxine or problems with resorption of levothyroxine in persons with hypothyroidism who are already receiving levothyroxine
Causes of a persistent increase in the thyrotropin level combined with a normal free T_4 level
Physiologic adaptation to aging (a widening of the reference range in elderly persons who have lived in regions with historical iodine sufficiency has been described)
Assay interference (e.g., caused by heterophilic antibodies)
Obesity
Adrenal insufficiency (very rare)
Thyrotropin-releasing hormone resistance or thyrotropin resistance (extremely rare)

* T_4 denotes thyroxine.

Table 2. Associations Between Subclinical Hypothyroidism and Clinical Outcome, and Consequences of Treatment.*

Outcome of Subclinical Hypothyroidism	Strength of the Association		Benefits of Treatment
	Thyrotropin 4.5–9.9 mIU/liter	Thyrotropin ≥10 mIU/liter	
Progression to overt hypothyroidism	Strong	Stronger	Early treatment before development of overt hypothyroidism with more severe symptoms
Symptoms of hypothyroidism (e.g., tiredness, decreased cognition)	Strong	Stronger	Inconsistent, with large trial involving persons with mildly elevated thyrotropin levels (<10 mIU/liter) and very few symptoms showing no effects, and small trials involving persons with thyrotropin levels >10 mIU/liter showing benefits
Surrogate markers of cardiovascular risk (e.g., elevation in total cholesterol and LDL cholesterol levels, increased carotid-wall intima–media thickness, and decreased cardiac function)	Strong	Stronger	Moderate for reduction in total cholesterol and LDL cholesterol levels but unclear whether this is accompanied by a decreased risk of cardiovascular events
Risk of coronary heart disease	Weak	Stronger	Insufficient data to inform benefits
Risk of congestive heart failure	Weak	Stronger	Insufficient data to inform benefits
Risk of stroke	Weak	Weak	Insufficient data to inform benefits
Cognitive decline	Weak	Weak	Insufficient data to inform benefits

* This table is adapted and updated from Surks et al.[3] LDL denotes low-density lipoprotein.

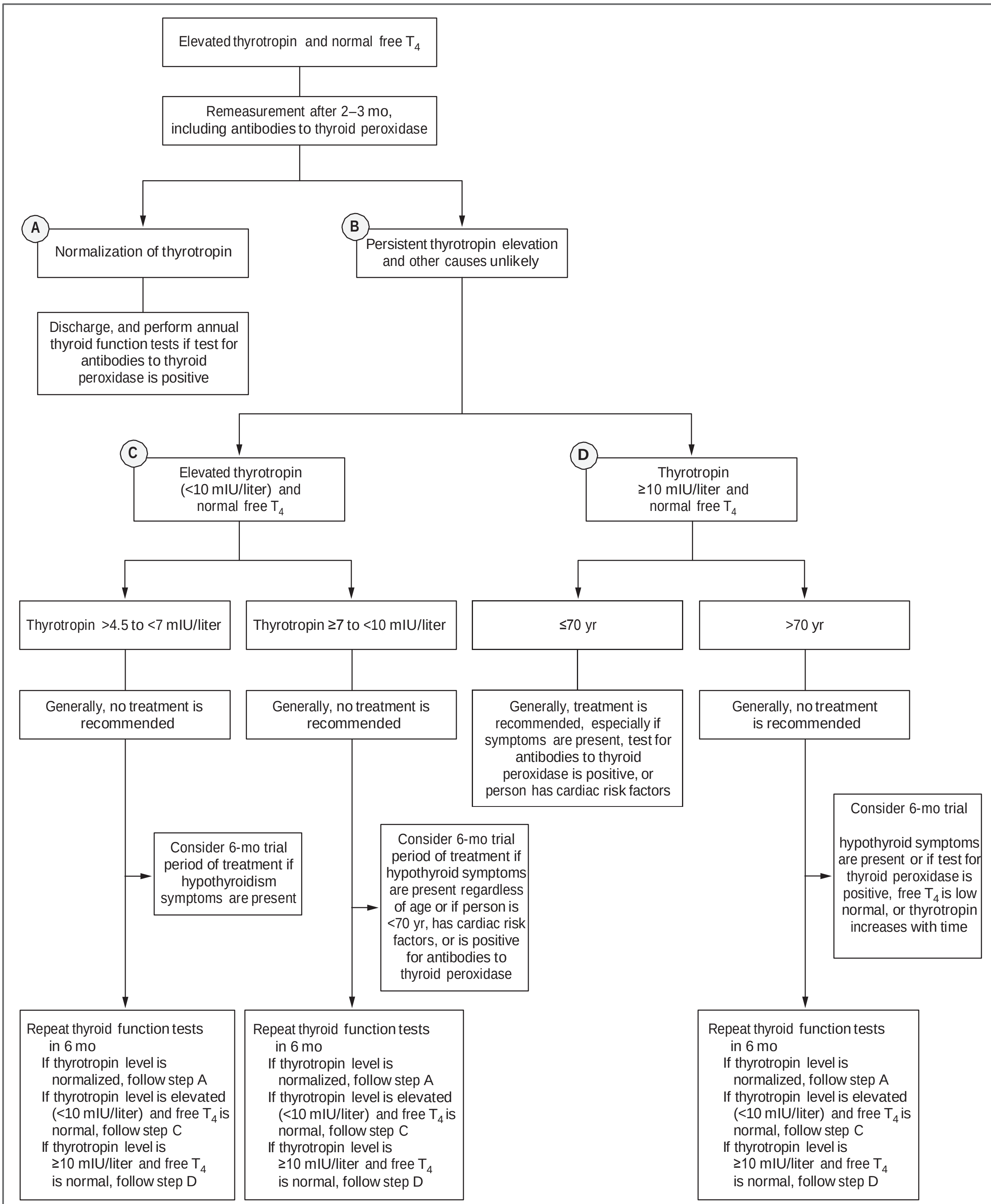

Figure 1. Treatment Algorithm for Subclinical Hypothyroidism.

This algorithm does not apply to pregnant women or to young women who may potentially seek pregnancy and is based on current U.S. and European guidelines.[26,27] However, the U.S. guidelines do not make an explicit distinction according to age, and neither guideline specifies differential management according to the degree of thyrotropin elevation below 10 mIU per liter.

Table 3. Differences Between American and European Guidelines Regarding Key Recommendations for Treatment of Subclinical Hypothyroidism.*

Degree of Subclinical Hypothyroidism	ATA and AACE†	ETA‡
Mildly increased thyrotropin levels (≤10.0 mIU per liter in the American guidelines; <10.0 mIU per liter in the European guideline)	Treatment should be considered on the basis of individual factors (i.e., symptoms suggestive of hypothyroidism, a positive test for antibodies to thyroid peroxidase, or evidence of atherosclerotic cardiovascular disease, heart failure, or associated risk factors for these diseases). (Grade B, because of a lack of randomized, controlled trials)	Younger patients (<65 to 70 yr): A trial period of treatment with levothyroxine should be considered when symptoms suggestive of hypothyroidism are present. (Grade 2, intervention short of a randomized, controlled trial or large, observational studies) Older patients (especially >80 to 85 yr): Careful follow-up with a wait-and-see strategy, generally avoiding hormonal treatment, is recommended. (Grade 3, expert opinion)
Markedly increased thyrotropin levels (>10.0 mIU per liter in the American guidelines; ≥10.0 mIU per liter in the European guideline)	Levothyroxine should be considered because of an increased risk of heart failure and death from cardiovascular causes. (Grade B, because of a lack of randomized, controlled trials)	Younger patients (<65 to 70 yr): Treatment with levothyroxine is recommended, even in the absence of symptoms. (Grade 2, large observational studies) Older patients (>70 yr): Treatment with levothyroxine should be considered if clear symptoms of hypothyroidism are present or if the risk of vascular events is high. (Not a graded recommendation, but part of the treatment algorithm)

* The American guidelines were cosponsored by the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE),[27] and the European guideline was developed by the European Thyroid Association (ETA).[26]

† The recommendations are evidence-based (grades A, B, and C, with A being the highest level of evidence) or are based on expert opinion because of a lack of conclusive clinical evidence (grade D). The "best evidence" rating level, which corresponds to the best conclusive evidence found, accompanies the recommendation grade.[27]

‡ The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used for the recommendations. The quality of the literature regarding each aspect of the statement was graded as high (evidence from a randomized, controlled trial; level [grade] 1); moderate (intervention short of a randomized, controlled trial or large, observational studies; level [grade] 2), or low (case series, case reports, expert opinion; level [grade] 3), according to modified GRADE criteria.[26]