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The 2015 European Thyroid Association Guidelines on Diagnosis and Treatment of Endogenous Subclinical Hyperthyroidism

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Abstract
Endogenous subclinical hyperthyroidism (SHyper) is caused by Graves' disease, autonomously functioning thyroid nodules and multinodular goitre. Its diagnosis is based on a persistently subnormal serum thyroid-stimulating hormone (TSH) level with free thyroid hormone levels within their respective reference intervals. In 2014 the European Thyroid Association Executive Committee, given the controversies regarding the treatment of Endo SHyper, formed a task force to develop clinical practice guidelines based on the principles of evidence-based medicine. The task force recognized that recent meta-analyses, including those based on large prospective cohort studies, indicate that SHyper is associated with increased risk of coronary heart disease mortality, incident atrial fibrillation, heart failure, fractures and excess mortality in patients with serum TSH levels <0.1 mIU/l (grade 2 SHyper). Therefore, despite the absence of randomized prospective trials, there is evidence that treatment is indicated in patients older than 65 years with grade 2 SHyper to potentially avoid these serious cardiovascular events, fractures and the risk of progression to overt hyperthyroidism. Treatment could be considered in patients older than 65 years with TSH levels 0.1–0.39 mIU/l (grade 1 SHyper) because of their increased risk of atrial fibrillation, and might also be reasonable in younger (<65 years) symptomatic patients with grade 2 SHyper because of the risk of progression, especially in the presence of symptoms and/or underlying risk factors or co-morbidity. Finally, the task force concluded that there are no data to support treating SHyper in younger asymptomatic patients with grade 1 SHyper. These patients should be followed without treatment due to the low risk of progression to overt hyperthyroidism and the weaker evidence for adverse health outcomes.

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Definition, Aetiology and Prevalence of Endogenous Subclinical Hyperthyroidism

The definition of subclinical hyperthyroidism (SHyper) is based exclusively on laboratory findings, not clinical criteria [1–6]. SHyper is defined biochemically by a subnormal serum thyroid-stimulating hormone (TSH) level, with normal levels of free thyroxine (FT_4), triiodothyronine (TT_3) and/or free triiodothyronine (FT_3) [1–6].

Current assays can detect TSH levels as low as 0.01–0.02 mIU/l. According to its severity, SHyper can be divided into two categories: grade 1 SHyper, which has low but detectable serum TSH levels (e.g. TSH 0.1–0.39 mU/l), and grade 2 SHyper, which has suppressed serum TSH levels (<0.1 mIU/l) [1–6].

Endogenous SHyper is most commonly due to Graves' disease (GD), toxic adenoma (TA) and toxic multinodular goitre (MNG) [3, 5] (table 1). While GD is the most common cause of SHyper in younger patients (<65 years) in iodine-replete areas, TA and toxic MNG are relatively more frequent in iodine-deficient areas and in older persons (≥65 years) [7].

The prevalence of endogenous SHyper varies considerably, between 0.6 and 16% [7–9], depending on diagnostic criteria and the age and sex of the population studied, the TSH assay used, and iodine intake. The Third National Health and Nutrition Examination Survey (NHANES) evaluated thyroid autoantibodies, serum TSH and serum free T_4 levels in persons older than 12 years who represented the geographic and ethnic distribution of the US population [10]. The prevalence of SHyper was 0.7% with a cutoff TSH value of <0.1 mIU/l, and 1.8% with a cutoff TSH value of <0.4 mIU/l [10]. SHyper is a relatively frequent condition in iodine-deficient regions, its prevalence being as high as 15% in subjects >70 years [11]. Suppression of TSH may also be iatrogenic (exogenous) due to thyroid hormone overtreatment, either intentionally (in patients with thyroid cancer), unintentionally (in patients with hypothyroidism) or surreptitiously [2, 3] (table 1).

The present guidelines focus on endogenous SHyper, which will be referred to as 'Endo SHyper' throughout this paper.

Is There a Need for Clinical Practice Guidelines on SHyper?

Given the controversies regarding the clinical significance and possible benefits of treatment of SHyper [1–4], in 2014 the European Thyroid Association (ETA) Executive Committee formed a task force to draft clinical practice guidelines on the treatment of Endo SHyper. A chairperson was selected to lead the task force (B.B.) and four additional ETA members were identified (L.B., L.H., P.L., G.J.K.) and subsequently approved by the ETA Guidelines Board and the ETA Executive Committee on the basis of their clinical expertise in this field. A member of the task force that drafted the American Thyroid Association's and the American Association of Clinical Endocrinologists' guidelines on hyperthyroidism (D.S.C.) [4] was selected by the ETA Executive Committee to provide additional input to the ETA task force. Each panel member declared no conflict of interest. The task force worked without any financial or commercial support. The draft guidelines with the panel's recommendations were put on the 'members-only' section of the ETA website for 4 weeks to receive comments. All suggestions and comments by ETA members were considered and incorporated into the paper. The final document was approved by the Guidelines Board and the Executive Committee of the ETA and submitted to the *European Thyroid Journal*.

Evaluation System and Grading for Recommendations

A systematic literature review of relevant articles was performed by searching Medline, using the search term 'subclinical hyperthyroidism' from May 1974 to July 2015. The search was restricted to reports published in English, but included translated articles. Records from personal files and references of relevant articles and textbooks were also included. The task force critically assessed the literature and identified high-quality studies on SHyper. They evaluated study designs, the quality and consistency of the results, and the statistical analysis used to assess the effects of SHyper treatment. Although the task force agreed that preference should be given to randomized controlled trials and longitudinal cohort studies in the evaluation of treatment of SHyper, it was appreciated that very few reports fulfilled the established criteria. Therefore, other types of clinical studies, as well as nonrandomized trials and expert opinions, were also considered. The task force rated the recommendations according to the GRADE system, which was used in guidelines issued by the ETA [12, 13], American Thyroid Association (ATA) and American Association of Clinical Endocrinologists (AACE) [4]. The strength of a recommendation was indicated by number 1 or 2. Level 1 was consid-

Table 1. Aetiology and differential diagnosis of SHyper

Causes of persistent SHyper
Endogenous causes
GD
TA
MNG
Exogenous causes
Excessive thyroid hormone replacement therapy
Intentional thyroid hormone suppressive therapy
Causes of transient SHyper
Treatment of overt hyperthyroidism with ATDs or radioiodine
Subacute thyroiditis, painless and silent thyroiditis
Causes of low serum TSH concentrations that are not SHyper
Pituitary or hypothalamic insufficiency
Psychiatric illness
Drugs
Severe non-thyroidal illness
Late first trimester of pregnancy
Can happen in black individuals as a consequence of racial differences
Smoking

ered a strong recommendation (for or against) because the benefits outweighed the risks (or vice versa). Level 2 was a weak recommendation (for or against) in which the treatment depended on the patient's preference because the benefits and risks were uncertain. The quality of the evidence that led to a specific recommendation was rated as follows: +++ (high, level A), ++0 (moderate, level B) and +00 (low, level C). The task force defined 'high-quality evidence' as consistent results obtained from population-based studies and randomized trials; 'moderate-quality evidence' was evidence derived from non-randomized trials and studies with methodological flaws, showing inconsistent or indirect evidence, and 'low-quality evidence' was evidence derived from data reported in case series, clinical observations and expert opinions. In accordance with other guidelines, meta-analyses performed on large prospective studies were considered high-quality evidence [14].

Diagnosing and Determining the Aetiology of Endo SHyper (table 1)

Serum TSH is the most sensitive test for the diagnosis and severity assessment of SHyper [1, 4, 15, 16]. FT_4 and FT_3 estimates are typically in the mid-to-high reference range in SHyper, and should be measured to distinguish SHyper from overt hyperthyroidism [2–4]. In hyperthyroidism, serum T_3 is often more elevated than serum T_4 caused by excessive thyroidal production of T_3. Measurement of TT_3 is frequently preferred in clinical practice because assays estimating FT_3 are less well validated than those evaluating FT_4 [4, 16]. However, serum FT_3 may be measured in addition to TSH to detect early thyroid hormone excess caused by focal or multifocal autonomy in patients with goitre living in areas of iodide deficiency [16]. In these patients with undetectable serum TSH levels and normal FT_4 and TT_3 levels, FT_3 (by tracer equilibrium dialysis) evaluation can distinguish SHyper from overt FT_3 toxicosis [17].

An accurate measurement and interpretation of thyroid function is necessary before diagnosing SHyper. Potential confounding factors, including alterations in normal physiology (e.g. pregnancy), intercurrent illness, drugs and laboratory assay artifacts in commonly used TSH or thyroid hormone immunoassays should be taken into consideration before diagnosing SHyper.

SHyper should be differentiated from other causes of low serum TSH levels of central origin such as drugs that suppress serum TSH (dopamine or high doses of glucocorticoids, somatostatin analogues, dobutamine, amphetamine, bexarotene, bromocriptine), psychiatric illness, non-thyroidal illness (euthyroid sick syndrome) and hypothalamic-pituitary disorders, which cause TRH or TSH deficiency. Serum free T_4 and free T_3 levels are generally normal to low-normal in people with the latter conditions [3, 5, 18]. Causes of transiently lowered serum TSH, due to subacute, silent or postpartum thyroiditis, should be excluded [2–5]. Pregnancy and advanced age may confound the diagnosis of SHyper [19, 20]. The increase in serum human chorionic gonadotropin concentration can lead to low serum TSH concentrations in up to 18% of pregnant women during early pregnancy, most of whom will have normal free T_4 concentrations [19]. In addition, a change in serum TSH levels may be observed in elderly patients due to potential changes in the hypothalamic-pituitary-thyroid axis with aging [20, 21]. Iodine intake and the frequent alterations secondary to non-thyroidal illnesses and/or drugs may further complicate the diagnosis of SHyper in the elderly [3]. Large population studies have demonstrated a shift in the TSH level towards higher concentrations with advanced age in healthy individuals in iodine-replete areas [22]. In contrast, TSH concentration may be below the normal range in some healthy centenarians in iodine-deficient areas [23, 24]. Low serum TSH, decline in serum T_3 and increase in serum reverse T_3 could suggest an age-dependent reduction of 5′-de-

Table 2. Diagnosis of SHyper

Level I To establish the diagnosis of persistent SHyper	Level II To establish the aetiology of SHyper	Level III To establish the risks associated with SHyper and appropriate treatment
TSH (initial screening) FT_4, TT_3 or FT_3 (if serum TSH is low)	Thyroid ultrasonography[1] Thyroid scan and possibly thyroid radioiodine uptake TSHR-Abs[2]	CT, MRI[3] ECG[4], Holter ECG[5], Doppler echocardiography[6] BMD[7]

[1] Ultrasonography can guide fine needle aspiration biopsy in cases of suspicious hypofunctioning thyroid nodules in nodular goitres. [2] TSH-receptor antibodies (TSHR-Abs) can be useful to identify autoimmune SHyper. [3] Computed tomography (CT) or magnetic resonance imaging (MRI) should be used in selected patients to assess airway compression. [4] ECG should be considered in symptomatic patients. [5] Holter ECG is useful to assess atrial arrhythmias. [6] Doppler echocardiography is recommended in patients with AF, CHD or HF and/or underlying heart disease. [7] BMD should be evaluated in postmenopausal patients, in elderly patients and in patients with underlying bone risk factors.

iodinase activity or changes in nutritional markers in very elderly patients with long-term iodine deficiency [24]. Finally, subnormal serum TSH concentrations are frequently observed in black people and in some healthy cigarette smokers [3, 5, 25].

Scintigraphy and a 24-hour radioactive iodine (RAI) uptake test can differentiate between: (1) normal diffuse and high normal uptake in patients with GD, (2) warm or hot nodule(s) in MNGs and autonomously functioning thyroid nodules, and (3) low or absent uptake in patients with thyroiditis and in those taking exogenous thyroid hormone or iodine-containing preparations [1–5, 15]. The measurement of 24-hour urinary iodine excretion may help to confirm suspected excessive iodine intake [3, 5]. Ultrasonography with colour flow Doppler provides relevant information on thyroid size, echogenicity, presence/absence of nodules and vascularization [15, 26]. Fine needle aspiration biopsy is useful to ascertain thyroid cancer in MNGs with suspicious hypofunctioning thyroid nodules [3–5, 15].

Recommendations on Biochemical and Morphological Diagnosis of Endo SHyper (table 2)

First Level of Investigation: To Establish the Diagnosis of Persistent SHyper

1 We recommend that serum TSH should be measured as an initial screening test to diagnose SHyper. If serum TSH is low, thyroid hormones (FT_4 and TT_3 or FT_3) should be measured [1, 4, 15, 16] (1/+++).
2 TSH assays should be used to assess the severity of SHyper and to distinguish grade 1 SHyper (serum TSH: 0.1–0.39 mIU/l) from grade 2 SHyper (serum TSH <0.1 mIU/l) [1, 4, 15, 16] (1/+++).
3 Causes of transient TSH or subnormal serum TSH not associated with SHyper, such as administration of drugs, pituitary or hypothalamic insufficiency, psychiatric illness and non-thyroidal illness (table 1), should be investigated [3–5, 16] (1/+00).
4 Patients with an initial subnormal serum TSH with thyroid hormone levels within or at the upper limit of the normal range should be retested within 2–3 months because SHyper is defined as a persistently subnormal TSH concentration [1–5] (1/+00).

Second Level of Investigation: To Establish the Aetiology of SHyper

5 We recommend that scintigraphy and possibly a 24-hour thyroid RAI uptake test be performed in nodular goitres with grade 2 SHyper to guide clinicians in the choice of treatment [1–5, 15] (1/+00).
6 Ultrasonography with colour flow Doppler can be helpful in patients with SHyper and nodular goitre [15, 26] (2/+00).
7 Measurement of TSH-receptor antibody levels can confirm the aetiology of autoimmune-induced hyperthyroidism [27] (2/+00). Furthermore, TSH receptor autoantibodies can identify autoimmunity even in nodular glands because approximately 17% of patients in iodine-deficient areas with scintigraphic criteria for toxic MNG may be positive for TSH receptor autoantibodies [28].

Third Level of Investigation: To Establish Appropriate Treatment

8 Computed tomography without contrast or magnetic resonance imaging should be used to assess airway compression in patients with large MNGs and compressive symptoms and signs [3–5, 29] (1/+++).

Risks Associated with Persistent and Untreated Endo Subclinical Hyperthyroidism

SHyper may progress to overt hyperthyroidism and may be associated with increased cardiovascular and skeletal risk [3, 5, 18]. Differences in the degree of TSH suppression, causes of SHyper, patient age and duration of TSH suppression may influence the adverse consequences of Endo SHyper [3, 5, 30].

Progression to Overt Hyperthyroidism

Patients with SHyper may have stable thyroid dysfunction, progress to overt hyperthyroidism or revert to euthyroidism over time. The degree of TSH suppression is the best parameter for predicting the progression from subclinical to overt hyperthyroidism [3, 5, 18, 31].

The progression of grade 1 SHyper to overt hyperthyroidism is uncommon, ranging from 0.5 to 0.7% over 7 years [32]. Low serum TSH levels may normalize in 25–50% of patients with grade 1 SHyper, as reported in two prospective studies with a long-term follow-up [33, 34]. In contrast, 5–8% of grade 2 SHyper patients may progress to overt disease each year [35, 36]. In a large retrospective study, SHyper progressed to overt hyperthyroidism in 20% of patients with grade 2 versus 6.8% with grade 1 SHyper ($p < 0.001$) during 7 years of follow-up [37]. Moreover, there was an association between undetectable serum TSH and the development of hyperthyroidism [hazard ratio (HR) = 3.4, 95% CI: 1.6–7.0] [37].

It is uncertain whether the underlying cause of SHyper is a predictor of progression to overt hyperthyroidism. The course of the disease may be less predictable in patients with GD than in those with MNG [38]. Patients with GD are more likely to progress to overt disease or to normalize serum TSH rather than having persistent SHyper [38, 39]. In the prospective Amsterdam Autoimmune Thyroid Disease Study, which evaluated the 5-year natural history of SHyper in patients with GD, the transition from SHyper to overt hyperthyroidism usually occurred within 1 year in patients younger than 65 years with autoimmune SHyper [40]. This progression was more frequent after stress and pregnancy. Patients with autoimmune SHyper, in whom serum TSH concentrations normalize spontaneously, may have transient episodes of thyroiditis or mild GD [5].

Patients with MNG-associated SHyper may have stable thyroid dysfunction over time [38, 41], and it is a long-term disease in areas where the natural iodine intake is relatively low. Progression of non-toxic MNG to toxic MNG occurred in about 10% of patients over a 4- to 5-year period in areas without iodine deficiency [42, 43].

Progression to overt hyperthyroidism frequently occurs in grade 2 SHyper due to toxic MNG in iodine-deficient areas, especially after supplementation with iodine or exposure to an iodine load ('iodine-induced hyperthyroidism'), often iatrogenic by iodine-containing contrast computed tomography scans or medications [44].

Symptoms of Hyperthyroidism, Quality of Life, Cognitive Impairment or Dementia in Patients with SHyper

SHyper may be associated with symptoms and signs of mild thyroid hormone excess, i.e. palpitations, tremor, heat intolerance, sweating, nervousness, anxiety and reduced exercise tolerance [45, 46]. Impaired quality of life, in terms of both mental and physical components, has also been documented in young patients with SHyper and undetectable serum TSH [45, 46]. The symptoms of adrenergic hyperactivity (palpitations, tremor, anxiety, etc.) may be improved with the use of cardioselective β-blocking drugs or treatment with antithyroid drugs (ATDs) [46–48]. In a study of 15 patients (aged 61–90 years) with SHyper and undetectable serum TSH, the mean Wayne score (a scale to rate symptoms and signs of hyperthyroidism) was similar to that of patients with overt thyrotoxicosis, and worse than in euthyroid subjects [49]. However, the absence of specific symptoms of hyperthyroidism does not exclude the diagnosis of overt and subclinical hyperthyroidism in the elderly because symptoms are often masked [50, 51]. Cardiovascular symptoms are the most frequent indicators of mild thyroid hormone excess in the elderly, similar to overt hyperthyroidism [52, 53].

There are conflicting data on the risk of dementia in elderly patients with SHyper, and the mechanism is unclarified [54–58]. A recent systematic review provided evidence for an association between SHyper or low serum TSH within the reference range and cognitive impairment or dementia [59]. Similarly, a subsequent population-based prospective study from Korea showed that low serum TSH levels are independently associated with the risk of cognitive impairment and dementia in the elderly [60]. At variance, two recent prospective studies did not find an association between low serum TSH levels and the risk of cognitive impairment and dementia or decreased functional capacity in the elderly [61, 62]. The risk of dementia, although increased in Endo SHyper, was not related to TSH concentration in the Thyroid Epidemiology, Audit and Research Study (TEARS), suggesting that it was not causally related [63]. Consequently, large prospective studies with a long-term follow-up are necessary to clarify the association between SHyper and cognitive impairment and dementia.

Risk of Adverse Cardiovascular Effects in Patients with Endo SHyper

Short-term overt hyperthyroidism is characterized by a hyperdynamic cardiovascular function, with high cardiac output and low systemic vascular resistance [64]. Sinus tachycardia and atrial premature beats are frequently observed in young SHyper patients with undetectable serum TSH [45, 46]. Moreover, prolonged exposure to thyroid hormone excess induces cardiomyocyte hypertrophy by increasing cardiac workload and acting on intracellular signalling pathways [2, 3, 5, 45, 46, 64–67]. In young adults with undetectable serum TSH levels, SHyper may increase left ventricular mass, arterial stiffness and left atrial size, and may induce diastolic dysfunction and impair left ventricular performance [45, 46, 67]. These alterations may be reversible or improve when euthyroidism is restored because thyroid hormone excess does not induce cardiac fibrosis [68]. On the other hand, two recent prospective studies did not find a link between SHyper and left ventricular mass in elderly subjects [69, 70], almost certainly because SHyper has not been associated with symptoms of adrenergic overactivity in the elderly [50]. The aforementioned prospective studies did not provide information about the treatment or progression of thyroid dysfunction [69, 70].

Risk of Atrial Fibrillation

A 2- to 3-fold increased risk of atrial fibrillation (AF) was associated with SHyper in elderly subjects in two large prospective studies [52, 53]. An increased incidence of AF has also been observed in elderly persons with low serum TSH (0.1–0.5 mIU/l) with an HR of 1.6 (95% CI: 1.0–2.5) [52] and 1.85 (95% CI: 1.14–3.00) [53].

Collet et al. [71] analysed the risk of AF in an individual participant data (IPD) meta-analysis (7,901 euthyroid and 810 participants with SHyper) from five prospective cohort studies. During a mean follow-up of 8.8 years, the overall HR for incident AF was higher in participants with SHyper than in those who were euthyroid, and the attributable risk for AF was 41.5% in patients with SHyper. After age- and sex-adjusted analyses, incident AF was significantly more common in participants with grade 2 SHyper (HR = 2.54; 95% CI: 1.08–5.99) than in those with grade 1 SHyper (HR = 1.63; 95% CI: 1.10–2.41; p for trend 0.02) [71]. The risk did not differ significantly by sex, age or pre-existing cardiovascular disease, and was similar after further adjustment for cardiovascular risk factors or pre-existing CVD [71]. Similarly, in a large retrospective case-control study, which was not included in the meta-analysis by Collet et al., an association between SHyper and increased risk of arrhythmia was reported in patients with grade 2 SHyper [63]. A greater risk of AF was also documented in individuals with serum TSH <0.1 mIU/l and underlying heart disease [72]. Atrial arrhythmia has been reported to occur more frequently in euthyroid persons with serum FT_4 levels at the upper limit of the reference [73].

Recently, a TSH level-dependent association with the risk of AF was found across the whole spectrum of thyroid function in a large population-based cohort study [74]. Compared to euthyroid individuals (TSH: 0.4–5 mIU/l), the risk of AF increased with decreasing levels of serum TSH from high-normal thyroid function [TSH: 0.2–0.4 mIU/l; adjusted incidence rate ratio (IRR) = 1.12] to mild SHyper (TSH: 0.1–0.2 mIU/l; IRR = 1.16) and grade 2 SHyper (TSH: <0.1 mIU/l; IRR = 1.41) [74].

Risk of Heart Failure

The pooled IPD data from six prospective cohort studies were analysed by Gencer et al. [75] in a meta-analysis to clarify the possible association between SHyper and heart failure (HF) events. Among the 648 participants with SHyper, the HR for HF events was significantly increased during a median follow-up of 10.4 years in age- and sex-adjusted analyses, although a limited number of participants were <50 years. The risk of HF was much higher in participants with grade 2 SHyper (HR = 1.94; 95% CI: 1.01–3.72) than in those with grade 1 SHyper (HR = 1.31; 95% CI: 0.88–1.95; p for trend across lower TSH categories 0.047). The risk of HF events did not differ after further adjustments for potential confounding risk factors and after the exclusion of patients with pre-existing HF or AF [75].

The risk of HF was increased in the Prospective Study of Pravastatin (PROSPER Study) in elderly patients with a history of cardiovascular disease [76]. A recent retrospective Danish cohort study, which was not included in the meta-analysis by Gencer et al. [75], reported a trend for increased risk for major adverse cardiac events and HF with increasing degree of hyperthyroidism [77]. HF was the leading specific cause of increased cardiovascular mortality in patients with SHyper [77]. In the age-stratified sensitivity analyses, the risk of major adverse cardiac events was mainly found in individuals older than 65 years [77].

Risk of Stroke

Stroke is a potential complication of AF in overt hyperthyroidism [68]. Moreover, hyperthyroidism itself has been associated with a prothrombotic state [78, 79]. The

risk of stroke was not higher in SHyper patients versus euthyroid controls in the meta-analysis performed by the Thyroid Studies Collaboration Group [71]. Conflicting results were reported on the association between SHyper and stroke in two Danish studies [77, 79]. A recent systematic review, based on six prospective studies, did not support an increased risk of stroke in SHyper patients [80]. Two studies included in this systematic review [79, 81] reported an increased risk of stroke in SHyper, and one study reported a statistically significant adjusted HR (3.39; 95% CI: 1.15–10.00) [79]. Contradicting this, two other studies included in this meta-analysis reported a non-significant decreased risk for stroke associated with SHyper [53, 82]. The overall pooled estimated HR using a random effects model showed no association of SHyper with stroke (HR = 1.17; 95% CI: 0.54–2.56), although the studies included in this meta-analysis were highly heterogeneous [80].

Cardiovascular Mortality and Coronary Heart Disease Events and Mortality

Both overt hyperthyroidism and SHyper have recently been associated with increased mortality [77, 83–88]. Five meta-analyses assessed the risk of cardiovascular and all-cause mortality in patients with SHyper [71, 89–93]. Two did not find a link between SHyper and mortality [89, 90], whereas four other meta-analyses found an association between SHyper and cardiovascular or all-cause mortality [71, 91–93], especially in elderly patients and in patients with co-morbidities [91, 92].

In an analysis of IPD data from 10 prospective cohorts, SHyper was linked to an increased risk of total mortality [71]. The IPD analysis showed an age- and gender-adjusted HR for total mortality in SHyper of 1.24 (95% CI: 1.06–1.46) compared to euthyroidism. Risks did not differ significantly by age or pre-existing CVD. All risks were similar after further adjustment for cardiovascular risk factors with an attributable risk of 14.5% for total mortality in SHyper [71]. The IPD analysis of the association between SHyper and coronary heart disease (CHD) events included six prospective cohorts [71]. Compared to euthyroidism, the age- and gender-adjusted HR for CHD events in patients with SHyper was 1.21 (95% CI: 0.99–1.46). The risk of CHD events was not significantly higher in grade 2 SHyper than in grade 1 SHyper [71]. However, in age- and sex-adjusted analyses, the overall HR for CHD mortality was significantly higher in patients with grade 2 SHyper than in euthyroid individuals (HR = 1.84; 95% CI: 1.12–3.00; p value for trend ≤0.03) [71]. Sensitivity analyses excluding patients receiving thyroid medication during follow-up or with previous CVD did not alter these results. Heterogeneity was present across studies for total mortality (I^2 = 49%), but not for CHD mortality and CHD events (all I^2 = 0%). Men had a slightly greater risk for total mortality and CHD mortality than women [71].

SHyper was associated with increased mortality in a population-based study [87] of 5,816 randomly selected adults not included in the meta-analysis by Collet et al. [71]. Mortality was higher in 493 participants aged 80 years or older with FT_4 levels in the high-normal range than in those with FT_4 levels in the middle range (HR = 1.7) [87]. In a large-scale population-based cohort, subclinical and overt hyperthyroidism were associated with increased all-cause mortality compared to euthyroid individuals [88]. A 137% increase in mortality risk was found per 5 years with decreased TSH, even after adjusting for confounders [88]. Recently, the Cardiovascular Health Study reported that lower TSH and higher FT_4 concentrations were associated with an increased risk of multiple adverse events, including mortality, in older people [94].

Data from all the available prospective cohort studies demonstrate that SHyper is associated with an increased risk of total mortality, CHD mortality and incident AF. The risks of CHD mortality and AF are greater among adults with grade 2 SHyper [71, 75]. Cardiovascular morbidity and mortality are particularly increased in men, in elderly patients with high-normal FT_4 levels and in patients with underlying heart disease [71–73, 76, 77, 87, 91, 92, 94].

The task force recognized that two recent meta-analyses have provided relevant information on the cardiovascular outcome of SHyper because they included IPD from all the available prospective studies [71, 75]. Moreover, these meta-analyses performed sensitivity analyses excluding participants with missing values of FT_4 and total FT_3, and used the I^2 statistic to assess heterogeneity across studies. They assessed baseline cardiovascular risk factors, pre-existing cardiovascular disease (CVD) and thyroid-altering medication use, and stratified the analysis by age, sex, race and TSH categories [71, 75].

Risk of Osteoporosis and Fractures in Patients with Endo SHyper

Thyroid hormone stimulates bone resorption, and overt hyperthyroidism is associated with increased bone turnover and an increased risk of osteoporosis and fractures [95]. It is still a matter of debate whether this holds true for persistent SHyper. In fact, the effects of SHyper are likely influenced by the duration of the disease and

associated risk factors for bone loss [30]. The major problem in assessing adverse skeletal effects of SHyper is the difficulty in establishing disease duration. There are conflicting results related to bone mineral density (BMD) [96–104]. However, the majority of studies show that Endo SHyper does not affect BMD in premenopausal women [96–98], whereas a decreased BMD has been reported in postmenopausal women [99–104].

Conflicting results have also been reported regarding the risk of fractures [63, 105, 106]. In a prospective cohort study of US community-dwelling adults (5,567 individuals 65 years or older followed for a median of 13 years), the incidence of hip fracture was higher in elderly men with SHyper than in euthyroid controls (HR = 4.91; 95% CI: 1.13–21.27), with no clear association in women [106]. In TEARS, SHyper was associated with an increased risk of fractures that was not related to TSH concentration [63]. In a population-based cohort study, a single first measurement of decreased TSH was associated with an increased long-term risk of hip fractures in older women [30]. This large-scale study demonstrated a clear correlation between level of TSH, duration of low TSH and risk of osteoporotic fractures in relation to age and sex [30]. In a subsequent study, the same authors demonstrated that the excess risk of major osteoporotic fractures in hyperthyroidism in postmenopausal women was associated with cumulative hyperthyroid time (excessive thyroxine dosing) [107].

A meta-analysis of the seven available prospective cohort studies assessed the risk for hip and non-spine fractures in patients with SHyper [108]. The pooled results indicate that SHyper was associated with an increased risk for hip fractures and non-spine fractures [108]. The HR was 1.46 (95% CI: 0.62–3.45) for hip fractures and 1.15 (95% CI: 0.75–1.77) for non-spine fractures in grade 1 SHyper and, respectively, 2.03 (95% CI: 0.27–15.00) and 1.97 (95% CI: 0.36–10.74) for grade 2 SHyper [108]. However, only two studies reported data on grade 2 SHyper. The HRs for participants with Endo SHyper were 2.16 (95% CI: 0.87–5.37) for hip fractures and 1.43 (95% CI: 0.73–2.78) for non-spine fractures [108]. No difference was found in women compared to men [108].

A very recent meta-analysis, including IPD from 13 prospective cohorts, confirmed that Endo SHyper is associated with an increased risk of fractures with an HR of 1.52 (95% CI: 1.19–1.93) for hip fracture, 1.42 (95% CI: 1.16–1.74) for any fracture and 1.74 (95% CI: 1.01–2.99) for spine fracture [109]. Grade 2 SHyper was associated with higher fracture rates with an HR of 1.61 (95% CI: 1.21–2.15; 47 events in 510 participants) for hip fracture, 1.98 (95% CI: 1.41–2.78; 44 events in 212 participants) for any fracture, 1.61 (95% CI: 0.96–2.71; 32 events in 185 participants) for non-spine fracture and 3.57 (95% CI: 1.88–6.78; 8 events in 162 participants) for spine fracture [109].

Therefore, the data reported in the available prospective cohort studies suggest an increased risk of hip fractures and non-spine fractures in SHyper, with the risk of fractures being greater in adults with grade 2 SHyper [108, 109].

Recommendations on Clinical Evaluation of Patients with Endo SHyper before Treatment

Third Level of Investigation: To Assess the Risks Associated with SHyper and Appropriate Treatment (table 2)

9 Electrocardiography (ECG), Holter ECG and Doppler echocardiography are recommended to assess cardiac rhythm and cardiovascular morphology and function in selected patients with grade 2 SHyper (i.e. in patients with atrial arrhythmias, CHD or HF) [3, 5, 14, 65, 68] (1/+00).

10 BMD and possibly biochemical markers of bone turnover should be performed in selected patients with grade 2 SHyper (i.e. postmenopausal women, elderly patients and patients with risk factors for osteoporosis) [3, 5, 108, 109] (1/+00).

Treatment of Endo SHyper: Effects of Treatment with ATDs and Radioiodine in SHyper

Few studies have assessed the potential beneficial effects of TSH normalization on quality of life and cardiovascular and skeletal risk in SHyper. Some studies suggest that cardioselective β-blockers [47, 48] or treatment of SHyper with ATDs [46, 67] may improve symptoms, heart rate and supraventricular arrhythmias in patients with grade 2 SHyper. A prospective study showed a significant improvement of cardiovascular parameters after treatment of hyperthyroidism [67]. However, no long-term prospective controlled trials have assessed whether treatment reduces the risk of AF and other cardiovascular events. Prospective studies conducted in postmenopausal women with SHyper showed an improvement in BMD after ATDs or RAI therapy [99, 100, 110–113], while BMD progressively declined in untreated patients [99, 100]. Femoral and lumbar spine BMDs were increased by 1.9 and 1.6%, respectively, 1 year after RAI treatment [99, 110]. However, there are no studies documenting that therapy of SHyper reduces the risk of fracture.

Recommendations on Treatment of Endo SHyper in Elderly Patients with SHyper and Low or Undetectable TSH (fig. 1)

11 Treatment of SHyper is recommended in patients older than 65 years with grade 2 SHyper to avoid the risks associated with untreated grade 2 SHyper (i.e. progression to overt hyperthyroidism, increased total mortality, CHD mortality, incident AF, hip fractures and non-spine fractures) [71, 75, 108, 109] (1/++0).

12 Treatment of symptomatic and asymptomatic patients older than 65 years with grade 1 SHyper may be considered to avoid the risk of AF [53] (2/+00). Given the risk of worsening potential cardiovascular events, we suggest that grade 1 SHyper be treated in patients older than 65 years, particularly in the presence of heart disease, diabetes, renal failure, previous stroke or transient ischaemic attack, left atrial dilatation, increased risk factors for stroke, HF, CHD, valvular heart disease, and coronary or peripheral arterial disease (2/+00).

Recommendations on Treatment in Young Patients with Endo SHyper and Low or Undetectable Serum TSH (fig. 1)

13 We suggest treating patients younger than 65 years with grade 2 SHyper if they have persistent disease and/or symptoms of thyroid hormone excess, especially when TSH receptor autoantibodies are persistently detectable and/or thyroid uptake is increased (2/+00). Treatment of SHyper might improve the quality of life and can attenuate the high risk of progression of these patients [35–37, 44]. Symptomatic patients can be treated with cardioselective β-blocking agents and/or therapies directed toward the thyroid dysfunction (2/+00). The dosage of the β-blocking agent can be guided by heart rate control [47, 48] (2/++0).

14 We recommend treatment of patients with grade 2 SHyper in patients with cardiovascular risk factors or co-morbidities [45–48] (1/+00).

15 Treatment of SHyper in young asymptomatic patients with low but detectable TSH is not recommended (no evidence for treating; 2/+00). These patients should be monitored without treatment due to the low risk of progression to overt hyperthyroidism [32–34, 37], the possibility of spontaneous remission of SHyper and the weak evidence of adverse health outcomes.

16 Observation is recommended in patients with grade 1 SHyper, lack of ultrasonographic findings of thyroid abnormalities, a normal radionuclide thyroid scan, normal heart rate on ECG, normal BMD and no cardiovascular or skeletal risks (1/+00).

17 Serum TSH, free T_4, and TT_3 or free T_3 should be evaluated every 6–12 months in untreated SHyper patients with persistently subnormal TSH, or as soon as the clinical picture changes (1/+00).

Recommendations on Treatment of Endo SHyper according to Aetiology (fig. 1)

The treatment of SHyper is similar to that of overt hyperthyroidism. Both ATDs and RAI treatment normalize thyroid function and may improve altered cardiovascular and bone parameters.

18 ATDs should be the first choice in young patients with GD and grade 2 SHyper and in patients older than 65 years with GD and grade 1 SHyper because remission of GD has been observed after ATD treatment in 40–50% of patients with overt hyperthyroidism 12–18 months after therapy [4] (1/+00). RAI should be considered if ATDs are not tolerated, in case of relapse and in patients with cardiac disease [4, 114–118] (1/+00).

19 Treatment with ATDs or RAI is recommended in patients with GD and grade 2 SHyper older than 65 years and when cardiac disease is present because these patients are at high risk of adverse cardiac events (1/+00).

20 RAI therapy or surgery should be the preferred option in patients older than 65 years with grade 1 and grade 2 SHyper due to MNG or TA because these patients are likely to have persistent SHyper [38]. Moreover, patients with grade 2 SHyper may progress to overt hyperthyroidism after excessive iodine intake [41, 44] (1/++0). In cases where RAI is not feasible (e.g. elderly nursing home patients who may be incontinent and patients with severe co-morbidity growing goitre or even pressure symptoms), lifelong low-dose ATDs is a possibility [119] (2/+00).

21 Surgery is recommended in patients with SHyper with large goitre, symptoms of compression, concomitant hyperparathyroidism or suspicion of thyroid malignancy [4, 5] (1/+++). Total thyroidectomy is the treatment of choice in the absence of associated conditions or factors, making grade 2 SHyper patients poor candidates for RAI treatment [4, 120, 121] (1/++0).

Potential Adverse Effects during Treatment with ATDs, RAI and Surgery

ATDs are associated with a variety of side effects that include rare but potentially life-threatening complications [4, 115, 116]. Side effects occur in about 3% of patients with overt hyperthyroidism treated with ATDs, although most

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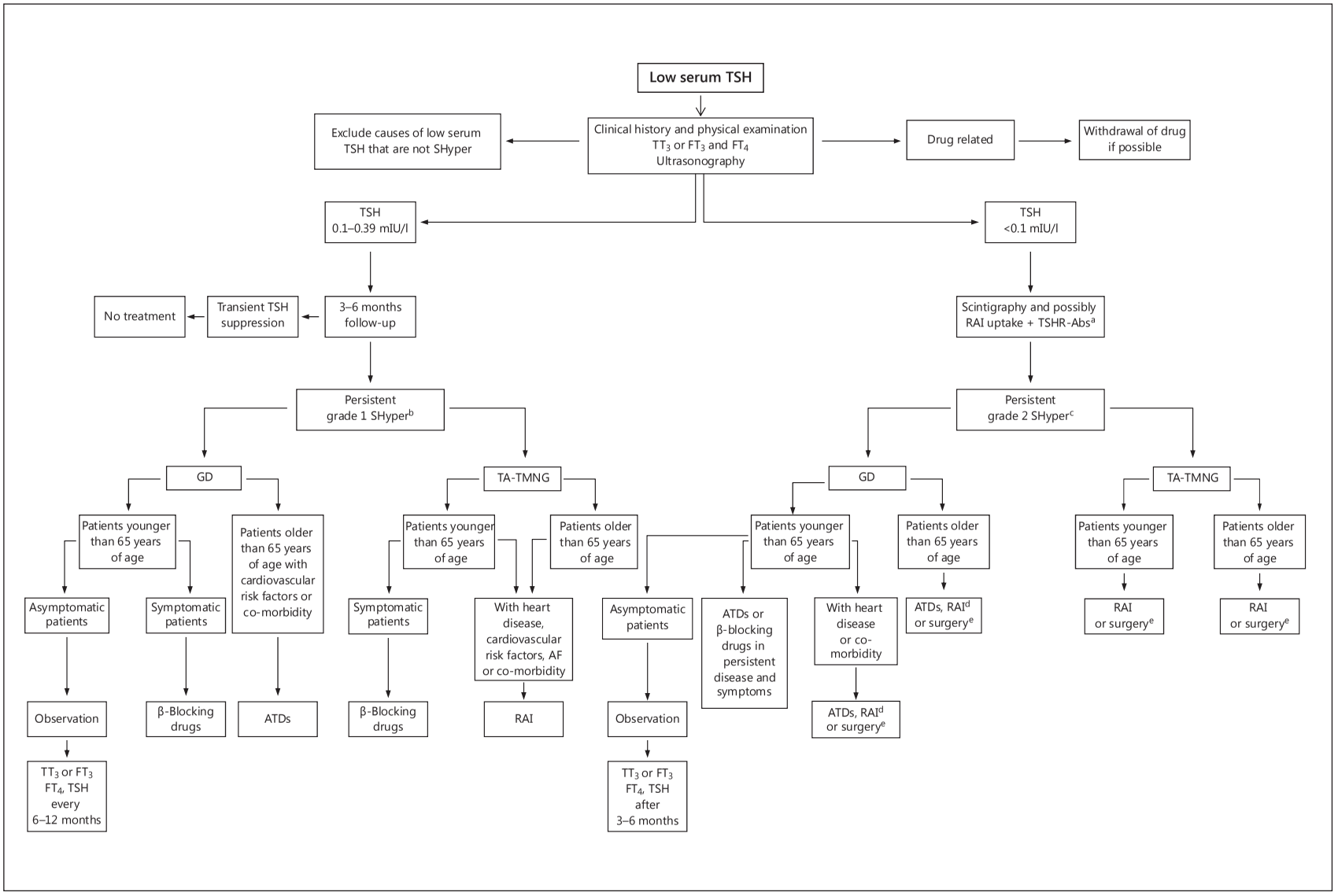

Fig. 1. Algorithm for the management of SHyper. [a] TSHR-Abs = TSH-receptor antibodies. [b] Grade 1 SHyper (TSH levels: 0.1–0.39 mIU/l). [c] Grade 2 SHyper (TSH levels <0.1 mIU/l). [d] RAI in patients with recurrences or if ATDs are not tolerated. [e] Surgery in patients with large goitre, symptoms of compression or thyroid malignancies.

are minor and transient. Minor allergic reactions may be controlled with antihistamine treatment [4]. Agranulocytosis is the most feared severe side effect of ATDs [115–117]. It occurs in about 0.1–0.15% of patients (usually within the first 3 months of treatment) [116]. The side effects of methimazole (MMI) are dose-related, whereas those of propylthiouracil are less clearly dose related [117]. Hepatocellular disease is rarely reported during MMI treatment [115, 117]. Some patients may develop a transient increase in thyroid hormones after RAI [115, 117]. A long-term increase in all-cause and vascular mortality has been detected in patients with overt hyperthyroidism after treatment with ATDs and RAI [4]. However, this risk is probably due to the consequences of prior severe hyperthyroidism rather than to RAI or ATDs. Increased mortality has been reported mainly in patients with overt hyperthyroidism and incomplete biochemical control, but not after treatment resulting in hypothyroidism [121]. In the same study, AF was independently associated with increased mortality [121]. The risk of cancer death after RAI was not significant in the majority of studies that assessed this risk [4]. Radioiodine may induce hypothyroidism and ATDs may increase and reduce the rate of hypothyroidism when given in the week before or after radioiodine treatment, respectively [122]. Radioiodine treatment may worsen Graves' ophthalmopathy and is not recommended for patients with active eye disease [123]. Hypothyroidism occurs after thyroidectomy, and permanent hypoparathyroidism and recurrent laryngeal nerve damage may also occur. However, in experienced hands, this risk is less than 1–2% [4].

Recommendations to Avoid Adverse Effects of Treatment of Endo SHyper

22 Low doses of MMI (5–10 mg/daily) should be used to rapidly restore euthyroidism in patients with SHyper (1/+00). Patients should be informed of the potential adverse effects of MMI (1/+00). A complete baseline blood count and liver profile should be obtained before MMI treatment (1/+00).

23 The goal of therapy with radioiodine should be to obtain a euthyroid state (with or without L-T_4 treatment; 1/+00).

24 Pretreatment with MMI before RAI or surgery might be considered in patients older than 65 years with cardiovascular disease (AF, CHD or HF) and in patients at an increased risk of complications due to worsening of hyperthyroidism, although there are no data supporting this suggestion (2/+00). A 10–15% increase in RAI activity should be considered after pretreatment with ATDs to maintain efficacy [122] (1/+++).

Table 3. Summary of recommendations

Recommendation	Statement
1–8	Recommendations on biochemical and morphological diagnosis of Endo SHyper
9, 10	Recommendations on clinical evaluation of patients with Endo SHyper before treatment
11, 12	Recommendations on treatment of Endo SHyper in elderly patients with SHyper and low or undetectable TSH
13–17	Recommendations on treatment in young patients with Endo SHyper and low or undetectable serum TSH
18–21	Recommendations on treatment of Endo SHyper according to aetiology
22–30	Recommendations to avoid adverse effects of treatment of Endo SHyper

25 Patients at high risk of Graves' ophthalmopathy progression (smokers, and those with markedly elevated serum FT_3 levels and detectable TSH receptor autoantibodies) should be identified before RAI [4, 123] (1/+00). Steroid prophylaxis is recommended in patients with clinically overt eye disease and in smokers [4, 123] (1/+00).

26 According to the American College of Cardiology/American Heart Association, we recommend that the first-line treatment of AF and HF in patients with thyroid dysfunction should be directed primarily towards restoring a euthyroid state because cardiovascular drugs are generally unsuccessful while thyroid hormone excess persists [14, 124]. Treatment of SHyper with ATDs should be the first-line therapy in elderly patients with grade 2 SHyper and AF and/or HF to obtain spontaneous conversion to sinus rhythm [14, 124] (1/+00).

27 Thromboembolism should be prevented in patients with AF. The American Heart Association suggests an anticoagulation with an international normalized ratio (INR) of 2.0–3.0 for patients with SHyper and AF [14, 124] (1/+00).

28 A periodic follow-up after RAI should be performed during the first year and then annually to assess normalization of thyroid function or the development of hypothyroidism (1 /+00).

29 L-Thyroxine in replacement doses should be started in hypothyroid patients after RAI or surgery (1/+++).
30 Near-total or total thyroidectomy should be the preferred surgical approach in GD patients to avoid the risk of recurrences after partial thyroidectomy [4]. In case of a solitary autonomous nodule, lobectomy and isthmus resection is sufficient [4]. Total or subtotal thyroidectomy should be performed in patients with toxic MNG [4], with a recurrence rate of <1% [4] (1/++0).

Conclusions

These ETA guidelines are in agreement with the ATA and AACE guidelines [4]. A summary of our recommendations is provided in table 3. In the absence of randomized controlled trials, the treatment of SHyper remains controversial because of conflicting opinions about the possible benefits of treatment. Three recent meta-analyses provide evidence, based also on IPD data, for treating SHyper with undetectable TSH because of an excess risk of total mortality, CHD mortality, HF, incident AF and fractures among adults with grade 2 SHyper [71, 75, 108, 109]. Although these meta-analyses do not show evidence that treatment is effective in improving the risks associated with untreated SHyper, they demonstrate that SHyper is a potentially life-threatening condition.

Despite the lack of randomized controlled trials, we recommend treating elderly patients with grade 2 SHyper given the results of the above-mentioned meta-analyses. We suggest considering treatment in patients with grade 1 SHyper older than 65 years because of the increased risk of AF, and in patients younger than 65 years with grade 2 SHyper because of the risk of progression especially in the presence of symptoms and/or co-morbidity. Currently, there is no evidence of a potential benefit of treating young patients with grade 1 SHyper because of their low cardiovascular and skeletal risks and the infrequent progression of SHyper to overt hyperthyroidism.

The Future

There are important limitations in all the prospective studies that provide relevant information on SHyper. First, thyroid function was measured only at baseline in the majority of these studies, and therefore the possible progression from subclinical to overt dysfunction is unknown. Second, FT_3 was measured in only a few cohorts. Third, the aetiology of hyperthyroidism was not considered. Adequately powered studies with relevant clinical outcomes are necessary to determine whether treatment of SHyper can prevent or improve the negative cardiovascular and skeletal repercussions of grade 2 SHyper in elderly patients. Large prospective studies are necessary to clarify the need to treat adults with grade 1 or 2 SHyper. Prospective trials are also needed to clarify the relationship between the aetiology of SHyper and the cardiovascular and skeletal risks in patients with SHyper. Such studies should be performed on large samples of SHyper patients with long-term evaluation. Patients should be selected for clinical trials with rigorous criteria, and confirmatory thyroid functions tests should be repeated during follow-up. However, this is not an easy task. Recently, two European trials, carried out to assess the potential benefits and risks of treatment of SHyper, were terminated because they did not complete their recruitment [125]. Pending larger studies, we hope that these guidelines will help clinicians improve their management of SHyper.

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