MANAGEMENT OF ENDOCRINE DISEASE

L-Thyroxine replacement therapy in the frail elderly: a challenge in clinical practice

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Abstract

The number of elderly people, mostly aged over 85 years (the 'oldest old'), is increasing worldwide. As a consequence, accompanying morbidity and disability have been increasing, and frailty, defined as an age-related condition of decline of physiological reserves and vulnerability, represents an emerging problem. Caring for older frail people may represent a challenge, since the elderly differ significantly from younger adults in terms of comorbidity, polypharmacy, pharmacokinetics and greater vulnerability to adverse drug reactions. Specific criteria of therapeutic appropriateness and modified goals of care are needed in such patients, also in endocrine care settings. Indeed, thyroid dysfunctions are among the most common conditions in older, multimorbid populations. The prevalence of overt and subclinical hypothyroidism is as high as 20% and thyroid hormone prescription is common in the elderly, with a trend toward levothyroxine treatment of more marginal degrees of hypothyroidism. In addition, older patients have the highest rate of overtreatment during replacement therapy and are more susceptible to developing adverse effects from thyroid hormone excess. Recently, results of a multicentric randomized controlled trial, the TRUST–IEMO collaboration trial, added further insights to the debated question of whether and when levothyroxine treatment is required and if it is beneficial in the elderly. With this in mind, we revised the relevant literature on the impact of thyroid dysfunction and replacement therapy among older people, with the aim to better define indications, benefits and risks of L-T4 replacement therapy in the frail elderly.

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An aging population: increasing comorbidity and risk of inappropriate medication

The number of elderly people is increasing worldwide. Over the last 25 years, the percentage of the population aged 65 years and older has increased, reaching 8.5% of

the total population in 2015, and this trend is projected to continue. By 2030, the world is likely to have 1 billion older people, accounting for 12–13% of the

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total population, and for the first time in history, people aged 65 and over will outnumber children under age 5, the so-called demographic transition (1). The greatest population increase has been in the number of those aged 85 and over, the 'oldest old'. They represent about 7% of the world's 65-and-over population (10% in developed countries), and the number is projected to grow because of increasing life expectancy. Indeed, they are the fastest growing demographic group (1, 2).

As a consequence, accompanying morbidity and disability have been increasing. In general, older people are more likely to suffer from two or more chronic medical conditions, and the prevalence of multimorbidity increases with age, affecting 1 out of 4 persons <65 and 3 out of 4 >65 years (3, 4, 5). Noteworthy, thyroid diseases are among the top 10 most common conditions in multimorbid patients, as reported in a Scottish study of primary care patients (6). Increased multimorbidity in turn leads to increased prescribing in the older population, resulting in a plethora of treatments that potentially interfere with each other and may harm, rather than aid, the patient (7, 8). Indeed, polypharmacy, defined as taking at least five drugs, has been consistently demonstrated as a risk factor for both drug interactions and/or adverse events (7, 8, 9). Old people differ from younger adults in many socio-demographic characteristics (loss of autonomy, social deprivation, long-term residence in nursing home) and physiologic reserves (disability, frailty) and are more vulnerable to the adverse effects of drugs, because of age-related changes in pharmacodynamics and pharmacokinetics (7, 9). For these reasons, current clinical guidelines for most chronic diseases may turn out to be potentially inappropriate for older people, since such guidelines derived from clinical trials that have not included older people or those with multimorbidity and have been mainly focused on separate disease management (10, 11). The extrapolation of evidence from younger and biologically different populations to older, often multimorbid, people may lead to inappropriate prescribing in a real-life scenario, exposing the patients to potential harm.

Inappropriate treatments are defined by Beers' criteria, developed in the USA, as 'medications or medication classes that should generally be avoided in persons 65 years or older because they are either ineffective or they pose unnecessarily high risk for older persons and a safer alternative is available' (12, 13). In a study of more than a thousand nursing home residents in North America, 40% of participants were prescribed at least one inappropriate

medication as above defined (12). More recently, a retrospective cohort study from Ireland including 931 community-dwelling patients aged >70 years reported a similar prevalence (42%) of potentially inappropriate medication prescribing, identified by the Screening Tool of Older Person's Prescriptions (STOPP) criteria (14). In conclusion, elderly people with multiple chronic diseases are at high risk of inappropriate prescribing and adverse drug reactions. Moreover, it should be taken into account that older people, in addition to being distinct from younger adults, represent a heterogeneous population, since individuals at the same age can greatly differ from each other in terms of disability and physiologic reserves.

Frailty: an emerging geriatric syndrome

Population aging is closely associated with an increasing prevalence of frailty, which makes elderly people highly vulnerable to adverse health outcomes (15). Frailty is not synonymous with multimorbidity and/or disability, but represents an independent geriatric syndrome (15). It has been defined as 'a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death' (15). Frailty develops as a consequence of age-related decline in multiple organ systems, which, all together, results in loss of physiological reserves and reduced stress tolerance, so that even minor stressor events trigger disproportionate changes in health status (15, 16). Sarcopenia, defined as a progressive loss of lean muscle mass and strength, is a major component of the syndrome (15, 16).

Contrary to common belief, frailty is not an unavoidable consequence of aging and not all elderly are frail. Only 3–7% of elderly people between the ages of 65–75 years are frail. The incidence of frailty increases steadily with advancing age, reaching about 26% in those aged >85 years and exceeding 32% in those above 90 years (17). Also, frailty is statistically more prevalent in women than that in men, in people living in southern Europe and in Hispanic and African-American people (17). Thus, between a quarter and half the people aged 85 and more are estimated to be frail, but on the other hand, up to three-quarters of them might not be (16, 17). Hence, distinguishing frail elderly people from those who are not frail is crucial.

In landmark studies, valid models have been developed to recognize frail individuals. The Cardiovascular Health

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Study Frailty Screening Measure proposed by Fried utilizes the presence of three or more of five components to identify a 'frail phenotype': unintentional weight loss, exhaustion, poor grip strength, slow walking speed or low physical activity (18). This model is centered on sarcopenia as the leading feature of frailty and does not consider cognitive and mood impairment nor comorbidity. As an alternative tool, proposed by the International Association of Nutrition and Ageing (IANA), the FRAIL scale utilizes five elements including fatigue, resistance, ambulation limitation, coexisting illnesses and loss of weight, with frailty represented by the presence of three or more of these elements (19). In addition, broader models of frailty have been proposed that also consider cognitive and psychosocial issues, diseases, disabilities and medications (for example, the comprehensive geriatric assessment (CGA) and the Frail Index (FI)) (20). Recently, a consensus group agreed that simple screening tests (for example, the clinical frailty scale by Rockwood *et al.*, the FRAIL scale or the Fried criteria) can be used to identify persons with physical frailty syndrome in routine clinical

practice (Table 1). People aged 70 years and older, as well as any person with significant weight loss ($\geq 5\%$ over the past year) should be screened for frailty by means of such validated tools (16).

Identification of frail patients should be the basis for appropriate selection of elderly people for invasive procedures or drug treatments, in order to minimize inappropriate medication (21). Indeed, frail elderly patients appear to be particularly at risk of adverse effects. They are also likely to be receiving several medicines, and polypharmacy has negative consequences above and beyond the risks of individual drugs, contributing to the pathogenesis of frailty itself. Thus, prescribing in frail older people should differ from that in non-frail older people. Instead of treating all diseases separately according to the current disease-specific guidelines, frail people should undergo a holistic, multidimensional approach, that takes into account factors such as patient's life expectancy, quality of life and risk-benefit estimate and that identifies the diseases with the highest priority for treatment (21, 22). The above-mentioned Beers criteria (12) and

Table 1 Examples of simple and well-validated screening tests to be used by physicians to identify persons with frailty or at risk of frailty.

Frailty model	Components	Measures	Definition of frailty
Clinical frailty scale (16)	Clinical judgment on physical and cognitive issues [^]	Visual and written chart for frailty with 9 graded pictures from 1=very fit, to 9=terminally ill	Frailty cut-off point ≥ 5 (continuous score)
Cardiovascular health study frailty screening measure (18)	Weight loss (unintentional)	$>5\%$ of body weight in prior year (by direct measurement of weight)	Frailty: ≥ 3 criteria Pre-frail: 1–2 criteria
	Weakness	Grip strength in the lowest 20% at baseline, (adjusted for gender and body mass index)	
	Poor endurance	Self-reported exhaustion at least 3–4 days/week*	
	Slowness	Walking time/15 feet slowest 20% (>7 or 6s, depending on gender, height)	
FRAIL scale (19)	Low physical activity	kcal expenditure per week lowest 20% [#] Males: <383 kcal/week Females: <270 kcal/week	Frailty: ≥ 3 items Pre-frail: 1–2 items
	Fatigue	Self-reported in the past month (all or most of time = 1)	
	Resistance	Any difficulty walking up 10 steps without resting (1 = Yes, 0 = No)	
	Ambulation	Any difficulty walking one block (1 = Yes, 0 = No)	
	Illness [§]	Participants are asked for 11 illnesses. The total illnesses are recorded as 0–4=0, and 5–11=1	
	Loss of weight	5% or more in the past year is scored as 1 and $<5\%$ as 0	

All the above reported tests require no more than 10 min to be administered (20).

[^]Each point on its scale corresponds with a written description of frailty, complemented by a visual chart to assist with the classification of frailty (16).

*Identified by two questions from the CES-D Depression Scale (18). [#]Based on the short version of the Minnesota Leisure Time Activity questionnaire (18).

[§]The illnesses include hypertension, diabetes, cancer (other than a minor skin cancer), chronic lung disease, heart attack, congestive heart failure, angina, asthma, arthritis, stroke and kidney disease (19).

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STOPP and Screening Tool to Alert Doctors to Right Treatment (START) criteria (14) may represent valid tools to reduce the inappropriate use of medication in this population, along with the available Guidance for Prescribing in Frail Adults (21, 22). According to this guidance, a drug review process should be conducted holistically by considering the impact and the cumulative effects of each medication on the individual clinical conditions of the patient (22). For each drug, need and indication, risk–benefit ratio and current dosages should be evaluated, in order to decide to initiate/continue or not the therapy. A list of drugs that are tolerated poorly in frail patients or are associated with falls is also provided (22). Modified goals of care and therapeutic targets should be developed to meet the unique needs of the frail population. A similar approach is also needed in thyroid care setting, since the prevalence of thyroid diseases increases with age and older patients have the highest rate of thyroid hormone prescription (23).

Prevalence of thyroid diseases with age: the need of age-appropriate reference ranges for TSH

It is well known that the prevalence of thyroid disorders increases with age, mostly in women and in white populations (24, 25, 26). Subclinical thyroid dysfunction represents the most common finding and is defined biochemically on the basis of only serum TSH alterations (27). Subclinical hypothyroidism (SHypo) refers to a raised TSH with normal free thyroid hormone concentrations and can be mild (TSH 4.5–9.9 U/L) or severe (TSH $\geq$ 10 U/L), while subclinical hyperthyroidism (SHyper) is defined as low ($<$ 0.4 U/mL) or undetectable ($<$ 0.01 U/mL) TSH with normal free thyroxine (FT4) and tri-iodothyronine (FT3) levels (27, 28). By contrast, overt thyroid dysfunction describes a more severe condition, in which serum concentrations of free thyroid hormones are outside of their reference ranges (27).

An increase in prevalence and incidence of overt thyroid dysfunction with age has been reported in all populations, with differences in epidemiology depending on genetic and environmental factors (24, 25, 26). While overt hyperthyroidism affects 0.5% to 2–4% of older people depending on iodine nutritional status, prevalence of SHypo ranges between 1% and 10% in most studies (24, 25, 26). Data from the Danish Investigation of Iodine Intake and Thyroid Diseases registry reported 33 new cases of overt hypothyroidism per 100 000 inhabitants

per year in the general population, whereas this was more than 120 cases per 100 000 per year in the elderly (aged 70 years and over) (29). Thus, older people had three-to-four-fold higher incidence rates of overt hypothyroidism than younger adults (29). These data are augmented by significant numbers of subjects with subclinical thyroid dysfunction, which is found in 10% and more of older people (24, 25, 26).

The Colorado Thyroid Disease Prevalence Study reported a prevalence of abnormal thyroid function in about 11% of the total study population, 9.5% presenting with elevated TSH and 2.2% with low TSH and demonstrated that the percentage of subjects with elevated TSH levels (i.e. $>$ 5.1 IU/L) increased with age, up to 21% of women and 16% of men aged 75 and more (30). Data from the National Health and Nutrition Survey (NHANES III) in the United States confirmed that TSH levels increased with age, as well as the frequency of anti-thyroid antibodies, and the percent with TSH $>$ 4.5 IU/L reached 14% of people aged 85 years and older, being greater in women than in men, and in whites than in blacks (31). Also, the frequency of anti-thyroid antibodies increased as TSH increased in the study population, providing evidence for underlying autoimmune thyroid disease (31). The same survey reported 2.5% of the general population as having low (1.8%) or fully suppressed (0.7%) serum TSH, after exclusion of ‘exogenous’ cases, with a higher prevalence in women and a rise in frequency with age (31). Similar findings were obtained in population prevalence studies from the United Kingdom (32, 33). Interestingly, a study of almost 6000 subjects over 65 years attending general practices in England revealed a comparable prevalence of SHyper in that age group (about 2%), but a lower population prevalence (2.9%) of SHypo (33). The same group had already reported a prevalence of SHypo of 11.6% in women and 2.9% in men aged over 60 years from the same geographical region (34). The authors attributed such a difference between the two community screening studies, conducted in the same area more than 10 years on, to more frequent testing of thyroid function and earlier treatment of raised TSH in primary care in the intervening years (35).

Indeed, data from a large UK population-based database demonstrated an increase in the rate of new levothyroxine (L-T4) prescriptions, and a trend toward L-T4 treatment of more marginal degrees of hypothyroidism over the years (36). During the study period (2001–2009), the median TSH threshold for initiation of treatment fell from 8.7 IU/L to 7.9 IU/L, reflecting a rise in the number of individuals treated for a TSH below

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10.0IU/L (up to 58.1%) (36). Moreover, 34.6% of subjects prescribed L-T4 had only one abnormal TSH reading, and no confirmatory testing was required before initiation of therapy (36). Subjects older than 70 years had the highest rates of L-T4 prescribing and the highest odds of being prescribed with a TSH level between 4.0 and 10.0IU/L and normal free thyroxine (FT4) levels (i.e. mild SHypo) (36). A substantial number of these individuals could have been inappropriately prescribed, and this is a relevant problem, since the indication for L-T4 therapy was rarely reviewed once initiated: more than 90% of individuals were still under L-T4 at the end of the study (36). However, a non-negligible rate of reversion of SHypo to euthyroid status has been reported in adults aged ≥ 65 years (37). In the same study population from the Cardiovascular Health Study, Somwaru *et al.* had evaluated the use of L-T4 over time and showed an increase from 8.9% to 20% during the 16 years of follow-up (23). The highest rates of L-T4 initiation were found in older patients, independently of sex and race: subjects aged 85 years and more initiated L-T4 more than twice as frequently as those aged 65–69 years (23). Once again, the most likely explanation for this phenomenon was prescription of L-T4 for the correction of SHypo (23). The authors concluded that such a trend in L-T4 therapy initiation in older people should prompt a more accurate evaluation of indications and benefits of thyroid hormone use in the elderly (23).

In the last few years, the emergence of age-specific reference ranges for TSH has added to the complexity of management of thyroid dysfunction in older people (38). There is a large body of evidence that TSH distribution curves shift to higher concentrations with increasing age in the general population. Data from NHANES III showed a progressive increase in median TSH and 97.5 centile with age, even in the reference population without thyroid antibodies; the upper limit of TSH rose from 3.5IU/L in individuals under the age of 50 to 7.5IU/L for those aged 85 years and over (31, 39). Similar findings have been reported in different population settings and also extended to Ashkenazi populations, who achieve exceptional longevity (40, 41, 42). Additionally, longitudinal studies confirmed a progressive increase of TSH in the same individuals over time, especially in the elderly, with no relevant changes in free-T4 concentrations nor association with increased mortality (43, 44). All studies concluded that such a rise in TSH concentrations did not reflect the increase in the prevalence of thyroid dysfunction with age, but rather a change in age-specific population distribution of TSH. It has been speculated that such a shift of TSH to higher levels with age may reflect an

age-associated alteration in TSH set point due to diminished sensitivity of the pituitary to negative feedback, a decrease in TSH biological activity or in thyroid gland sensitivity to TSH (30, 43, 44). On this basis, the use of an age-specific reference range for TSH has been recommended, especially in those aged over 70 years, to avoid patients being misclassified with subclinical thyroid dysfunction and inappropriately treated with thyroid hormone (39, 40, 41, 43, 44). This raises the debated question of the clinical relevance of such mild thyroid abnormalities in terms of symptoms and potential associations with health outcomes in elderly, and hence, to the much-debated question of whether to treat or not.

Thyroid status, morbidity and mortality in the elderly

Studies on the relationship between thyroid dysfunction, mostly subclinical forms, and health outcomes in older adults still provide inconsistent findings, and large randomized trials of treatment for those with subclinical dysfunction are lacking.

While in younger adults there is strong evidence that SHypo is associated with lipid alterations, cardiac dysfunction and increased cardiovascular risk, which may be partially reversed by hormone replacement therapy (45), most studies in older populations have not shown such a clear association, suggesting that the burden of mild thyroid failure on cardiovascular outcomes becomes less and less evident with increasing age and almost disappears in the oldest old (26, 45, 46). Several studies failed to demonstrate any relationship between SHypo and coronary heart disease, cerebrovascular and peripheral arterial disease (47, 48, 49, 50, 51, 52), whereas some found an association (mostly with heart failure) only at TSH values greater than 10IU/L (53, 54, 55, 56). Also, the impact on cardiovascular outcomes of known risk factors (i.e., serum lipid alterations, diastolic blood hypertension, endothelial function) that may be improved by replacement therapy is substantially influenced by age, since it appears less pronounced in the elderly compared to the middle aged (57, 58). Thus, even if treatment of subclinical disease may result in lipid profile and/or blood pressure improvement, there is no evidence that such an improvement is associated with a decrease in cardiovascular morbidity and/or mortality in elderly patients. These data are reinforced by the results of two comprehensive meta-analyses, suggesting that increased risk for adverse cardiovascular outcomes may

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be present in SHypo patients <65 years of age, but not in those >65 years (59, 60).

On the other hand, higher serum TSH has been associated with prolonged life span. In the Leiden 85+ Study, which included 599 participants who were aged 85 years at enrolment and were followed up through age 89 years, individuals with higher TSH levels did not experience adverse effects and had lower mortality than their euthyroid counterparts, suggesting a protective effect of SHypo in this age group (61). Higher TSH levels were also found in centenarians compared to younger controls (42) and in nonagenarians with reported familial longevity (62), also providing a genetic basis for this raised TSH contributing to extreme longevity (42, 62). Other studies did not confirm such a protective effect of elevated TSH levels, but also failed to find a harmful association with mortality in very old people (44, 46, 47, 48, 50, 51). Two recent retrospective cohort studies depicted the association between subclinical thyroid disease and excess mortality in the elderly at higher degrees of TSH elevation, even if different TSH threshold values were proposed (>10IU/L and >6.3IU/L respectively) (63, 64). In the study by Grossman *et al.* (64), the most significant association was found at 1 year from initial analysis; then, it decreased (instead of increasing, as expected) as time of follow-up was more prolonged, the lowest being at 10 years. The authors hypothesized that when individuals were followed for longer periods, their comorbidities led to mortality that was not dependent on their thyroid status (64). This raises the question of how patients may really benefit from replacement therapy in the long term. Interestingly, a long-term observational study found no significant association between high-normal TSH levels and all-cause mortality among participants aged >60 years, despite the observation of a significantly increased risk of mortality among participants aged <60 years with high-normal TSH levels (65).

By contrast, low TSH concentrations have been associated with an increased risk of dysrhythmias in older, as well as in younger adults, even in the absence of elevated thyroid hormone levels (i.e. SHyper) (45, 47, 66). The risks appeared to be greatest at levels of TSH <0.1IU/L (45, 66). Most studies also demonstrated an association between SHyper and risk of fatal and nonfatal cardiovascular diseases and all-cause mortality (55, 61, 66, 67), even if other studies did not (47, 49). Moreover, an association has been reported between SHyper and frailty (68). In a large cohort of more than 1000 community-dwelling men aged >65 years, subjects with SHyper, mostly those aged >74 years, had an

increased risk of frailty at baseline and were more likely to be weak than euthyroid men (OR: 3.41; 95% CI: 1.03–11.30) (Table 2). An increased risk of developing frailty over time was also observed in prospective analyses, but the results did not reach statistical significance (68). The authors suggested that SHyper might contribute to the development of frailty among elderly individuals because of its effects on bone and muscle (osteoporosis, muscle weakness, weight and lean body mass loss) and its association with cognitive decline (68). Contrary to expectations, no relationship was found between SHypo and either frailty at baseline or subsequent frail status after a 5-year follow-up (68). Other two cross-sectional studies have assessed the relationship between TSH levels and frailty among older subjects and both have failed to find any (69, 70) (Table 2). In a cohort of women (641 participants aged 70–79 from the Women's Health and Aging Studies), Wang *et al.* reported an inverse association between thyroid antibodies and frailty, irrespective of thyroid functional status. Even though the group of subjects seropositive for thyroid antibodies had a higher prevalence of abnormal serum TSH concentrations, this inverse correlation persisted after adjusting for TSH values and was therefore independent of TSH (69). A similar lack of association between TSH and frailty was reported in men also (among more than 3000 participants ≥70 years) (70). Simonsick *et al.* showed that older individuals with elevated TSH levels do not demonstrate increased risk of mobility problems; rather, those with mild TSH elevation showed a slight functional advantage (71). The authors evaluated functional motility in relation to TSH levels in a large cohort of 2290 community-dwelling subjects aged 70–79 years from the Health, Aging and Body Composition (Health ABC) Study (71). At cross-sectional analysis, the mild SHypo group (TSH >4.5 to <7.0IU/L) demonstrated better mobility (increase walking speed) and retention of cardiorespiratory fitness compared to the euthyroid group. After 2 years, persons with SHypo experienced a similar decline to the euthyroid group, and those with mild elevations in TSH levels maintained their mobility advantage (Table 2) (71). Similarly, Virgini *et al.* reported no consistent association between subclinical thyroid dysfunction (SHypo or SHyper) and self-reported functional capacity or decline, in a large population of 5182 well-functioning community-dwelling older people (mean age of 75.3 years) (72) (Table 2).

From the same studies, it emerged that serum FT4 levels, even within the reference range, might predict health outcomes relevant to aging, irrespective of TSH values. In the Leiden 85+ study, increasing levels of

Table 2 Summary of the studies evaluating the relationship between thyroid functional status and frailty or related parameters of physical performance.

Study	Place	Sample/follow-up	Mean age (s.d.)	Components (frailty criteria)	Results
(68)	USA	1455 community-dwelling men/5 year	73.6 (5.8) year	Weight loss, weakness, exhaustion, slowness, low activity level (Fried criteria)	Increased risk of frailty at baseline in SHyper subjects (OR: 3.41, CI: 1.03–11.30) No relationship between SHypo and frailty either at baseline nor at 5-year follow-up Prevalence (6.7%) and likelihood (OR: 0.30, CI: 0.10–0.85) of frailty were lower in subjects seropositive for thyroid antibodies, irrespective of TSH values
(69)	USA	641 community-dwelling women	74.0 (2.7) year	Weight loss, weakness, exhaustion, slowness, low activity level (Fried criteria)	FT4 in the highest two quartile of normal range was associated with frailty (OR: 1.32, CI: 1.01–1.73, and OR: 1.36, CI: 1.04–1.79, respectively)
(70)	Australia	3943 community-dwelling men	75.3 (4.1) year	Fatigue, resistance, ambulation, illness, loss of weight (FRAIL scale)	No association between TSH and frailty Neither SHyper (OR: 0.69, CI: 0.21–2.31) nor SHypo (OR: 1.17; CI: 0.90–1.53) was associated with frailty
(71)	USA	2290 community-dwelling individuals (47.5% women)/2 year	74.6 year	Self-reported and performance-based measures of mobility (usual and rapid gait speed, endurance walking ability)	SHypo was not associated with increased risk of motility problems The mild SHypo group showed a slight functional advantage both at baseline and at 2-year follow-up
(72)	USA	5182 community dwelling people (47.5% women)/3.2 year	75.3 (3.3) year	Self-reported functional capacity (self-care and mobility by Barthel index and instrumental activities of daily living scores)	No association between persistent subclinical thyroid dysfunction (either SHypo or SHyper) and functional capacity at baseline or during follow-up ($P > 0.05$)
(77)	The Netherlands	403 independently living men/4 year	77.8 year	Activities of daily living (ADL), physical performance scale (standing balance, walking speed, and ability to rise from a chair), muscle strength, body composition	High FT4, within the normal range, was related with a lower physical performance and muscle strength, as well as with a worst 4-year survival No association between SHyper and SHypo and physical performance, ADL and mortality
(78)	Italy	933 independently living individuals (58% women)/3 year ($n = 713$)	74.2 year men 76.6 year women	Physical performance scale (standing balance, walking speed, and ability to rise from a chair), muscle strength and mass	Subjects with SHyper had a significantly lower lean body mass than euthyroid and SHypo subjects SHyper men were more likely to have poor physical performance (OR: 2.97, CI: 1.01–8.71)
(79)	Italy	450 hospitalized individuals (66.4% women)	83.8 (0.3) year	Autonomy in daily living activities (self-care and mobility) before admission and at discharge Length of stay, in-hospital mortality and long-term survival	High FT4, within the normal range – but not TSH – was associated with steeper decline of physical performance at the 3-year follow-up, in men Low T3 syndrome was associated with frailty and in-hospital mortality risk (OR: 2.7, CI: 1.1–6.5) High FT4, within normal range, was associated with a slightly greater long-term mortality (HR: 2.12, CI: 0.99–4.54)

CI, 95% confidence interval; HR, hazard ratio; OR, odds ratio; SHyper, subclinical hyperthyroidism; SHypo, subclinical hypothyroidism.

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free thyroxine were associated with increased all-cause mortality (HR: 1.16, 95% CI: 1.04–1.30 per 2.7 pmol/L increase), after adjusting for sex, disability and health status, and subjects with abnormally low levels of TSH (i.e. subclinical hyperthyroidism) had the highest mortality rate (61). By contrast, increasing levels of TSH and decreasing levels of FT4, both representing lower thyroid function, were associated with a survival benefit (61). The authors speculated that low thyroid function might lead to low metabolic rate and reduced energetic expenditure, resulting in increased survival, as already described in animal models (73). A significant association between higher FT4 levels and both cardiovascular and all-cause mortality was reported in the cohort of oldest old of the Cardiovascular Health Study All-Stars, despite no association with TSH levels (44). Gammage *et al.* also found that FT4 (but not TSH) was independently associated with prevalence of atrial fibrillation among 5860 adults aged ≥ 65 years (74). In another study by Murphy *et al.*, evaluating 1278 healthy euthyroid postmenopausal women, higher FT4 within the normal range was associated with lower hip bone mineral density, increased bone loss and non-vertebral fracture risk (75). In a cohort of 3485 euthyroid men aged 70–89 years from the Health In Men Study, higher FT4 levels were found to be associated with all-cause mortality, independently of conventional risk factors and medical comorbidities (76). Noteworthy, in the same cohort from the Health In Men Study, higher FT4 was an independent and significant predictor of frailty, suggesting that circulating FT4, even within the normal range, might contribute to weight loss and reduced physical capability (70). Similar findings had been reported by van den Beld *et al.* who noted that in euthyroid men aged 73–94 years, higher serum FT4 concentrations were associated with reduced physical function, while low serum FT4 was associated with better 4-year survival (77). Interesting data came from a study by Ceresini and coworkers who evaluated the relationship between physical function and thyroid hormones in a large cohort of independently living ≥ 65 years subjects (78). In the study population, the authors measured muscle strength and mass and physical performance, all parameters that are closely related to frailty. At longitudinal analysis, they found that higher FT4 concentrations at enrolment, although within the normal range, were associated with steeper decline of physical performance at a 3-year follow-up in elderly men, while TSH concentrations were not (Table 2) (78). In very old and frail hospitalized patients (450 participants

with a mean age of 84 years), low T3 syndrome was clearly associated with frailty and in-hospital mortality risk (OR: 2.7, CI: 1.1–6.5), while increasing levels of FT4 were associated with a slightly greater mortality (HR: 2.12, CI: 0.99–4.54; $P=0.053$), suggesting that FT4 (but not TSH) might represent a predictor of long-term survival in older euthyroid subjects (Table 2) (79). More recently, data analysis of 14 cohorts with thyroid function measurements at baseline and prospective follow-up of cardiovascular outcomes reported no association of TSH levels within the reference range with risk of coronary heart disease morbidity or mortality, but found a U-shaped association with FT4 levels within the reference range, since participants with FT4 levels in the second quartile had lower risks of coronary heart disease events compared with participants with high (highest quartile) FT4 levels (80).

In conclusion, even in euthyroid subjects with normal levels of TSH, higher FT4 levels seem to be predictors of poor health outcomes including frailty, while FT4 levels in the low-normal range may contribute to healthy aging and improved survival in late life. Lower thyroid hormone levels decrease energy production and requirements, preventing catabolism and reducing oxidative stress. Thus, blunted thyroid function may represent a protective factor against frailty. Also, shifting the accent from a negative (frailty) to a positive aspect, it might contribute to biological resilience, i.e. the ability to adapt in the face of adverse conditions and stress and to recover (81). Therefore, FT4 rather than TSH alone, may better represent clinical thyroid status in the elderly population, mostly in frail individuals.

Replacement therapy with levothyroxine (L-T4): benefits and risk in older people

There is no doubt about the benefits and indication of replacement therapy for treating overt hypothyroidism in the elderly. Thyroid hormone replacement therapy provides symptomatic relief, has positive effects on cardiac, executive and cognitive functions, which are strongly affected by overt hypothyroidism in the elderly and avoids progression to myxedema, a life-threatening condition with a mortality rate as high as 40% (24, 25, 26, 29, 82, 83, 84).

On the contrary, benefits and indication for treatment of SHypo in the elderly are still controversial. The main reasons to treat SHypo are to avoid progression to overt

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disease, relieve symptoms and reduce cardiovascular risk. None of these seems truly relevant for health outcomes in late life.

Firstly, although SHypo is usually progressive, the annual rate of progression to overt disease is low and recovery of thyroid function is more frequent than thought in the elderly, mostly in mild forms (27, 45, 82). In the study by Gussekloo *et al.*, 11 out of 21 (52%) ≥ 85 -year patients with SHypo (most of whom with TSH < 10 U/mL) normalized their thyroid function, and none progressed to overt disease after 3 years (61). Also in a large community-based study, involving 5888 ≥ 65 -year adults from the Cardiovascular Health Study (37) of whom 459 were sub-clinically hypothyroid (mean TSH at baseline 6.7 ± 2.6 U/L), 35% of subjects, that is over a third, normalized TSH values over a 2-year period. In the same period, less than a 10th (9%) of subjects progressed to overt hypothyroidism and/or initiated thyroid hormone replacement, while the majority (56%) remained sub-clinically hypothyroid (37). In a cohort of elderly Japanese (mean age 70-year) with SHypo (mean TSH at baseline 6.10 ± 1.71 U/mL), TSH levels normalized spontaneously in half of the patients, and progression to overt hypothyroidism occurred in 7% of them after an average follow-up period of 4.2 years (85). Noteworthy, normalization was not observed in patients whose baseline serum TSH level was > 8 IU/L (85). A previous study in a geriatric population by Rosenthal *et al.* had reported a slightly higher degree of progression to overt disease, since one-third of patients developed overt hypothyroidism during a 4-year duration follow-up. However, the small number of subjects with elevated TSH levels ($n=26$) and the inclusion of individuals with markedly high TSH levels (> 20 IU/L) may have biased the results of the study (86). Pearle *et al.* reported on the evolution of 73 patients > 60 -year with SHypo (55 with TSH values between 5 and 10 U/L and 18 with TSH > 10 U/L) (87). They found that, after 12 months, 5.5% of these patients normalized TSH levels and less than a fifth (17.8%) developed overt dysfunction, while the large majority (76.7%) remained without progression to overt hypothyroidism (87). Once again, patients with the highest TSH values at baseline (> 10 U/L) did not normalize TSH during follow-up, and their rate of progression to overt dysfunction was threefold higher than patients with initially lower (< 10 U/L) TSH (33% vs 12%) (87). A high degree of persistence of SHypo over the years was also reported in selected populations of younger adults (88, 89, 90), as well as in the general population (91, 92). In a 20-year follow-up evaluation of the Wickham Survey, the annual risk of developing

overt hypothyroidism was 2.6% with elevated serum TSH (> 6 U/L) alone and 4.3% with both elevated TSH and positive anti-thyroid antibodies (91). In a large, non-selected population of 422242 subjects aged 21 to > 80 years, the progression rate from slightly increased serum TSH (> 5.5 to ≤ 10 U/L) to high TSH (> 10 U/L) was even lower, occurring in only 2.9% of cases during a 5-year duration follow-up (92). Moreover, serum TSH levels became normal in 62% of subjects with TSH value < 10 U/L, when the test was repeated during the follow-up (92). Serum TSH levels > 10 IU/L, female sex and the presence of anti-thyroid antibodies are associated with an increased risk of progression from subclinical to overt hypothyroidism, while normalization of thyroid function is more likely to occur when serum TSH concentrations are lower than 10 U/L and anti-thyroid antibodies are negative (27, 45, 82). On this basis, it is reasonable that a large subset of older individuals with a mildly increased TSH may not require substitutive treatment, as TSH may normalize within a few years or remain stable over time, while a minority, with higher degree of TSH elevation, are at risk of developing overt thyroid dysfunction. In these patients, close monitoring of thyroid function could be the best option, given the low rate of annual progression, and both life expectancy and quality of life should be taken into account prior to initiating replacement therapy (27, 37, 45).

Concerning health-related quality of life and relief of symptoms, SHypo seems to be less symptomatic in elderly people (27, 45, 82), and many symptoms are nonspecific, as confirmed by studies demonstrating that clinical signs and symptoms were poor predictors of thyroid status in older patients (93, 94). Also, an interview survey of more than 800 subjects with a mean age of 74.1 years did not reveal any differences in the age-adjusted frequency of self-reported symptoms between subjects with mildly elevated serum TSH (< 10 IU/L) and those with normal TSH concentrations (95). Furthermore, SHypo was not associated with impairment of physical and cognitive function or depression, and L-T4 replacement therapy did not improve cognitive function and mood in elderly individuals (50, 61, 96, 97, 98). Rather, in a large cohort of geriatric patients, SHypo was associated with better physical performance compared to euthyroidism across a 2-year duration follow-up (71). As a consequence, decision to treat or not to treat older patients with SHypo should not be based only on the assessment of clinical symptoms and signs (27, 99).

Finally, in clinical decision-making processes, the presence of cardiovascular risk factors is commonly

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considered an element in favor of intervention with L-T4 in SHypo subjects, even at older ages. Indeed, Somwaru *et al.* who demonstrated a steady trend in thyroid hormone initiation with increasing age reported the highest rate of L-T4 initiation in patients with coronary heart disease (23). However, most studies in older populations have provided insufficient evidence that treatment of SHypo could be beneficial in preventing cardiovascular events and/or reducing mortality (25, 26, 27, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 56). From a cardiovascular viewpoint, it seems reasonable to be concerned about treating SHypo in the elderly, since a mild thyroid deficiency may exert protective effects on the heart, by lowering metabolic rate, oxygen consumption and adrenergic tone, which in turn would reduce the risk of acute events, while initiation of replacement therapy could increase oxygen demand of the heart and precipitate ischemic heart disease as well as arrhythmias (27, 45, 82). Furthermore, an observational study of real-life practice performed from data obtained from the United Kingdom General Practitioners Research Database (GPRD) showed that treatment of SHypo with L-T4 was associated with fewer ischemic heart disease events and a reduced all-cause mortality in younger individuals (40–70 years), but this was not evident in older people (>70 years) (100). Similarly, in a large cohort of primary care patients from Denmark, no beneficial effects were found in L-T4 treated patients regarding myocardial infarction, cardiovascular death or all-cause mortality, except in patients <65 years, where it seems that L-T4 has some protective effect on all-cause mortality (101). Thus, the cardiovascular benefits of L-T4 therapy are lower in older patients than in younger adults. On the other hand, overtreatment may cause net harm in older people (46, 100, 101).

Unfortunately, the risk of over-treating during thyroid hormone replacement therapy is high, mostly in older people, and it seems to increase with longer time from therapy initiation, and with increasing age (30, 36, 102, 103). Moreover, in a British study in one general practice, it emerged that the finding of abnormal levels of TSH in patients under L-T4 therapy was often disregarded and did not result in any treatment changes: 23.4% of patients had decreased serum TSH, but physicians did not adjust the dose in 89% of patients (102). The Colorado Thyroid Disease Prevalence Study confirmed that approximately 20% of L-T4-treated patients have decreased serum TSH (30). Data from the United Kingdom Clinical Practice Research Datalink (36) demonstrated that the percentage of subjects with decreased or suppressed TSH following replacement therapy increased as time from therapy

initiation increased. Overall, 16% of individuals had a TSH level lower than 0.50IU/L 5 years after L-T4 therapy was initiated (36). Such rates of overtreatment were even higher in older people. In a population of community-dwelling individuals aged 65-year and older, Somwaru *et al.* found a very high prevalence of thyroid function testing abnormalities in people under thyroid hormone therapy (103). Of the 339 thyroid hormone users, only 43% were in the euthyroid range, 16% had a high TSH and as many as 41% had a low TSH (of whom 8% were overtly hyperthyroid) (103). Thus, older people are at higher risk of overtreatment and are more susceptible to developing skeletal and cardiovascular adverse effects from thyroid hormone excess. Somwaru *et al.* also sought to describe the factors associated with thyroid hormone over- or under-replacement in older men and women and found that, apart from comorbidities (diabetes, kidney failure), lower weight was independently associated with low TSH levels in multivariable analyses ($P < 0.001$): for every 10kg lower weight, the likelihood of having low TSH increased by 65% (OR: 1.65; 95% CI: 1.31–2.07) (103). On this evidence, frail individuals who suffer from weight loss and reduced lean mass, appear to be particularly at risk of overtreatment among older people, and thyroid hormone excess may have negative consequences beyond the well-known adverse effects, contributing to the pathogenesis of frailty itself. Indeed, besides lowering TSH, thyroid replacement therapy excess affects serum FT4 levels, which are independent predictors of frailty (68, 70, 77, 78). Several studies have demonstrated that patients under L-T4 therapy have higher levels of FT4 than controls, even if within normal values, and serum FT4 concentrations are often at the upper limits of normal range (27, 45). Also, the well-known harmful effects from overtreatment with L-T4, which include cardiovascular and skeletal side effects, could be particularly deleterious in the frail elderly.

The major risk is represented by atrial fibrillation (AF). The threshold for AF decreases with age, and the coexistence of ischemic and degenerative heart disease likely predisposes elderly individuals to the development of AF, even in the presence of mild thyroid hormone excess (27, 45, 82). There is a large body of evidence showing that the frequency of AF is increased in patients with low TSH (47, 74, 104, 105, 106). In a retrospective cross-sectional study of more than 23000 hospitalized patients aged 65–70 years, most of whom had underlying cardiovascular disease, the prevalence of AF in patients with low serum TSH concentrations (<0.4 U/L) was 13.3% compared with 2.3% in euthyroid controls (106). Low

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serum TSH was associated with a >5-fold higher likelihood for the presence of AF with no significant difference between subclinical and overt hyperthyroidism (106). A prospective study by Cappola *et al.* (47) confirmed a higher incidence of AF in older individuals with SHyper (TSH <0.44 IU/L, mean age 73-year) than in the euthyroid group ($P < 0.001$) (47). After adjustment for age, sex, clinical cardiovascular disease at baseline, medications and other known risk factors for AF, subjects with SHyper had nearly twice the risk of developing AF, irrespective of whether serum TSH was less than 0.1 U/L or 0.1–0.44 U/L (47). Gammage *et al.* showed a higher prevalence of AF in those with SHyper compared with euthyroid subjects (9.5% vs 4.7%) among 5860 adults aged ≥ 65 years, without differences between people with serum TSH <0.1 U/L and those with minimally suppressed serum TSH (0.1–0.4 U/L). Moreover, they reported that, also in euthyroid subjects with normal serum TSH levels, serum FT4 concentration was independently associated with AF (74). Similar findings were reported by Heeringa *et al.* who demonstrated that old persons with high-normal thyroid function parameters (the highest quartile of FT4 and the lowest quartile of TSH within the normal range) were at an increased risk of AF (107). In addition, increases in other cardiovascular disorders (atherosclerotic cardiovascular events and stroke) and in cardiovascular or all-cause mortality have been recorded in most (55, 61, 66, 67) but not all (46, 49) studies in SHyper (27, 45). A meta-analysis of aggregated data from cohort studies and life-tables demonstrated a 41% increase in all-cause mortality in subjects with SHyper vs euthyroid control subjects. Mathematical modeling suggested that excess mortality increased progressively over time beyond the age of 60 years, with the highest risk in the elderly and in men (108).

Concerning the skeletal effects of thyroid hormone excess, it is still a matter of debate whether persistent exogenous SHyper can affect bone metabolism and increase the risk of fractures (27, 45, 82). In a meta-analysis of 41 controlled cross-sectional studies (including about 1250 patients), TSH-suppressive therapy was associated with significant bone loss at lumbar spine and hip in postmenopausal, but not in pre-menopausal, women (109). In a cohort of 686 women aged 65 years or older who were followed up for about 4 years, occurrence of vertebral fractures was four times higher and occurrence of hip fractures was three times higher in women with serum TSH <0.1 U/L than in those with normal TSH concentrations (110). In another prospective study in older men and women, who were followed up

for 13 years, the incidence of hip fracture was higher in men, but not in women, with SHyper than in euthyroid controls (111). Also in euthyroid postmenopausal women, thyroid status within the upper normal range (FT4 and/or FT3 levels in the highest quintile) was associated with lower hip bone mineral density, increased bone loss and non-vertebral fracture risk (74). Current thyroid hormone therapy was significantly associated with a significantly increased risk of fracture among adults aged 70 or more, in a dose–response manner. High (>0.093 mg/day) and medium (0.044–0.093 mg/day) cumulative doses of L-T4 were associated with a significantly increased risk of fracture compared with low cumulative doses (<0.044 mg/day). Thus, dosages commonly used in clinical practice, mostly over 0.093 mg/day, might be excessive for an older population (112). Similarly, Ko *et al.* reported a strong dose–response relationship between L-T4 therapy and risk of fractures in women aged ≥ 65 years according to their history of osteoporosis, but at higher cumulative doses. Higher (>150 µg/day) L-T4 dosages were associated to increased risk of fractures compared with lower dosages (51–100 µg/day) in women with osteoporosis (HR: 1.56; 95% CI: 1.03–2.37), but not in women who were not diagnosed with osteoporosis (113). Moreover, in a study population of 1278 healthy euthyroid postmenopausal women (not including subjects suffering from any thyroid disease and/or taking any drugs affecting thyroid function, as well as bone metabolism), individuals with higher FT4 and/or FT3, within the normal range, had lower bone mineral density (mostly at hip), compared to women with FT4 and/or FT3 in the lowest quintile. Also, the risk of non-vertebral fracture was increased by 20% and 33% in women with higher FT4 or FT3 respectively, whereas higher TSH was protective and the risk was reduced by 35% (75). These findings might bring concern that L-T4 overtreatment, affecting serum concentrations of either TSH or FT4 or both, might favor osteoporosis and increase the risk of fractures. Moreover, thyroid hormone excess affects muscle strength and mass. Both thigh strength and cross-sectional area were found to be reduced in patients with either overt ($n=30$) or subclinical ($n=24$) hyperthyroidism compared to euthyroid controls ($n=48$), and both improved after restoration of a euthyroid state (114). This finding may have particular relevance for elderly frail patients, who have concurrent sarcopenia and are prone to falls.

Large prospective therapeutic trials are needed to clarify whether hormone replacement therapy is beneficial in these patient groups or not, and if any benefits may be offset by adverse effects (115, 116). At this juncture, there

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are two currently ongoing trials investigating whether L-T4 treatment improves outcomes in older patients affected by SHypo: the TRUST trial (Thyroid hormone Replacement for Untreated older adults with Subclinical hypothyroidism; a randomized placebo-controlled Trial; <http://www.trustthyroidtrial.com>) and the IEMO 80+ Thyroid Trial (The Institute for Evidence-based Medicine in Old age; <http://www.iemo.nl>). The TRUST trial is a European multicenter, double-blind placebo-controlled randomized trial including 3000 adults aged 65 and older (117). The IEMO 80+ is a randomized controlled trial recruiting 450 subject aged 80 years and more in the Netherlands (118). The two studies joined the TRUST Project with one research question: what is the safety and efficacy of thyroid hormone replacement in older adults with SHypo? They evaluate, prospectively, the effects of thyroid hormone therapy on the same endpoints, from cognitive and physical function and quality of life to cardiovascular disease and mortality, in old (>65 year) (117) and very old (>80 year) people (118). Both trials started recruiting participants in 2013 and are following them over a 3 (IEMO 80+) to 5 (TRUST trial) year period. Very recently, Stott and coworkers for the TRUST study group published the first results of a randomized placebo-controlled trial involving 737 adults aged 65 years and more (mean age 74.4 year), affected by persistent SHypo (mean serum TSH: 6.40 ± 2.01 U/L, range: 4.60–19.99 U/L, with normal FT4) (118). Of these, 368 patients were randomly assigned to receive L-T4 treatment and 369 were assigned to receive placebo, and all were followed up for 12 months. The primary outcome of the study was thyroid-specific quality of life, evaluated by means of specific scores (hypothyroid symptoms score and tiredness score); secondary outcomes included generic health-related quality of life, executive and cognitive function, hand grip strength, activities of daily living, body weight and body mass index, all parameters that are closely related to frailty. Despite no adverse effects occurring during the study period, L-T4 treatment had no beneficial effects on either primary or secondary outcomes compared to placebo. Thus, the first available results of the TRUST trial indicate that hormone replacement therapy does not provide symptomatic relief in old patients with SHypo (119). Moreover, during recruitment, it clearly emerged that many old persons (three out of 5 patients eligible for the study because of biochemical findings consistent with SHypo) had spontaneous reversion to euthyroid state during follow-up, without any treatment. The results of the study are impressive, especially considering that a common argument in favor of treatment of older

people is to improve physical and cognitive performance and quality of life. Therefore, the results of the study by Stott and coworkers may be relevant in decision-making processes and may impact future guidelines. However, there are some limitations that the authors themselves have highlighted. Firstly, few patients included in the study had baseline TSH levels above 10 U/L, so that the question of whether there are benefits from treatment in this subgroup could not be addressed. Secondly, the study was underpowered for cardiovascular outcomes, so that no conclusions could be drawn concerning any effects of L-T4 therapy on cardiovascular events (119). Once full results of such randomized controlled trials are available, they may be able to give an answer regarding the benefits and drawbacks of L-T4 replacement therapy in older and oldest old patients.

Thyroid replacement therapy in the frail older patient: what can we extrapolate from the evidence of literature and the current guidelines

As clearly indicated in Guidance for Prescribing in Frail Adults (21, 22), L-T4 therapy should, in almost all cases, be prescribed/continued in frail patients with overt hypothyroidism, since the drug is replacing a vital hormone. By contrast, no clear recommendations can be stated concerning treatment of SHypo, due to insufficient data (27, 45, 46, 82). Evidence from literature suggests that in late life a mildly increased TSH level do not deserve substitutive treatment, and that it does not provide any real benefit but rather exposes older patients (mostly the frailest) to potential harmful effects. The balance of risks and benefits is mainly influenced by the degree of TSH elevation and by individual clinical conditions. It is advisable that the decision to treat or not should be taken on an individual basis, by taking into account degree of thyroid dysfunction, patient's age and life expectancy, associated risk factors and comorbid conditions and health-related quality of life (21, 22, 27, 82). In any case, age-specific reference ranges for serum TSH should be considered for the establishment of diagnosis and confirmatory testing performed before initiation of therapy, to avoid inappropriate prescribing (27, 82).

As first proposed by Cooper and Biondi (27), the recent European Thyroid Association (ETA) guidelines (120) emphasized the importance of categorizing patients affected by subclinical hypothyroidism by age (60–70 years as moderately old, >70 years as older and >80–

85 years as oldest old) for the decision-making process. A wait-and-see approach with close monitoring of thyroid function has been proposed in very old patients (>85 years), avoiding replacement therapy, especially in the presence of a mildly elevated TSH (<10 IU/L) (120, Recommendation 15). Two different management algorithms have been suggested for individuals under or over the age of 70, even if it has been clearly highlighted that a net chronological demarcation is impossible to draw and clinicians are expected to use their discretion and judgment in interpreting this age threshold (120). It has been proposed not to treat individuals ≥ 70 years in the presence of a mildly elevated TSH (<10 IU/L), without considering symptoms of hypothyroidism, unlike what has been suggested in younger adults. For more severe degrees of TSH elevation (>10 IU/mL), treatment should be considered if clear symptoms of hypothyroidism or high cardiovascular risk are found (120). However, any decision regarding treatment of old (>70 year) and moderately old (60–70 year) patients cannot ignore comorbidities and frailty, even if no statements can be firmly established, and this issue is intensely debated (120, 121, 122, 123). Regular monitoring of thyroid function and cardiovascular outcome is recommended in subjects not prescribed with thyroid hormone replacement therapy (27, 82, 120).

Once the decision to treat has been made, oral L-T4 is the treatment of choice (81, 120, 124). Current evidence does not suggest use of either liothyronine (T3) or combined L-T4/T3 treatment in elderly individuals, above all if they are frail (82, 124, 125). The starting dose of L-T4 varies depending upon the cause and severity of thyroid dysfunction, age and sex of the patient, BMI and any underlying physiological and pathological conditions, which may affect the L-T4 requirement (82). Lower doses of L-T4 are usually required to normalize serum TSH in elderly patients in relation to the reduced T4 metabolism, which in turn is due to decrease in lean body mass (82). It has been estimated that older hypothyroid patients need approximately 25% less than younger ones, and that the mean half-life of T4 increases with age, from 6.7 days for adults aged 18–27 years, to approximately 9 days for those ≥ 65 (126, 127). However, other factors, such as physiological decrease in intestinal absorption, concomitant drug use and comorbidities, which are common in the elderly and may counterweight the effects of decreased T4 metabolism, should be taken in account, and L-T4 dose individualized and carefully titrated in the elderly (Table 3) (82, 120, 124). As suggested by Biondi and Wartowsky (82), it is prudent not to start a full L-T4 dosage in older individuals: replacement therapy should

Table 3 Factors that may affect L-thyroxine requirements in elderly.

Determinants	Dosage requirements
Age-related changes in pharmacodynamics and pharmacokinetics	Decrease in L-T4 requirement (about 25% less), mainly due to reduced lean body mass Increased mean half-life of L-thyroxine (9 days)
Deiodinase activity	Reduced activity in elderly patients, with consequent increment in L-T4 requirement
Adherence to therapy	Poor medication-taking behavior/poor compliance (related to socio-economic status, burdens of medications, no immediate satisfaction, loss of autonomy, cognitive decline) may falsely suggest increased requirements
Comorbidities	Concomitant disease may impair levothyroxine's proper absorption or action (atrophic gastritis, Helicobacter pylori infection, intestinal chronic inflammatory diseases, liver and pancreatic diseases, previous gastrointestinal surgery, to mention the most common in elderly)
Interferences	Increment or decrement in dosage
Nutritional habits	Food and beverages (coffee, grapefruit juice, cereals, soya)
Drugs	A large number of drugs may interfere with the L-T4 requirement by impairing absorption of L-T4 or by other mechanisms (proton-pump inhibitors and other anti-acid drugs, calcium carbonate, ferrous sulfate, to mention a few)

be started at a low dosage and gradually increased until euthyroidism is achieved. Starting doses of 25–50 µg/day are suggested in individuals >60 year, and lower doses of 12.5 µg/day, with a progressive increase of 12.5 µg/day every 4–6 weeks, are recommended in very old individuals with severe hypothyroidism, as well as in patients suffering from ischemic heart disease (82). Both the ETA and the American Thyroid Association (ATA) guidelines agree on the 'start low, go slow' recommendation for thyroid hormone replacement in the elderly (120, 124). Although a randomized trial showed that starting with a full dose of L-T4 is safe and feasible even in older patients unless not diagnosed with heart disease (128), the practice of starting L-T4 therapy slowly in the elderly should not be abandoned (82, 129). Above all, a similar approach should be taken in frail subjects, to avoid the risk of precipitating clinical conditions. ETA guidelines recommend a starting dose of 25–50 µg daily, in the elderly as well as in patients of any age suffering from heart diseases (120). In the same

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subgroups of patients, the ATA guidelines suggest an even lower starting dose of L-T4 (12.5–25 µg daily) (124). Then, the L-T4 dose should be slowly increased by no more than 12.5–25 µg daily every 4–8 weeks based on serum TSH levels, until the TSH target has been reached (120, 124).

In addition to lower thyroid hormone requirements, also the target serum TSH should be raised in older persons, especially the oldest old (>80 years), given evidence that that serum TSH levels rise with age and the 97.5% confidence interval for serum TSH in healthy elderly persons has been estimated at 7.5 IU/L (37). Accordingly, a TSH target value of 4–7 U/L has been proposed in the elderly to mimic physiological values (27, 82), and the ATA guidelines agreed to raise the target serum TSH to 4–6 IU/L in persons >70–80 years (124). Also ETA guidelines propose a higher therapeutic target for serum TSH in older patients (>70–75 years) compared to younger adults (120, Recommendation 21). Moreover, a double-blind, randomized clinical study clearly showed that targeting TSH in the lower part of the reference range does not improve symptoms or quality of life in middle-aged and elderly patients with hypothyroidism (130). Thus, based on current evidence, an age-adjusted range of TSH values should be targeted in elderly patients (82). However, a very recent retrospective study (including 611 patients, mean age 61 ± 6 years) showed that older patients with treated overt hypothyroidism, whose median TSH level was between 0.5 and 5.0 IU/L, had a significantly lower mortality rate than those with a median TSH between 5.0 and 10.0 IU/L, while FT4 level did not influence mortality. On this basis, the authors proposed that a TSH in the normal range may be an appropriate target also in older patients (131). Despite limitations, the study raises interesting issues for future prospective studies.

Finally, once the TSH target has been reached on L-T4 therapy, then serum TSH should be regularly monitored at least annually, since thyroid hormone requirements may change with age, comorbidities and concurrent use of other medications (Table 3) (82, 120, 124). In addition to the TSH level, the assessment of serum FT4 targeting the mid reference range should be considered when evaluating adequacy of therapy in old people (82). Regular monitoring of thyroid function is particularly relevant for older patients (especially the oldest old and the frail), since the elderly are more susceptible to the adverse cardiovascular and skeletal muscle effects of overtreatment with L-T4 (82, 120, 124). More frequent evaluations of thyroid function are necessary in patients receiving drugs that interfere with thyroid function, those with malabsorption and/or those losing body weight

(82). In conclusion, as clearly stated in guidelines from professional societies and expert opinions, in the elderly, hormone replacement therapy should be individualized, gradual and closely monitored, and this statement is even truer for the frail elderly (27, 82, 120, 124).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Author contribution statement

Rosaria M Ruggeri drafted the manuscript. Francesco Trimarchi and Bernadette Biondi participated in writing and critical reviewing of the manuscript. All authors read and approved the final version.

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