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Consensus

Management of thyroid dysfunctions in the elderly. French Endocrine Society consensus statement 2019. Long version

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1. Introduction

During the last quarter of a century, the population over 65 years has grown steadily, reaching 18% of the general population, and 9% over 75 in France. This aging is both a source of physiological repercussions on the tissues, and of the accumulation of pathological processes, which can themselves alter these major functions of the organism, notably the functioning of the thyrotropic axis.

2. Thyroid aging

Thyroid aging is accompanied by subtle changes in functioning that cause adaptations in the synthesis and secretion of its hormonal products. The clinician must not attribute to a pathological process what is only the reflection of a physiological evolution. The morphological vicissitudes of the thyroid with age testify to its aging. The main clinical translation is the propensity for nodularity, especially in women [1,2]. From the pathological point of view, this corresponds to a dilation of the vesicles with a tendency to fusion, generating colloid cysts, and a loss of functional mass. In microscopy, more or less functional micro-follicles are also observed [3]. Diffuse or focal lympho-plasmocytic infiltrates corresponding to areas of thyroiditis are readily present and may participate in a moderate reduction in the ability to produce thyroxine (T4).

3. Iodine status

Iodine intake frequently decreases with age (less consumption of marine products, reduced sodium intake supplemented with iodine). Iodine metabolism gradually deteriorates, and medications frequently reduce digestive iodine absorption, which may have consequences on thyroid physiology. In addition, iodine uptake by the thyroid cells decreases with age [4]. The result is a decrease in T4 secretion in the elderly. This phenomenon is compensated by the reduction in the metabolic clearance of T4 which leads to slightly modified circulating thyroxine concentrations (see below).

4. Changes in thyroid biological parameters

4.1. TSH

The gold standard for assessing primary thyroid function is TSH level. Several studies have shown an increase in TSH level during normal aging [5–9], but there are exceptions [10], after excluding the risks bias (people with thyroid dysfunctions or with antithyroid antibodies). The variations in TSH concentrations may be due to physiological adaptation, the repercussion of a general pathology on the thyrotropic axis as can be observed in low T3 syndromes, or have a pathological significance in favor of thyroid dysfunc-

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tion, without the distinction between these three clinical situations being easy in the elderly with poly-pathology. This question of the "physiological" evolution of TSH with age is central because it should raise questions about the use of specific reference intervals for the elderly, essential in current practice to distinguish the "normal" from the pathological, before to begin the discussion of therapeutic indications and intervention thresholds.

4.2. Thyroxine (T4)

Serum free thyroxine (FT4) concentration seems to change little with aging [7,9], although a recent study reported a slight increase [10]. This stability despite aging may be due to a combination of reduced T4 synthesis and secretion by the thyroid cells and reduced metabolic thyroxine clearance [4,11]. High FT4 concentration, on the other hand, may be associated with increased mortality [12], at least in men [13], and diminution with increased life expectancy in over-85 year-old patients [14].

4.3. Triiodothyronine (T3)

Serum total and free T3 concentrations tend to decrease with age [15]. This may be due to reduced activity of 5'mono-deiodase, which catalyzes deiodination of T4 into T3, or reduced stimulation by TSH caused by resistance to TSH action with aging. In rat, deiodinase type 1 tissue concentrations and activity decrease with age in the liver and later in the kidneys, as T4 transformation into T3 is reduced [16]. In-vitro data confirm these in-vivo results [17]. Increased FT3 after the age of 75 years may be associated with reduced mortality in women [13]. Likewise, a study from the Netherlands reported an association between FT3 reduction and increased life expectancy in over-85 year-old patients [14].

4.4. Reverse T3 (rT3)

Serum rT3 concentration depends on confounding factors such as general, severe or consumptive disease. When such pathologies are absent, aging is often accompanied by reduced deiodinase type 1 activity, leading to rT3 elevation [16], although decrease may also be found [9].

4.5. Autoimmunity

The enzymatic equipment of thyrocytes enables them to combat free radicals effectively. However, excessive free radical production with aging can cause oxidative stress that is harmful for the thyroid, giving rise to thyroiditis or even cancer [4]. Autoimmunity targeting the thyroid is more frequent in women, increasing with age, especially after the menopause. Auto-antibody prevalence reaches 20% in over-60 year-old women [4], especially Caucasian, Hispanic and Black [18]. Anti-thyroglobulin antibodies, when elevated and especially without anti-TPO (thyroid peroxidase) antibodies, are not associated with onset of thyroid dysfunctions [18]. Thyroid hypo-echogenicity on ultrasound correlates with the level of circulating anti-thyroglobulin antibodies, which in turn expresses thyroid damage [4].

5. Q.1. Whom to screen for thyroid dysfunction?

The symptoms of thyroid dysfunctions are relatively non-specific in the elderly, who tend to show fewer symptoms overall. A high level of clinical vigilance is required not to overlook thyroid dysfunction. However, this needs weighing against the risk of over-prescription of thyroid examinations, which often reveal transient hormonal abnormalities that are actually secondary to other general diseases or medical treatments, unrelated to any thyroid pathology and almost always without any clinical impact, giving rise to unnecessary treatment and pointless and costly iterative check-ups.

> Guideline 1.1. Hormonal thyroid exploration is indicated in patients with previously unknown atrial fibrillation, cognitive disorder of recent onset, unexplained depression or other signs of thyroid dysfunction. (Grade 1+++)

> Guideline 1.2. Thyroid function screening is not indicated in the elderly. (Grade 1++)

In case of clinical symptoms prompting thyroid assessment that finds normal TSH level, there is no reason to repeat the assay within 6 months or a year in the absence of new clinical events.

> Guideline 1.3. In the absence of new clinical events, there is no reason to repeat thyroid function exploration that came out normal. (Grade 1+++)

Thyroid function tests are often non-specifically disturbed in general non-thyroid disease, especially when acute. Thyroid evaluation is better avoided in case of intercurrent pathology without strong suspicion of thyroid dysfunction if a diagnosis of thyroid dysfunction would alter the ongoing treatment (for example, recent atrial fibrillation). Thyroid evaluation work-up is better performed outside of the acute episode. This is especially true for hospital patients. There are no data determining a particular interval to be respected, but work-up in practice is usually repeated at a 4–12 months interval, although this depends on the context and particularly on the progression of the thyroid dysfunction.

> Guideline 1.4. Except if diagnosis of thyroid dysfunction would alter ongoing treatment, thyroid assessment is best not performed during acute episode of intercurrent diseases, and especially during unscheduled hospital stay. (Grade 1+++)

6. Q.2. How to screen for thyroid dysfunction in the elderly?

Small changes in FT4 concentration are accompanied by much greater changes in TSH levels. This remains true in the elderly, whatever the relation between the two parameters (linear, sigmoid or logarithmic) [19–21] and is a good reason for assaying TSH level for thyroid exploration in this age group, except in case of central pathology (hypothalamic or pituitary).

Brown et al. [20] showed that, for T4 concentrations within normal limits, TSH levels are higher in elderly than younger subjects. In moderate to severe hypothyroxinemia, elderly subjects show less TSH elevation than younger subjects [19].

Interpreting TSH level in the elderly should always take account of variations that may be due to medications or to non-thyroid pathologies.

> Guideline 2.1. Diagnosis of thyroid dysfunction is based on TSH assay alone in first line. (Grade 1+++)

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Schneider et al. [22] showed lack of benefit for simultaneous TSH and FT4 assays in first line: 93% of the 4471 patients had normal TSH level and 89.2% had normal values for both; thus, 96% of subjects with normal TSH level also had normal FT4 concentration. Eighty-five percent of those with normal TSH but FT4 concentrations outside the normal range (3.8%; $n = 168$) showed FT4 at < 2 pmol/L outside the range. Thus, isolated TSH assay is preferable to FT4 in first line, the latter being reserved to patients with TSH level outside the normal range.

Guideline 2.2. In first line there is no reason to perform FT4 or FT3 assay, and screen for antithyroid antibodies or perform thyroid ultrasound scan. (Grade 1++)

7. Q.3. What are the TSH reference values in the elderly?

One difficulty in thyroid function exploration in the elderly is defining TSH reference values. The reference range for a biological parameter is a statistical concept (range including 95% of subjects without the pathology in question) and does not in itself determine what is pathological, and should therefore not be used alone for treatment decision-making.

TSH reference values in adults range between 0.4 and 4.0 mIU/L [23–25] – but this may not hold for "older" subjects in our aging population.

Prevalence of subclinical hypothyroidism depends on where the upper limit of normal is set. Hennessey reviewed 18 descriptive studies of subclinical hypothyroidism, and found prevalence to vary between countries and especially according to the TSH threshold employed: from 0.4% in Japanese men, to 16.9% in American women [26]. Generally speaking, TSH level and anti-TPO prevalence are higher in women and increase with age [18].

The American NANHES III study reported TSH level according to age. Low and median values differed little between elderly and younger subjects, whereas the upper value was more difficult to determine in the elderly due to a rightward skew in the TSH distribution. These data have been confirmed on other cohorts in different regions of the world (Australia, Japan, Europe) [26–28], while others do not find an increase in TSH level with age [10,29]. Some have even shown that TSH level decreases with age [30].

Longitudinal studies [7] found that individual TSH level increased more strongly when low at initial assessment, without change in FT4, indicating less bioactive TSH molecule or a change in TSH/T4l set point: subjects with slightly higher initial TSH showed less increase over 13 years' follow-up.

From all these studies, covering large cohorts, we realize that the adoption of universal reference values to be used in the elderly is not possible at the present time. Many advocate the use of values adapted to elderly subjects [31], but studies carried out on cohorts representative of a state or a region of the world are rarely transposable and therefore usable on the scale of a doctor or from a patient from another country. This is why the TSH values of older subjects are still very widely interpreted using the commonly accepted values of 0.4 to 4.0 mIU/L as the reference interval.

7.1. How can reference values be determined?

TSH reference values, according to the American National Academy of Clinical Biochemistry (NACB), should be determined from samples of "euthyroid" out-patients without anti-TPO antibodies, personal or familial history of thyroid dysfunction or visible goiter. After normalization using various mathematical models [32], lower and upper limits are calculated from the 2.5 and 97.5 percentiles so as to have a range including 95% of normal subjects. The TSH values will not show a normal distribution, even after logarithmic transformation, as the curve is skewed rightward (toward higher values), perhaps corresponding to occult hypothyroid patients (without anti-TPO antibodies) [33].

Takeda et al. tested various methods for calculating reference values without prior selection of healthy controls, which is required by the NACB but unfeasible in everyday practice and unrepresentative when particular age groups are the focus [34]. They concluded that the reference range suited to Japan is wider than for the USA and that calculation using classical rejection rules regardless of presence of anti-TPO antibodies provides the same results in a large cohort as studies selecting only patients free of thyroid autoimmunity. Applying various mathematical models of normalization to TSH values for a patient cohort, Strich showed that the upper and lower TSH limits varied widely depending on the model, unlike the FT4 range [32]. TSH probably has physiological variations that cannot be modeled [32], revealing wide inter-individual differences in the FT4/TSH relation. This argues for individualizing rather than normalizing reference values.

These mathematical constraints added to the difficulty of recruiting sufficiently large cohorts representative of all the age groups studied make it impossible to achieve reference values within a laboratory when all the recommendations suggest the opposite.

7.2. Uncertainty

Like any other biochemical parameter, TSH is subject to both analytic and biological variation, which must be fully taken into account, as TSH level is interpreted in terms of threshold values.

The analytical variability is linked to a measurement uncertainty, which reflects the dispersion of the values that can be observed between the different assays implemented and also the intra-laboratory differences, from day to day or from batch to batch. This measurement uncertainty is the quantification of the doubt linked to the measurement, or rather of "guarantee" that the result is well understood within the proposed range. This analytical variability is relatively well mastered for TSH and the re-harmonization work in progress of the International Federation of Clinical Chemistry, which aims to harmonize the reagents of the different suppliers with each other, will further reduce it [35].

TSH is also subject to inherent individual biological variation. Repeated measures taken in the same subjects over 1 year's follow-up showed scatter that was sometimes wider than the reference range [36,37]. Circadian variation is also well described, with a stronger nocturnal peak in men.

Sleep deprivation considerably increases TSH levels in the acute phase [38]. Many treatments directly impact TSH level: amiodarone, lithium, corticosteroids, metoclopramide, amphetamines, dobutamine, dopamine and, more rarely, somatostatin receptor ligands. It is worth bearing in mind that, so far as possible, TSH assay should be performed only at an interval after treatment of acute pathology. This intra-subject variability argues for repeating assay when the TSH values fall outside the reference range.

Individual TSH levels, in the light of the above variations, nevertheless do not show variation greater than the reference range, which corresponds to inter-individual variability. The reference values concern a population, not an individual [24], and are thus unsuited to monitoring an individual over time [37]; rather, repeated checks are needed, with the subject serving as his/her own control. Individual pathological variation can be masked using reference values adapted for a population but too wide for following

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individual variation. A difference in TSH levels between two assays should only be considered clinically significant if it exceeds 40% [36].

7.3. Classical interferences in TSH assay

In elderly subjects, "classical" immune analysis interferences are liable to be found in TSH assay: interfering antibodies, macro-TSH, and drug-related interference [39].

In elderly subjects, TSH molecule may show impaired biological activity [40] despite conserved immune activity (biologically inactive isoforms recognized on immune-assay). In such situations, TSH elevation without increased FT4/FT3 ratio may indicate decreased TSH activity [41]. In the view of some authors, the issue of subclinical hypothyroidism cannot be settled so long as TSH assay continues to recognize these less bioactive forms [41].

There are also many iatrogenic causes of interference in thyroid diseases and thyroid function work-up: history of radioactive iodine treatment or cervical radiation therapy, and certain drugs such as amiodarone. Elderly patients are also often poly-medicated, and their prescriptions need to be studied attentively to identify molecules liable to disturb thyroid function assessment.

7.4. Summary

TSH remains the parameter to be measured to explore primary thyroid dysfunctions in the elderly.

The low value to be used is not modified compared to younger individuals (0.4 mIU/L).

The high value of the reference interval can be modified given the shoulder on the right of the distribution of TSH levels in the population.

> Guideline 3.1. The lower limit of normal for TSH assay is usually 0.4 mIU/L. This threshold is relatively unaffected by age. (Grade 2+)

For the upper limit, the TSH distribution is skewed rightward, and no universal threshold can be set. Given the above-mentioned reservations, we propose a pragmatic solution: for over-60 year-old patients, the upper limit of normal is the patient's age (decade) divided by 10: e.g., TSH $\leq$ 7 for a 70 year-old, or $\leq$ 8 mIU/L for an 80 year-old patient.

> Guideline 3.2. The upper threshold of the TSH reference interval increases with age. For reasons of simplicity, it is recommended to use from the age of 60 years as a reference in clinical practice the value of the decade of the patient's age divided by 10 (ex: TSH $\leq$ 8 mIU/L for an over 80-years old patient). (G2 +)

8. Q.4. What to do in front of a low TSH?

A low TSH value should always be checked in light of the many circumstances that may influence the concentration of TSH level. The time limit for carrying out this check depends on the clinical situation. The measurement of TSH level in patients hospitalized for an acute condition should probably be avoided in the absence of clinical evidence clearly suggesting thyroid dysfunction. In the vast majority of patients, these TSH values moderately decreased in the acute phase will normalize after a few days to a few weeks. If there is a suspicion of thyrotoxicosis, the diagnosis of which would modify the management of the patient (presence of atrial fibrillation AF), the control can be done within 48 hours by combining a dosage of free T4 and if necessary free T3. In the other cases, the control of TSH is advised a few days to a few weeks after resolution of the acute intercurrent problem.

> Guideline 4.1. Low TSH should be systematically controlled except in the context of clinical emergency. (Grade 1++)

The inter-assay interval depends on the clinical situation, initial TSH value and cardiovascular context.

> Guideline 4.2. If TSH > 0.1 mIU/L, TSH monitoring alone is recommended. Below 0.1 mIU/L, a TSH control must be carried out by associating the free T4 assay, and if free T4 is normal, that of free T3. (G2 +)

Free T3 concentration should be interpreted in the light of the clinical context and ongoing medication.

8.1. Q.4.3. What procedure if TSH level later normalizes?

There are no data on follow-up after transient TSH decrease in the acute phase. Apart from the context of iodized contrast medium administration (cf. Guideline 4.8.4), such decrease is not predictive of subsequent thyroid dysfunction, and we do not recommend systematic monitoring in these patients.

> Guideline 4.4. There is no need for systematic control of TSH in the absence of clinical signs. (Grade 1++)

Very few patients with isolated TSH decrease go on to develop hyperthyroidism within 5 years, and most recover a normal thyroid profile.

In case of TSH decrease after iodine overload, any further iodine injection requires control of thyroid function test (cf. Guideline 4.8.2).

8.2. Q.4.5. What complementary examinations are needed in case of confirmed thyrotoxicosis?

Thyrotoxicosis is defined as the clinical and biological consequences of an excess of thyroid hormones at the tissue level. The term hyperthyroidism is reserved for situations of hyperfunction of the thyroid gland. In the elderly, the most common cause of thyrotoxicosis is an overdose of levothyroxine.

The main etiologies of hyperthyroidism in the elderly are the same as in the young, but with a different distribution in terms of frequency. Toxic multi-nodular goiter (GMNT) becomes the number one cause, followed by toxic adenoma (TA) and then Graves' disease. If the etiological assessment is strongly recommended in the young patient presenting a hyperthyroidism [42] because likely to modify the therapeutic choices, this is much more discussed in the old patient. Indeed, "radical" treatments are indicated in the case of autonomous hyperthyroidism (GMNT, AT) in order to ensure a definitive cure, at the cost of an assumed risk of hypothyroidism. In Graves' disease of the elderly, the treatment proposed in younger subjects (synthetic antithyroid drugs for 12 to 18 months) is considered by many experts to be unsuitable.

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Guideline 4.5.1. Etiological assessment depends on the clinical context and treatment objectives, but in most elderly patients treatment options are relatively unaffected by the etiology of the hyperthyroidism. Work-up in first line comprises thyroid scintigraphy (Tc99 or I-123 as available) to provide etiologic and pre-treatment data (Grade 2+). It should not postpone treatment initiation.

Guideline 4.5.2. The usefulness of anti-TSH receptor antibody assay is to be assessed according to context and the likelihood of Graves' disease. (Grade 2+)

Guideline 4.5.3. Thyroid ultrasound should not be performed as a first line because it does not provide information on the etiology of hyperthyroidism and exposes to the risk of overdiagnosis of thyroid nodules. It must be reserved for specific situations: anomalies of the cervical palpation, pre-therapeutic evaluation (in particular before radioactive iodine treatment), or amiodarone-associated thyrotoxicosis. (G2+)

8.3. Q.4.6. What specificities of hyperthyroidism treatment and follow-up in the elderly?

Autonomous pathology (TMNG, TA) is more frequent than Graves' disease [43] especially in iodine-deficient regions.

In the elderly hyperthyroidism is often accompanied by an increased risk of supraventricular rhythm disturbances and heart failure [44,45], definitive treatment is generally preferred, in particular radioactive iodine therapy (I-131) if there is no contraindication.

Guideline 4.6.1. In elderly subjects with permanent atrial fibrillation, tachy-arrhythmia, ischemic cardiopathy or risk of acute coronary syndrome, or with cardiovascular symptomatology triggered or aggravated by their hyperthyroidism, the objective is definitive treatment, with iodine^{131} ablation in first line after medical control of thyrotoxicosis (synthetic antithyroid drugs). (Grade 2++)

The guidelines of the European and American Thyroid Associations (ETA, ATA) for the management of hyperthyroidism in elderly patients advocate ablative treatment, either by surgery or by iodine^{131} [46,47], the latter being preferable for autonomous thyroid nodules (TMNG, TA).

In the elderly, primary thyrotoxicosis treatment, before undertaking any radical treatment is the same as in younger patients: antithyroid drugs associated to beta-blockers, unless contraindicated, notably for cardiovascular reasons.

The advantage of iodine^{131} therapy in TMNG lies in reducing thyroid volume by up to 40% within one year, with a 10–20% risk of hypothyroidism [48].

The risk of definitive hypothyroidism after iodine^{131} treatment ranges between 4% and 82% depending on the reports, the differences seeming to relate especially to the etiology of the hyperthyroidism and to duration of follow-up. Ceccarelli et al. [49], in a retrospective analysis of clinical outcome in 346 patients receiving iodine^{131} treatment, found that hypothyroidism was confirmed in 60% of patients 20 years after treatment for toxic nodule. Another retrospective study with a long follow-up of patients with hyperthyroidism treated with I-131 showed that hypothyroidism can be observed in the first year in at least a quarter of patients with Graves' disease and 4% of patients with GMNT, and can go up to 82% in Graves' disease and 32% in GMNT at 20 years post-treatment [50].

Other risk factors for post-iodine^{131} hypothyroidism were suggested by other studies: patient age, thyroid or nodule size (small glands showing greater risk), and level of iodine^{131} fixation and uptake [51].

Pre-treatment with antithyroid drugs and presence of thyroid autoimmunity are also factors for onset of hypothyroidism according to a retrospective analysis of 105 patients with autonomous nodules treated by iodine^{131} [52].

Guideline 4.6.2. In fragile patients without serious cardiovascular pathology with moderate hyperthyroidism and contraindications to total thyroidectomy or if iodine^{131} is unavailable, long-course low-dose antithyroid drugs may be used. (Grade 2++)

Guideline 4.6.3. In the absence of contraindications, total thyroidectomy is indicated in case of large goiter, signs of compression and/or thyroid cancer. (Grade 1++)

In over-65 year-old patients with large multi-nodular goiter (> 40–60 mL) and TSH < 0.4 mIU/L, radical treatment such as total thyroidectomy is recommended in the absence of major cardiovascular risk factors, as iodine^{131} was reported to be ineffective in some retrospective studies [53,54]. If surgery is contraindicated, repeated low-dose iodine^{131} therapy can restore euthyroidism and reduce goiter volume (by 40% in 6–12 months) [53,55,56].

Surgery is also indicated in some other situations: thyroid cancer, primary hyperparathyroidism [47,57].

8.4. Q.4.7. What procedure in case of persistent low TSH with normal FT4?

This situation corresponds to subclinical hyperthyroidism. In the literature, TSH level normalizes at a variable delay of months to years, and progression to proven or clinical thyrotoxicosis is rare [58,59]. There is, however, a notable risk of cardiovascular complications with atrial fibrillation.

Guideline 4.7.1. A durably low TSH level with normal free T4 and free T3 justifies an endocrinologic opinion. (G1 ++) (Grade 1++)

Guideline 4.7.2. When TSH is low with normal free T4 and free T3, thyroid scintigraphy is recommended to identify autonomisation (AT, GMNT) as well as an assessment of comorbidities and risk factors for complications, in particular cardiovascular and bone complications. (G2 +)

In the absence of evidence from randomized trials, management is based on expert consensus. The aim is more to prevent complications such as atrial fibrillation (AF) than to treat the disease itself: a large majority of patients are asymptomatic, and their biological abnormality is revealed fortuitously.

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8.5. Q.4.8. Should subclinical hyperthyroidism in the elderly be treated?

Decision factors to treat or not to treat comprise: patient age, etiology of hyperthyroidism, TSH level (< or > 0.1 mIU/L), and risk of complications (notably AF). The international guidelines (ETA, ATA) are not fully concordant: roughly, the ETA recommends treating all "older" subjects (> 65 years) [46], while the ATA recommends treating all over-65 year-old patients with TSH < 0.1 mIU/L [47]; for those with moderately decreased TSH (0.1–0.4 mIU/L), treatment is indicated in case of osteoporosis, atrial fibrillation or cardiopathy.

In the absence of interventional studies assessing the risk/benefit ratio, and taking account of:

- the lack of evidence that treating subclinical hyperthyroidism significantly reduces the risk of AF;
- the risk of definitive hypothyroidism following treatment for hyperthyroidism;
- several reports that achieving balance in levothyroxine substitutive treatment is difficult in the elderly, with high frequencies of low or high TSH levels [60–62], we recommend a cautious attitude weighing risk and benefit for each patient.

Guideline 4.8.1. The decision between treatment and surveillance for subclinical hyperthyroidism is to be discussed with the individual patient and/or family, taking account of expected benefit (reduced risk of AF) and possible risk (onset of definitive hypothyroidism).

Advanced age, the degree of decrease in TSH (with an arbitrary threshold generally set at 0.1 mIU/L), the etiology of hyperthyroidism (autonomous pathologies have a higher risk of developing over or clinical thyrotoxicosis) and the field (existence of heart disease or osteoporosis) are elements that encourage the choice of treatment. Their absence prompts discussion of regular monitoring with the patient. (G2 +)

Guideline 4.8.2. When a treatment has been chosen, modalities are the same as for clinical hyperthyroidism. (Grade 2++)

Guideline 4.8.3. If surveillance without treatment is chosen, it is based on TSH and free T4 monitoring (plus free T3 if free T4 is normal) at 3 months then every 6 months, without limit. A clinical check-up should also be made, notably to ensure maintained sinus rhythm. (Grade 2+)

In elderly patients with goiter, that is usually nodular [63], or with history of thyroid dysfunctions following iodized contrast medium injections, there is proven risk of either thyrotoxicosis or of hyperthyroidism.

The data available in the literature do not allow the recommendation of a specific validated regimen for the prevention of an iodine overload induced by iodinated contrast media. A single prospective randomized study has shown the advantage of prevention either by antithyroid drug or by sodium perchlorate [64], which would allow rapid urinary elimination of excess iodine and avoid overloaded iodine.

A treatment of a few days framing the radiological examination with antithyroid drug or sodium perchlorate (if available), could be used with empirical dosages and durations (according to the Société française d'endocrinologie–Groupe de recherche en thyroïde–Société française de radiologie 2010 recommendations concerning administration of iodinated contrast agents in case of thyroid pathology). A check of thyroid function a few weeks after the examination is justified. If there is a foreseeable need for repeated administrations of iodized products (oncology monitoring for example), and if the risk of thyrotoxicosis is considered significant, ablative treatment with iodine 131 (at a distance from the injection of iodinated contrast agents) can be discussed.

Guideline 4.8.4. In case of thyroid pathology, and notably multi-nodular goiter, and especially if TSH level is transiently low, prophylactic treatment may be implemented around iodized contrast medium administration. (Grade 2+)

Amiodarone treatment for thyroid dysfunctions was the focus of very recent European Thyroid Association guidelines [65]. This will not be reviewed here, as patient age does not affect diagnosis or treatment.

Guideline 4.8.5. Amiodarone is a frequent cause of thyrotoxicosis or hypothyroidism in the elderly. Treatment does not differ from that in younger patients (Grade 2++). However, given the potential severity of thyrotoxicosis and the complexity of management, an endocrinologic opinion is indispensable. (Grade 2+++)

9. Q5. What procedure in TSH elevation in the elderly?

9.1. Q.5.1. What diagnostic attitude in case of elevated TSH?

9.1.1. The prevalence of hypothyroidism

The prevalence of hypothyroidism depends on the populations studied and the diagnostic criteria [18,66,67,60,68]. In the Framingham study, the prevalence of hypothyroidism (TSH > 10 mU/L) was 4.4% (5.9% in women, 2.3% in men) in those over 60 years of age [66]. Most often found in subjects over 60 years: 0.5 to 5% of clinical hypothyroidism and up to 15% of subclinical hypothyroidism, especially in Caucasian women and in case of significant iodine intake [69].

9.1.2. Clinical diagnosis of hypothyroidism

Clinical diagnosis of hypothyroidism in the elderly is difficult, due to similarities with simple aging and frequent non-specific or atypical manifestations, and possible comorbidities [70–72]. The diagnosis can be mentioned when the patients present [73,74,4]:

- general signs: asthenia, muscle cramps or myalgia, weight gain, cold intolerance, acquired constipation, hoarseness, alopecia and dryness of the skin;
- other manifestations can be predominantly diastolic hypertension, discomfort, cerebellar disorders, carpal tunnel syndrome or arthromyalgia;
- neuropsychological signs include slow ideation, concentration disorders, somnolence, memory disorders, depressive syndrome or signs of dementia, impaired quality of life, and cognitive impairment;

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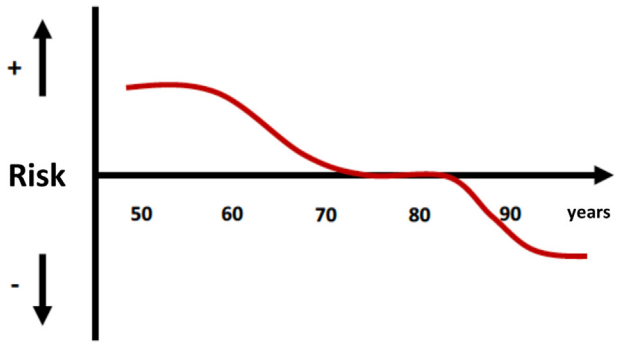

Fig. 1. Possible relation between age and cardiovascular risk in subclinical hypothyroidism [74].

- biological signs include macrocytic anemia, hypercholesterolemia and increased creatinemia [75].

Onset or recent aggravation of these signs should suggest hypothyroidism [75]. Signs are weaker and less frequent in over-60 year-old patients [4,76]. Clinical signs increase with increasing TSH levels [76]. Symptoms may regress when euthyroid status is restored with levothyroxine replacement therapy.

9.1.3. Complications of hypothyroidism in the elderly

As clinical hypothyroidism is systematically treated when diagnosed, observational studies focused on complications in subclinical hypothyroidism.

9.1.3.1. Cardiovascular disorders. In the elderly, the cardiovascular impact of subclinical hypothyroidism is complicated by the cardiovascular risk factors and comorbidities associated with aging [77,78], making interpretation of epidemiological series controversial [79].

Clinical thyroid failure is a classic risk factor for coronaropathy. Hypothyroidism is associated with cardiovascular alterations, the best known of which is elevation of circulating total and LDL cholesterol [60], increasing the risk of coronary atherosclerosis [80,81]. Changes in intracellular calcium metabolism combined with endothelial dysfunction account for increased arterial rigidity and peripheral arterial resistance and onset of diastolic and then systolic dysfunction, aggravating the cardiovascular risk associated with clinical hypothyroidism [57]. A cardiovascular impact of subclinical hypothyroidism, especially in the elderly, on the other hand, remain to be demonstrated.

Several meta-analyses reported significant but slight increase in risk of ischemic cardiopathy and cardiovascular mortality in subclinical hypothyroidism [82,83], although this is not found in studies focusing on over-65 year-old patients. A study of over-85 year-old patients suggested lower cardiovascular mortality in case of subclinical hypothyroidism [12]. These findings suggest that the cardiovascular risk associated with subclinical hypothyroidism decreases with age (Fig. 1). The most recent and largest meta-analysis in the field, with more than 55,000 subjects including almost 3500 with subclinical hypothyroidism, found no greater cardiovascular risk in the latter except in case of TSH > 7 mIU/L [84]. This increased risk was not analyzed according to age, but previous studies reported an association between TSH elevation and cardiovascular risk (atheroma) in over-65 year-old patients [85,86].

Several interventional studies assessed the impact of levothyroxine treatment in subclinical hypothyroidism, and reported improvement in lipid profile and other cardiac functional parameters [57]. However, these biological effects did not reduce intima-media or plaque thickness [87]. Finally, the benefit of levothyroxine therapy in reducing the rate of cardiovascular events applies only to under-70 year-old subjects, disappearing thereafter [88]. The TRUST study randomized more than 70 patients aged over 65 years presenting subclinical hypothyroidism (TSH = 6.4 ± 2.0 mIU/L) and found no benefit of levothyroxine replacement therapy over placebo in terms of cardiovascular event rate [89].

There is no present evidence in favor of levothyroxine replacement therapy to prevent cardiovascular events in subclinical hypothyroidism, probably because the TSH threshold for expected benefit in elderly patients needs to be progressively increased with age. Even so, risk factors such as high blood pressure, type 2 diabetes and dyslipidemia should be managed according to the thresholds set in the European Society of Cardiology guidelines, taking account of adaptation for advanced age (> 85 years) [90].

9.1.3.2. Cognitive disorders. Clinical or over hypothyroidism is classically associated with intellectual slowness and is thus a recognized reversible cause of secondary dementia, requiring screening and systematic treatment in any assessment of recent acquired cognitive disorder.

In subclinical hypothyroidism, data are less clear: an American case-control study reported extra risk of dementia [91], but subsequent reports were contradictory [92–94].

A recent meta-analysis [95] included seven prospective studies (7401 patients) on the cognitive impact of subclinical hypothyroidism and found no extra risk of dementia compared to euthyroid patients; cognitive decline on the Mini Mental State Examination was not significantly greater over a mean study period of 32 months.

Unexpectedly, a recent prospective cohort study of 9446 patients with a mean age of 65 years at inclusion, assessed over an 8-year period [96], found lower dementia risk with higher TSH level (whether in the normal range or above the upper limit), with higher values associated with better overall cognitive performance scores. Another cohort study with 2558 patients during 9 years' follow-up found no significant association [97].

9.1.3.3. Depression. Clinical hypothyroidism can induce mood disorders and depression syndrome that can mimic melancholic depression in case of severe hypothyroidism [98,99]. Such impact is major in the elderly, notably due to associated social isolation.

For subclinical hypothyroidism, there is no evidence of increased risk of depression:

- a transversal study of 5865 over-65 year-old patients in the United Kingdom [100], including 168 patients with subclinical hypothyroidism, found no association between subclinical hypothyroidism and anxiety/depression;
- a study [12] of 599 over-85 year-old patients in the Netherlands, including 30 patients with subclinical and 37 others with clinical hypothyroidism, at a mean 3.7 years' follow-up, found no association between depressive symptoms and high TSH levels;
- a recent cohort study on 503 subjects with a mean age of 70 years in the Netherlands found no association between TSH level at the upper limit of the normal range and more frequent depression [101].

9.1.3.4. Bone risks. Clinical hypothyroidism decreases bone remodeling, with reduced osteoblastic bone formation and osteoclastic resorption, affecting cortical more than trabecular bone [102]. However, such very slow changes in patients in whom treatment is indicated have been rarely studied [103–105].

Concerning subclinical hypothyroidism:

- a recent meta-analysis [106] covering more than 70,000 patients focused on the bone impact of subclinical thyroid dysfunctions,

there was no increased risk of fracture associated with subclinical hypothyroidism. Subgroup analysis by age found no increased risk of hip fracture in the 897 over-75 year-old patients with subclinical hypothyroidism, and likewise in the 520 patients assessed for all risks of fracture;
- another recent meta-analysis [107] focused on the impact of subclinical hypothyroidism on bone mineral density: in 5458 patients with a median age of 72 years, including 451 patients with subclinical hypothyroidism, there was no association between subclinical hypothyroidism and bone loss, whatever the site.

9.1.3.5. Mortality. Gussekloo et al., reporting a cohort of 599 over-85 year-old patients, showed that high TSH level was associated with longer life expectancy [12].

These findings were not replicated in the meta-analysis by Rodondi, with 2345 over-80 year-old subjects, including 228 patients with subclinical hypothyroidism, and no association emerged between subclinical hypothyroidism and mortality for whatever cause [86]; there was likewise no significant association in the 16,785 65–79 year-old patients, including 1636 with subclinical hypothyroidism, although there was increased risk of cardiovascular mortality.

The Chianti Area Study [108] also found no association between subclinical hypothyroidism and all-cause mortality in over-65 year-old patients, while higher TSH level was associated with lower overall mortality in euthyroid subjects.

Atzmon et al., reporting an exceptionally long-lived Ashkenazi population, found significantly higher TSH levels in a group with median age 98-years compared to the group with median age 72 years or a control group of Americans with a median age of 68 years [109]. Jansen reported that relatives of centenarians had higher TSH levels than controls [110].

9.1.3.6. Briefly. No increased cardiovascular, musculoskeletal or neurocognitive risks in elderly subjects with TSH < 7 mIU/L [111].

No proven extra all-cause mortality, or possibly even increased life expectancy, in elderly subjects with subclinical hypothyroidism.

9.1.4. Biological diagnosis of hypothyroidism in the elderly

The diagnosis of hypothyroidism is difficult based on clinical symptoms or signs alone. Elevation of TSH is often the only way to diagnose it [66] with normal free T4 (subclinical hypothyroidism) or low free T4 (over or clinical hypothyroidism).

The presence of symptoms or clinical signs guides the hormonal diagnosis of thyroid dysfunction [112]. Given the high frequency of thyroid dysfunctions and the impossibility of confirming the diagnosis without hormonal analysis, several recommendations recommend a systematic dosage of TSH level after a certain age [113–115]. The group, like others [116], does not recommend routine screening for hypothyroidism in the elderly.

The differential diagnosis of elevated TSH in the elderly must take into account many factors [117]:

- the physiological increase in TSH concentration with age;
- the evolution of functional thyroid parameters after certain serious non-thyroid conditions;
- the temporary increase in TSH level after an injection of iodine-based contrast media, unrelated to an underlying thyroid disease;
- the presence of heterophilic anti-TSH antibodies, of macro-TSH.

Autoimmune thyroiditis is the main cause of hypothyroidism in the elderly. Antithyroid peroxidase (TPO) antibodies are the most frequent serum markers of thyroid autoimmunity, but their prevalence increases with age: the American NHANES III cohort showed 20–23% prevalence in over-60 year-olds patients: 11–13% in men and 27–30% in women, versus 1.7–2.1% and 18–21% respectively in 40–60 year-old patients [18]. In the Whickham cohort [67] at 20 years' follow-up, 55% of patients with high TSH level and positive antithyroid antibodies developed hypothyroidism, versus 33% in case of high TSH level without antithyroid antibodies.

Examination should screen for history of thyroid disease (Hashimoto thyroiditis, insufficient levothyroxine replacement treatment, prior iodine^{131} therapy, history of Graves' disease, history of thyroidectomy) and of certain drugs (lithium, amiodarone, tyrosine kinase inhibitors).

> Guideline 5.1. All high TSH levels should be controlled: within the month in case of clinical signs, and within 3 months in the absence of symptoms or if the TSH level is < 10 mIU/L. (Grade 2+)

9.2. Q.5.2. What examinations are mandatory or contributive in case of high TSH level (checked on repeat assays)?

On the practical level, no additional examination modifies the management of elderly patients with a high TSH level, in particular: the search for antithyroid antibodies, the free T4 assay, the serum lipid profile, thyroid ultrasound (except abnormality of cervical palpation). These examinations are unnecessary and are not recommended in practice in the elderly with hypothyroidism.

> Guideline 5.2. No complementary examinations are needed in case of high TSH level in the elderly (Grade 2+)

Many factors and circumstances can transiently disturb thyroid function tests, and high TSH level should be checked before diagnosing primary thyroid failure [118,119].

Several older studies, with relatively small samples, reported that TSH level normalized over time in more than half of patients diagnosed with subclinical hypothyroidism with moderate high TSH [59,120,121]. Risk of progression to clinical hypothyroidism is greater when baseline TSH level is higher and antithyroid antibody screening is positive [122].

9.3. Q.5.3. What are the indications for treating hypothyroidism?

Thyroid hormone replacement should be implemented for clinical hypothyroidism with high TSH and low free T4 concentrations. Although formal or definitive proof is lacking, the present group recommends levothyroxine replacement therapy when TSH is > 20 IU/L in two controls. In the absence of proven benefit [89,121], given the risk of iatrogenic thyrotoxicosis [60–62], the group advises against treatment when TSH level is < 10 mIU/L on several successive controls. When TSH is in the range of 10–20 mIU/L, treatment should be considered on a case-by-case basis with the patient and family, depending on context, comorbidities, clinical signs, expected benefit, baseline TSH level and progression over successive controls.

9.4. Q.5.4. What are the follow-up modalities for hypothyroidism in the elderly?

In the elderly, the treatment of hypothyroidism is based on levothyroxine. The combination of triiothyronine (T3) with

Guideline 5.3.0. Levothyroxine therapy should be initiated only when hypothyroidism is diagnosed by high TSH level confirmed on two controls. (Grade 2+++)

Guideline 5.3.1. Levothyroxine replacement therapy is indicated in case of TSH > 20 mIU/L in at least two controls. (Grade 2+)

Guideline 5.3.2. There is no evidence of favorable risk/benefit ratio for replacement therapy in case of TSH < 10 mIU/L. (Grade 2+)

Guideline 5.3.3. In patients with TSH level between 10 and 20 mIU/L on several controls, levothyroxine replacement therapy should be considered on a case-by-case basis, taking account of the patient's wishes, expected benefit and TSH level progression. (Grade 2+)

levothyroxine is debated, and given the lack of evidence of superior efficacy, such use is not recommended in the more frail elderly, particularly in cardiac terms. In a patient already treated previously by a levothyroxine + T3 combination, the advancement of age must lead to questioning a therapy containing T3 in favor of a substitution with levothyroxine alone.

Levothyroxine is usually administered in tablets, although a drop form is also available, which some authors recommend for fragile elderly patients as it allows more progressive dose adjustment [123]. The procedure depends on clinical habits, and there are no risk/benefit studies comparing the two presentations. Apart from the uncertainty regarding daily dose, administration by drops can lead to medication error and is not to be considered in the elderly unless prepared and delivered by a third party. In patients with psychological disorders precluding reliable daily intake, twice weekly or weekly administration in a health center or at home under supervision can be considered [124]. Injectable forms of levothyroxine are indicated only in emergency for myxedema coma or in patients hospitalized in gastroenterology or visceral surgery.

The usual attitude consists in an initial 0.25 or 0.5 μg/kg/day dose (12.5–25 μg/day). Under clinical and especially cardiovascular surveillance, the daily dose is increased by 12.5–25 μg every 4–6 weeks until normal thyroid function is achieved. Alternatively, the replacement dose of 1.1–1.3 μg/kg/day may be administered at the beginning [125]; normal thyroid function was achieved more quickly (13–19 weeks), with comparable results in terms of symptomatology and quality of life, without side-effects (notably cardiovascular). In Ross's study, patients were selected based on normal baseline stress test or stress echocardiogram [125].

Unstable coronary failure may require more progressive increment. In 1980, Levine, in 51 patients with coronary failure aged 33–88 years (median age 72 years), normal thyroid function is obtained in only 40% of patients, due to angina pectoris episodes on introducing or increasing levothyroxine treatment [126]. Associating beta-blockers made no significant difference. These older findings would be worth updating, as intraluminal revascularization is frequently performed in elderly patients.

In elderly, various factors can impact levothyroxine therapy, requiring dose adjustment [119]:

- in case of impaired endogenous metabolic clearance, the initial dose on diagnosis of hypothyroidism should be about 20 micrograms lower, and the replacement dose about 40 micrograms lower than in young or middle-aged patients [127,128];
- decreased lean mass is a major factor for decreasing levothyroxine requirement with aging [129], malnutrition being common in the elderly and a cause of frailty;
- reduced digestive absorption of levothyroxine: according to Hays [130,131], levothyroxine absorption (in the absence of drug interaction or digestive disorders) decreases by about 10% after the age of 70 years: 62.8 ± 13.5% for > 70 years versus 69.3 ± 11.9% for 20–70 years ($P < 0.001$);
- abnormal absorption is frequently induced by medical treatments and gastro-intestinal pathologies;
- poly-medication (calcium or iron supplementation, proton pump inhibitors) is frequent in the elderly, due to the prevalence of chronic diseases [132];
- etiology of primary thyroid failure: levothyroxine dose decreases over time for hypothyroidism secondary to autoimmune thyroiditis or total thyroidectomy, increases for hypothyroidism secondary to iodine^{131} treatment, and is stable for iatrogenic hypothyroidism [132];
- in case of difficulty taking levothyroxine 30 to 60 minutes before breakfast or away from other treatments, it is possible in the evening 2 to 4 hours after the last meal.

Overall, in elderly patients, the replacement dose of levothyroxine needed to achieve normal thyroid function depends on physiological factors, concomitant treatments and progression of thyroid disease.

Guideline 5.4.1. Treatment is based on levothyroxine at a replacement dose of 1.1–1.3 μg/kg/day. (Grade 2+)

Guideline 5.4.2. There are no indication for associating levothyroxine (T4) + liothyronine (T3). (Grade 2+++)

Guideline 5.4.3. Levothyroxine should be introduced progressively, especially if TSH level is markedly elevated and the patient's cardiovascular status is unknown. (Grade 1+++)

Monitoring of levothyroxine replacement therapy in patients with peripheral thyroid insufficiency is based on the determination of TSH level (and not on free T4 assay, to be considered in the event of central hypothyroidism). When the replacement dose is obtained, it is advisable to check the concentration of TSH level 3 to 6 months later and then once a year if the elderly person's condition is stable.

On the other hand, there is no consensus established for the definition of the interval of "normality" of TSH in the elderly and treated patient. We can consider obtaining a TSH level in the standards for the dosing method used (1 to 4 mIU/L) [133] but it seems more logical to recommend a higher TSH value adapted to age, in particular in very old patients (age divided by 10). On the other hand, for all patients, it is advisable to maintain the TSH above 1 mIU/L to prevent the risk of thyrotoxicosis; 20% in the Colorado Thyroid Disease [60], 50% in the Mammen study [62], which is all the more frequent as older patients lose weight, with cardiac and bone consequences. These same patients found it difficult to understand a decrease in treatment dose with advancing age. This decrease is then perceived as being able to deteriorate their clinical situation. This need for "supervision" of the elderly during the treatment of thyroid insufficiency is advocated by several authors [134,135].

And lastly, any change during levothyroxine treatment in elderly patients, TSH level should be assayed 6–8 weeks after any modification.

10. Q.6. Can levothyroxine therapy be withdrawn?

Hypothyroidism is usually definitive. In the elderly, some patients have often been taking levothyroxine for many years, frequently at low doses, and the initial reasons for prescription may be unknown. It may sometimes be justifiable to try reducing and

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Guideline 5.4.4. Surveillance of levothyroxine treatment for primary thyroid failure is based on TSH level alone. Assays should be conducted between 6 weeks and 3 months after achieving replacement dose or any dose adaptation. (Grade 1+++)

Guideline 5.4.5. The treatment objective is to have TSH level within the normal-for-age range (cf. Guideline 3.2), avoiding risk of overdose if TSH < 1 mIU/L; e.g., the upper limit of normal is 7 mIU/L for 70–79 years and 8 mIU/L for > 80 years. (Grade 2+)

Guideline 5.4.6. Once normal thyroid function is achieved, annual checks are sufficient. (Grade 2+)

Guideline 5.4.7. When a treatment known to impact levothyroxine bioavailability is introduced or withdraw, TSH level should be checked 6–8 weeks later. (Grade 2++)

Guideline 5.4.8. If levothyroxine therapy is not indicated, TSH level should be assayed every 6 months for 2 years to assess the kinetics of progression. If TSH level is stable, annual checks are sufficient. (Grade 2+)

withdrawing a non-beneficial treatment, although obviously making sure that there was no formal indication (total thyroidectomy, previous iodine^{131} therapy, proven autoimmune hypothyroidism), informing the patient and securing consent. Treatment may then be withdrawn, but a TSH assay should be check at 4–6 weeks.

Guideline 6. If the indication for levothyroxine therapy is not clear, withdrawal may be attempted, with the patient's consent with TSH check at 4–6 weeks. (Grade 2+)

11. Q.7. When should an endocrinologic opinion be sought?

In case of thyroid dysfunctions in an elderly patient, whether endocrinologic opinion should be sought depends on the context and is at the physician's discretion. Given the possible complexity of situations and treatment considerations, the present group recommends endocrinologic opinion for all patients with prolonged low TSH level. Endocrinologic opinion should also be sought in the following situations:

- at diagnosis:
  - signs of severity (coronary context, auto-immune polyendocrinopathy, profound hypothyroidism, myxedema coma, etc.),
  - discordance between clinical and biological findings,
  - according to etiology: iatrogenic, central hypothyroidism,
  - discussion of treatment objectives;
- during levothyroxine therapy:
  - doubt regarding treatment objectives,
  - difficulty in interpreting results (central hypothyroidism),
  - onset of symptoms with severity,
  - lack of improvement (treatment resistance, drug interactions, malabsorption, poor adherence, etc.),
  - poor tolerance,
  - need to change formulation (e.g., impossibility of oral administration).

Guideline 7. Endocrinologic opinion should be sought in proven hyperthyroidism or persistent low THS level. (Grade 2++)

Disclosure of interest

J. Abeillon: HAC, Sanofi, Uni-pharma.
A. Cailleux: Sanofi, HAC.
P. Caron: Merck-Serono, HAC, Genevrier, Uni-pharma.
B. Goichot: Merck-Serono, Uni-pharma, HAC.
L. Groussin: Merck-Serono, HAC.
G. Kaltenbach, O. Lairez, P. Wolff declare that they have no competing interest.
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R. Leroy: Merck-Serono, HAC, Sanofi.
V. Raverot: Abbott Diagnostic, Roche Diagnostic, IDS, HAC.

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