The American Thyroid Association/American Association of Clinical Endocrinologists Guidelines for Hyperthyroidism and Other Causes of Thyrotoxicosis: A European Perspective

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The new management guidelines of the American Thyroid Association (ATA) and American Association of Clinical Endocrinologists (AACE) for the management of hyperthyroidism and other causes of thyrotoxicosis are an important and informative accomplishment (1). The authors of this precisely written, evidence-based document provide 100 clearly written recommendations, summarizing the rationale for each with pertinent references. The following are among the many recent and relevant clinical issues that are extensively discussed.

- The newly described severe hepatotoxicity of propylthiouracil (PTU) in pediatric patients with Graves' hyperthyroidism (2)
- The limitation of PTU treatment, foremost to the first trimester of pregnancy (3)
- The increasing role of the antithyroid drug (ATD) treatment as the primary therapy for patients with new onset Graves’ disease (GD) and the clear trend towards prescription of methimazole (4)
- The introduction of the helpful classification pertaining to the clinical activity and severity of Graves’ orbitopathy (GO) according to the recently published, in this journal, Consensus Statement of the European Group on Graves’ Orbitopathy (5)
- The evidence-based recognition of the radioactive iodine (RAI)-induced deterioration of GO, or its de novo onset (5–7)
- The beneficial effect of steroids to prevent RAI-induced exacerbation of GO (8)
- The strong recommendation for a “high-volume thyroid surgeon” to keep the rate of local post-surgical complications of thyroidectomy as low as possible (9,10)
- The clear recommendations to treat all patients with subclinical thyrotoxicosis (isolated suppressed serum thyrotropin [TSH] values) who are older than 65 years (11) and to treat them the same as those with subclinical thyrotoxicosis who are below age 65 and have risk factors (cardiovascular morbidity, osteoporosis, postmenopausal) and/or hyperthyroid symptoms (8)
- The usefulness and clinical relevance of thyroid ultrasound (US) with the color-flow Doppler device for the rapid differentiation between the two main types of amiodarone-induced thyrotoxicosis, and its help for accurate treatment of these conditions (12–15)
- The recommendation to measure TSH-receptor (TSH-R) autoantibodies in pregnant women with a previous history of autoimmune thyroid disease (3,16) and, if present, to closely monitor the TSH-R autoantibody level in pregnant patients with GD, especially in the third trimester.

The fact that nearly all authors of the guidelines for thyrotoxicosis (1) are from North America (with the exception of one from Europe) might have influenced the interpretation of the science on which the recommendations are based. Much focus is on GD, the predominant form of thyrotoxicosis in North America, while nodular toxic goiter still prevails in many areas in Europe (17). Moreover, although the recommendations are evidence based, the potential influence of questionnaire-based studies among specialists should also be considered (18). Importantly, these almost exclusively deal with GD, show a wide variation in management aspects regarding virtual patient(s), and originate from two decades ago. Lack of interaction with a real patient suggests that any recommendation should be viewed with caution. Tradition, availability of economic and human resources, and origin of the scientific evidence greatly impact the implementation of any technology/recommendation. Rarely are the recommendations based on randomized clinical trials (RCTs) and, when available, these cover only a limited spectrum of the potential patients to be treated. Although quality of life (QoL) and costs are increasingly taken into consideration when designing studies, and suggest that there may be little difference between the main therapeutic options for hyperthyroidism (19), we know little of what determines QoL in the individual patient and how this can be improved (20). Finally, the evidence rarely if ever concerns the individual patient who certainly deviates from the norm of any published study. On top of this, despite the strength of the evidence, recent events may
have a greater impact on the responses and weighting that physicians or even experts assign to a particular issue. Any guideline must, as its hallmark, allow for preserving the art of medicine.

Not only the strength of evidence needs focus but also the relative importance of the recommendations. It is clear that not all 100 recommendations are equally important, independent of the strength of the evidence. However, a kind of hierarchical structure could have been offered, to leave no doubt in the mind of the reader as to which recommendations are the most important. Guidelines represent a useful tool in clinical practice, but they must be implemented by measures aimed at analyzing the degree of adherence with them and at improving them.

For obvious reasons, an in-depth commentary regarding the majority of issues dealt with is not feasible. However, from the eastern side of the Atlantic Ocean some eye-catching differences regarding ideal content and priorities may be described. For a European thyroidologist, it is very surprising that US imaging of the thyroid gland and the neighbor neck organs, as a highly sensitive and reliable diagnostic tool, more than 30 years after introduction of this helpful method in our circles, still is not recognized as the primary imaging procedure for thyroid diseases in the United States. In contrast, the American guidelines start with the following recommendation: “a radioactive iodine uptake should be performed when the clinical presentation is not diagnostic of GD and a scan should be added if nodules are present.” Also surprising is the different rating system of recommendations used in these hyperthyroidism management guidelines as opposed to the one used in the ATA guidelines taskforce on thyroid nodules and differentiated cancer, published in late 2009 in this journal (21).

As previously published, ATD treatment is the primary therapy of choice for autoimmune hyperthyroidism in Europe (22). In line with this, measurement of TSH-R autoantibodies, for monitoring patients during treatment as well as for definitive therapy in case of relapse, is more widely used in the Old World (23). It is also difficult to disagree regarding the recommendations on the use of ATD, where the last half century unfortunately has seen little progress. Therefore, the fascinating perspective of targeted biological therapy—whether for obtaining remission of hyperthyroidism or for the management of GO or both—could have been mentioned, despite the limited available data (24). Further, European guidelines would probably focus less on a detailed ATD dose calculation for various causes of hyperthyroidism, although such calculations are more widely used in Europe than in America, where many opt for fixed RAI activities. Thus, in the new American guidelines (1), approximately one fifth of the text extensively discusses indications, methods of application, and various doses of this first line treatment in North America.

In the following sections we focus on a few selected topics.

**Thyroid US**

Thyroid US is a highly sensitive, convenient, inexpensive, and noninvasive technique to aid in determining the underlying pathophysiology of thyrotoxicosis (25–29). Thyroid US and thyroid scintigraphy are equally accurate at diagnosing GD; in a large study they were able to make the correct diagnosis in 95.2% and 97.4% of patients, respectively (30). US imaging offers the additional advantage of obtaining the diagnosis without exposing the patient to ionizing radiation. US probes have excellent spatial resolution; nodules as small as 2–3 mm are readily visualized with the current technology (10). Addition of color-flow Doppler US improves the diagnostic spectrum and accuracy through its ability to quantify thyroid vascularity (31–36). This method accurately distinguishes GD from destructive thyroiditis. In a recent study, increased peak systolic blood flow through the inferior thyroidal artery was seen in 32 of 34 patients with GD, whereas low flow was seen in all patients with destructive thyroiditis (34). These results correlated significantly with findings on pertechnetate scanning, establishing a comparable sensitivity and specificity of 95% and 96%, respectively. Recognition of its superior diagnostic accuracy has led to increasing reliance on US among endocrinologists, and training in neck US is a part of the educational curriculum for many European endocrine fellows.

While it is most commonly used for the detection of thyroid nodules (10,37–39) and guidance for fine-needle aspiration, US is also an important tool in the initial workup of patients with hyperthyroidism. US has been found to be more sensitive than antibody testing for predicting autoimmune thyroid dysfunction. In one study, reduced echogenicity predicted future thyroid dysfunction in 100% of patients (40,41) and was present prior to antibody positivity in 14%; whereas, no individual with normal echogenicity went on to develop autoimmune thyroid dysfunction during the 3 years of follow up (27). Also, serial US exams after initiation of medical therapy help predict relapse or remission of GD, aiding the clinician in determining the optimal therapy. Patients requiring ATD treatment had significantly lower thyroid echogenicity compared with those in whom the disease was inactive (25,42). Prospective trials have confirmed that echogenicity after ATD treatment helps to predict remission (43,44) and revealed a relationship between thyroid echogenicity and the clinical course and immunologic parameters in GD (43,45). Patients who had a hypoechoic, micronodular appearance on US were more likely to have a high TSH-R antibody titer and were at a higher risk of recurrence of hyperthyroidism after ATD withdrawal (45).

Vascularity, an objectively quantifiable US parameter, also has an established value in predicting the relapse of hyperthyroidism in GD patients after withdrawal of ATD (46–48) and retains its predictive value in multivariate analyses (46). Significantly increased blood flow parameters were observed in patients with active hyperthyroidism before treatment (49) and in euthyroid patients who had a relapse after withdrawal of ATD treatment compared with normal controls (50). On the other hand, those patients who remained in stable remission had no significant difference in the blood flow parameters versus normal controls. Finally, this method is very useful in thyrotoxic pregnant women, in whom it accurately differentiates between GD and gestational thyrotoxicosis and/or destructive thyroiditis (51). In this recent report (51), thyroid vascularity and inferior thyroidal artery flow velocity were significantly greater in the GD group compared with the gestational thyrotoxicosis patients.

**Thyroid Nuclear Scan**

Although thyroid uptake and nuclear scan are widely employed in the management of thyrotoxicosis, the value of
thyroid scintigraphy in the differential diagnosis of hyperthyroidism is controversial. With the advent of modern sensitive TSH-R immunoassays (52,53) and bioassays (54–57) for the diagnosis of GD, the etiology of thyrotoxicosis can be established in most cases on clinical and immunological grounds without resorting to scintigraphy. RAI uptake scans are also performed in the assessment of patients prior to RAI therapy for hyperthyroidism. However, it is unclear whether pretherapeutic uptake studies offer enough prognostic information to justify their routine use in patients receiving RAI. These considerations are relevant given that radionuclide imaging is costly, often inconvenient to the patient, and involves added exposure to radioactive isotopes. With this in mind, in a large retrospective study with 881 hyperthyroid patients, thyroid scan and RAI uptake studies did not influence diagnosis or treatment outcomes in most cases of hyperthyroidism (58) and the corresponding findings did not justify their routine use. Hence, selective scanning will reduce cost and exposure to radioisotopes without compromising diagnostic accuracy or treatment outcomes.

When compared with US, scintigraphy is significantly less sensitive for diagnosing thyroid nodules (30,59). In a large prospective study of 426 patients with GD, US identified 68 (16%) thyroid nodules, whereas pertechnetate scanning only detected nine (2.1%) nodules (p < 0.001) (30). In another study, US uncovered nodules that palpation and scintigraphy failed to identify in 12.1% of patients (59). Radionuclide scanning may not distinguish thyroid nodules measuring less than 1–1.5 cm (60). Even when considering only those nodules measuring over a centimeter, scintigraphy performs poorly; for example, it was only able to localize 30% of cold nodules (30). In this same cohort, 30/68 (47.7%) patients were diagnosed with thyroid cancer, which scintigraphy identified in only four cases.

Another drawback of radionuclide scanning is the significant cost. Cost analysis comparing pertechnetate scanning and US in the initial workup of GD found that the total cost to obtain a diagnosis by US for all patients in the study was €14,645.34 compared with €19,922.71 for scintigraphy (30). Based on these findings, we recommend US imaging as a first step in the diagnosis of all thyrotoxic patients (61). Thyroid scintigraphy could be limited to just uncommon cases in which the diagnosis cannot be made with clinical clues and laboratory data and/or to evaluate the function of nodules >1 cm.

Radioiodine and GO

Scientific evidence has accumulated that RAI ablation treatment for GD is associated with a clinically significant increased de novo risk, or risk of progression, of preexisting GO compared with ATD and thyroid surgery (5,7,62–65). Recently, the results of a large trial with a 4-year follow-up provided evidence that RAI treatment was a significant risk factor for development of GO in GD (6). In this intention to treat study, patients with a recent diagnosis of GD were randomly assigned to either RAI (n = 163) or to ATD (n = 150). Early substitution with levothyroxine (LT4) was given in both groups. Worsening or development of GO was more common in the RAI group (n = 63, 38.7%) compared with the ATD group (n = 32, 21.3%) (p < 0.001). The risk for de novo development of GO was greater (p < 0.001) in patients treated with RAI (53 of 141, 38%) than with ATD (23 of 131, 17.5%). Steroid treatment for GO was required in more patients in the RAI group (n = 15, 9.2%) than in the ATD group (n = 4, 2.7%). Smoking influenced the risk of worsening or development of GO (p < 0.001), and smokers treated with RAI had the overall highest risk for GO. Cox regression analysis revealed two major risk factors regarding worsening or development of GO: RAI vs. ATD (OR 7.72, 95% CI 2.31–25.75, p < 0.001) and current smoking (OR 9.80, 2.75–34.90, p < 0.001).

All in all, the risks of developing new GO or worsening of pre-existing GO is around 20% after RAI and around 5% after ATD (5,7). The risk of developing severe GO after RAI is around 7%. Smoking, high levels of pretreatment serum triiodothyronine, and post RAI hypothyroidism are associated with increased risk of GO (64), whereas a high TSH-R autoantibody titer is an independent risk factor for the progression of GO. In patients with mild pre-existing GO, thyroid propylthiouracil is effective in preventing deterioration (66,67). Also, routine use of prophylactic oral steroids with RAI therapy should be considered in GD patients without overt GO but at higher risks of eye complications. Hence, post RAI de novo onset and/or deterioration of eye signs foremost occurs in patients with preexisting and/or active GO. However, even in those without overt GO or with inactive eye disease, RAI-induced exacerbation may still occur, especially in smokers. Therefore, effective low-dose steroid prophylaxis (e.g., 0.2 mg prednisone or equivalent/kg bodyweight for 4–6 weeks) as recently demonstrated (8) and/or regular ophthalmic monitoring, in case steroids are not administered, would be cautious and wise.

RAI Ablation Therapy for Hyperthyroidism

Based on the low remission rates on ATD the majority of patients with GD and thyrotoxic nodular thyroid disease ultimately are treated with thyroid ablative therapy, i.e., RAI or surgery. In most European countries the radiation regulations are more rigorous than in North America, necessitating in-house therapy in some countries even with very small activities of RAI. For this and other reasons, many European centers aim for activities that are as low as possible and meticulously calculate the RAI dose. The consequence of this approach is recurrence of thyrotoxicosis or prolongation of the thyrotoxic phase until euthyroidism and frequently hypothyroidism ultimately occur. It has been shown that thyroid size can be normalized by RAI, independent of initial size (68), and therefore many European centers rarely use surgery unless thyroid malignancy is suspected. Also in uni- and multinodular toxic goiter the standard therapy is RAI since the remission rate is close to nil and thyroid size can be adequately reduced in the vast majority (69). Despite difficulties in demonstrating any advantage by the extensive calculations, fixed RAI activities are generally higher and are aimed at rendering the patients hypothyroid as quickly as possible. Little is known regarding the consequences of administering such higher activities, aside from the higher incidence of hypothyroidism. However, the increasing focus on the imperfections of thyroid hormone therapy and the vast number of patients dissatisfied with their QoL suggests that the debate on whether to maintain endogenous thyroid function for as long as possible is not over, the latter point being of particular...
relevance in view of therapy of progressively younger individuals. Although most patients, with negligible risks, can be given RAI without ATD pretreatment, one important reason for offering ATD is the fact that many patients, when hyperthyroid, have cognitive and attention impairment that makes it difficult to comprehend the extensive information in the context of RAI therapy. If used, the impact of such ATD therapy for the efficacy of RAI has been extensively reviewed (70). A meta-analysis based on 14 RCTs suggests that methimazole and PTU have similar radioprotective abilities (70) and that ATD administration before, during, and after RAI therapy is associated with treatment failure and a lower frequency of hypothyroidism. However, the meta-analysis is based on incongruent materials as for nearly all potential variables. Therefore, to some surprise, the individual well-designed RCTs suggest that pre- or post-RAI therapy with ATD has at worst very limited negative impact on efficacy. Thus, no single RCT has been able to demonstrate an increased failure rate by the use of methimazole or carbimazole in the pre-RAI period, and most RCTs found a neutral effect of ATD resumption in the early post-RAI period. PTU pretreatment was associated with a reduced cure rate, but only after adjustment for the concomitant increase in serum TSH (71). Since the use of PTU is discouraged, these findings have little importance. Overall, the beneficial rapid normalization of thyroid function and limitation of the post-RAI surge of thyroid hormones may well override any marginally decreased efficacy due to ATD administration. Therefore, it may be concluded that in many European countries patients are given ATD pretreatment prior to RAI administration.

**Recombinant Human TSH and US-Guided Thyroid Nodule Ablation Therapy**

While the use of recombinant human TSH (rhTSH) in patients with benign goiter, independent of thyroid status, is off-label, a more nuanced statement than “use of recombinant human TSH is not indicated in toxic multinodular goiter due to risk of exacerbating the patient’s hyperthyroidism” could have been used, if mentioned at all. rhTSH, in doses currently used and given 24 hours before RAI therapy, has no serious side effects compared with RAI without rhTSH. However, it augments the goiter-reducing effect by around 30%–50%, in superiority studies (72,73), or allows reduction of the radioactivity by around 70% with retained efficacy (74). Use of modified rhTSH in even lower doses (0.03 mg) possibly further reduces the risk of side effects without compromising efficacy (75). These results also hold for patients with mild hyperthyroidism.

**US-Guided Nodule Ablation**

An area receiving little attention in the present guidelines is US-guided nodule ablation therapy, probably due to the limited use and availability in North America. It is striking that focus is on the beneficial effect of percutaneous ethanol injection which, with the exception of the treatment of solitary cysts (which is not the focus of the present guidelines) and based on limited long-term efficacy and serious side effects, has long been abandoned by those with the most experience in this field (76). In contrast, neglecting the fact that the effects and side effects of radiofrequency therapy and laser therapy for hyperfunctioning thyroid nodules is very favorable (76,77) is surprising. Notably, the latter has been compared in a randomized study with RAI (77). This therapy has attractive features, at least in solitary nodules. It acts only on the hyperfunctioning portion of the nodule, decreasing its size and avoiding hypothyroidism by not affecting perinodular tissue.

In summary, the new management guidelines of the ATA and AACE for the management of hyperthyroidism and other causes of thyrotoxicosis contain many important recommendations. Here we provide our viewpoint of some aspects of the guidelines, sending our thoughts around the world to underline a “European perspective.”

**Author Disclosure Statement**

No competing financial interests exist.

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