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# Survey of Clinical Practice Patterns in the Management of 992 Hyperthyroid Patients in France

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Hyperthyroidism · Diagnosis · Echography · Treatment · Antithyroid drugs · Radioiodine therapy · Surgery

**Abstract**
***Background:*** Considerable variations in diagnosis and therapeutic practices are reported for hyperthyroidism (HT) between countries. ***Methods:*** A clinical study was conducted among a representative sample of 263 endocrinologists in France. All consecutive patients seen for HT during the study period were included. Diagnosis and treatment modalities were recorded from hyperthyroid patients with Graves disease (GD, *n* = 802), multinodular goiter (MNG, *n* = 121), and toxic adenoma (TA, *n* = 69). ***Results:*** Antithyroid antibodies were measured in half of the population (anti-TPO in 48.5% and anti-TSH receptor in 57.8%). Patients had thyroid ultrasonography and scintigraphy in 93.8 and 40.3%, respectively. Therapeutic management depended on the etiology: for the first episode of GD, antithyroid drugs (ATDs) were the first-line treatment in 91% of the patients, combined with surgery in 6.1% and with radioiodine in 2.9%. Surgery was preferred to radioiodine in MNG (52.6 vs. 22.4%) and TA (59.1 vs. 24.2%). Euthyroid status was achieved after 3 months in 64.4% of GD. A "block and replace" protocol was used in 41.2% of patients. After 3 months, 73% of patients were euthyroid in the "block and replace" group compared to 56.2% in the group with ATDs alone ($p = 0.009$). For MNG and TA, more than 75% of patients were euthyroid at the 3-month follow-up. ***Conclusions:*** Large discrepancies remain between clinical practice and international guidelines. These results should boost efforts to improve adherence to these guidelines.



## Introduction

The etiological diagnosis of hyperthyroidism (HT) is considered by many experts to be an important step in therapeutic decision-making, although clinical practices in this field appear to vary greatly between countries, as attested to by some recent controversies [1–3]. In addi-

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tion, regardless of etiology, at least for the 3 main causes, i.e., Graves disease (GD) (autoimmune HT), toxic multinodular goiter (MNG), and toxic adenoma (TA), which account for over 90% of HT, few studies have compared the results of the 3 available treatment options: medical treatment with synthetic antithyroid drugs (ATDs), treatment with iodine 131 ($^{131}$I), or surgery. Medical treatment blocks hormone synthesis and the release of thyroid hormones. This may be sufficient in GD in which the autoimmune process disappears in approximately 50% of patients after a few months or years. The other 2 are radical treatments which usually cure the HT, although often at the cost of permanent hypothyroidism. One of the difficulties in comparing these treatments is to determine relevant end points which may range from rapidity to control of the HT to the long-term consequences of permanent hypothyroidism, such as the effect(s) on quality of life.

Considerable variability in clinical practices is seen both between and within countries in the diagnosis and treatment of the disease, whereas reliable observational studies are only available in a few countries throughout the world. This lack of data and the paucity of comparative available studies explain the difficulty of drawing up guidelines, which are based mostly on expert opinions and are controversial [1, 2]. This is particularly regrettable as HT is a common disease and, apart from affecting the patients' demands for quality care, this variability in practices probably has consequences in terms of costs at a time in which health system resources must be used optimally in the majority of countries around the world.

The aim of this work is to describe the diagnostic and therapeutic management to HT patients in France, a country in which, until now, there have only been limited and nonrepresentative data. Unlike most of the studies performed [4–6], this is not a general declarative survey of practices, but an observational study of investigations and treatments performed in patients seen by French endocrinologists in order to avoid bias due to a possible difference between declared practices and those effectively used in "real life."

## Patients and Methods

The complete methodology of the study has been previously published [7] and is summarized below. All of the 1,538 endocrinologists in France were invited to take part in the study. Of these, 337 agreed to participate and 263 included at least 1 patient. There was no difference in the characteristics (sex, age, practice) between participants and nonparticipants.

*Patients*

All consecutive patients with a recent (<3 months) diagnosis of HT managed by the endocrinologists taking part in the study were included. Two questionnaires were completed for each patient, one about clinical and paraclinical findings at the time of diagnosis and the second on treatment modalities and thyroid status after a 3-month follow-up (see www.karger.com/doi/10.1159/000453260 for online suppl. data 1 and 2). Data on clinical findings have been published elsewhere [7]. The questionnaires included clinical findings, comorbidities (particularly heart disease), and smoking status, i.e., whether an active smoker or having smoked in the past. The endocrinologists were asked to record their requests for the results of laboratory and imaging investigations and to indicate the etiological diagnosis of HT. Treatment was described in a detailed manner, especially the drugs used (names and dosage of synthetic antithyroid drugs, concomitant treatments (L-thyroxine in the "block and replace" protocol, β-blockers, anxiolytics). At 3 months, the questionnaire reported thyroid status (euthyroid, hyper- or hypothyroid), treatments, results of thyroid profiles, and any side effects.

Two hundred and sixty-three endocrinologists included at least 1 patient. These endocrinologists (67% women) were on average 50.6 ± 8.5 years old and 72% worked exclusively in private practice. The endocrinologists included 1,667 patients, of whom 95 were excluded subsequently as they did not meet the criteria or because of missing data (HT present for over 3 months, etc.). In this study of diagnostic and therapeutic practices, only the 3 main causes (GD, MNG, TA) were included. The diagnostic approach to suspected iatrogenic HT or thyroiditis is often guided by the pharmaceutical context or related symptoms (fever, neck pain, etc.) and treatment is different. The diagnosis of relapsed GD does not usually justify repeated etiological investigations. Therefore, the analysis was based on a population of 992 hyperthyroid patients.

*Statistics*

For this observational study, the number of patients recruited was based on the proportion of patients expected in subcategories, and on the size of the confidence intervals of proportions calculated in these subcategories. The following 2 formulas were used for the confidence interval calculation and for the number of patients to be included respectively:

$$\mathrm{CI}_{95\%} = p \pm 1.96\sqrt{\frac{p \times q}{n}}$$

$$n = 1.96^2 \times \frac{p \times q}{\text{required\_precision}^2}.$$

Accordingly, it was estimated that a population of 1,000 patients would be sufficient to meet the study objectives.

To verify the representativeness of the physicians participating in the study, their characteristics were compared to those of all French physicians (age, gender, type and place of work). The representativeness of the patients included in the study was checked by a comparison with patients of the noninclusion registry.

Quantitative or continuous variables were described by means and standard deviation (SD). Qualitative variables were described by absolute frequency and percentage per modality. Quantitative variables were compared between groups by Student tests in case

**Table 1.** Characteristics of the hyperthyroid patients according to the different etiologies

| | Graves disease ($n$ = 802) | Multinodular goiter ($n$ = 121) | Toxic adenoma ($n$ = 69) | $p$ value |
|---|---|---|---|---|
| Sex | | | | 0.7 |
| No response | 1 | – | – | |
| Female | 651 (81.3) | 101 (83.5) | 54 (78.3) | |
| Male | 150 (18.7) | 20 (16.5) | 15 (21.7) | |
| Age, years | 43.3±13.8 | 63.6±15.7 | 58.7±14.4 | <0.0001 |
| BMI | 23.3±4.4 | 25.5±4.8 | 25.8±5.1 | <0.0001 |
| Smoking habit | | | | 0.014 |
| No response | 13 | 4 | 1 | |
| Current smoker | 183 (23.2) | 17 (14.5) | 8 (11.8) | 0.013 |
| Ex-smoker/never smoked | 606 (76.8) | 100 (85.5) | 60 (88.2) | |

Values are presented as $n$ (%) or means ± SD. BMI, body mass index.

**Table 2.** Diagnostic investigations into etiology

| | Graves disease ($n$ = 802) | Multinodular goiter ($n$ = 121) | Toxic adenoma ($n$ = 69) | $p$ value |
|---|---|---|---|---|
| Prescription of TRAb | | | | |
| No response | – | 1 | – | |
| Yes | 486 (60.6) | 56 (46.7) | 31 (44.9) | 0.0013 |
| No | 316 (39.4) | 64 (53.3) | 38 (55.1) | |
| Results of TRAb | | | | |
| No response | 5 | 1 | 1 | <0.0001 |
| Positive | 461 (95.8) | 8 (14.5) | 2 (6.7) | |
| Negative | 20 (4.2) | 47 (85.5) | 28 (93.3) | |
| Request for anti-TPO Ab | | | | |
| Yes | 413 (51.5) | 47 (39.2) | 21 (30.4) | 0.0003 |
| No | 389 (48.5) | 73 (60.8) | 48 (69.6) | |
| Results of anti-TPO Ab | | | | |
| No response | 6 | – | – | |
| Positive | 311 (76.4) | 4 (8.5) | 2 (9.5) | <0.0001 |
| Negative | 96 (23.6) | 43 (91.5) | 19 (90.5) | |
| Blood count | | | | 0.007 |
| No response | 60 | 7 | 9 | |
| Yes | 653 (88.0) | 94 (82.5) | 45 (75.0) | |
| No | 89 (12.0) | 20 (17.5) | 15 (25.0) | |
| Thyroid scan | | | | |
| No response | 117 | 10 | 3 | |
| Yes | 213 (31.1) | 75 (67.6) | 59 (89.4) | <0.0001 |
| No | 472 (68.9) | 36 (32.4) | 7 (10.6) | |
| Ultrasonography | | | | |
| No response | 56 | 6 | 6 | |
| Yes | 695 (93.2) | 105 (91.3) | 59 (93.7) | 0.8 |
| No | 51 (6.8) | 10 (8.7) | 4 (6.3) | |

Values are presented as $n$ (%).

of normal distribution or the Wilcoxon-Mann-Whitney test. Qualitative variables were compared between groups using the Pearson $\chi^2$ test if all theoretical sample sizes were ≥5 or the Fisher test if <5. All tests were performed with a significance level of 5%. All statistical analyses were performed using SAS 9.2 software (SAS Institute, Cary, NC, USA).

According to French law, the approval of the Ethics Committee was not required although the study was approved by the CNIL (French National Data Protection Commission) for the anonymized data processing. Patients were provided with written information and gave their verbal consent to participate. The study took place from April 2010 to March 2011.

## Results

### *Patients*

The characteristics of the population are summarized in Table 1. The vast majority of patients had GD and approximately 80% were women. There was no difference in sex ratio according to etiology. Patients with GD were significantly younger ($p < 0.0001$). The body mass index at diagnosis was significantly lower ($p < 0.0001$) and the proportion of smokers was significantly higher in patients with GD ($p < 0.02$) compared to the other 2 etiologies (MNG and TA).

### *Laboratory Investigations*

A complete blood count was requested for the majority of patients, most likely with the idea to treat with antithyroid drugs. Anti-TSH receptor antibodies (TRAb) were tested in slightly less than 60% of the patients and surprisingly in only 61% of GD and approximately 45% of MNG and TA. They were positive in 95.8% of patients

**Table 3.** Combinations of diagnosis investigations

| | Graves disease ($n$ = 802) | Multinodular goiter ($n$ = 121) | Toxic adenoma ($n$ = 69) | Total ($n$ = 992) |
|---|---|---|---|---|
| No test | 34 (4.2) | 8 (6.6) | 3 (4.3) | 45 (4.5) |
| TRAb only | 42 (5.2) | 2 (1.7) | 1 (1.4) | 45 (4.5) |
| Echography only | 147[a] (18.3) | 19 (15.7) | 1 (1.4) | 167 (16.8) |
| Scintigraphy only | 10 (1.2) | 3 (2.5) | 3 (4.3) | 16 (1.6) |
| TRAb and echography | 303[a] (37.8) | 15 (12.4) | 4 (5.8) | 322 (32.5) |
| TRAb and scintigraphy | 16 (2.0) | 2 (1.7) | 2 (2.9) | 20 (2.0) |
| TRAb, echography, and scintigraphy | 125 (15.6) | 37 (30.1) | 24 (34.8) | 186 (18.8) |
| Echography and scintigraphy (without TRAb) | 62 (7.7) | 32 (26.4) | 30 (43.5) | 124 (12.5) |

Values are $n$ (%). [a] 58 additional patients (7.2%) had echography and antiTPO testing without TRAb.

with GD. Anti-TPO antibodies were tested in almost 50% of patients, with slightly more in patients with GD in whom they were positive in 76.4% of patients (Table 2).

*Imaging*

Thyroid ultrasound was performed in 94% and scintigraphy in 40% of patients. Thyroid ultrasound was performed independently of etiology ($p = 0.8$), whereas thyroid scintigraphy was performed in 31.1% of GD, 67.6% of MNG, and 89.4% of TA ($p < 0.0001$) (Table 2). Combinations of the investigations are shown in Table 3. It was not possible with the study design to examine the reasons or chronology for requesting the different biological or imaging investigations. In terms of scintigraphy in GD for example, we were unable to determine whether some endocrinologists performed this routinely or in the occasional patient when anti-TSH receptor antibodies were negative. In light of the frequency with which this investigation was performed, however, it is likely that this was principally a routine practice at the time of diagnosis and not guided by immunological results. When we compared diagnosis practices conducted for patients seen by endocrinologists who included at least 6 patients ($n$ = 800) to that of patients seen by endocrinologists who included less than 6 patients ($n$ = 192), no statistically significant differences were observed.

*Treatment*

For GD, 91% of patients were treated with synthetic ATDs, 6.1% with surgery and 2.9% with radioiodine, most of whom received initial preparation with ATD for both of these treatments with a view to restoring euthyroid status (Fig. 1). Surgery was used in 52.6 and 59.1% of patients with GMN and TA, respectively, and radioiodine for 22.4 and 24.2%, respectively. Some patients were only treated during the 3 months of the study with ATDs in these groups (25.0% for MNG and 16.7% for TA). The limited follow-up period makes it impossible to determine whether this was preparation for a radical treatment or whether long-term ATD treatment was being considered. In the subgroup of GD patients treated with ATDs, 392 (53.9%) were treated with ATDs alone and 300 (41.2%) with a combination of ATDs and levothyroxine ("block and replace" protocol).

*Outcomes*

The change in thyroid function at 3 months is summarized in Figure 2. Three quarters of the patients with MNG or TA were euthyroid at the 3-month follow-up, regardless of treatment, compared to only 64.4% of GD ($p < 0.001$). For GD patients, 17% of patients were still clinically hyperthyroid or had laboratory parameters of HT, and the same proportion was hypothyroid. Following medical treatment for 3 months, significantly more patients treated with the "block and replace" protocol were euthyroid compared to those treated with ATDs alone ($p < 0.0001$, Fig. 3).

## Discussion

Diagnostic and therapeutic management of HT varies according to regions of the world for reasons of availability of certain examinations or treatments, and for reasons of clinical practices. These differences are not based on scientific reasons because there are no studies comparing

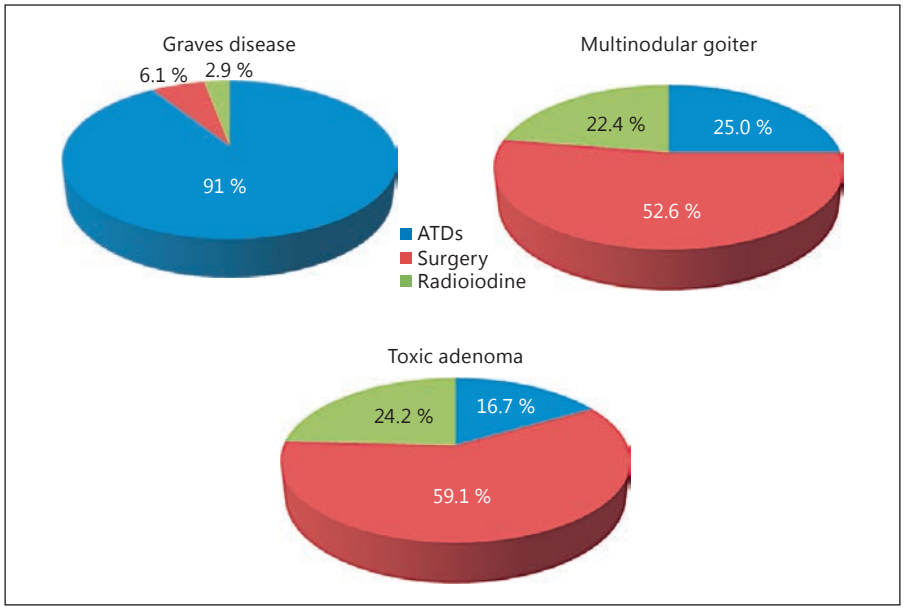


**Fig. 1.** Therapeutic management of hyperthyroidism depending on cause. ATDs, antithyroid drugs.

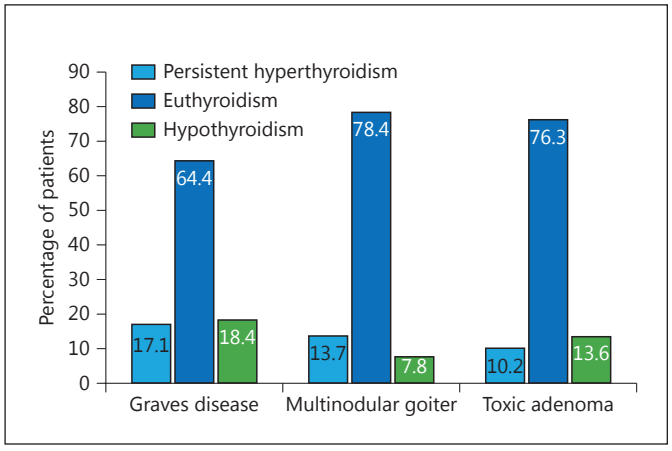


**Fig. 2.** Thyroid status after 3 months of treatment in patients with Graves disease ($n = 762$), multinodular goiter ($n = 111$), and toxic adenoma ($n = 62$).

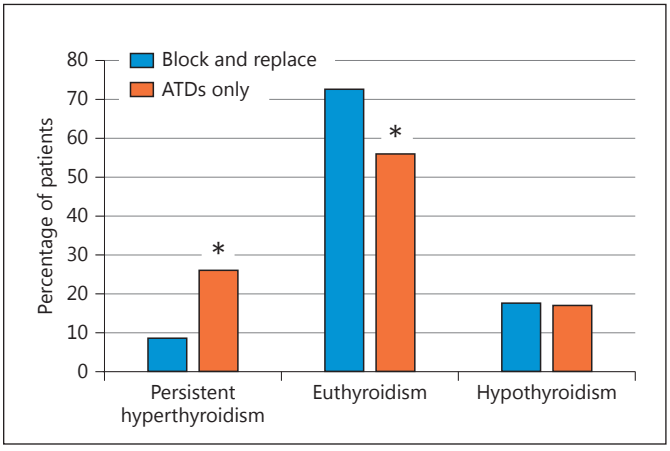


**Fig. 3.** Thyroid status after 3 months of antithyroid drugs (ATDs) alone or in association with levothyroxine ("block and replace") in 692 patients with Graves disease (* $p < 0.0001$).

practices, including diagnostic, from one country to another. The main published recommendations are those of the ATA, which were recently updated [1, 8]. Their level of evidence is weak, and some have been challenged by other experts [2, 3, 9–11]. We report the largest survey on diagnostic and therapeutic practices in HT from a representative sample of French endocrinologists. It is an observational study describing real practices, not a questionnaire completed from clinical "vignettes" like most studies published on diagnostic and therapeutic practices [4–6]. This approach avoids the frequent discrepancy between real-life and declared practices. Moreover, as mentioned in the Methods section, our panel was more representative of endocrinologists in practice in France as they were not contacted through scientific societies. Previous studies probably reflect the opinions and practice of "thyroidologists," i.e., endocrinologists with a high recruitment of thyroid diseases, whereas in France, endocrinology and diabetology belong to the same specialty, and most endocrinologists have a relatively low recruitment of thyroid diseases. This could also explain the major discrepancies between international guidelines and

the clinical practices observed in this study. In terms of diagnostics, the main relevant information is the highly prevalent prescription of thyroid ultrasound and the relative underuse of anti-TSH receptor antibodies which offer extremely good performance for the diagnosis of GD. In terms of treatment, our study confirms the common use of ATDs as a first-line treatment, either alone or in combination with levothyroxine ("block and replace") in patients with GD.

After the diagnosis of thyrotoxicosis, the clinical approach is generally etiological, particularly when there are not enough clinical clues available to confirm the cause. While the etiological diagnosis of HT for most endocrinologists is an important step in the management of the disease and guides the choice of treatment, some contest this approach [3, 9]. The need for imaging in the management of HT has been controversial in recent years [1–3, 9–11]. Two different questions arise when morphological or morphofunctional investigations are performed in HT. The first relates to the cause, the answer to which has a definite prognostic benefit. The second one is the impact that the etiological diagnosis may have on the choice of treatment, although at this stage other factors may be important in this decision, such as sex and the desire for pregnancies, related symptoms (ophthalmopathy in GD), or severity and cardiac complications which occasionally justify urgent treatments. In addition, due to the complications of HT, particularly cardiovascular outcomes, most clinicians prefer hypothyroidism, which is usually relatively easy to control, to persistent subclinical HT.

In laboratory evaluation, the relative underprescription of anti-TSH receptor antibodies in patients with GD is extremely surprising as this is considered in Europe as the first-line investigation because it is seen as both necessary and sufficient in most cases, particularly in younger patients. Conversely, the frequent prescription of anti-TPO antibodies is surprising as the utility of this test in GD is considerably lower than that of the anti-TSH receptor antibodies and are known to offer poor specificity as they are present in 8–20% of the general population depending on age and sex. Concerning laboratory screening, a recent review [11] has underlined the differences between clinical practices and recommendations, in particular between Europe and the USA.

Thyroid ultrasonography was used very commonly in our study (in over 90% of patients), whereas its benefit for the etiological diagnosis is debatable. It is unlikely that the large prescription of thyroid ultrasound could be due to financial issues as most thyroid ultrasonographies in France are done by general radiologists and not by the endocrinologists themselves. In a survey on GD and based on a questionnaire from clinical vignettes, thyroid ultrasound was requested by 26% of practitioners in the USA [4], 70.6% of European thyroidologists [5], and more than 90% in Italy [6]. Thyroid ultrasound in functional thyroid diseases contributes to the overdiagnosis of thyroid nodules with resultant anxiety caused to patients, an increase in the number of investigations performed, and occasionally unnecessary surgery [12, 13]. The previous ATA guidelines stated that ultrasound was not indicated in most cases of HT as it has very limited input concerning management [1]. This position has been strongly contested by a European expert group in an article published in the same issue of *Thyroid* [2]. The same controversies apply to the indication of scintigraphy or at least measurement of radioiodine uptake, which is rarely used in France outside of the phase prior to therapeutic administration of $^{131}$I. Thyroid scintigraphy was performed in 40% of all patients although there were considerable differences according to etiology. In the absence of guiding clinical elements and when anti-TSH receptor antibodies are negative, scintigraphy is generally considered to be the best examination to establish the cause of the HT. It was the recommended first-line investigation in the 2011 ATA guidelines (at the time of our survey), but once again this position is controversial. Indeed Okosieme [9] has demonstrated in 900 consecutive patients firstly that clinical and laboratory findings were sufficient to correctly classify the cause of the HT, but also that the cause remained uncertain when scintigraphy was performed in 50% of patients. In addition, in a very large study reporting the management of HT in an English center, no etiology was identified in almost 50% of patients prior to initiation of treatment [14]. The revised ATA guidelines have been recently published and have slightly nuanced recommendations concerning diagnosis practices [8]. When clinical presentation is typical of GD, no further etiological investigation is necessary. In the other cases, measurement of TRAb, determination of the radioactive iodine uptake, and measurement of thyroidal blood flow on ultrasonography may be used depending on available expertise and resources. However, TRAb evaluation is probably the most cost-effective because when it is positive it confirms the diagnosis of GD, especially in France where it is largely available with results obtained in a few days at a cost of EUR 31.05.

Results of ablative treatment (surgery or $^{131}$I) are usually obtained at the cost of permanent immediate (for surgery) or delayed (for $^{131}$I) hypothyroidism in patients with autonomous thyroid disease (TA or GMN). The use

of synthetic ATDs is discussed in those patients as their effects are suspensive and require treatment for life. The question is more complex in GD and practices are much more variable. ATDs are preferred by the majority of thyroidologists in Europe, whereas $^{131}I$ is used more frequently in the USA, although this difference is less evident in more recent studies [4, 5]. The main problem is the choice of end point, which should lie at the heart of the discussion concerning HT treatment, i.e., the objective of treatment. Many outcomes can be considered: the rapidity of resolution in signs and symptoms of thyrotoxicosis and of obtaining euthyroid status; the percentage of HT permanently cured (without risk of relapse), notably at the expense of permanent hypothyroidism; the respective cardiovascular morbidity and mortality risks; bone, metabolic, and cognitive consequences of the different treatments; long-term quality of life and patient preference; and overall cost to the health care system, which may vary greatly between countries, but should incorporate not only the cost of initial treatment (investigations and treatment) but also the cost of the iatrogenic hypothyroidism in terms of treatment and monitoring.

Euthyroid status was usually obtained at 3 months more frequently for autonomous diseases (MNG and TA) than for GD patients in our study. Medical treatment of GD is not as effective to restore euthyroid status, and the "block and replace" method using a higher dose of ATDs combined with levothyroxine to avoid development of hypothyroidism has been extremely controversial [15–17]. However, the "block and replace" protocol remains widely used by French endocrinologists. Interestingly, the percentage of patients who are euthyroid at 3 months was significantly higher with the "block and replace" protocol than with ATDs alone ($p < 0.0001$). Classically, "block and replace" carries an increased risk of side effects (agranulocytosis) and is reported not to increase the long-term recovery rate although the main argument of the supporters of the "block and replace" protocol is that euthyroidism is obtained more rapidly and that it reduces the number of laboratory assessments needed during follow-up [15–17].

Our results should be interpreted with caution as this is an observational study. However, they suggest that the "block and replace" protocol, which is widely used in France, should be reassessed in a prospective study in order to confirm the potential gain in terms of rapidity of achieving euthyroidism, the reduction in the number of laboratory monitoring thyroid tests, and the real incidence of hematological and hepatic adverse effects.

In conclusion, our study is the first report of "real life" practices in the management of patients with HT in France. It confirms the major differences in clinical practice compared to other regions in the world and the discrepancies between these practices and international expert guidelines [1, 8, 18]. Faced with such a frequent incidence of thyroid disease, it would seem necessary to conduct prospective studies to better evaluate the management of HT patients even if it is not clear how to identify the appropriate treatment aims and end points to be used in these studies.


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## Disclosure Statement

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