

A 2015 Italian Survey of Clinical Practice Patterns in the Management of Graves' Disease: Comparison with European and North American Surveys

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Key Words

Hyperthyroidism · Graves' disease · Orbitopathy · Thyroid ·
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Abstract

Background: Patients suffering from Graves' disease (GD) are quite frequent in endocrine clinical practice. In particular, overt hyperthyroidism may be complicated by serious adverse events and requires careful treatment, but its management has changed over the years in both the USA and European Union (EU). **Objectives:** To evaluate the current diagnosis and management of patient's with GD in Italy, and compare results with those obtained in previous similar surveys in the USA and EU. **Methods:** Members of the Italian Association of Clinical Endocrinologists (AME) were asked to participate in a Web-based survey on management of GD. **Results:** In total, 947 responses were obtained. The preferred diagnostic modality in Italy is TSH receptor antibody determination in conjunction with ultrasound, while radioactive iodine uptake/scan is preferred in the USA. Methimazole (MMI) 20–30 mg/day with a β -blocker is the initial treatment of choice in Italy and the EU, whereas the USA opts more fre-

quently for radioactive therapy. If Graves' orbitopathy occurs, orbit CT/MRI scans are more often obtained in Italy and the EU than in the USA. In case of planned pregnancy in 6–12 months, surgery is more frequently suggested in Italy than in the EU and USA. Propylthiouracil is generally preferred to MMI in the first trimester. **Conclusions:** Italian endocrinologists have shown significantly different patterns in diagnosis and management of GD compared to both the USA and EU.

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Introduction

Graves' disease (GD) is one of the most common causes of hyperthyroidism, with a prevalence rate in the USA of about 1.2% (0.5% overt and 0.7% subclinical) [1]. The severity of GD is variable; it may be associated with peculiar complications like orbitopathy, and may lead to serious adverse events like atrial fibrillation and heavily influence the patient's quality of life. Four years ago Burch et al. [2, 3] reported the results of a questionnaire-based survey of clinical practice patterns in the management of GD among

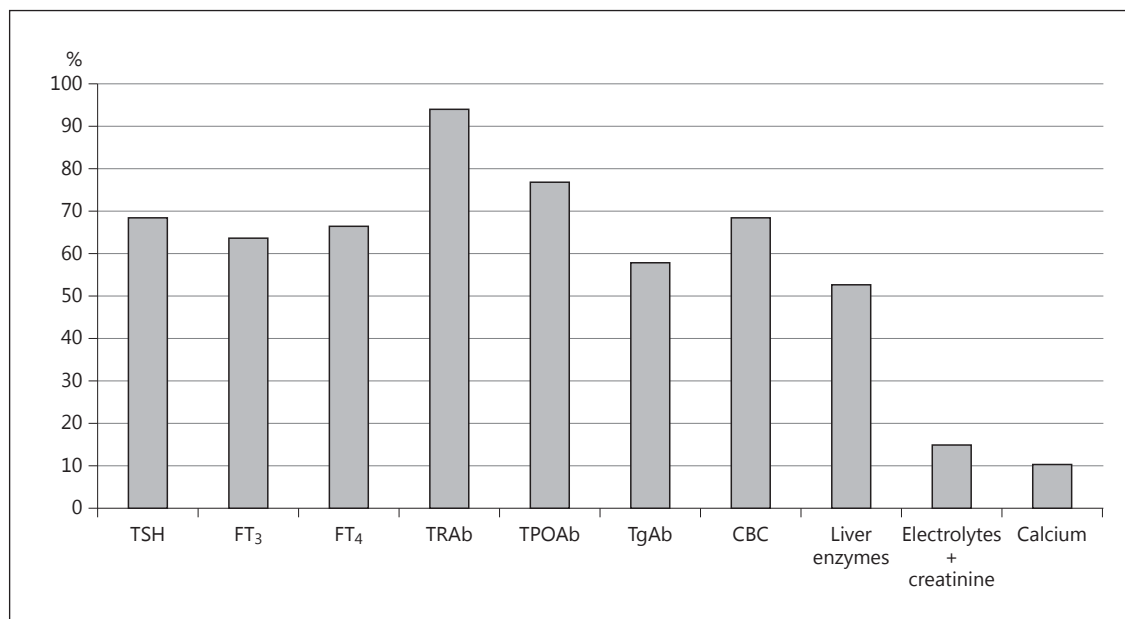


Fig. 1. Rates of laboratory tests requested in the index case.

members of the Endocrine Society, the American Thyroid Association and the American Association of Clinical Endocrinologists, and 2 years ago Bartalena et al. [2, 3] conducted the same survey among members of the European Thyroid Association. In order to assess the extent to which Italian endocrinologists are similar or different to their American and European colleagues, we conducted a survey, analogous to those used by Burch and Bartalena, and distributed it among the members of the Italian Association of Clinical Endocrinologists (AME).

Materials and Methods

A Web-based survey was used. The index case (a 42-year-old woman with uncomplicated GD) was the same as in the previous surveys, with two variants, including a patient with associated Graves' orbitopathy (GO) and a patient anticipating pregnancy over the next 6–12 months. The survey was constructed by using LimeSurvey, an open access platform that provides many different question templates. The questionnaire included 33 questions. AME members ($n = 1,824$) received an initial e-mail including an electronic link to the questionnaire, and a weekly reminder from the AME secretariat from March 1 to March 31, 2015. Survey responses were anonymously collected and stored electronically by the survey service, accessible in a password-protected manner. Repeat submissions from the same IP address were automatically blocked by the survey service. Responses were then compared with those of specialists extracted from the American and European surveys.

Statistical Analysis

Summary statistics were prepared for responses to each question. Since not every participant answered all questions, the percentage of respondents providing a given answer was calculated individually for each question, using the number of respondents to that question in the denominator. χ^2 analysis was used to compare the results of the present survey with those of the previous American and European surveys.

Results

Survey on Management of GD

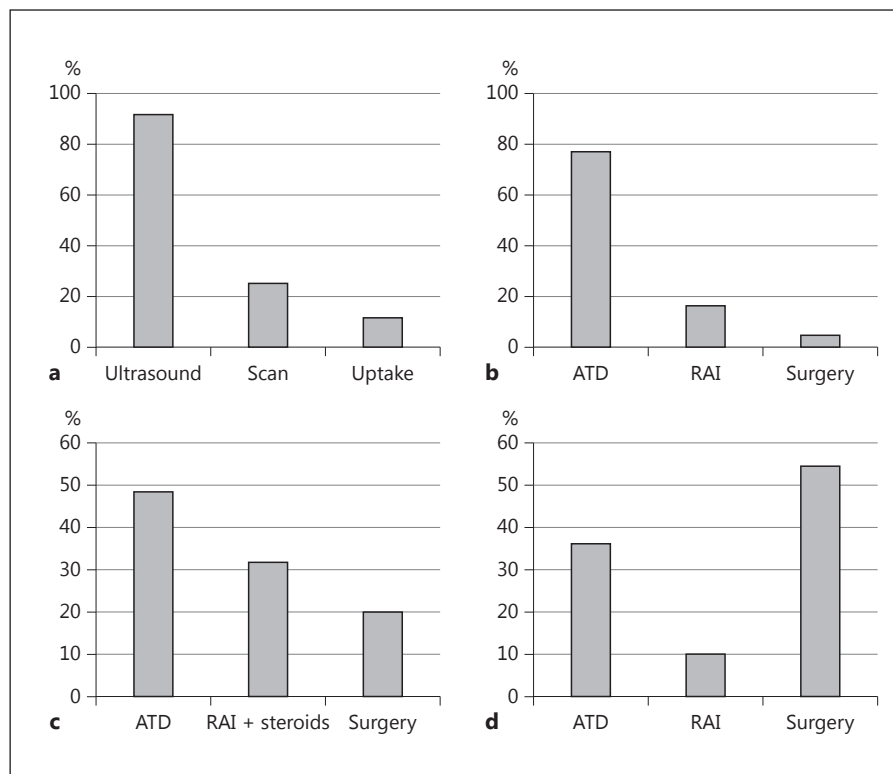
Response Rate and Respondent Demographics

947 respondents (51.9% of AME members) participated in the survey, 709 of whom completed all the sections. 53.1% of respondents were female, 25% graduated after 2000, and 50% graduated after 1990. 90.7% were endocrinologists, 5.5% were internal medicine physicians, and 3.8% were other specialists. 42% usually deal with more than 10 newly diagnosed Graves' patients/year.

Diagnostic Evaluation of the Index Case

Serum TSH and FT₄ determination would be repeated by 68.5 and 66.5%, respectively. TSH receptor antibodies (TRAb), peroxidase antibodies (TPOAb), and thyroglobulin antibodies (TgAb) would be requested by 93.9, 76.8, and 58%, respectively. Complete blood count (CBC) is

Fig. 2. Rates of functional and anatomic investigations requested in the index case (a), rates of preferred treatment modality in the index case (b), rates of preferred treatment modality when GO occurs (c), and rates of preferred treatment modality for a woman planning pregnancy (d).



considered by 68.2%, and liver enzymes by 52.7%, whereas a minority would ask for electrolytes + creatinine (15%), and for calcium (10.4%) (fig. 1).

Thyroid ultrasound would be requested by 92.1%, while 1/4 of the respondents would order a thyroid scan (technetium-99) and only a minority would use radioactive iodine uptake (RAIU; ^{131}I) (fig. 2a).

Therapy

Preferred First-Line Treatment in the Index Case. As β -blockers, propranolol would be used by 80.6%, with the aim of reducing heart frequency below 80 bpm in 46.7%, and below 90 bpm in 39.2% of cases. Antithyroid drug (ATD) therapy was by far the preferred first-line treatment (77.1%), while radioactive iodine (RAI) treatment was selected by only 16.2%, and thyroidectomy by 4.5% of the participants (fig. 2b).

ATD Treatment. Methimazole (MMI) was the preferred ATD for 98.6% of respondents, with a preferred starting dose of 20 mg/day (35.9%).

Monitoring ATD Treatment. After the treatment has been started, 67.1% would monitor TSH after 4–6 weeks, and once the patient is euthyroid, the scheduled monitoring would be every 2–3 months in 87.5% of cases. Other

than thyroid hormones, 77.7% of physicians monitor liver enzymes, and 88.4% CBC. In the event of a pruritic macular rash, 83.6% would change the ATD, 10.5% would change strategy (surgery or RAI), 4.4% would add antihistamines, 0.7% would reduce ATD dose, and 0.8% would add steroids.

Duration of ATD Therapy. Before changing strategy (surgery or RAI) ATD treatment would be continued for 18 months by 38.5%, and globally for 12–24 months by 82.5% of respondents.

Adjunctive ATD Treatment in Patients Receiving RAI. In patients receiving RAI treatment, pretreatment with ATDs was suggested as a routine by 63.2% of respondents, selectively by 25.5%, and not used by 11.3%. ATD treatment would be stopped 5–7 days before RAI administration in 58.6% of cases. In the early posttreatment period, ATDs would be employed only selectively by 45.6% of respondents, were routinely used by 24.5%, and were never used by 29.9%.

Perioperative Management of Patients Undergoing Thyroidectomy. In hyperthyroid patients undergoing thyroidectomy, 98.4% of endocrinologists would like to restore euthyroidism before surgery, and Lugol's solution would be used in 35.9% of cases. After surgery, 53.6%

Table 1. Respondent rates in Italy, the EU, and the USA

	Italy	EU	USA	p
Number of respondents	947	147	730	Italy and USA vs. EU <0.001
Ultrasound	92.1%	70.6%	25.8%	Italy vs. EU and vs. USA <0.01
Scan	25.2%	31.5%	41.9%	Italy and EU vs. USA <0.01
RAIU	11.5%	6.2%	47.0%	<0.001
β-Adrenergic blocking agents	94.8%	93.6%	91.9%	n.s.
MMI as preferred ATD	97.7%	79.3%	83.5%	n.s.
MMI starting dose (20–30 mg)	57.7%	67.3%	68.8%	n.s.
PTU as preferred ATD	1.4%	2.9%	2.7%	n.s.
Monitor TSH in 4–6 weeks	67.9%	30.9%	68.3%	EU vs. Italy and USA <0.05
Long-term TSH monitor (2–3 months)	87.5%	83.1%	90.1%	n.s.
Monitor liver enzymes	77.7%	42.3%	53.8%	Italy vs. EU and vs. USA <0.001
Monitor CBC	88.4%	57.8%	48.4%	Italy vs. EU and vs. USA <0.001
Change ATD for pruritic macular rash	83.6%	55.3%	75.3%	Italy and EU and vs. USA <0.001
Duration treatment with ATD (18 months)	38.4%	50.8%	35.4%	Italy and USA vs. EU <0.001
Stop ATD before RAI (7 days)	39.5%	41.2%	37.1%	n.s.
ATD not used after RAI	29.9%	19.1%	31.9%	Italy and USA vs. EU <0.05
Render patient euthyroid preoperatively	98.4%	94.2%	91.2%	n.s.
Use Lugol's solution preoperatively	35.6%	37.0%	37.0%	n.s.
Vitamin D + calcium postoperatively	53.6%	30.7%	39.3%	Italy vs. EU and vs. USA <0.001
Ophthalmologist consultation	76.9%	66.4%	81.1%	Italy and USA vs. EU <0.001
Orbital imaging	30.2%	29.9%	16.1%	Italy and EU vs. USA <0.01
Steroids administered by endocrinologist	80.1%	83.2%	60.9%	Italy vs. EU and vs. USA <0.001
Use of PTU in first trimester pregnancy	82.2%	75.3%	75.6%	n.s.
Switch PTU-MMI in second trimester	47.2%	60.0%	45.9%	n.s.

would prescribe calcium and vitamin D supplementation regardless of serum concentration of calcium at discharge.

Variant 1: Hyperthyroidism with Concurrent Moderate and Active GO

If the index case presented with concurrent active moderate-severe GO (Clinical Activity Score: $\geq 3/7$ points), the majority of respondents would require an ophthalmological consultation (76.9%), while less than 1/3 would obtain orbital imaging (26.5% visual field, 27.1% CT scan, 27.1% MRI, 30.2% orbital ultrasound). If required, high-dose glucocorticoid treatment for GO would be administered by the endocrinologists in 81.8%. In the presence of GO, half of the respondents (48.5%) would continue treating hyperthyroidism with ATD therapy, 31.6% would opt for thyroidectomy, and 19.9% would suggest RAI associated with high-dose glucocorticoids (fig. 2c).

Variant 2: Hyperthyroidism Management in a Patient Planning Pregnancy

If the hyperthyroid patient desired to have pregnancy in the next 6–12 months, 54.3% would suggest thyroidec-

tomy, whereas 36% would continue ATD treatment, and 9.7% would suggest RAI (fig. 2d). If the chosen treatment is ATD, 61% would suggest using propylthiouracil (PTU) rather than MMI before the pregnancy, and PTU would be continued by 55.1% of physicians during all the three trimesters; if the patient became pregnant on MMI, 82.2% would switch to PTU as soon as the pregnancy is confirmed.

Comparison with the 2011 American Survey and 2013 European Survey

Number of Respondents

In the Italian survey the number of respondents ($n = 947$) was higher than the US ($n = 730$) and EU ($n = 147$) surveys ($p < 0.001$; table 1).

Diagnosis

Less frequently than US and EU respondents, Italian endocrinologists would repeat serum TSH as well as FT₄ ($p < 0.001$). A significantly higher number of Italian and European endocrinologists would obtain TRAb determination compared to their American counterparts ($p < 0.001$; fig. 3). Thyroid ultrasound would be ob-

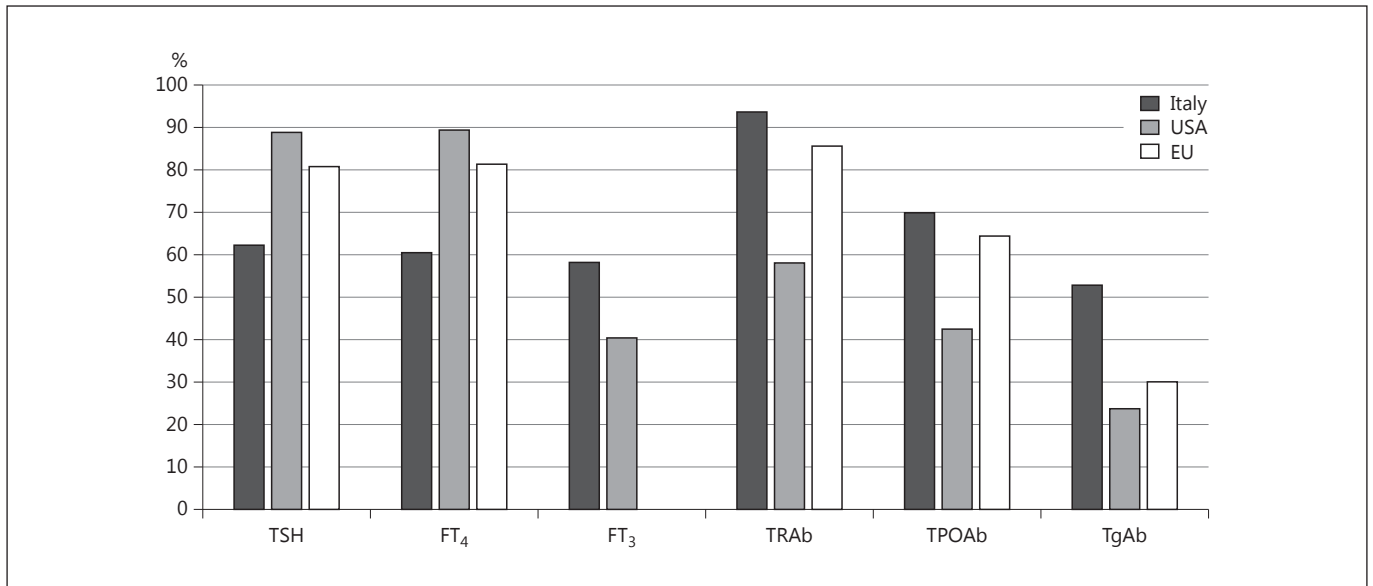


Fig. 3. Rates of laboratory tests requested in Italy, the USA, and the EU.

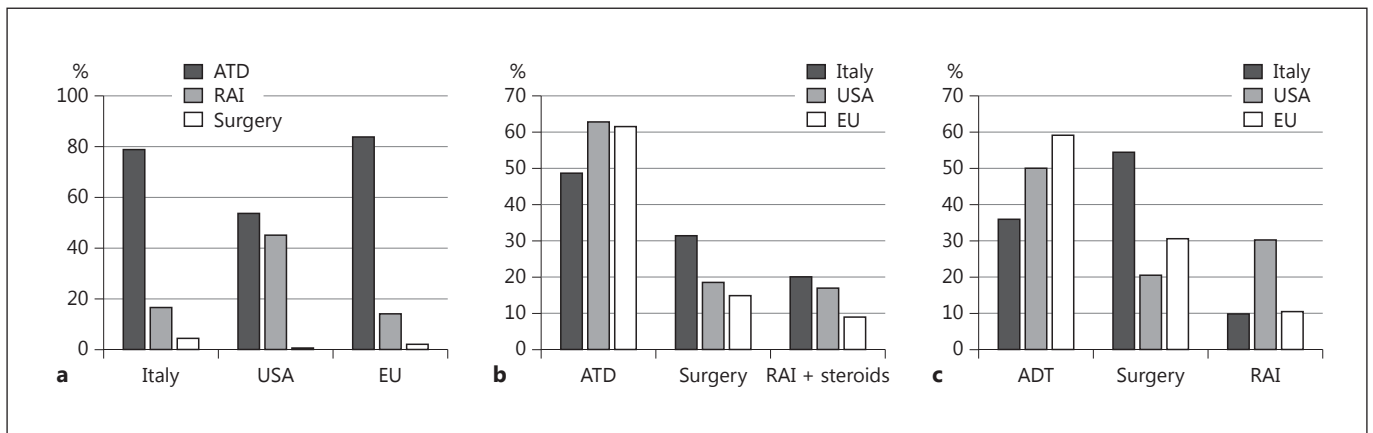


Fig. 4. Rates of preferred treatment modality in Italy, the USA, and the EU (a), rates of preferred treatment modality when GO occurs (b), and rates of preferred treatment modality if pregnancy is planned in the next 6–12 months (c).

tained more frequently in Italy than in the EU and USA ($p < 0.001$); less frequently than US endocrinologists, Italian and EU endocrinologists would obtain a thyroid radioisotope scan ($p < 0.001$). Significant differences were observed also for RAIU between the EU and USA (table 1).

Therapy

The Use of β -Adrenergic Blocking Agents. β -Blockers would initially be used (definitely or possibly), without

any significant difference, by the large majority of respondents of the three surveys (table 1).

Preferred Primary Treatment Modality in the Index Case. The preferred primary treatment modality was ATD for Italian and EU endocrinologists, while RAI is the preferred modality in the USA ($p < 0.001$); surgery is the preferred treatment in a minority of cases (fig. 4a).

Preferred Drug and Doses for ATD Therapy. Most of the respondents, without significant difference, would opt for MMI as the drug of choice, with a starting dose of

20–30 mg. PTU would be the drug of choice in a minority of cases (table 1).

Monitoring ATD Therapy. Most of the respondents in Italy and the USA would evaluate TSH 4–6 weeks after instituting ATD therapy. After restoring euthyroidism, thyroid function tests would be most frequently performed every 2–3 months for the three surveys. Routine monitoring of liver-associated enzymes and CBC was more frequent in Italy than in the EU and USA. In the event of a pruritic macular rash, Italy and the EU would change the ATD more often than would be done in the USA (table 1).

Duration of ATD Therapy. Respondents were asked how long they would use ATDs in an attempt to achieve a remission from GD. The most frequent answer was 18 months in all the three surveys (table 1).

Adjunctive ATD Therapy in Patients Receiving RAI. Less than 15% in the three surveys never routinely pre-treat patients with an ATD. When using pretreatment with ATDs before RAI therapy, the relative majority of respondents stopped ATD treatment 7 days before; in the early posttreatment period, ATDs were never used by 20–30% of respondents (table 1).

Perioperative Management of Patients Undergoing Thyroidectomy. The vast majority of respondents in the three surveys would render patients euthyroid with ATDs preoperatively. More than one third would use a saturated solution of potassium iodide or Lugol's solution. Prophylactic calcium and vitamin D would be given at discharge in Italy more than in the EU and USA (table 1).

Variation 1: Hyperthyroidism with Concurrent Orbitopathy

In the presence of active moderate-severe GO, the majority of Italian and American physicians would refer the patient to an ophthalmologist; Italian and European respondents would obtain orbital imaging (CT, MRI, ultrasound) more frequently than the American respondents (table 1). The primary treatment modality for hyperthyroidism would change as US and EU endocrinologists tend to opt for prolonged ATD treatment, while Italian endocrinologists opt for surgery ($p < 0.05$; fig. 4b). High-dose glucocorticoid treatment for GO is mostly administered by endocrinologists in the EU and Italy (table 1).

Variation 2: Hyperthyroidism Management in a Patient Planning Pregnancy

For a hyperthyroid woman planning pregnancy over the next 6–12 months, Italian respondents preferred surgery, whereas the EU and US respondents opted for ATD

($p < 0.01$; fig. 4c). When a pregnancy is confirmed, the majority of physicians in the three surveys would switch from MMI to PTU (table 1).

Discussion

The present study depicts the attitude of Italian endocrinologists in the management of GD. To date, this is the survey with the highest number of respondents, compared with the North American and European surveys [2, 3]. Whereas the Italian study derived from a limited area, the study from North America derived from the USA for the 59% of the cases, and outside the USA for the remaining cases; the European survey was representative of the relative area, but counts the lowest number of respondents (147), of whom just 38% with clinical interests.

For the diagnostic assessment of our hyperthyroid patient, in Italy, other than serum TSH and FT_4 , nearly all would require TRAb. The use of TRAb in conjunction with ultrasound (requested by 92% of Italian physicians), delineates a significant difference, especially compared with American respondents, who would obtain a thyroid scan or RAIU in about half of the cases. The Italian respondents clearly deviate from ATA/AACE guidelines that suggest a 'radioactive iodine uptake when the clinical presentation of thyrotoxicosis is not diagnostic of GD', and affirm that as 'ultrasonography does not generally contribute to the differential diagnosis of thyrotoxicosis, it should be used only when RAI is contraindicated (pregnancy or breastfeeding)', and that 'TRAb as well should be utilized when a thyroid scan and uptake are unavailable or contraindicated' [4].

Some American and European authors are doubtful about the recommendations from the abovementioned guidelines, and outline the utility of the TRAb test because of its elevated accuracy and low cost [5–11]. Moreover, the objection that the TRAb test may be appropriate for diagnosis, but does not offer a morphologic assessment, is clearly outdone by the use of ultrasound as an imaging tool, which in turn is by far more accurate than RAIU/scan and is cheaper and devoid of irradiation [12]. As a treatment modality, ATD is the first choice for all the respondents, but with a significantly higher rate for Italy and the EU, while RAI presents a significantly higher rate in the USA than in Italy and the EU. It is plausible that given the decline in RAI use with a proportionate increase in the use of ATD in the USA, nowadays this difference might be less evident [13]. The majority of respondents in all the three surveys would suggest MMI with a starting

dose of 20–30 mg/day, and after achieving euthyroidism, the patient's control is 2–3 months later. Italian endocrinologists monitor liver enzymes and CBC more frequently than their colleagues in the EU and USA. The Italian attitude in monitoring the side effects of ATDs seems to be unjustified and too prudent, as most side effects are rare, minor, and transient [14, 15]. It should be kept in mind that the European Thyroid Association guidelines suggest to obtain a CBC and liver profile before MMI treatment [16].

After thyroid surgery, supplementation with calcium and calcitriol is more frequent in Italy than in the EU and USA; this strategy carries several advantages and relatively little downside, especially in the outpatient setting [17].

When GD is complicated by orbitopathy, the great majority of Italian physicians would refer the patients to an ophthalmologist. The reason why Italian physicians obtain more orbital imaging (CT, MRI, ultrasound) compared with their colleagues in the USA may rely on the availability of imaging techniques through the national health service as a routine assessment of orbital disease. However, imaging in most cases appears useless for the assessment of disease activity and thus for planning immunosuppressive treatment in moderate-severe GO [18]. As a treatment modality, thyroidectomy has a neutral effect on active GO and this may be reassuring when opting for a definitive therapy in comparison with RAI.

Surgery is also the treatment of choice for a woman planning pregnancy over the next 6–12 months, and PTU is the preferred drug before pregnancy and during the first trimester. In this latter field, Italian endocrinologists seem to adhere to American guidelines about the use of PTU in the first trimester [19, 20]. The unlucky occurrence of so-called 'methimazole embryopathy' clearly convinced endocrinologists to suggest PTU more than MMI.

In conclusion, the main findings of the present study may be summarized as follows: other than TSH, FT₃, and FT₄, Italian endocrinologists frequently obtain TPOAb, TgAb, and TRAb; EU respondents prefer TRAb determination associated with ultrasound as a diagnostic modality, whereas US respondents prefer RAIU/scan. MMI 20–30 mg/day with a β -blocker is the treatment of choice in the EU, but doctors in the USA opt more frequently for RAI. Liver enzymes and CBC are globally monitored by 50–70% of physicians, and thyroid function is tested every 2–3 months. In case of pruritic macular rash, EU endocrinologists switch ATDs more often than their US counterparts; however, both in the USA and the EU, physicians wait 12–24 months before changing strategy (RAI/surgery). If GO occurs, about 30% of respondents would ask for CT/MRI in the EU, while only 15% would do so in the USA; ophthalmologist consultation is required by 75%, and ATD is the treatment of choice, followed by surgery. In case of planned pregnancy in 6–12 months, surgery is more frequently suggested in Italy than in the EU and USA; PTU is generally preferred to MMI in the first trimester.

As a whole, Italian endocrinologists showed significantly different patterns in diagnosis and management of GD compared with the USA and EU. These findings confirm the opportunity of joint clinical practice guidelines, endorsed by the national endocrine societies, for a cost- and risk-effective management of thyroid diseases.

Disclosure Statement

The authors have nothing to disclose.

References

- 1 Hollowell JG, Staehling NW, Flanders WD, et al: Serum TSH, T(4), and thyroid antibodies in the United States population (1988–1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* 2002;87:489–499.
- 2 Burch HB, Burman KD, Cooper DS: A 2011 survey of clinical practice patterns in the management of Graves' disease. *J Clin Endocrinol Metab* 2012;97:4549–4558.
- 3 Bartalena L, Burch HB, Burman KD, Kahaly GJ: A 2013 European survey of clinical practice patterns in the management of Graves' disease. *Clin Endocrinol (Oxf)* 2016;84:115–120.
- 4 Bahn RS, Burch HB, Cooper DS, et al: American Thyroid Association; American Association of Clinical Endocrinologists: Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Endocr Pract* 2011;17:456–520.
- 5 Barbesino G, Tomer Y: Clinical review: clinical utility of TSH receptor antibodies. *J Clin Endocrinol Metab* 2013;98:2247–2255.
- 6 Tozzoli R, Bagnasco M, Giavarina D, Bizzaro N: TSH receptor autoantibody immunoassay in patients with Graves' disease: improvement of diagnostic accuracy over different generations of methods. Systematic review and meta-analysis. *Autoimmun Rev* 2012;12:107–113.

- 7 McKee A, Peyerl F: TSI assay utilization: impact on costs of Graves' hyperthyroidism diagnosis. *Am J Manag Care* 2012;18:e1–e14.
- 8 Daniels GH: The American Thyroid Association and American Association of Clinical Endocrinologists' guidelines for hyperthyroidism and other causes of thyrotoxicosis: an appraisal. *Endocr Pract* 2011;17:325–333.
- 9 Kahaly GJ, Bartalena L, Hegedus L: The American Thyroid Association/American Association of Clinical Endocrinologists guidelines for hyperthyroidism and other causes of thyrotoxicosis: a European perspective. *Thyroid* 2011;21:585–591.
- 10 Mariotti S, Caturegli P, Piccolo P, et al: Anti-thyroid peroxidase autoantibodies in thyroid diseases. *J Clin Endocrinol Metab* 1990;71:661–669.
- 11 Morita T, Tamai H, Oshima A, et al: The occurrence of thyrotropin binding-inhibiting immunoglobulins and thyroid-stimulating antibodies in patients with silent thyroiditis. *J Clin Endocrinol Metab* 1990;71:1051–1055.
- 12 Sipos JA, Kahaly GJ: Imaging of thyrotoxicosis. *Am J Med* 2012;125:S1–S2.
- 13 Emiliano AB, Governale L, Parks M, Cooper DS: Shifts in propylthiouracil and methimazole prescribing practices: antithyroid drug use in the United States from 1991 to 2008. *J Clin Endocrinol Metab* 2010;95:2227–2233.
- 14 Cooper DS: Antithyroid drugs. *N Engl J Med* 2005;352:905–917.
- 15 Nakamura H, Miyauchi A, Miyawaki N, Imagawa J: Analysis of 754 cases of antithyroid drug-induced agranulocytosis over 30 years in Japan. *J Clin Endocrinol Metab* 2013;98:4776–4783.
- 16 Biondi B, Bartalena L, Cooper DS, et al: *Eur Thyroid J*. 2015;4:149–163.
- 17 Terris DJ, Inabnet WB 3rd, Kandil E, et al; American Thyroid Association Surgical Affairs Committee Writing Task Force: American Thyroid Association statement on outpatient thyroidectomy. *Thyroid* 2013;23:1193–1202.
- 18 Bartalena L, Baldeschi L, Dickinson AJ, et al; European Group on Graves' Orbitopathy (EUGOGO): Consensus statement of the European Group on Graves' orbitopathy (EUGOGO) on management of GO. *Eur J Endocrinol* 2008;158:273–285.
- 19 De Groot L, Abalovich M, Alexander EK, et al: Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2012;97:2543–65.
- 20 Stagnaro-Green A, Abalovich M, Alexander E, et al: Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid* 2011;21:1081–1125.