A 2011 Survey of Clinical Practice Patterns in the Management of Graves' Disease

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Context: More than two decades have passed since members from the American Thyroid Association (ATA), European Thyroid Association, and Japan Thyroid Association were surveyed on management practices for patients with hyperthyroidism due to Graves' disease (GD).

Objective: We sought to document current practices in the management of GD and compare these results both to those documented in earlier surveys and to practice recommendations made in the 2011 ATA/American Association of Clinical Endocrinologists (AACE) hyperthyroidism practice guidelines. Lastly, we sought to examine differences in GD management among international members of U.S.-based endocrine societies.

Methods: Members of The Endocrine Society (TES), ATA, and AACE were invited to participate in a web-based survey dealing with testing, treatment preference, and modulating factors in patients with GD.

Results: A total of 730 respondents participated in the survey, 696 of whom completed all sections. Respondents included 641 TES members, 330 AACE members, and 157 ATA members. The preferred mode of therapy in uncomplicated GD was antithyroid drugs (ATDs) by 53.9% of respondents, radioactive iodine (RAI) therapy by 45.0%, and thyroid surgery in 0.7%. Compared with 1991, fewer U.S. (59.7 *vs.* 69%) and European (13.3% *vs.* 25%) respondents would use RAI therapy. Methimazole and carbimazole were the preferred ATDs, with only 2.7% of respondents selecting propylthiouracil. Patients with Graves' ophthalmopathy were treated with ATDs (62.9%) or surgery (18.5%) and less frequently with RAI plus corticosteroids (16.9%) or RAI alone (1.9%).

Conclusions: Striking changes have occurred in the management of GD over the past two decades, with a shift away from RAI and toward ATDs in patients with uncomplicated GD. Apparent international differences persist but should be interpreted with caution. Current practices diverge in some areas from recently published guidelines; these differences should be assessed serially to determine the impact of the guidelines on future clinical practice. **(*J Clin Endocrinol Metab* 97: 4549–4558, 2012)**

The management of Graves' disease (GD) has been influenced by a number of clinical advances over the past two decades. Included among these are the recognition of an association between new or worsened Graves' ophthalmopathy (GO) and antecedent radioactive iodine (RAI) therapy (1–3), a heightened awareness of life-threatening adverse effects of propylthiouracil (PTU) (4), the once-favored antithyroid drug (ATD) (5), and a refine-

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Abbreviations: ATD, Antithyroid drug; CBC, complete blood count; GD, Graves' disease; GO, Graves' ophthalmopathy; MMI, methimazole; PTU, propylthiouracil; RAI, radioactive iodine; RAIU, RAI uptake; TBII, TSH-binding inhibitory Ig; TRAb, TSH-receptor antibody; TSI, thyroid-stimulating Ig.

ment of optimal management goals for thyroid dysfunction during pregnancy (6). Additional data pertaining to the role of adjunctive ATD treatment before (7–9) or after (10) RAI therapy, the effect of radioiodine on TSH-receptor autoantibody levels (11), the association between tobacco smoking and GO (12), and an overall improved understanding of the pathogenesis of GO (13) have each affected clinical practice.

In 2011, the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE) published practice guidelines pertaining to the management of hyperthyroidism (14). Although these guidelines are intended to positively affect change in patient management, it is not clear to what extent current clinical practice differs from these recommendations, because the last systematic survey of management practices for GD in the United States was published nearly a quarter of a century ago (5). That survey, which included members of the ATA, and contemporary surveys including members of the European Thyroid Association (ETA) (15) and the Japanese Thyroid Association (JTA) (16) and later in South America (17) and Asia (18) demonstrated dramatic international differences in the manner in which GD is managed (19).

The objectives of the current study were 1) to document current practices in the management of GD, 2) to compare current practice with that previously reported and with that recommended in the 2011 ATA-AACE hyperthyroidism guidelines, and 3) to assess current international differences in the management of GD.

Materials and Methods

Survey design

A web-based, commercial survey management service (Survey Monkey, Palo Alto, CA) was used to administer the survey. The survey included questions pertaining to diagnostic evaluation, choice of therapy, and follow-up of an index case of uncomplicated GD (Table 1), followed by two clinical variants including a patient with mild-moderate ophthalmopathy and a patient anticipating pregnancy over the next 6–12 months (the complete survey is included in Supplemental Material, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). The index case (Table 1) was similar to that in the earlier surveys to members of the ETA, JTA, and ATA (5), with the exception that the current case specified smoking status.

TABLE 1. Clinical impression: uncomplicated GD

INDEX CASE: A 42-yr-old woman presents with moderate hyperthyroid symptoms of 2 months duration. She is otherwise healthy, takes no medications, and does not smoke cigarettes. She has two children, the youngest of whom is 10 yr old, and does not plan on being pregnant again. This is her first episode of hyperthyroidism. She has a diffuse goiter, approximately two to three times normal size, pulse rate of 105 beats per minute, and has a normal eye examination. Thyroid hormone levels are found to be twice the upper limit of normal (free T4 = 3.6 ng/dl; normal range = 1.01-1.79 ng/dl), with an undetectable thyrotropin level (TSH < 0.01 mIU/liter).

Strategy for question design

Most questions required a single best response to be selected from multiple choices. Diagnostic preference questions allowed multiple items to be simultaneously selected. To limit bias, questions were carefully constructed to omit phrasing that could influence respondents' answers, and a broad range of answers were included, arranged alphabetically or numerically. The survey was constructed specifically with fewer clinical variants than earlier surveys and designed and tested to allow a completion time of approximately 10 min. Before general release, the survey was vetted through council members of the three societies and the research committee of the ATA.

Contact of potential respondents

The target groups for the survey were clinically active international members of The Endocrine Society (TES), the ATA, and the AACE. Respondents were contacted according to the current bylaws, regulations, and philosophies of the individual society. Members of TES who were listed by the society as clinically active received a single e-mail from TES administrators describing the survey and containing an electronic link to the survey website. The authors did not contact potential respondents directly, and no reminders were sent to nonrespondents. Members of the ATA received notice of the survey opportunity in distributed newsletters to society membership, and an electronic link was included on the ATA website. Members of AACE were notified by newsletter.

Collection and summary of responses

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. The survey website was open to respondents for the three month period from 19 April to 18 July 2011.

Geographical region of respondents

The geographical location was localized to country of the respondents' clinical practices. To preserve anonymity, the city or town of origin of individual respondents was not requested. Respondents were grouped according to the United Nations country grouping of the following geographical regions: Africa, Asia, Europe, Latin America, the Middle East, North America (United States and Canada), and Oceania. Responses from Asia and Oceania (the latter principally Australia and New Zeeland) were pooled as were responses from Northern Africa and the Middle East.

Statistical analysis

Summary statistics were prepared for responses to each question. Because not every participant answered all questions, the

TABLE 2. Existing GD management surveys

First author (year published)	Number of surveys sent	Number of responses analyzed	Target group
Glinoer (1987) (15)	NS	100	ETA
Nagayama (1989) (16)	698	138	JTA
Solomon (1990) (5)	380	197	ATA
Mithal (1993) (21)	45	32	Endocrine Society of India
			Indian Thyroid Association
Romaldini (1997) (17)	235	NS	Latin Thyroid Association
Tominaga (1997) (18)	115	60	JTA
	164	64	Korea Thyroid Association
	NS	17	Chinese Thyroid Association
Escobar-Jiménez (2000) (22)	70	53	Spanish endocrinologists
Walsh (2000) (20)	310	130	Endocrine Society of Australia
Current study (2012)	1852[a]	730[b]	TES, AACE, and ATA

NS, Not stated.

[a] This number represents the number of directly contacted Endocrine Society Members who opened the e-mail invitation. This does not include any additional responses received independently from ATA and AACE newsletter and webpage links (see text).

[b] Among 730 individuals participating in the survey, 696 completed all sections. All responses to individual questions were included in the analysis of that question.

percentage of respondents providing a given answer was calculated individually for each question, using the number of respondents to that question in the denominator. Statistical analysis explored the relationship between respondent demographics and key diagnostic or treatment preferences for the index case. Fisher's exact test (two-tailed) was used to compare both the decade of medical school graduation and the geographical region of respondents to preferred treatment modality (ATDs, RAI, or surgery) or testing preference. Data were analyzed using IBM SPSS Statistics version 19 software (SPSS, Chicago, IL).

Results

Response rate and society membership

Seven-hundred thirty respondents participated in the survey, and 696 (95.3%) completed all sections. This response compares favorably to previous GD management surveys (5, 16–18, 20–22) (Table 2). Respondents consisted of 648 TES members, 333 AACE members, and 162 ATA members. Among 689 respondents providing society membership information, 297 (43.1%) belonged only to TES, 26 (3.8%) belonged only to AACE, and 11 (1.5%) belonged solely to the ATA. Dual membership in TES and AACE was noted by 204 respondents (29.6%), TES and ATA in 47 respondents (6.8%), and ATA and AACE in four respondents. Membership in all three societies was noted by 100 respondents (14.5%).

Among TES members, 6278 physicians received the e-mail, and 1852 (29.5%) opened it. The response rate for TES members opening the e-mail was 35.0% (648 of 1852), assuming that TES members learned of the survey through the direct e-mail rather than the newsletter or webpage links provided through the ATA or AACE. The relatively small number of respondents belonging solely to either ATA or AACE or both but not TES supports this assumption. The manner in which the ATA and AACE contacted potential respondents precluded estimates of independent response rates for these societies.

Respondent demographics

The type of medical practice reported by respondents was adult endocrinology (92.2%), pediatric endocrinology (8.3%), general internal medicine (4.6%), nuclear medicine (2.2%), and general surgery (0.6%). The geographical regions of the respondents' practices were diverse (Fig. 1), including North America (United States, 59.0%; Canada, 4.0%), Europe (12.9%), Latin America (11.3%), Asia and Oceania (9.5%), and the Middle East and Africa (3.4%). The median year of graduation from medical school was 1987 (mean, 1986 ± 12). Seventy percent of respondents noted treatment of more than 10 new cases of GD annually. No demographic data were able to be collected on nonrespondents.

Diagnostic evaluation of the index case

Figure 2A shows the percentage of respondents ordering the listed laboratory tests for the index case. Among 726 respondents, baseline assessments of the complete blood count (CBC) and liver function tests would be obtained by 361 (49.7%) and 348 (47.9%) of the respondents, respectively. TSH-receptor antibody (TRAb) testing was selected by 422 respondents (58.1%), among whom 72.2% would obtain thyroid-stimulating Ig (TSI) alone, 10.4% TSH-binding inhibitory Ig (TBII) alone, and 17.3% who would obtain both TSI and TBII. Regional differences were noted in test-ordering patterns, with a higher use of TRAb testing in Europe (77.5%) than in

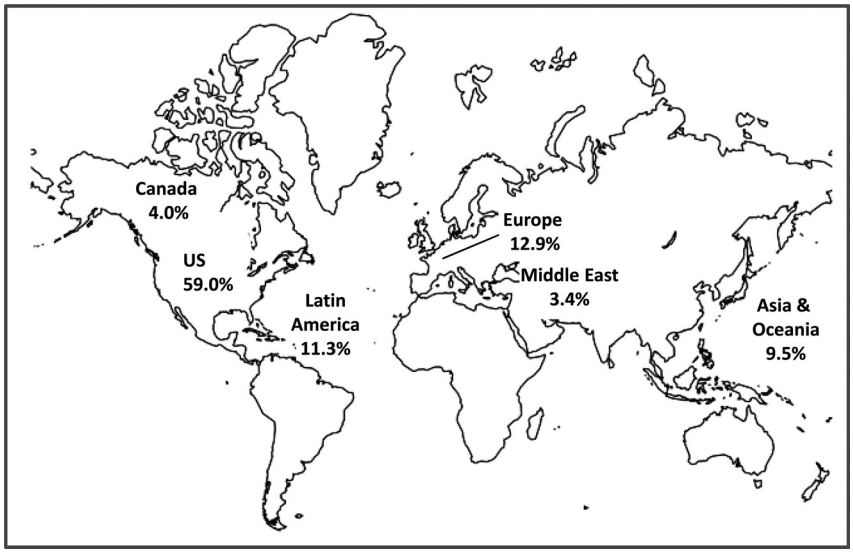

FIG. 1. Geographical distribution of survey participants. Regions were defined using the United Nations country grouping system.

North America (54.3%; $P < 0.001$) and, conversely, a higher use of isotopic studies [RAI uptake (RAIU) or thyroid scanning] in North America (70.9%) than in Europe (30.3%; $P < 0.001$), with intermediate values obtained for Asia/Oceania for both TRAb testing (65.3%) and isotopic studies (54.2%). T_3 and /or free T_3 measurement was similar by region, being requested by 73.6% of respondents from Asia and Oceania, 73.7% from North America, and 63.7% from Europe ($P = 0.126$ for between-group differences).

Figure 2B shows the percentage of respondents who would request the listed anatomical or functional test for the index case. At least one type of functional or anatomic study would be obtained by 524 (72.2%) respondents. A RAIU measurement would be obtained by 47.0% of respondents, including 119 (16.4%) who would request a study using ^{131}I and 222 (30.6%) who would use ^{123}I (two respondents indicated the use of both ^{123}I and ^{131}I for measuring RAIU in their practice). A technetium-99m scan would be requested by 138 respondents (19.0%) and a scan using ^{123}I by 166 respondents (22.9%). A single imaging or functional modality was obtained by 20.9% of respondents, including RAIU (10.9%), thyroid scan (4.7%), and ultrasound (5.4%). One-hundred eighty-seven respondents (25.8%) would obtain a thyroid ultrasound, the majority (58.2%) of whom would not order a radioisotope thyroid scan.

Therapy

The use of β-adrenergic blocking agents

β-Adrenergic blocking drugs would definitely or possibly be used in the index patient by 654 (91.9%) of 712 respondents, including 444 (62.4%) who would definitely use these agents and an additional 210 (29.5%) who would possibly use them. Propranolol was the preferred agent in 400 (61.3%) of 656 respondents, followed by atenolol in 27.9%, metoprolol in 9.5%, and other medications in this class in less than 2% of respondents. The target heart rate was 80–90 beats per minute in 34.8% of respondents, 70–80 beats per minute in 32.7%, and 90–100 beats per minute in 29.2% of respondents.

Preferred primary treatment modality in the index case

ATD therapy was the preferred primary mode of treatment for hyperthyroidism due to GD in 383 (53.9%) of 711 respondents to this question, followed by radioiodine therapy in 320 (45.0%), and thyroidectomy in five

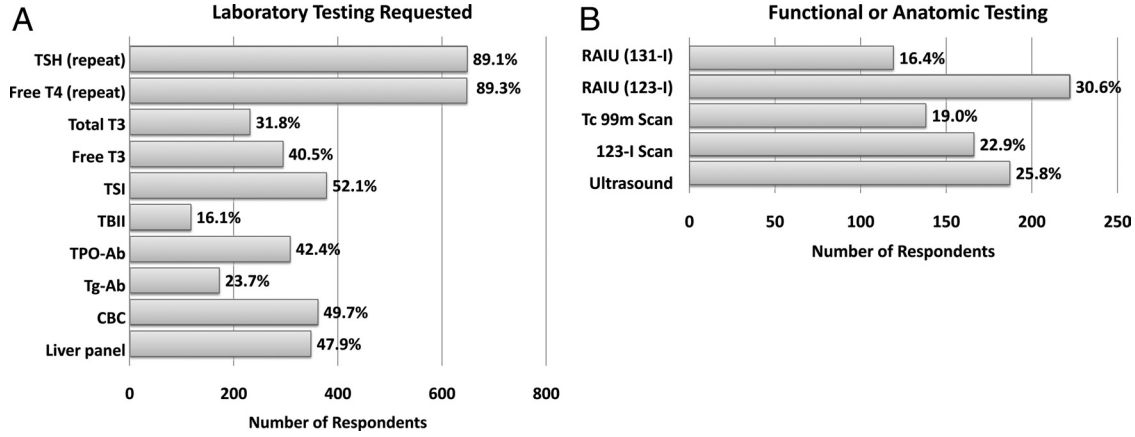

FIG. 2. Percentage of participants who would obtain the listed laboratory test (A) or functional and anatomic study (B) in a patient with uncomplicated GD. Some form of imaging would be obtained by 72.1% of respondents. A single functional or anatomic imaging modality was obtained by 20.9% of respondents, including RAIU (10.9%), thyroid scan (4.7%), and ultrasound (5.4%). Among respondents obtaining an ultrasound, 58.2% would not obtain a thyroid scan. Tg-Ab, Thyroglobulin antibody; TPO-Ab, thyroperoxidase antibody.

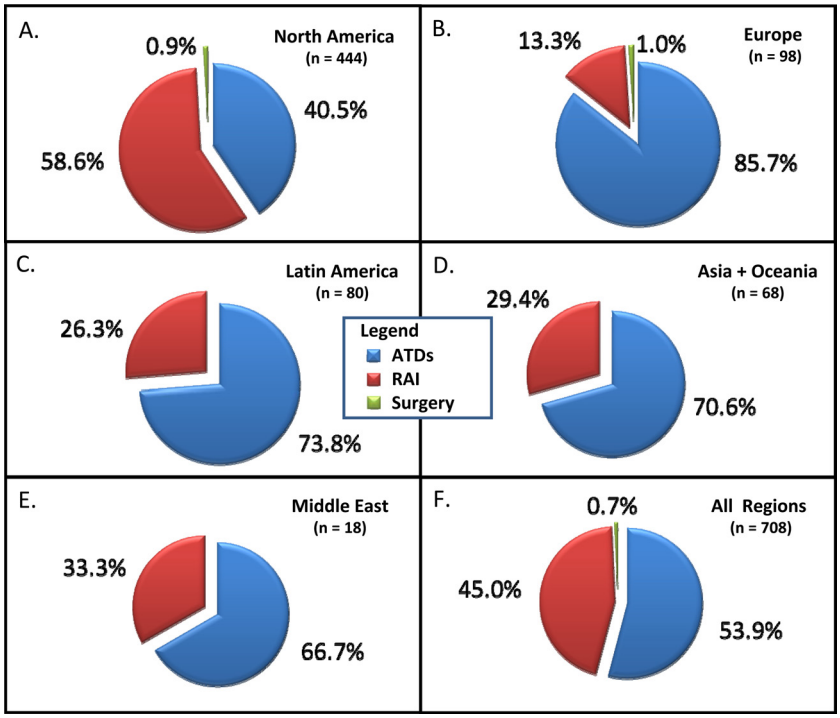

FIG. 3. International differences in the selection of primary treatment modality for the index case of uncomplicated GD.

(0.7%). Less than 1% of respondents would use β-blockers alone in the index case.

Primary treatment preferences were further analyzed by the geographical region and compared with the results of similar surveys performed from 1985–1990 (5, 15, 16), as summarized in 1991 (19). Among respondents with clinical practices in North America, 58.6% would now choose RAI therapy and 40.5% ATDs as the primary mode of therapy, compared with rates of 69 and 30%, respectively, for ATA members surveyed in 1990 (5). There was no change in preference for surgery (less than 1%) during this time interval (Fig. 3). Within the North American group, primary treatment preferences differed between the United States (414 respondents) and Canada (30 respondents), with 56.7% of the Canadians and 39.4% of U.S. respondents preferring ATDs. In comparison with earlier surveys, a greater number of respondents from Asia/Oceania (29.4 *vs.* 10%) and fewer respondents from Europe (13.3 *vs.* 25%) would now use RAI therapy as primary therapy in the index case (Fig. 4). Within the Asia/Oceania group, similar percentages of respondents from Asia and Oceania, respectively, preferred ATDs (73.0 *vs.* 67.7%) and RAI therapy (27.0 *vs.* 32.3%). Treatment preferences compared by major geographical region were significantly different, with significantly less use of ATDs in the United States than in Europe ($P < 0.001$), Latin America ($P < 0.001$), and Asia/Oceania ($P < 0.001$), a higher use of ATDs in Europe than in Latin America ($P = 0.035$) or Asia/Oceania ($P = 0.017$), and no difference in ATD use between Latin America and Asia/Oceania ($P = 0.777$). The low number of respondents from the Middle East/Northern Africa prevented meaningful statistical comparison. There was no apparent effect of decade of graduation from medical school upon preferred primary treatment modality for hyperthyroidism due to GD ($P = 0.644$).

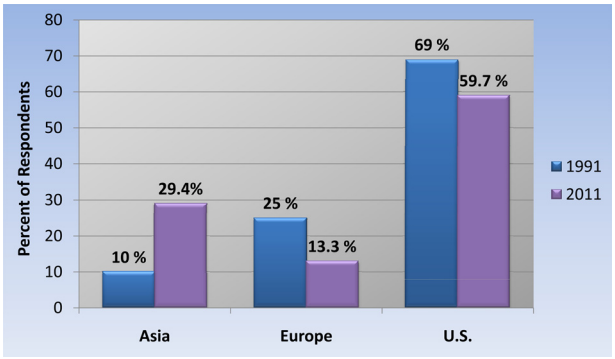

FIG. 4. Potential changes in the use of RAI therapy for the management of hyperthyroidism due to uncomplicated GD by geographical region over a 20-yr period from 1991–2011. Apparent changes in Europe and Asia should be interpreted with caution (see Discussion).

Preferred drug and doses for ATD therapy

Among 704 respondents indicating a preference, 588 (83.5%) would select methimazole (MMI), 13.8% carbimazole, and 2.7% PTU. This contrasts sharply with the 1990 ATA member survey at which time 73% of respondents would have selected PTU as the preferred ATD (5). The preferred starting dose of MMI in the index case was 20 mg once daily by 40.6% of respondents, followed by 30 mg once daily (28.2%), with 10 mg daily (13.0%), 20 mg twice daily (11.3%), and 40 mg once daily (6.9%). The most common starting doses of PTU were 100 mg three times daily by 47.0% of respondents, 50 mg three times daily (14.2%), and 100 mg twice daily (13.9%).

Monitoring ATD therapy

After instituting ATD therapy, thyroid labs would be first checked at 2 wk by 11.3% of 701 respondents, at 3 wk by 9.8%, at 4 wk by 41.8%, and at 6 wk by 26.5% of respondents. After attaining euthyroidism using ATDs, 407 (62.4%) of 652 respondents would perform fol-

low-up thyroid labs at 3-month intervals, 28.5% at 2-month intervals, and 9.0% at 1-month intervals.

Routine monitoring of liver-associated enzymes during ATD therapy was performed by 375 (53.8%) of 697 respondents and serial complete cell count monitoring by 48.4%. The remaining respondents (40.2%) would not perform routine monitoring of either of these parameters.

If a patient being treated with ATDs developed a pruritic, macular rash that failed to respond to antihistamine therapy, 389 (55.3%) of 703 respondents would switch to an alternate ATD, and 38.1% would switch from ATDs to an alternate mode of therapy, including either RAI or surgery; 6.5% would continue the same ATD with additional antihistamine therapy.

Duration of ATD therapy

Respondents were asked how long they would use ATDs in an attempt to achieve a remission from GD. Among 678 respondents to this question, 19.3% would treat for 24 months, 35.4% for 18 months, 30.2% for 12 months, and 13.9% for less than 1 yr.

Adjunctive ATD therapy in patients receiving RAI

Respondents were asked whether they routinely use ATDs to prepare patients for RAI therapy. Among 709 respondents, 352 (49.6%) used ATD preparations only in selected patients, 37.7% routinely pretreat most patients, and 12.7% do not use ATD pretreatment at all. Respondents citing selective use of ATD pretreatment indicated that the presence of underlying heart disease (88.1%), multiple comorbidities (77.7%) and age over 65 yr (60.6%) were indications for ATD pretreatment. When using pretreatment with ATDs before RAI therapy, among 660 respondents, 37.1% stopped ATDs 7 d before RAI, 25.2% at 5 d, 12.1% at 4 d, and 15.8% at 3 d before RAI therapy. Respondents were next asked whether they routinely start ATDs after RAI therapy (posttreatment ATDs). Among 709 respondents to this question, 313 (44.1%) use posttreatment ATDs only selectively, 24.0% routinely in most patients, and 31.9% not at all.

Perioperative management of patients undergoing thyroidectomy

Respondents were queried about perioperative management practices in patients who elect to undergo thyroidectomy as primary therapy for GD. Among 697 respondents, 91.2% would render patients euthyroid with ATDs preoperatively, and 8.8% would not. Preoperative use of iodine drops in the form of saturated solution of potassium iodide or Lugol's solution would be used by 37.0% of 700 respondents, and not used by another 52.0%; 11.0% were unsure whether this was a usual practice at their medical facility. Finally, respondents were asked whether patients at their medical facilities are routinely discharged with calcium and/or vitamin D therapy after thyroidectomy, even if the serum calcium level is normal at the time of discharge. Among 695 respondents, 422 (60.7%) replied that they do not routinely prescribe postoperative calcium and/or vitamin D in this setting, and 39.3% replied that this is indeed a routine practice at their facility.

Variation 1: hyperthyroidism with concurrent ophthalmopathy

The index case was modified to include a history of current tobacco smoking and active GO, consisting of pain with eye movement, moderate scleral injection, eyelid edema, proptosis to 23 mm bilaterally (clinical activity score 3), but normal visual acuity. Respondents were first asked about additional testing or consultation in the presence of active GO. Among 679 respondents, 551 (81.1%) would obtain consultation with an ophthalmologist, and 16.1% would obtain either a noncontrast computed tomography scan or magnetic resonance imaging of the orbits.

The preferred primary treatment modality for hyperthyroidism changed in the presence of active GO, with 439 (62.8%) of 699 respondents now selecting prolonged therapy with ATDs, 18.5% selecting thyroidectomy, 16.9% selecting RAI therapy with prophylactic corticosteroids, and 1.9% selecting RAI therapy alone (Fig. 5). We further examined changes in modality preference by individual respondents in the presence of active GO. Among 320 respondents initially selecting RAI as the principal mode of therapy in the index case, 49.4% would switch to ATD therapy in the presence of active GO, 22.8% would change to RAI plus prophy-

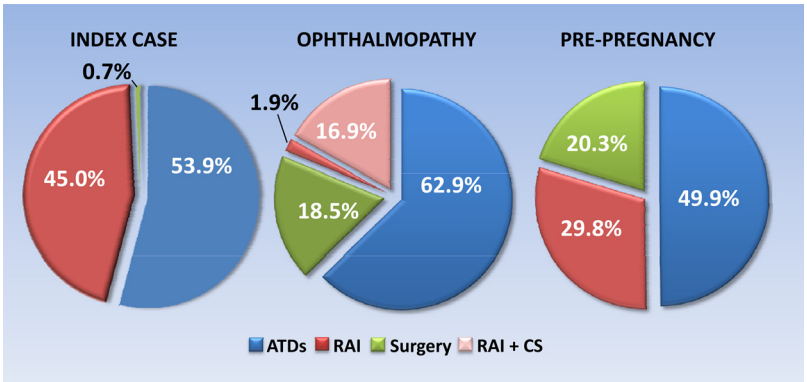

FIG. 5. The effect of clinical variation on the selection of therapy for GD. Clinical variants are described in the text. CS, Prophylactic corticosteroid therapy.

lactic corticosteroids, 22.2% would refer the patient for thyroidectomy, and only 3.4% would continue to use radioiodine without concurrent corticosteroids. Among 278 respondents selecting ATDs as the primary mode of therapy for the index case, 72.6% would still use ATDs in the presence of moderate ophthalmopathy, 13.6% would now choose thyroid surgery, 11.5% would use radioactive iodine plus corticosteroids, and 0.3% would change to radioiodine alone; 2.1% of individuals providing a response for the index case failed to answer this question.

Lastly, when asked to indicate the physician responsible for administering corticosteroid therapy to a patient with active GO, 421(60.9%) of 691 respondents indicated the endocrinologist, 38.9% indicated the ophthalmologist, and less than 1% indicated the primary care physician.

Variation 2: hyperthyroidism management in a patient planning pregnancy

The index case was next modified to a 22-yr-old woman with hyperthyroidism due to confirmed GD and planning pregnancy over the next 6–12 months. Respondents were first asked to indicate their preferred primary mode of therapy in this setting. Among 694 respondents, 346 (49.9%) indicated a preference for prolonged ATD therapy, 29.8% would use RAI therapy, and 20.3% would use thyroidectomy as definitive therapy for the patient's hyperthyroidism, suggesting a shift from RAI to surgery in this setting (Fig. 5). We next examined changes in modality by individual respondents in the setting of a woman planning pregnancy. Among 320 respondents selecting RAI in the index case, 39.1% would now use ATDs, 38.4% would still use RAI therapy, and 20.3% would now refer the patient for thyroidectomy; 2.5% of individuals providing a response for the index case failed to answer this question. Likewise, among 383 respondents who would use ATDs in the index case, 56.7% would still use ATDs in the prepregnant patient, 21.9% would switch to definitive therapy with RAI prepregnancy, and 18.5% would now refer the patient for thyroidectomy; 2.9% of respondents citing preferred therapy in the index case failed to answer this question.

Respondents were asked which ATD they preferred in patients selecting this modality 6–12 months before pregnancy. Among 693 respondents, 376 (54.3%) stated a preference for PTU, and the remaining 45.7% preferred MMI. For respondents electing to use MMI before pregnancy, 238 (75.6%) of 315 respondents would switch to PTU when pregnancy was confirmed, and the remaining 24.4% would continue MMI into the first trimester. For those respondents who used PTU during the first trimester of pregnancy, it was now asked whether they would switch back to MMI upon entering the second trimester, as has been recently recommended (4, 14). Among 680 respondents to this question, 368 (54.1%) would not switch from PTU to MMI upon entering the second trimester and the remainder (45.9%) would in fact change from PTU to MMI at that time.

Discussion

The current study represents the largest survey to date of management practices in patients with hyperthyroidism due to GD and includes responses from a geographically diverse collection of respondents, by virtue of international membership in the academic societies that were surveyed. The results demonstrate a progressive increase in the use of ATD therapy at the expense of RAI therapy, a near elimination of the use of PTU in uncomplicated GD, and an infrequent use of thyroidectomy in the absence of extenuating circumstances such as ophthalmopathy or pregnancy planning.

The reduction in the use of RAI therapy in the United States and potentially in Europe in the past two decades is perhaps the most significant trend demonstrated in the current study. When considering the prevalence of GD to be 0.5 cases per 1000 (23) and the population of the United States to be approximately 300 million, the decline in RAI use translates to approximately 15,000 fewer patients being treated with RAI therapy in the United States each year, with a proportionate increase in the use of ATDs. In fact, a recent U.S. study found an 8-fold increase in the number of prescriptions written annually for MMI between 1991 and 2008, with little change in the number written for PTU (24). In the presence of preexisting ophthalmopathy, there was a 20-fold increase in the use of thyroid surgery, largely at the expense of radioiodine therapy. A similar but more pronounced avoidance of RAI was noted in a recent survey of ETA members regarding treatment of hyperthyroidism in a patient with more severe ophthalmopathy than our clinical variant (25). Although our survey was not designed to determine the factors influencing the changes in preference for ATD use, fear of causing new or worsening GO after RAI therapy seems a likely contributor. Just after publication of the previous GD management surveys in the late 1980s, two randomized trials showed new or worsened GO rates of 33 and 15%, respectively, after RAI therapy compared with rates of 16 and 2.7%, respectively, in patients treated with ATDs (1, 3). Although most affected patients in these studies developed only mild, reversible eye changes, four (10%) of 39 and eight (5%) of 150 patients, respectively, required a specific eye intervention such as high-dose cor-

ticosteroid therapy or orbital radiotherapy. Conversely, a recent randomized trial comparing RAI therapy with ATDs in patients with GD found that those who were smokers or had preexisting GO were no more likely to experience worsening GO after RAI than after ATD therapy, but new GO occurred more frequently after RAI (38%) than with ATDs (18%) (2). A second potential contributor to the declining use of RAI therapy in GD may relate to reports of higher rates of radiation-induced malignancies after treatment of hyperthyroidism with RAI (26), compared with non-hyperthyroid patients in the general population. In contrast to the findings from the United States and Europe, there was an apparent increase in RAI use among respondents from Asia and Oceania. However, due to the small number of survey participants from this area and potential selection bias among international members of U.S.-based endocrine societies, the significance of this finding is uncertain.

Another major change in clinical practice patterns compared with previous surveys has been a near-elimination of the selection of PTU as the preferred ATD in patients with GD undergoing medical management. In the 1990 study by Solomon and colleagues (5), 73% of respondents using ATD therapy would have selected PTU in the index case, compared with less than 3% in the current survey. Although hepatotoxicity due to PTU, including fatal hepatic necrosis, has been known for many years (27), an increased awareness of the potential magnitude of this problem in adults and children has emerged from a series of recent publications and a new black box warning in the package insert for PTU (28–30). Evidence that these are relatively recent changes is apparent in a 2010 paper showing that the number of prescriptions written for PTU in the United States was relatively stable in the years between 1991 and 2008 (24). PTU is no longer available in many countries, which has further contributed to a decline in its use.

The management trends identified in the current study mirror the 2011 ATA/AACE hyperthyroidism practice guidelines in some areas while diverging significantly in others (14). In the case of diagnostic evaluation, these guidelines state that neither RAIU nor TRAb testing are needed in patients with clinical findings consistent with GD, but nearly one half of respondents would obtain an RAIU and more than half would perform TRAb testing in the index case. The ATA/AACE guidelines also recommended against serial monitoring of the CBC and liver function in patients receiving ATDs, yet approximately one half of practicing endocrinologists routinely follow these parameters. For the selection of the primary treatment modality, the guidelines suggest that any of the three modalities should be used to treat uncomplicated GD, but it is clear that thyroidectomy is almost never selected in this setting, with less than 1% of respondents recommending thyroidectomy in the index case. Conversely, there was a nearly 20-fold increase in the use of thyroidectomy when the index case was modified to a patient with mild-moderate ophthalmopathy or a woman planning pregnancy in the next 6–12 months. The selection of MMI and carbimazole as the preferred ATDs by nearly all respondents closely mirrors recommendations made in the ATA/AACE guidelines. However, the selection of ATD before and during the pregnancy differs substantially from guideline recommendations. The ATA/AACE guidelines suggest that MMI be used until pregnancy is confirmed to minimize the potential for PTU-related hepatotoxicity and that PTU should be used for the duration of the first trimester to avoid potential embryopathy associated with MMI use during this trimester. Finally, the guidelines recommend that MMI be restarted at the beginning of the second trimester. Most respondents would use PTU before pregnancy, and many of those using MMI would continue this into the first trimester. Furthermore, more than half of respondents using PTU in the first trimester would continue this medication as needed throughout pregnancy rather than switching to MMI. A selective use of ATD pretreatment before RAI therapy was recommended by the guidelines, and half of respondents favored this approach as well. Likewise, the ATA/AACE guidelines suggested that patients with moderate-severe GO should not be treated with RAI, and our modification of the index case to include active (clinical activity score of 3 of 7) mild-moderately severe GO resulted in only 1.9% of respondents using RAI alone and an additional 16.9% using radioiodine with prophylactic corticosteroids. This suggests a reluctance to use RAI therapy at all in the presence of even mild GO by more than 80% of respondents.

Our study has both strengths and limitations. First, the number of respondents was greater than all previous surveys and represented a diverse international group of endocrinologists. The use of a web-based service minimized presurvey down time and optimized the cataloging of results. The electronic mail invitation to participate (TES members) provided an opportunity for nearly 7000 potential respondents to learn about the survey. An important limitation of the current study is the relatively low percentage of active society membership participating in the survey. Despite the large number of respondents who completed the study, the 648 TES members who completed the survey represented approximately 10% of the clinically active members at the time of the study. Likewise, approximately 13% of ATA members and 6% of AACE members are represented by the current respondents. Another major limitation of the current study is an

underrepresentation of non-U.S.-based endocrinologists and potential selection bias when including international members of U.S.-based endocrine societies. Although the number of European respondents was similar to the 1987 survey of ETA members, it is unlikely that our survey responses or response rates would approximate those obtained with a modern direct survey to members of the ETA. Furthermore, ETA members include a mix of other specialists such as nuclear medicine and surgeons who were less likely to be represented among international members of U.S.-based endocrine societies. Additionally, although regional differences in diagnostic testing were identified in our study, it is possible that the greater use of TRAb testing and lower reliance on isotopic testing in Europe compared with North America reflects greater difficulty distinguishing GD from small toxic multinodular goiters or smaller solitary toxic adenomas in Europe due to persistent subtle iodine deficiency in many European countries. Next, the Asian and Oceania respondents to our survey were limited (n = 68) and were not queried about JTA membership, so although their preferred primary mode of therapy was similar to one another, this subgroup is not strictly comparable to the 1988 survey of JTA members that analyzed 138 responses. Finally, it is possible that international members of U.S. endocrine societies have practices more aligned to those in the U.S. than nonmembers of U.S. societies from the same country. Although this represents a major limitation in our ability to generalize the trends identified in our study to management practices in Europe, Asia, and Latin America, it also makes the stark international differences identified in our study all the more noteworthy.

In summary, our survey shows striking changes in the delivery of healthcare to patients with GD over the past two decades, with a shift away from RAI and toward ATDs in patients with uncomplicated GD. The implication of this change in terms of the incidence of GO and occurrence of major adverse effects from ATDs remains to be determined. International differences persist with a continued greater reliance on RAI therapy in the United States compared with all other geographical regions, albeit at a 10% lower rate than in 1990. Although international endocrinologists accounted for 40% of our respondents, this sampling was limited and subject to selection bias, so updated surveys by thyroid associations in these regions are needed to more accurately determine international practice differences. Finally, current practices diverge from recently published guidelines in multiple areas, and these differences will need to be assessed serially to determine the impact of the guidelines on future clinical practice.

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References

1. **Tallstedt L, Lundell G, Tørring O, Wallin G, Ljunggren JG, Blomgren H, Taube A** 1992 Occurrence of ophthalmopathy after treatment for Graves' hyperthyroidism. The Thyroid Study Group. N Engl J Med 326:1733–1738
2. **Träisk F, Tallstedt L, Abraham-Nordling M, Andersson T, Berg G, Calissendorff J, Hallengren B, Hedner P, Lantz M, Nyström E, Ponjavic V, Taube A, Törring O, Wallin G, Asman P, Lundell G** 2009 Thyroid-associated ophthalmopathy after treatment for Graves' hyperthyroidism with antithyroid drugs or iodine-131. J Clin Endocrinol Metab 94:3700–3707
3. **Bartalena L, Marcocci C, Bogazzi F, Manetti L, Tanda ML, Dell'Unto E, Bruno-Bossio G, Nardi M, Bartolomei MP, Lepri A, Rossi G, Martino E, Pinchera A** 1998 Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. N Engl J Med 338:73–78
4. **Bahn RS, Burch HB, Cooper DS, Garber JR, Greenlee CM, Klein IL, Laurberg P, McDougall IR, Rivkees SA, Ross D, Sosa JA, Stan MN** 2009 The role of propylthiouracil in the management of Graves' disease in adults: report of a meeting jointly sponsored by the American Thyroid Association and the Food and Drug Administration. Thyroid 19:673–674
5. **Solomon B, Glinoer D, Lagasse R, Wartofsky L** 1990 Current trends in the management of Graves' disease. J Clin Endocrinol Metab 70:1518–1524

6. **Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce EN, Soldin OP, Sullivan S, Wiersinga W** 2011 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 21:1081–1125
7. **Burch HB, Solomon BL, Wartofsky L, Burman KD** 1994 Discontinuing antithyroid drug therapy before ablation with radioiodine in Graves disease. Ann Intern Med 121:553–559
8. **Burch HB, Solomon BL, Cooper DS, Ferguson P, Walpert N, Howard R** 2001 The effect of antithyroid drug pretreatment on acute changes in thyroid hormone levels after ^{131}I ablation for Graves' disease. J Clin Endocrinol Metab 86:3016–3021
9. **Braga M, Walpert N, Burch HB, Solomon BL, Cooper DS** 2002 The effect of methimazole on cure rates after radioiodine treatment for Graves' hyperthyroidism: a randomized clinical trial. Thyroid 12: 135–139
10. **Walter MA, Briel M, Christ-Crain M, Bonnema SJ, Connell J, Cooper DS, Bucher HC, Müller-Brand J, Müller B** 2007 Effects of antithyroid drugs on radioiodine treatment: systematic review and meta-analysis of randomised controlled trials. BMJ 334:514
11. **Laurberg P, Wallin G, Tallstedt L, Abraham-Nordling M, Lundell G, Tørring O** 2008 TSH-receptor autoimmunity in Graves' disease after therapy with anti-thyroid drugs, surgery, or radioiodine: a 5-year prospective randomized study. Eur J Endocrinol 158:69–75
12. **Bartalena L, Martino E, Marcocci C, Bogazzi F, Panicucci M, Velluzzi F, Loviselli A, Pinchera A** 1989 More on smoking habits and Graves' ophthalmopathy. J Endocrinol invest 12:733–737
13. **Bahn RS** 2010 Graves' ophthalmopathy. N Engl J Med 362:726–738
14. **Bahn RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, Klein I, Laurberg P, McDougall IR, Montori VM, Rivkees SA, Ross DS, Sosa JA, Stan MN** 2011 Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Thyroid 21:593–646
15. **Glinoer D, Hesch D, Lagasse R, Laurberg P** 1987 The management of hyperthyroidism due to Graves' disease in Europe in 1986. Results of an international survey. Acta Endocrinol Suppl (Copenh) 285:3–23
16. **Nagayama Y, Izumi M, Nagataki S** 1989 The management of hyperthyroidism due to Graves' disease in Japan in 1988. The Japan Thyroid Association. Endocrinol Jpn 36:299–314
17. **Romaldini JH** 1997 Case selection and restrictions recommended to patients with hyperthyroidism in South America. Thyroid 7:225–228
18. **Tominaga T, Yokoyama N, Nagataki S, Cho BY, Koh CS, Chen JL, Shi Y** 1997 International differences in approaches to ^{131}I therapy for Graves' disease: case selection and restrictions recommended to patients in Japan, Korea, and China. Thyroid 7:217–220
19. **Wartofsky L, Glinoer D, Solomon B, Nagataki S, Lagasse R, Nagayama Y, Izumi M** 1991 Differences and similarities in the diagnosis and treatment of Graves' disease in Europe, Japan, and the United States. Thyroid 1:129–135
20. **Walsh JP** 2000 Management of Graves' disease in Australia. Aust NZ J Med 30:559–566
21. **Mithal A, Shah A, Kumar S** 1993 The management of Graves' disease by Indian thyroidologists. Natl Med J India 6:163–166
22. **Escobar-Jiménez F, Férnandez-Soto ML, Luna-López V, Quesada-Charneco M, Glinoer D** 2000 Trends in diagnostic and therapeutic criteria in Graves' disease in the last 10 years. Postgrad Med J 76: 340–344
23. **Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, Evans JG, Young E, Bird T, Smith PA** 1977 The spectrum of thyroid disease in a community: the Whickham survey. Clin Endocrinol (Oxf) 7:481–493
24. **Emiliano AB, Governale L, Parks M, Cooper DS** 2010 Shifts in propylthiouracil and methimazole prescribing practices: antithyroid drug use in the United States from 1991 to 2008. J Clin Endocrinol Metab 95:2227–2233
25. **Perros P, Baldeschi L, Boboridis K, Dickinson AJ, Hullo A, Kahaly GJ, Kendall-Taylor P, Krassas GE, Lane CM, Lazarus JH, Marcocci C, Marino M, Mourits MP, Nardi M, Orgiazzi J, Pinchera A, Pitz S, Prummel MF, Wiersinga WM** 2006 A questionnaire survey on the management of Graves' orbitopathy in Europe. Eur J Endocrinol 155:207–211
26. **Metso S, Auvinen A, Huhtala H, Salmi J, Oksala H, Jaatinen P** 2007 Increased cancer incidence after radioiodine treatment for hyperthyroidism. Cancer 109:1972–1979
27. **Cooper DS** 2005 Antithyroid drugs. N Engl J Med 352:905–917
28. **Rivkees SA** 2010 63 years and 715 days to the "boxed warning": unmasking of the propylthiouracil problem. Int J Pediatr Endocrinol pii:658267
29. **Rivkees SA, Szarfman A** 2010 Dissimilar hepatotoxicity profiles of propylthiouracil and methimazole in children. J Clin Endocrinol Metab 95:3260–3267
30. **Rivkees SA, Mattison DR** 2009 Ending propylthiouracil-induced liver failure in children. N Engl J Med 360:1574–1575