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Shifting Trends and Informed Decision-Making in the Management of Graves' Disease

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Graves' disease (GD) is the most common cause of hyperthyroidism in the United States and is associated with impaired quality of life (1) and, when untreated, an increased risk of significant morbidity and mortality (2–6). Treatment options for GD include thionamide antithyroid drugs (ATDs), radioactive iodine (RAI) ablation, and thyroidectomy, each of which has unique indications and associated risks that inform patient and provider decision-making. ATDs, most commonly methimazole, have the highest risk of relapse and are associated with adverse events, including pruritic rash, agranulocytosis, and hepatotoxicity (7,8). RAI is more successful in causing hypothyroidism in patients with GD after an initial dose, but can cause transient worsening of thyrotoxicosis and concerns for Graves' orbitopathy (7–10). The surgical management of GD with total thyroidectomy is associated with very low recurrence rates, but poses the risk of permanent hypoparathyroidism and recurrent laryngeal nerve injury, which may be more common when surgery is performed by low-volume surgeons and can contribute to long-term morbidity (11). Recently updated American Thyroid Association (ATA) guidelines for the management of hyperthyroidism highlight that treatment decisions should be made by physicians and patients together, focusing on the ''logistics, benefits, expected speed of recovery, drawbacks, potential side effects, and costs'' (12). However, socioeconomic factors, regulations, and regional practice patterns have a significant influence on the primary treatment modality for GD, with prior studies showing RAI ablation more commonly used in North America and ATDs more common in Europe and Asia (13,14). Up until now, population-based data on the comparative risks and benefits of ATDs, RAI ablation, and thyroidectomy have been lacking, which has limited informed decision-making by patients and providers.

In this issue of *Thyroid*, Brito *et al.* (15) report the findings of a retrospective cohort study using the OptumLabs Data Warehouse that describes treatment patterns for GD in a privately insured and Medicare Advantage population in the United States and documents the comparative effectiveness and safety of ATDs, RAI, and thyroidectomy in this group. The authors report the percentage of patients undergoing each therapy and unadjusted rates of treatment failure and adverse events. They then used Cox proportional hazards regression models to identify risk factors for treatment failure. With this analysis, they found that the majority of patients were initially treated with ATDs (60%), followed by RAI (33%) and thyroid surgery (6%), with 26% of patients ending up on long-term ATD therapy. When assessing treatment efficacy, they found that GD treatment was successful (based on not receiving further treatment) in only 50% of patients who received ATDs, 93% of patients who received RAI, and 99% of patients who underwent surgery. Thyroid surgery had the highest rate of adverse events (24%) based on their definitions, with hypoparathyroidism (combined transient and permanent) being the most common. Based on these findings, the authors recommended (1) further investigation of the safety, risks, and costs of long-term ATD therapy and (2) use of their results to facilitate shared decision-making with GD patients.

This study is the first to document practice patterns for the management of GD and treatment efficacy in a large national patient population in the United States, which will improve our ability to counsel and effectively care for these patients. Before this publication, our understanding of treatment decisions in GD was based predominantly on single center studies and surveys administered through national endocrine societies, which were subject to selection bias and did not account for the influence of patient preference and shared decision-making on treatment choice (14,16–18). In contrast, this claims-based retrospective cohort study was well designed to document how privately insured patients with GD are being managed in a real-world setting. The comprehensive data within the OptumLabs database were appropriately used to assess first- and second-line treatments employed for a nationally representative patient population with GD. By restricting cohort inclusion to patients with continuous enrollment 2 years after treatment initiation, the authors were able to provide longitudinal follow-up on a geographically diverse group of patients with GD, who were treated with all three available treatment modalities, and compare both treatment efficacy and adverse events.

Limitations of the study, as highlighted by the authors, are related to the absence of granular clinical information in the OptumLabs database. Laboratory data such as thyroid

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function tests and antibody status could not be extracted, so we are unable to assess disease severity, confirm treatment failure based on biochemical parameters, or identify patients at risk for relapse based on degree of thyroid stimulating immunoglobulin elevation at diagnosis or while on ATD therapy (19–21). Information on the presence and size of an associated goiter or thyroid nodules was not available, which would affect the decision to pursue surgical management up front, and claims data fail to distinguish between treatment failure or a change in patient preference. In addition, relevant patient factors, such as pregnancy status of female patients in fertile age groups, were not reported. This is important, as pregnancy is the most common indication for definitive surgical intervention in this population due to concerns about the teratogenicity of ATDs and the need to wait at least 6 months to conceive after RAI ablation (12,22). Finally, patients with private insurance tend to be diagnosed at earlier stages of disease and are more likely to receive therapeutic interventions than patients who are uninsured, underinsured, or on Medicaid (23–26), so these results may not be representative of or generalizable to all patients with GD in the United States.

Nevertheless, the results of this study highlight shifting trends in the management of GD in the United States, away from RAI and toward initial and long-term ATD therapy. This trend was foreshadowed by a 2011 survey of providers from the ATA, Endocrine Society, and American Association of Clinical Endocrinologists (AACE), which showed that RAI use was decreasing in popularity as the preferred initial therapy for uncomplicated GD when compared with a similar survey performed in 1991 (14). Potential factors contributing to this practice change include concern over the risks of RAI ablation in patients with Graves' orbitopathy, a better understanding of the risk profile of methimazole given frequent long-term use in other countries, a preference to avoid hypothyroidism and lifelong hormone replacement, and concerns about the long-term risks of secondary malignancies with RAI administration (27,28). There is continued debate regarding the validity of these concerns, with better data still needed. But, a national change in practice patterns favoring ATDs is now confirmed, requiring us to refocus research efforts to evaluate if this trend will lead to improved outcomes and quality care for patients with GD. In addition, the study by Brito *et al.* provides the first estimate of the prevalence of surgical management for GD, which was the initial treatment strategy in 6% of patients in this cohort. Recent endocrine surgery publications have documented a trend toward increased utilization of thyroidectomy for the management of GD at high-volume institutions, most commonly after failure or intolerance to ATDs, but this appears to be an uncommon practice in the general population with GD based on this cohort (29,30).

This study also identified some shortcomings in the care for patients with GD, including the finding that in clinical practice, the time from ATD treatment initiation to treatment break is often shorter than recommended by the ATA and AACE guidelines. The authors showed that the median time to treatment break was 214 days in the overall cohort, but that if the length of ATD therapy was extended to 1 year, the rate of treatment failure decreased from 50% to 25%. Although we agree that there are other potential explanations for early discontinuation of ATDs by patients in this study, these results are in agreement with other analyses that have shown that extended, 18-month ATD treatment significantly increases the likelihood for remission in GD (31) and support guideline recommendations for a minimum of 12–18 months of initial ATD therapy to maximize efficacy (12). Although this study also provides some insight into which patients are most likely to fail first-line ATD therapy, including young and black patients, these results raise a number of questions about the validity of these associations and whether disease severity, access to care, or other unmeasured confounding factors may be contributing. Without further research incorporating more granular clinical and biochemical data, these new findings are unlikely to improve patient selection for initial ATD therapy when compared with prior instruments, such as the Clinical Severity Score or Graves' Recurrent Events After Therapy (GREAT) score, which has been validated but is not widely used in clinical practice (32–34).

With new insight into the predominant treatment strategies used to treat patients with GD in the United States, further research is needed to weigh efficacy against associated risks and develop a patient-centered approach to treatment decisions. With a recent publication documenting an increased risk of death from solid organ malignancies in hyperthyroid patients treated with RAI (28), practice patterns may again shift and drive endocrinologists and patients further away from RAI and toward ATDs or thyroidectomy. Although these results are in conflict with prior studies, and debate on this topic is likely to continue (35–37), we agree it is imperative to evaluate the risks and costs associated with long-term treatment with ATDs, given one in four patients with GD end up in this group. In addition, a well-designed population-based evaluation of perioperative complications in GD patients treated with thyroidectomy is needed, given the alarmingly high rates of hypoparathyroidism and other adverse events after thyroidectomy that were reported in this study. Although this may be explained by the use of nonspecific ICD-9 codes to define complications (i.e., ''other disorders of calcium metabolism'' as criteria for hypoparathyroidism) and failure to use available pharmacy claims or other available data to corroborate these findings, this certainly warrants further investigation. While transient hypoparathyroidism is more common after thyroidectomy for GD than for many other benign and malignant indications and is generally manageable with short-term administration of calcium and calcitriol (38), permanent hypoparathyroidism is associated with significant morbidity, impaired quality of life, and substantial cost if recombinant parathyroid hormone is prescribed (39,40). Therefore, more granular analysis of the OptumLabs data or follow-up population-based studies are needed to document the risks and benefits of surgical therapy in GD, ideally with consideration of surgeon volume.

Overall, the findings of this study will improve the ability of endocrinologists to provide GD patients with accurate information regarding the efficacy and risks of each treatment modality and highlight high-priority topics for future research. Each patient has different priorities and preferences that will determine which initial treatment strategy is best for them, so updated estimates of treatment efficacy and associated adverse events will inform shared decision-making and help individualize GD treatment decisions. Cardiovascular risk and mortality is increased in patients with persistent hyperthyroidism after initial treatment (41), so priority should be given to rendering patients euthyroid in an

expeditious manner with whatever treatment modality is preferred by the patient and deemed appropriate by their endocrinologist based on disease severity and associated clinical features. A more detailed assessment of long-term treatment risks that goes beyond this study's findings will improve patient and provider decision-making, and priority should be given to developing tools to predict which patients are most likely to respond to treatment with ATDs and RAI or benefit from thyroidectomy. We commend the authors for reporting results that will have a significant impact on the management of patients with GD and look forward with anticipation to the research it will inspire to facilitate individualized treatment decisions in GD.

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