Current Evidence and Research Gaps on the Economic Burden of Graves' Disease: A Targeted Literature Review

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BACKGROUND

- Graves' disease (GD) is an autoimmune disease, and the most common cause of hyperthyroidism, where systemic manifestations can affect the heart, eyes, liver, bone, skeletal muscle, and skin[1,2]
- Current guidelines for GD recommend first-line therapy with antithyroid drugs (ATDs), and while ablative therapies (ie, thyroidectomy, radioactive iodine [RAI]) are also available, patients and providers aim to avoid these treatments due to resulting lifelong hypothyroidism[3]
- Patients with GD are at increased risk of heart failure, depression, dementia, diabetes, and other conditions, even after treatment[4-9]
- The economic burden of GD, including direct and indirect costs and healthcare resource use (HCRU), has not been comprehensively reviewed in recent years

OBJECTIVES

- To evaluate available economic evidence among GD populations, including information pertaining to the disease and treatment costs and HCRU
- To identify knowledge gaps related to economic burden that could be used to guide future research

METHODS

- This analysis included a targeted review of scientific literature published from January 1, 2019, through August 2, 2024
  - Literature searches were conducted in Embase, MEDLINE, the Cochrane Library, and Econlit using a predefined search strategy designed to identify articles describing economic outcomes in GD
- Relevant conference proceedings published between January 1, 2021, and August 2, 2024, were also identified via handsearching
- One independent reviewer screened all records, first as titles/abstracts and then as full texts, and a second independent reviewer performed a quality control check of 10% of records
  - The following conferences were searched: American Thyroid Association, British Thyroid Foundation, European Thyroid Association, and ISPOR

RESULTS

Study attrition

- From 2,152 unique records evaluated, only eight relevant citations were identified, including two from the US, three from Europe, and three from China (**Table 1**)
  - Study designs included retrospective observational studies (n=5), a prospective interventional study (n=1), and economic models (n=2)

Table 1. Characteristics of included economic studies in GD

Author, Year	Study Design	Country/ Region	Study Period	Median Follow-up Time, Months	Sample Size, N	Mean Age, Y	Female, %
Akram, 2020[10]	Retrospective observational	US	2007–2015	NR	228	39	83
Aung, 2019[11]	Retrospective observational	UK	2006–2015	80	576	51	74.5
Karmisholt, 2022[12]	Prospective interventional	Denmark	2007–2011	NR	208	43.8-44.6[a]	83.6-92.0[a]
Liu, 2021[13]	Retrospective observational	China	2006–2018	90	6,385	45.6	72.6
Liu, 2022[14]	Retrospective observational	China	2006–2018	79	3,443	45.1	73.0
Zhu, 2021[15]	Retrospective observational	China	2015–2019	NR	3,558	43.3[b]	83.3[b]
Ma, 2023[16]	Cost-effectiveness analysis	US	NA	NA	NA	NA	NA
Lindholm, 2023[17]	Cost-utility analysis	Sweden	NA	NA	NA	NA	NA

[a]Demographics were provided separately for ATD-treated patients with ADRs (n=25) and without ADRs (n=183). [b]Demographics were provided for 36 patients who were hospitalized with ATD-induced agranulocytosis.

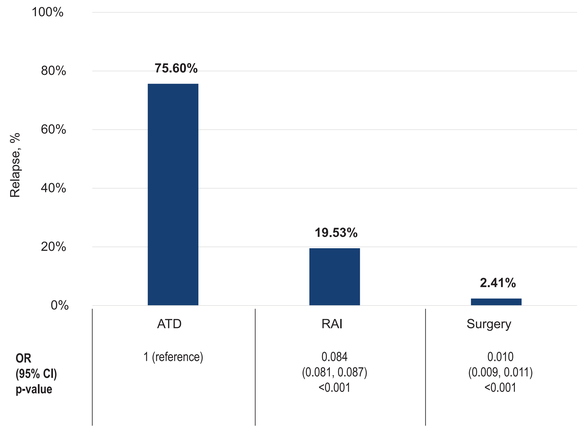
ADR, adverse drug reaction; ATD, antithyroid drug; GD, Graves' disease; NR, not reported; NA, not applicable; UK, United Kingdom; US, United States.

RESULTS

Costs of ATD, RAI, and thyroidectomy

- Three real-world evidence studies included data on costs; all focused on costs associated with specific treatments
  - In a Chinese retrospective study examining 6,365 patients who initiated first-line treatment with ATD (74.93%), RAI (19.95%), or thyroidectomy (5.12%) between 2006 and 2018, the relapse rate was significantly higher for patients treated with ATD than for RAI or thyroidectomy (**Figure 1**)[13]
  - Ten year cumulative costs were $23,915, $24,260, and $20,202, respectively[13]
    - This included costs related to clinic visits, hospitalizations, surgical procedures, and relevant medications
  - In a second Chinese study in patients with persistent or relapsed GD who initiated second-line treatment over the same time period (n=3,443), 10-year cumulative costs were €17,390 for ATD, €17,918 for RAI, and €14,754 for thyroidectomy[14]
  - In both Chinese studies, the highest annual expenses were incurred in the first year for all treatments[13,14]
    - Year 1 costs in 6,365 patients:
      - ATD: $5,269
      - RAI: $7,759
      - Thyroidectomy: $12,063
  - ATD and RAI had similar long-term costs in patients with GD, but relative thyroidectomy costs differed across studies[12-14]

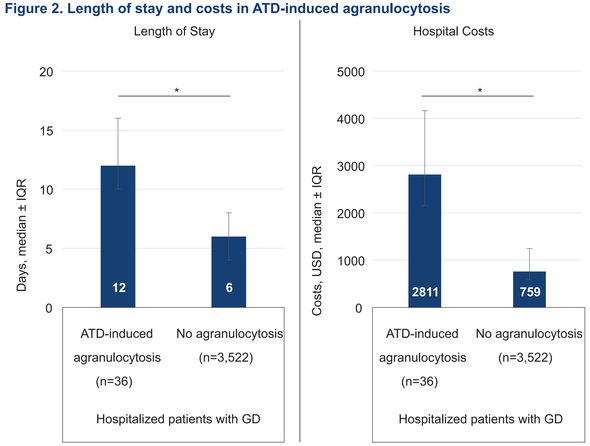
Figure 1. Long-term relapse rates in GD (N=6,385)[13]



p<0.001 relative to ATD. ATD, antithyroid drug; CI, confidence interval; OR, odds ratio; RAI, radioactive iodine

  - Another study calculated the lifetime costs of treating GD with ATD, thyroidectomy, or RAI in a Danish population, depending on the age at treatment initiation[12]
    - Thyroidectomy: approximately €9,250 (age 20) to €6,000 (age 85)
    - RAI: approximately €4,000 (age 20) to €1,000 (age 85)
    - ATD: approximately €4,750 (age 20) to €0 (age 85)
    - ATD + levothyroxine: approximately €8,000 (age 20) to €0 (age 85)
    - Costs included the treatment only and not any other associated costs (eg, for monitoring)
    - This study also reported that 10% of ATD-treated patients experienced adverse drug reactions (ADRs), most within 6 months of treatment initiation, and 16% of which were considered severe. However, costs and HCRU associated with these ADRs were not provided
- Three real-world evidence studies included information pertaining to HCRU in patients with GD
  - A retrospective study examining the impact of agranulocytosis in hospitalized patients with GD found that those with this rare, serious side effect of ATD had higher hospitalization costs and length of stay than those without (**Figure 2**)[15]
    - Recovery time was related to agranulocytosis severity (severe cases [i.e., neutrophil count <0.1 × 10^9/L], 9.77±2.61 days; non-severe cases, 4.00± 1.67 days, P<0.001)
  - Another study looking at impact of new American Thyroid Association guidelines for thyroidectomy patients found a mean (standard deviation [SD]) length of stay ranging from 0.7 (0.5) to 0.8 (1.1) days, with 2.9%–3.2% of patients subsequently visiting the emergency room, 1.1%–2.0% requiring hospital readmission, and 1.1%–2.0% requiring further surgery[10]
  - A retrospective study including 474 patients who received RAI treatment for GD showed that 2.1% had an unscheduled hospital admission within the first 100 days of therapy[11]
    - Approximately half of patients who received RAI had previous treatment with ATD
    - One-quarter of ATD-treated patients who later received RAI failed RAI treatment
  - Disparate treatment-related HCRU outcomes were reported across these studies[10,11,15]
- Two economic analyses found that thyroidectomy was more cost-effective than RAI therapy (**Table 2**)[16,17]

Figure 2. Length of stay and costs in ATD-induced agranulocytosis



* p<0.001. ATD, antithyroid drug; GD, Graves' disease; IQR, interquartile range

Table 2. Economic models evaluating treatments for GD

Author, Year (Country)	Study Overview	Key Results
Ma, 2023 (US)[16]	• Cost-effectiveness comparison based on a Markov decision analytic model • Thyroidectomy vs RAI was evaluated in hypothetical, ATD-refractory patients • Time horizon was the lifespan of patients	• Thyroidectomy was more cost-effective than RAI • ICER of thyroidectomy vs RAI: $2,982 USD / QALY, which was below the WTP threshold of $100,000 USD / QALY
Lindholm, 2023 (Sweden)[17]	• Cost-utility analysis using quality-of-life data from two studies (1996 and 2012) • 8-year time horizon	• Thyroid surgery was more cost-effective than RAI • ATD dominated over RAI • Thyroid surgery was more costly and more effective* than ATD

*Effectiveness was not defined.

ATD, antithyroid drug; GD, Graves' disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; RAI, radioactive iodine; US, United States; USD, United States dollar; WTP, willingness-to-pay.

Key evidence gaps

- Limited evidence on the cost-effectiveness of GD treatments, particularly for ATD, was identified, with no US-based cost-effectiveness evidence identified in the first-line setting
- No evidence on costs or resource use for:
  - Patient monitoring
  - Adverse events associated with treatment
  - Contribution of systemic manifestations of GD or subclinical hyperthyroidism
  - Indirect costs (e.g., time lost from work) of GD
- No US-based evidence on the long-term treatment-related costs associated with GD was identified, including costs associated with permanent hypothyroidism as a result of ablative treatments

CONCLUSIONS

- **Evidence on the short- and long-term costs and HCRU related to treatments for GD, particularly with ATD as the preferred first line therapy, was extremely limited**
- **No evidence on the contribution of systemic manifestations of GD to overall HCRU or costs (direct or indirect) was identified**
- **Data appear limited to the US, northern Europe, and China**
- **Long-term registries and other real-world studies are necessary to fully capture the economic burden of GD, including treatment-related costs and costs related to systemic manifestations associated with GD (e.g., cardiovascular conditions, autoimmune disorders, and depression)**

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DISCLOSURES

LAMW and **KT** are employees of Immunovant, Inc. **EM**, **SR**, and **SN** are employees of PPD™ Evidera™ Health Economics & Market Access, Thermo Fisher Scientific. **NA** was an employee of Immunovant, Inc., at the time this work was carried out.