

Long-term prognosis after medical treatment of Graves' disease in a northern Swedish population 2000–2010

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Abstract

Objective: To investigate the long-term prognosis of patients with Graves' disease (GD) after antithyroid drug (ATD) treatment and follow-up outside of highly specialised care.

Design and methods: Medical records of all patients diagnosed with first-time GD in 2000–2010 with at least 6 months ATD treatment at a central hospital and follow-up in primary health care in the county of Norrbotten in northern Sweden were retrospectively reviewed. Patients were followed for relapse until 31st December 2012. We included 219 patients (mean age 46 years, 82.5% women) with follow-up of maximum 10 years and 829 observed patient years. Data were analysed using Kaplan–Meier estimates and log-rank test.

Results: During the observation period, 43.5% of the patients had relapsed into active GD. The cumulative relapse rates were 22.6, 30.2, 36.9 and 41.5% after 6 months, 1, 3 and 5 years respectively. The presence of goitre ($P=0.014$) predicted relapse. Previous smoking was protective against relapse ($P=0.003$). The levels of free thyroxine or free tri-iodothyronine, age, gender, current smoking and ophthalmopathy did not predict relapse. Agranulocytosis was found in 1.7% (95% CI 0.7–4.0%).

Conclusion: A long-term remission of 56.5%, in an iodine-sufficient area where ATD is offered to most patients in the real world of central and district hospitals, is higher than in most studies. Relapse was most common during the first year, and prognosis was excellent after 4 years without relapse. The protective effect of previous smoking merits further research.

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Introduction

Graves' disease (GD) may be treated with antithyroid drugs (ATDs) or by ablative treatment, i.e. radioiodine (RAI) or surgery. ATDs have traditionally been favoured as first-line treatment in Europe and Japan, while RAI has been preferred in the USA (1). A recent survey among endocrinologists indicates increased use of ATDs both in the USA and Europe (2).

A major disadvantage with ATD treatment is the high risk of relapse. In a Cochrane review of 26 randomised clinical trials (RCTs) with a total of 3388 patients, the

1-year relapse rates after discontinuation of ATDs were 51 and 54%, for block–replace and dose titration respectively (3). The review concluded that an optimal duration of treatment is 12–18 months and that the RCTs were heterogeneous regarding rates of relapse. The relapse rates may vary due to differences in patient selection for ATD, population differences and the length of follow-up. A more recent Greek study has noted a 39% relapse rate after 4 years (4). The relapse rate after 5 years post-ATD treatment is little studied, and modern studies are lacking.

Some factors are associated with relapse or poor prognosis: young age (5, 6, 7); smoking (8, 9, 10, 11); large goitre (5, 6, 7, 8, 10); high thyroid hormone levels (7, 8); severe ophthalmopathy (12) and thyroid receptor antibodies (TRAbs) level after, and in some studies also before, treatment (6, 13, 14, 15). Hypothyroidism, defined as increased thyroid-stimulating hormone (TSH) during treatment, was protective against relapse (16). The importance and magnitude of these risk factors varies between studies.

Sweden is considered iodine sufficient (17, 18) with an iodine fortification programme of table salt since 1936. Only a few small observational studies from the 1970s and 1980s have reported on the prognosis after ATD treatment in Sweden, and only a minority of the eligible patients had been treated with ATDs (7, 19, 20). The cumulative relapse rates were 44–53%.

We report an observational retrospective study of patients diagnosed with GD over an 11-year period with the aim to evaluate the long-term outcome after ATD in a real world clinical setting. Our aim was to facilitate the individualisation of treatment and to better inform the decision makers, both physicians and patients.

Subjects and methods

Norrbottnen is the most northern county in Sweden, and the population in 2005 was 200 251 adult (≥ 18 years) inhabitants. It covers 97 257 km² of land, which includes a large and sparsely populated mountainous inland area and a more densely populated coastal area. The health care in Sweden is government funded and organised in national, regional and local levels. In Norrbotten County there are four local hospitals and one central hospital with specialist care and 36 primary health care centres with general practitioners. GD is treated within the specialist care. The majority of cases are treated at Sunderby Central Hospital in Luleå. In Sweden, every patient is identified by a unique personal number, and all visits are coded according to the ICD-10 in a diagnosis-related group (DRG) registry. In Norrbotten, all hospitals and health centres share the same electronic medical record system.

Study design

A search in the DRG registry identified 657 adult patients with ICD-10 code E05.0 (thyrotoxicosis with diffuse goitre) who were registered to an in- or outpatient visit at the Department of Internal Medicine at the hospitals

or at the primary health care centres in Norrbotten between 1st January 2000 and 31st December 2010 (Fig. 1).

The search was carried out in December 2012, and according to the population registry 59 patients were deceased. The living patients ($n=598$) were contacted by letter with information on the study, and the possibility to deny participation in the study was given. Of those patients, nine (1.5%) were not possible to contact due to wrong address or emigration and 22 (3.7%) did not allow their data to be used.

The medical files of the remaining 626 patients (95.3%) were reviewed to confirm the diagnosis. GD was defined as the combination of overt hyperthyroidism (TSH <0.1 mU/l and increased free thyroxine (fT₄) and/or free tri-iodothyronine (fT₃) on either two separate occasions or on one occasion in close temporal association to the start of treatment) and TRAb positivity ($n=270$). If TRAb was negative or missing, diffuse uptake on thyroid radionuclide scintigraphy ($n=11$) or thyroid-associated

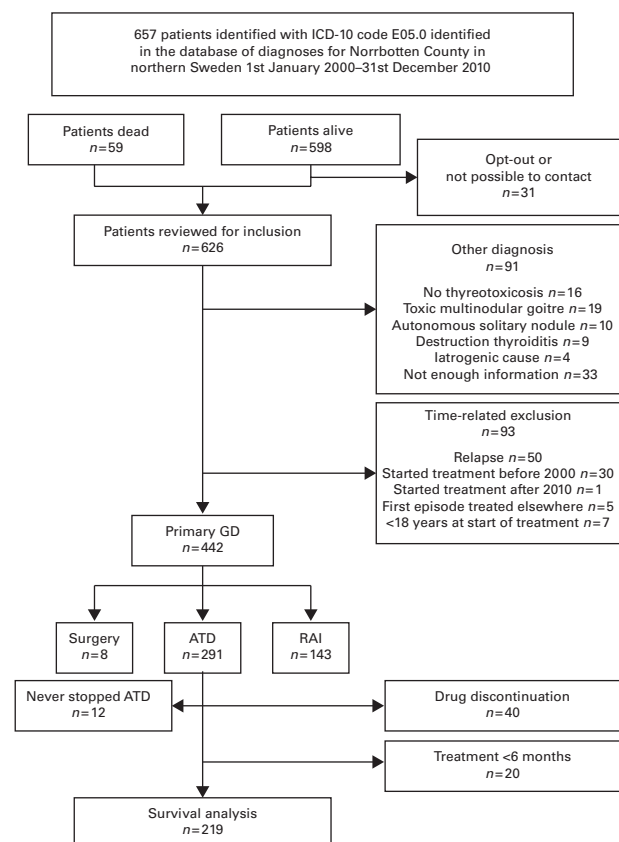


Figure 1

Process of selection of patients from all cases found in the database search to survival analysis-group. GD, Graves' disease; ATD, antithyroid drug; RAI, radioactive iodine.

ophthalmopathy (TAO; $n=10$) was used as the base for the diagnosis of GD. We considered TRAb as positive above the lower cut-off of the TRAb assays (including borderline positive results), as it was considered so in clinical practice, and it has been shown that either cut-off is highly specific for GD (21).

In routine health care, patients were instructed to leave blood samples for white blood cell counts during ATD treatment when they experienced signs of infection. Granulocyte counts were recorded as agranulocytosis if $<0.5 \times 10^9/l$ and granulocytopenia if $<1.5 \times 10^9/l$. After drug withdrawal, patients generally provided blood samples for fT_4 and TSH every 3 months during the 1 year. Thereafter, they were referred from the hospitals to the primary health care centres and were informed to contact the health care services if they experienced any symptoms of thyrotoxicosis. The digital medical record system allows for overview of all laboratory values recorded at every clinic in the county, ensuring that a relapse would not be missed.

The patients with a verified diagnosis of GD were followed for relapse until 31st December 2012, when they were censored in the survival analysis (Fig. 1A). During follow-up, six patients died, three patients moved out of the county, three patients went to private clinics which were not included in the digital medical record system and one patient had ATD reinstated without overt hyperthyroidism. These 13 patients were censored at the last time point we could ensure a follow-up that would have noted a relapse.

Possible predictors for relapse were defined as follows:

- i) fT_4 and fT_3 levels were the highest recorded value within 3 months before start of treatment.
- ii) Goitre (any degree of enlargement on palpation) or no goitre.
- iii) Eye involvement was coded as one of three categories: no eye signs or symptoms, TAO-specific, or non-specific eye-involvement (including grittiness and/or only lid signs).
- iv) Daily smoking was recorded in respect to the time when treatment was started. Tobacco cessation ≥ 6 months before start of treatment was classified as previous use, while cessation < 6 months before start of treatment was classified as current use.
- v) Treatment regimens were classified as block-replace if T_4 was added during treatment, except for a few cases when it was added at the end of treatment to maintain euthyroidism while on minimal ATD doses. Otherwise treatment was classified as dose titration.

The cessation of treatment was not based on levels of TRAb but most commonly on euthyroidism with low (2.5–5 mg) doses of methimazole after 12–18 months of treatment. Date of relapse were registered as the first health care contact or laboratory test in association with overt hyperthyroidism, which was considered to be a relapse by the attending physician.

Patients

Patients were included in this study if they had a verified diagnosis of GD, primary ATD treatment, start of treatment between 1st January 2000 and 31st December 2010 and were 18 years or older at start of treatment. Patients were not included if they had previously been treated for GD. Previous GD was based on the physicians' assessment of the patients' history and the availability of the computerised medical records with coverage for diagnoses, history and laboratory values back to 1995. Furthermore, to be included in the survival analysis, an ATD-treatment period of at least 6 months was required. Of the 627 patients found in the DRG search, 535 patients were verified as GD and 93 were excluded due to relapsed disease or treatment start outside the study period or age < 18 years (Fig. 1). The primary treatment was (RAI) in 143, surgery in eight and ATD in 291 patients.

Among the patients with ATD treatment as primary intention, 12 patients moved, died during treatment or had not ended medical treatment at the end of the observational period. In addition, 40 switched over to ablative treatment (Fig. 1). The reasons for switching were as follows: adverse reactions in 16 patients, failure to control thyroid function while tapering drug in 13 patients, development of severe ophthalmopathy in three patients, change in treatment preference in three patients, fluctuating hormone levels on ATD in two patients, poor compliance in two patients and decision by the treating doctor that likelihood of long-term remission was poor in one patient. An additional 20 patients had < 6 months' treatment duration at the end of the follow-up period and were excluded from the survival analysis, but included in the safety analysis, leaving 219 patients with primary GD treated for ≥ 6 months.

Ethical approval

The Regional Ethical Review Board, Umeå, Sweden, approved the study. Patients received written information of the study and were given the opportunity to decline participation and were otherwise included. The study was carried out according to the Declaration of Helsinki.

Laboratory analysis

The levels of TSH, fT₄ and fT₃ were measured by electrochemiluminescence immunoassays (Roche Diagnostics). The upper reference intervals varied between 20.0 and 22.0 pmol/l for fT₄ and between 6.5 and 7.8 pmol/l for fT₃. For simplicity and due to the small variations, values are compared on common scales. Two TRAb assays were used during the study period. During the first part (2000–2004) TRAK assay (B.R.A.H.M.S Diagnostica, Henningsdorf, Germany) was used (<9 U/l negative, 9–14 U/l borderline positive and >14 U/l positive). Thereafter, TRAK human RIA (B.R.A.H.M.S Diagnostica; <1.0 IU/l negative, 1.0–1.5 IU/l borderline positive and >1.5 IU/l positive) was used.

Statistical analysis

Patient characteristics are reported as proportions and means or medians, as indicated. The χ^2 -test and Fisher's exact test were used to compare proportions within large and small groups respectively. Kaplan–Meier estimates were calculated and survival curves were plotted to illustrate rates of relapse during follow-up. Patients who moved out of the county or died during follow-up were censored at the last time when we could ensure that a relapse would have been recorded. The log-rank test was used to compare prognosis between groups. Age, fT₃ and fT₄ levels are reported using a cut-off at the median of patients in the survival analysis. IBM SPSS Statistics for Windows, version 20.0 (IBM Corp.) was used for statistical analysis.

Results

A total of 442 patients fulfilled the criteria for primary GD, corresponding to an incidence in adults of 20.1/100 000 per year, and 219 patients were included with a treatment period of more than 6 months.

General characteristics

The mean age of GD patients at the start of treatment was 51 years. Patients who received ATD as primary treatment were younger (mean 46 years) than those who were treated with RAI (mean 61 years, $P < 0.001$, ANOVA). Those who were treated with surgery were the youngest (mean 31 years, s.d. 11). Mean age was the same for men and women treated with ATD and RAI, while no men underwent primary surgery. Baseline characteristics for the 291 patients receiving primary ATD treatment are

given in Table 1. Only 17.5% of the patients were men. A majority of patients, 96%, started treatment with methimazole, and dose titration and block–replace were equally common. Goitre was found among 51.1%, and 25.8% of the patients had TAO, out of whom 37.3% were regular smokers, while 31.2% of patients without TAO were smokers ($P = 0.4$).

Long-term prognosis

In total, follow-up includes 829 patient years with a median follow-up of 2.8 years and maximal follow-up of 10 years. The long-term remission rate during 10 years was 56.5% (Fig. 2A and Table 2). The risk of relapse was highest during the first 6 months, after which 77.4% remained in remission. After 1 year, 69.8% of patients were in remission. A total of 63.1 and 58.5% were in remission after 3 and 5 years respectively. Between 5 and 10 years of follow-up, only two patients relapsed.

Table 1 Baseline characteristics of the 291 patients who received ATD treatment. Data on fT₃ were missing in 17 subjects.

Characteristics	Values
Gender	
Women	240 (82.5%)
Men	51 (17.5%)
Regimen	
Dose titration	151 (51.9%)
Block–replace	140 (48.1%)
Drug	
Methimazole	280 (96.2%)
Propylthiouracil	11 (3.8%)
Goitre	
Yes	152 (54.1%)
No	129 (45.9%)
Data missing	10
Eye involvement	
TAO	69 (25.8%)
Non-specific	66 (24.7%)
None	132 (49.4%)
Data missing	24
Smoking	
Current smokers	90 (32.1%)
Previous smokers	41 (14.6%)
Non-smokers	149 (53.2%)
Data missing	11
Biochemical values	
fT ₄ ^a	49.6 (s.d. 21.7)
fT ₃ ^a	18.7 (s.d. 10.4)
Daily starting dose	
Methimazole ^b	23.5 ± 7.2
Propylthiouracil ^b	127.3 ± 74.6

TAO, thyroid-associated ophthalmopathy.

^aMeans (pmol/l).

^bMeans (mg).

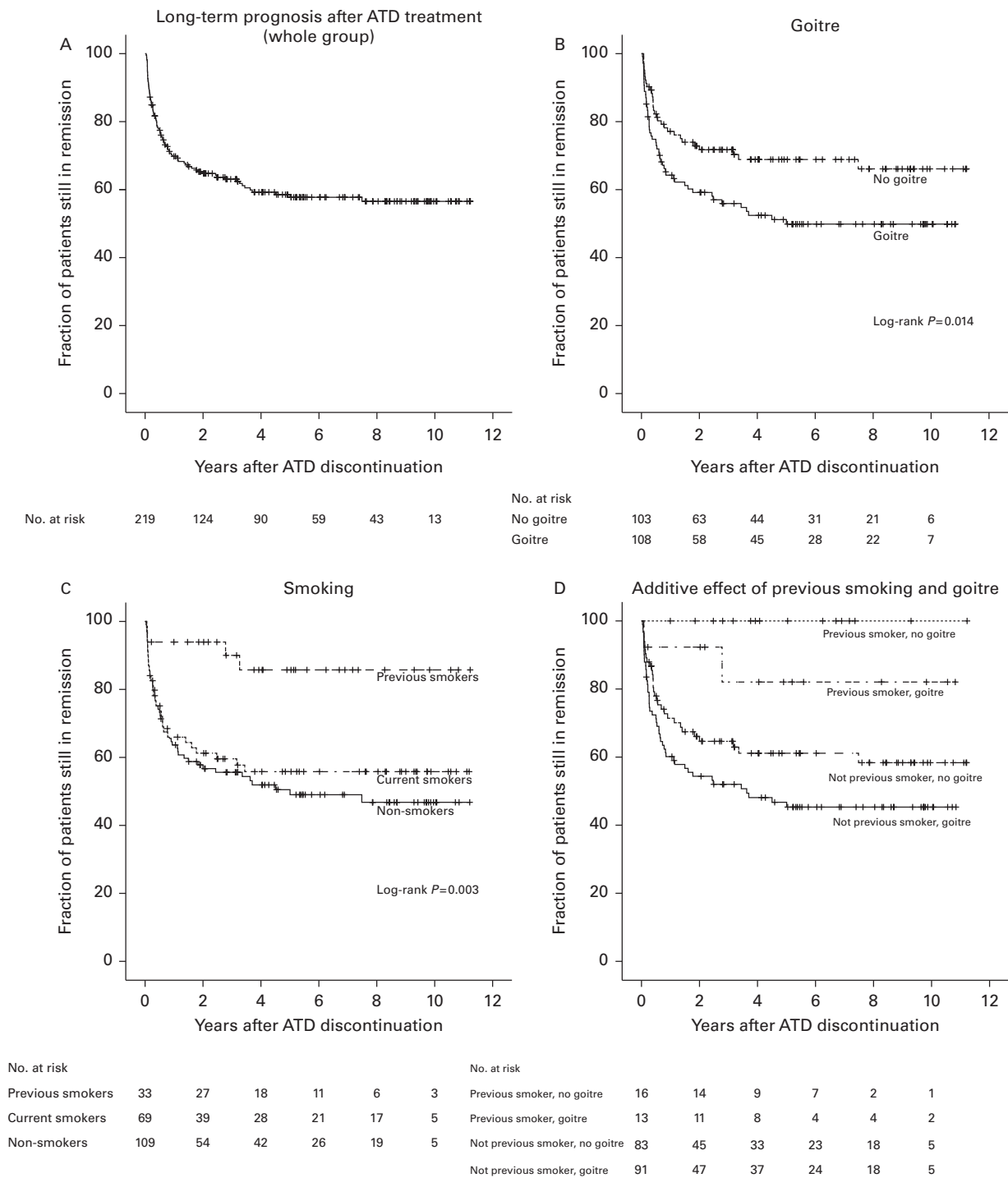


Figure 2

Kaplan–Meier estimates of fraction of patients in remission at different time points after ATD discontinuation. (A) All 219 patients with >6 months’ treatment. (B) Presence of goitre on palpation at start of treatment. (C) Smoking status. (D) Additive effects of previous smoking and goitre. Significance testing

with log-rank test, overall comparison. Pairwise comparisons: current vs non-smokers, $P=0.51$; current vs previous smokers, $P=0.004$ and non-vs previous smokers, $P=0.001$. ATD, antithyroid drug.

Table 2 Percentage of patients in remission at various time points after ATD discontinuation. Values are percentages. Data according to Kaplan–Meier estimates for whole cohort and subgroups. Subgroup data limited to 5 years because of low number at risk at 10 years.

	6 months	1 year	3 years	5 years	10 years	P value ^a
All patients	77.4	69.8	63.1	58.5	56.5	NA
FT ₃ (median)						
< 15 pmol/l	78.6	72.3	66.9	62.6	NA	0.47
≥ 15 pmol/l	77.3	67.3	60.6	56.6	NA	
FT ₄ (median)						
< 44 pmol/l	82.8	76.8	68.3	64.6	NA	0.11
≥ 44 pmol/l	72.3	62.9	57.8	53.7	NA	
Goitre						
Palpable goitre	73.9	64.2	55.9	51.2	NA	0.014
No goitre	82.3	77.1	71.7	68.9	NA	
Smoking						
Non-smokers	73.2	63.7	55.6	50.5	NA	0.003
Current smokers	75.2	66.0	59.6	55.8	NA	
Previous smokers	93.9	93.9	90.0	85.7	NA	
Gender						
Women	76.6	67.8	61.4	59.0	NA	0.74
Men	81.6	78.9	70.5	56.4	NA	
Age (median)						
< 47 years	80.9	76.2	65.3	60.4	NA	0.48
≥ 47 years	73.9	62.9	60.6	56.6	NA	
Eye involvement						
None	73.6	70.6	65.3	61.2	NA	0.75
Non-specific	81.2	71.4	60.8	57.2	NA	
TAO	85.0	71.0	68.9	64.0	NA	
Regimen						
Block–replace	75.8	64.4	57.5	54.4	NA	0.09
Dose titration	79.3	75.4	68.9	62.3	NA	
PS+/-goitre						
PS+no goitre	100	100	100	100	NA	0.001
PS+goitre	92.3	92.3	82.1	82.1	NA	
NPS+no goitre	77.9	71.4	64.6	61.1	NA	
NPS+goitre	71.3	60.1	52.0	46.7	NA	

TAO, thyroid-associated ophthalmopathy; PS, previous smokers; NPS, not previous smokers; NA, not applicable.

^aLog-rank test (overall comparison).

Prognostic factors

FT₄ and fT₃ were not significant prognostic factors, using a cut-off at the median (Table 2). Palpable goitre was associated with worse prognosis compared with no goitre (51.2 vs 68.9% in remission after 5 years; $P=0.014$; Fig. 2B and Table 2). There was no difference in prognosis between smokers and non-smokers (Fig. 2C and Table 2). Previous smokers had a higher remission rate than either current smokers or non-smokers (85.7 vs 55.8 vs 50.5% respectively, in remission after 5 years; $P=0.003$).

No significant differences were seen in prognosis for gender, age <47 vs ≥47 years or eye involvement (Table 2). The difference for regimen was not statistically significant. The remission rate was 62.3% for dose titration and 54.4% for block–replace ($P=0.09$). When stratified for duration of therapy: 6–12 months (10% of the participants),

12–18 months (44%) and >18 months (46%), no differences in the risk of relapse could be seen ($P=0.4$).

The impact of previous smoking and goitre on relapse is shown in Fig. 2D and Table 2. In both non-smokers and previous smokers, the presence of goitre was associated with a higher risk of relapse ($P=0.001$).

Adverse reactions

Rash was experienced by 23 patients (7.9%; 95% CI 5.3–11.6) and arthralgia by 20 (6.9%; 95% CI 4.5–10.4). There was no difference in starting dose between those with rash or arthralgia and those without. Five of these developed both arthralgia and rash. It was significantly more common in patients with one reaction to develop the other one ($P=0.014$, Fisher's exact test). Five (1.7%; 95% CI 0.7–4.0) patients had agranulocytosis; none of them

had a fatal outcome. Seventeen patients had granulocytopenia, with three of them prompting ATD discontinuation. Mean starting dose for Methimazole was 23.5 mg for the whole group, 26.0 mg for the five patients with agranulocytosis and 21.5 mg for the 16 patients with granulocytopenia ($P=0.4$, ANOVA). Other adverse effects that were severe enough to warrant ATD discontinuation were loss of taste in one patient, elevation of transaminases in one patient and various diffuse symptoms in one patient. Three patients died during treatment. No death was attributable to thyroid disease or treatment.

Discussion

The long-term remission rate after ATD treatment between 2000 and 2010 in the real world of central and district hospitals in a Swedish, iodine-sufficient area is higher than in most published studies. Relapse rates decreased sharply with time. Half of the relapses occurred within 6 months after ATD withdrawal and two-thirds occurred within 1 year. The long-term prognosis was excellent after 4 years without relapse. Patients in remission at that time have a high probability to remain in remission for at least the coming 6 years.

Sweden is considered long-term iodine sufficient (17, 18) with an iodination programme since 1936 (22). The level of fortification has been stable for 40 years, which probably rules out the increased risk of iodine-induced hyperthyroidism (23) and the risk of autoimmune thyroid diseases in susceptible individuals (24) seen after introduction of iodination programmes. However, iodine levels also positively influence the degree of elevation of thyroid hormones (25), and as higher fT_4 and fT_3 are a prognostic factor for relapse (7, 8) the low relapse rates found in Sweden are surprising.

The 1-year relapse rate of 30% compares favourably with ~50% in the systematic review from the Cochrane Collaboration (3, 5). Swedish studies from the 1970s and 1980s report somewhat higher relapse rates than our study (7, 20) even though definite ablative methods were used more frequently, and that would supposedly lead to fewer and more easily ATD-treated patients at that time. However, TRAb methods are more sensitive today (26), probably affecting the number of patients diagnosed with GD by such assays, as used in 2004 in our study, and may have a better prognosis with ATD.

This study reflects the practice in the real world of routine care at district and central hospitals where analysis of TRAb was not part of the clinical decision on if or when to end ATD treatment. This also means that a pre-selection occurs. Some of the patients with large goitres, very high

thyroid hormone levels and pregnancy intentions or with medical conditions that would risk worsening if relapse occurred would primarily be treated with RAI or surgery. This will narrow the group with primary ATD to patients with a reasonably good chance of successful treatment, which may contribute to low relapse rates. Nevertheless, the presence of goitre and was still associated with worse prognosis, as previously reported (5, 6, 7, 8, 10).

Current smoking was more common among GD patients (34% of women and 24% of men) than in the general population (27). In 2004, 16% of the women and 9% of the men in northern Sweden were smokers, which underlines the importance of smoking as a risk factor for GD. The association between smoking and an increased relapse rate (9, 10, 15) was not confirmed. The reasons are unclear, but some degree of selection bias towards ablative treatment may exist, as smoking has been seen as a poor prognostic factor among endocrinologists. Smoking status at the time of diagnosis cannot be verified but we have shown in a study from the same area that self-reported tobacco habits, both among smokers and ex-smokers, were highly reliable when validated by plasma nicotine and cotinine (28). The effect of smoking on TAO is dose-dependent (29) and the mean numbers of cigarettes smoked in Sweden has declined for many years. In 2010, the average Swedish smoker now smokes only ten cigarettes per day compared with the average in Europe (14) and in Southern Europe (28). Thus a lack of relationship between smoking and TAO may be due to the low exposure in Swedes.

Unexpectedly, previous smokers had a much better prognosis than smokers and non-smokers, which has not previously been described. This finding should be interpreted with caution as the analysis was not pre-specified and smoking status was based on retrospective medical files where some earlier smokers might have been classified as non-smokers. We recorded smoking status at start of treatment, and the few patients who quit smoking within 6 months before, during or after treatment were classified as smokers. The results should be interpreted in the light of a recent case-control study where smoking cessation was followed by a sharp but transient rise in the risk of developing autoimmune hypothyroidism (30).

Smoking cessation has also been associated with increasing thyroid peroxidase and thyroglobulin antibodies (31). It has been proposed that autoimmune hyperthyroidism and hypothyroidism represent the two ends of a spectrum, and environmental factors may influence which phenotype is manifested (32). Smoking cessation may thus influence the phenotype of autoimmune disease, perhaps towards hypothyroidism also in

GD patients. In earlier studies a pooling of previous and never-smokers studies may have biased the conclusions that smoking is a poor prognostic factor.

The most feared side effect of ATDs is agranulocytosis with a risk of 0.35% (33). Therefore, the high rate of agranulocytosis (1.7%) in our study deserves special note. The high starting doses of ATD and common use of the block–replace regimen may contribute to this.

This study is strengthened by the recruitment method that ensures that patients from every clinic in a defined area and population would be recorded. Although this was not an epidemiological study, the incidence was in accordance with previous Swedish incidence studies (34, 35, 36). Thus, we probably have included almost all eligible subjects and only a small proportion of the patients chose to opt-out from participation. Loss of follow-up was low and the probability of identifying a relapse was high, which ensured a high validity of the results.

Otherwise, the major limitation in this retrospective design was the dependence on routine medical records. In a real-life study, or effectiveness study, there is an impact of how the physicians select which patients should undergo ATD treatment. Treatment selection could hide differences between groups, i.e. if patients with several known risk factors for relapse are more often referred to primary ablative treatment or treated with longer courses of ATD. Some such bias may also exist towards block–replace in patients with more severe disease. This confounding by indication may bias observational studies when evaluating causal effects of treatments. The multiple comparisons carried out on different predictors of relapse make spurious associations possible and *P* values above 0.01 should be interpreted cautiously.

As all data came from medical files from many doctors, variables such as goitre and ophthalmopathy may have been assessed and recorded differently. Furthermore, in an optimal prospective setting, objective evaluation of goitre size by ultrasound and grading of TAO according to a validated scoring system would provide more information than the dichotomous data to which we were limited. On the other hand, our study shows that even a routine clinical examination may be helpful in risk stratification.

In conclusion, ATD treatment may be used for a large fraction of GD patients in a Swedish population with a good chance of inducing long-term remission and thereby avoiding the risk of worsening ophthalmopathy with RAI and, especially in young patients, possibly lifelong T₄ replacement therapy for iatrogenic hypothyroidism. If a patient remains euthyroid for 4–5 years after completion of the treatment, the risk of a further relapse is small.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

M Eliasson designed the study and drafted the final manuscript. E Mohlin performed the study, the statistical analyses and wrote the manuscript. H Filipsson Nyström advised on design and participated in the analysis and writing of the manuscript.

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