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Thyroid function test variability and cardiovascular morbidity in hyperthyroidism

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Abstract

Objective: The variability of thyroid function tests (TFTs) during antithyroid drug (ATD) therapy and its association with adverse health outcomes have not been previously studied. The aim of this study was to evaluate the association of TFT variability and cardiovascular morbidity during ATD therapy.

Design: Retrospective cohort study.

Patients and Measurements: Hyperthyroid patients ($n = 394$) treated with ATD therapy at Tampere University Hospital between March 2016 and December 2018 were followed up for a median time of 1.5 years (interquartile range 0.8–2.0). The coefficients of variation (CVs) of the follow-up thyroid-stimulating hormone (TSH), free thyroxine (fT4) and free triiodothyronine (fT3) measurements were determined. The associations of TFT variability and baseline clinical factors with cardiovascular disease (CVD) -associated hospital visits were assessed with logistic regression analyses.

Results: In the multivariable analyses, age (odds ratio [OR]: 1.06, 95% confidence interval [CI]: 1.03–1.09), male gender (OR: 2.33, 95% CI: 1.03–5.28) and fT4-CV (OR: 1.02, 95% CI: 1.01–1.04) were independent risk factors for cardiovascular morbidity, whereas baseline positive thyrotropin receptor antibodies (TRAbs) were associated with lower cardiovascular morbidity (OR: 0.29, 95% CI: 0.14–0.61). When the patients with baseline TRAb positivity were studied separately, fT4-CV was associated with cardiovascular morbidity (OR: 1.03, 95% CI: 1.00–1.05).

Conclusions: During ATD therapy, fT4 variability is associated with an increased cardiovascular morbidity. Although positive TRAbs are associated with a lower cardiovascular morbidity compared with hyperthyroidism with negative autoantibodies, the variability of fT4 is associated with cardiovascular morbidity also in patients with positive TRAbs.

KEYWORDS

antithyroid agents, cardiovascular diseases, Graves disease, hyperthyroidism, thyroid function tests, thyroid hormones, thyrotropin receptors

1 | INTRODUCTION

The clinical course of hyperthyroidism can vary significantly depending on several factors, such as the cause and severity of the disease, patient characteristics and response to the treatment.[1,2] Graves' disease (GD) is an autoimmune disease characterized by circulating antibodies against the thyrotropin receptor and the most common cause (70%–80%) of hyperthyroidism in iodine sufficient areas.[3,4] Other common causes of hyperthyroidism include toxic multinodular goitre and solitary toxic adenoma, characterized by nodular autonomy.[3,4]

The three treatment options for hyperthyroidism include long-term ATD therapy, radioactive iodine (RAI) and surgery.[1] In Europe, ATD therapy is commonly preferred as the first-line treatment of GD, and if hyperthyroidism recurs, second-line treatment with either RAI or surgery is recommended.[1,5,6] The recurrence rate of hyperthyroidism after ATD therapy is high (40%–60%), increasing the risk of associated health problems, for example cardiovascular complications.[7–9] As thyroid hormones have a major role in the regulation of the cardiovascular system, acute cardiovascular manifestations are common during hyperthyroidism and cardiovascular morbidity remains increased for years even after restoring normal thyroid function.[2,10–13]

In the treatment of hyperthyroidism, recent evidence highlights the importance of rapid elimination of hyperthyroidism and early definitive treatment with RAI or surgery, if remission with ATD therapy is unlikely, as patients with poor biochemical control of hyperthyroidism have an increased mortality.[14–18] Rapid restoration of euthyroidism has been shown to improve the survival of the patients regardless of the treatment modality.[14,18] The response to ATD therapy, however, is difficult to predict and a substantial number of patients will eventually need lifelong thyroid hormone replacement regardless of the first-line treatment option chosen.[19,20] Several studies with partly conflicting results have recognized factors that predict the recurrence of hyperthyroidism after ATD therapy in GD,[8,21–26] whereas the response to ongoing ATD therapy regarding thyroid hormone variability during the treatment and its clinical relevance have not been studied previously.

The aim of this study was to evaluate the association of the thyroid function test (TFT) variability with the risk of cardiovascular morbidity after the initiation of ATD therapy. Furthermore, the aim was to identify baseline clinical factors related to a high TFT variability during ATD therapy.

2 | MATERIALS AND METHODS

In this retrospective study, all consecutive patients with a newly diagnosed hyperthyroidism and treated with a first-line ATD therapy at the endocrinology outpatient clinic of Tampere University Hospital between March 2016 and December 2018 were included and followed up until March 2019 (Figure 1). A majority of the hyperthyroid patients in our hospital district are treated at Tampere University Hospital, as the regional clinical guidelines instruct primary

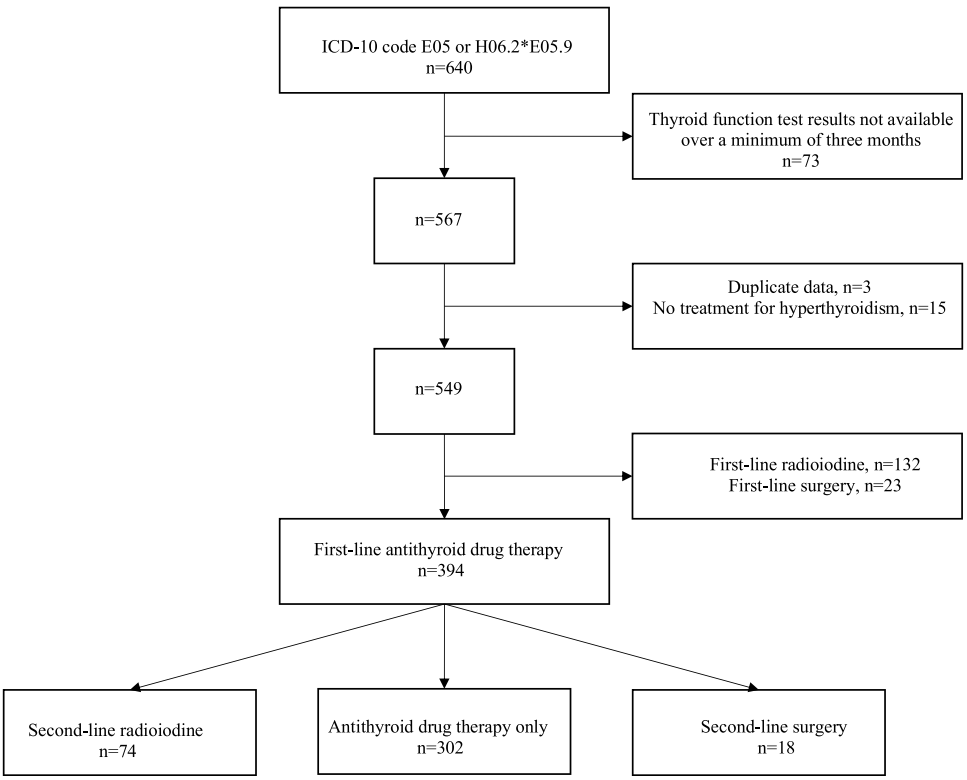

FIGURE 1 Formation of the study cohort.

health care providers to refer all adult patients (age ≥ 15 years) with a newly diagnosed hyperthyroidism to the endocrinology clinic of Tampere University Hospital. The catchment population was 442,960 at the end of year 2018.[27]

First, a cohort was formed of patients with the first outpatient visit to the endocrinology clinic due to a diagnosis code E05 or H06.2*E05.9 according to the Tenth Revision of the International Classification of Diseases (ICD-10). Then, 73 patients who did not have TFT results available over a minimum follow-up period of 3 months after the first visit were excluded. Eighteen patients were excluded, because they did not need any treatment for hyperthyroidism, or due to technical errors. Finally, after excluding 132 patients treated with first-line RAI and 23 patients treated with first-line surgery, a study cohort of 394 patients was formed.

The patients of the study cohort and the clinical data on their treatment were gathered from the hospital patient record system of endocrinology (Endo registry), which is an electronic system used in the endocrinology clinic aimed to support clinical practice. The data obtained from the Endo registry included clinical characteristics of the patients registered on the first endocrinology clinic visit (Table 1) and follow-up information on possible second-line treatments with RAI or thyroid surgery. Cardiovascular morbidity was evaluated based on hospital visits to Tampere University Hospital due to a cardiovascular disease (CVD) between the first visit to the endocrinology clinic and the end of the follow-up on March 31, 2019. The data on the CVD-associated inpatient and outpatient hospital visits were obtained from the data administration services of the hospital. The outpatient visits also included remote contacts. The cardiovascular diagnoses (ICD-10 diagnosis codes I10-99) were divided into nine subgroups presented in Table 2 and a hospital visit was included in the analyses, if the primary diagnosis or one of the two

TABLE 1 Clinical characteristics of the hyperthyroid patients treated with first-line antithyroid drug therapy according to the cardiovascular morbidity status during the follow-up.

		Cardiovascular morbidity during the follow-up						
		All patients *n* = 394		No *n* = 337		Yes *n* = 57		
	Data available	*n*/median	%/IQR	*n*/median	%/IQR	*n*/median	%/IQR	*p*
Age, years	394	46	34–64	42	32–58	66	58–72	<.001[a]
Gender, male	394	86	22	63	19	23	40	<.001[a]
Body mass index, kg/m^2	375	25.9	22.5–29.8	25.2	22.2–29.7	27.0	24.0–30.4	.045[a]
Systolic blood pressure, mmHg	373	131	121–146	130	121–142	142	125–155	.007[a]
Diastolic blood pressure, mmHg	373	80	73–86	80	73–86	82	74–87	.427
Heart rate, beats/min	368	76	68–85	76	68–85	74	64–87	.579
Smoking, current	377	79	21	72	22	7	13	.105
Smoking, current and ex-smokers	377	133	35	115	36	18	33	.668
Previously diagnosed hypertension	371	100	27	68	21	32	62	<.001[a]
Previously diagnosed diabetes	372	39	11	25	8	14	26	<.001[a]
Previously diagnosed hypercholesterolaemia	361	47	13	29	9	18	36	<.001[a]
Family history of thyroid disease	363	106	29	98	31	8	16	.022[a]
Symptoms of hyperthyroidism	394	376	95	324	96	52	91	.158
Eye symptoms:	390							.048[a]
Mild		96	25	86	26	10	18	
Severe		15	4	15	5	0	0	
Baseline TSH, mU/L	378	0.01	0.01–0.04	0.01	0.01–0.03	0.01	0.01–0.12	.167
Baseline fT4, mU/L	377	18.0	13.3–25.5	17.8	13.2–24.8	21.1	14.7–31.8	.038[a]
Baseline fT3, mU/L	375	6.0	4.5–8.3	6.1	4.6–8.4	5.4	4.1–8.0	.164
TRAb positive	352	264	75	243	79	21	46	<.001[a]
TPOAb positive	357	202	57	187	60	15	32	<.001[a]

Abbreviations: ft3, free triiodothyronine; fT4, free thyroxine; IQR, interquartile range; TPOAb, thyroid peroxidase antibody; TRAb, thyrotropin receptor antibody; TSH, thyroid-stimulating hormone.

[a]Statistical difference between the patients with and those without cardiovascular morbidity during the follow-up (Mann–Whitney *U* or χ^2 test, as appropriate).

first secondary diagnoses of the visit was included in the above-mentioned subgroups.

2.1 | Thyroid laboratory tests

All the TFTs were analysed at Fimlab Laboratories. Plasma TSH, fT4, fT3 and thyroid peroxidase antibody (TPOAb) concentrations were analysed by an electro-chemiluminescence immunoassay (Elecsys Cobas e immunoassay analyser, ECLIA; Roche Diagnostics). A fluoroenzymeimmunoassay (EliA anti-TSH-R method, Phadia AB) was used for the measurement of TRAbs. The reference ranges for TSH, fT4 and fT3 values for patients over 20 years of age were 0.27–4.2 mU/L, 11.0–22.0 pmol/L and 3.1–6.8 pmol/L, and for 15–20-year-old patients 0.5–4.3 mU/L, 12.6–21.0 pmol/L and 3.9–7.7 pmol/L, respectively. Due to a change of the assay, the reference range for TRAb measurements was 0–1 IU/L until February 14, 2018, and since then 1–2.9 IU/L. The reference range for TPOAb measurements was less than 34 kU/L.

It is noteworthy that according to the clinical practice in our hospital district, ATD therapy is initiated already at the time of diagnosing hyperthyroidism in primary health care and the first visit to the endocrinology clinic is scheduled at 3–6 weeks after the initiation of ATD therapy. Thus, the TFTs at the first endocrinology clinic visit represent the initial response to ATD therapy, which is mostly started with carbimazole 30 mg per day 4–6 weeks before the first visit, but adjusted individually based on the severity of the disease. ATD adjustments were made by trained nurses, by using a standardized protocol of adjusting the ATD dose according to the TFT results and the ATD dose used during the previous 4–6 weeks.

The study was undertaken in accordance with the Declaration of Helsinki. The ethics committee of the Pirkanmaa Hospital District approved the study protocol (study number R18099).

TABLE 2 Types of cardiovascular morbidity diagnosed during the follow-up of the hyperthyroid patients treated with first-line antithyroid drug therapy.

	Patients (n = 394)	
	n	%
Any cardiovascular disease	57	14
All arrhythmias	38	10
Atrial fibrillation	30	8
Valvular diseases and cardiomyopathies	22	6
Hypertension	15	4
Coronary artery disease	9	2
Cerebrovascular diseases	5	1
Heart failure	5	1
Diseases of arteries and veins	3	0.8
Diseases of pulmonary arteries	2	0.5

2.2 | Statistical analysis

IBM SPSS Statistics version 27.0 was used in the statistical analyses. A p-value < .05 was considered statistically significant. Continuous variables presented in Tables 1 and 3 were compared with the Mann–Whitney U test and χ^2 test was used to compare categorical variables.

The visit-to-visit variability of thyroid hormone measurements was evaluated by using the coefficient of variation (CV) as a statistical measure. The CV provides information about the dispersion of the measurements around the mean and it is commonly used, for example, in the clinical practice of diabetology to assess glycaemic variability.[28–30] The CV is a dimensionless number, commonly presented as the percentage of the SD of the mean, and therefore it allows the comparison of measurements with different reference

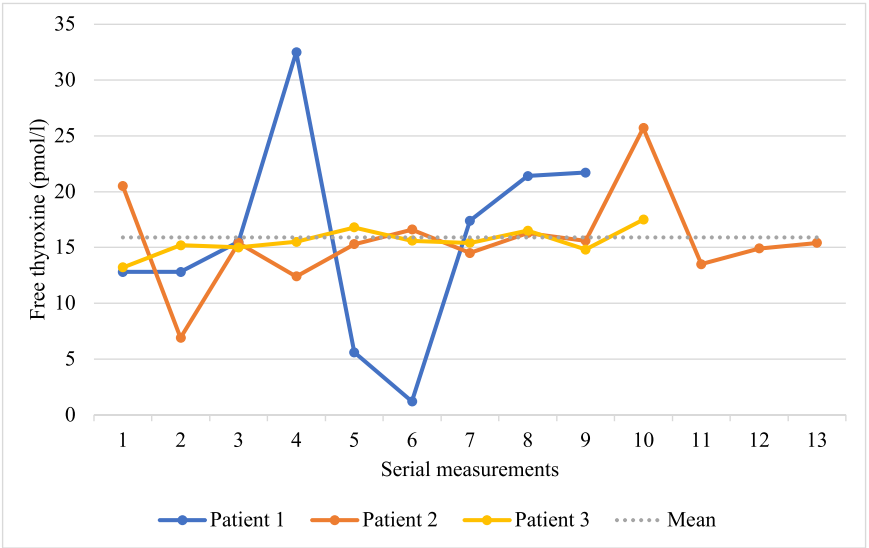

FIGURE 2 Demonstration of three patients in the study cohort with a similar free thyroxine (fT4) mean 16 pmol/L, but different fT4 coefficients of variation (CV): fT4-CV is 56% for Patient 1, 26% for Patient 2 and 7% for Patient 3.

ranges. Figure 2 demonstrates three patients of the study cohort with the same follow-up fT4 mean but differing fT4-CVs; the difference between the patients in the biochemical course of hyperthyroidism becomes apparent, when the fT4 variability is observed instead of the mean fT4 value.

The CVs of the TSH, fT4 and fT3 measurements for each individual patient were calculated by dividing the SD of the measurements by the mean of the measurements. Then, the CV was divided by the factor $\sqrt{[n/(n-1)]}$ to correct for the possible impact the number of measurements (n) had on the variation, as the variance would be wider, if only a few measurements were available due to a shorter follow-up period.[29,30] All thyroid hormone measurements starting 2 months before the first endocrinology clinic visit until March 31, 2019 were included in the calculations. For the sake of comparison, also the medians of the TFTs measured during the follow-up were calculated.

The associations of baseline clinical factors and thyroid hormone variability with cardiovascular morbidity were assessed with binary logistic regression analyses. The analyses were repeated including only the patients with a baseline positive TRAb measurement, to evaluate the above-mentioned associations among GD patients and to eliminate the possible effect of the aetiology of hyperthyroidism on thyroid hormone variability or on cardiovascular morbidity. The covariates entered in the analysis of cardiovascular morbidity were age, gender, body mass index, smoking, previously diagnosed hypercholesterolaemia, diabetes or hypertension, a need for a second-line treatment with RAI or surgery, baseline TRAb positivity and, one at a time, the median or the CV of the TSH, fT4 or fT3 values measured during the follow-up. Cardiovascular morbidity due to arrhythmias was evaluated separately. In addition, baseline clinical factors were evaluated in relation to the median and CV of the TFTs, to identify factors associated with TFT variability during ATD therapy.

3 | RESULTS

Of the 549 patients referred to the endocrinology clinic for hyperthyroidism, 72% (n = 394) were treated primarily with ATD therapy and were included in the analyses (Figure 1). During a median follow-up time of 1.5 years (interquartile range [IQR]: 0.8–2.0) a second-line treatment was necessary for 23% (n = 92) of the patients: 19% (n = 74) were treated with RAI and 5% (n = 18) with surgery (Figure 1). Of the patients who received a second-line treatment, 64% (n = 52) were TRAb positive and 36% (n = 29) TRAb negative (p = .011). There was no difference in the frequency of second-line treatments with RAI or surgery during the follow-up between the patients with cardiovascular morbidity (30%, n = 17) and those without it (22%, n = 75) (p = .121). The median follow-up time was 1.6 (IQR: 1.0–2.1) years in patients with cardiovascular morbidity and 1.4 (IQR: 0.8–2.0) years in patients without cardiovascular morbidity (p = .270).

The clinical characteristics of the study cohort registered at the first endocrinology clinic visit according to the follow-up cardiovascular morbidity status are represented in Table 1. The median age of the patients was 46 years (IQR 34–64) and most of them (78%, n = 308) were female. Seventy-five percent (n = 264) of the patients had positive TRAbs and 57% (n = 202) had positive TPOAbs.

Fourteen percent of the patients (n = 57) had a CVD-associated hospital visit during the follow-up (Tables 1 and 2). Altogether, 340 CVD-associated hospital visits were registered for these 57 patients during the follow-up and the median number of CVD visits per patient was 4 (IQR: 2–6). Of the visits, 61 (18%) were inpatient admissions. The median time between the first visit to the endocrinology clinic and the first CVD-associated hospital visit was 84 days (IQR: 14–202). The patients with cardiovascular morbidity were older and more often male, had a higher body mass index and systolic blood pressure, and more often previously diagnosed hypertension, hypercholesterolaemia and diabetes, and less often eye symptoms, family history of thyroid disease or TRAb positivity than those without cardiovascular morbidity (Table 1).

Altogether, 3860 TSH measurements, 3851 fT4 measurements and 3649 fT3 measurements were made during the follow-up of the study cohort. The median number of TFT measurements was 9 (IQR: 5–12) among patients with cardiovascular morbidity and 9 (IQR: 6–13) among patients without cardiovascular morbidity (p = .498). There was no difference in the medians or the CVs of the TSH, fT4 and fT3 measurements during the follow-up among patients with cardiovascular morbidity compared to patients without cardiovascular morbidity (Supporting Information: Table 1).

In the univariable analyses including the whole study cohort, age, male gender, hypercholesterolaemia, diabetes, hypertension and baseline TRAbs were associated with cardiovascular morbidity (Table 3). In the multivariable analysis, age (odds ratio [OR]: 1.06, 95% confidence interval [95% CI]: 1.03–1.09), male gender (OR: 2.33, 95% CI: 1.03–5.28), positive TRAbs (OR: 0.29, 95% CI: 0.14–0.61) and fT4-CV (OR: 1.02, 95% CI: 1.01–1.04) were significantly associated with cardiovascular morbidity (Table 3). When cardiovascular morbidity due to arrhythmias was studied separately in a multivariable analysis including the whole study cohort, age (OR: 1.07, 95% CI: 1.03–1.11), male gender (OR: 2.99, 95% CI: 1.07–8.35) and positive TRAbs (OR: 0.21, 95% CI 0.08–0.54) were associated with arrhythmias and the association of fT4-CV (OR: 1.02, 95% CI: 1.00–1.04) was nearly significant (p = .06).

When fT4 median during the follow-up was evaluated in the multivariable analyses, age (OR: 1.06, 95% CI: 1.03–1.09), male gender (OR: 2.46, 95% CI: 1.09–5.56) and positive TRAbs (OR: 0.34, 95% CI: 0.17–0.70) were significantly associated with cardiovascular morbidity, but the fT4 median was not (OR: 1.06, 95% CI: 0.97–1.15) (Supporting Information: Table 2). When arrhythmias were studied separately, age (OR: 1.08, 95% CI: 1.04–1.12), male gender (OR: 2.99, 95% CI: 1.05–8.50), fT4 median (OR: 1.13, 95% CI: 1.04–1.23) and positive TRAbs (OR: 0.25, 95% CI: 0.10–0.61) were associated with arrhythmias.

When the multivariable analyses were performed separately on the patients with positive TRAbs, age (OR: 1.06, 95% CI: 1.02–1.11)

TABLE 3 Cardiovascular morbidity in the univariable and multivariable analyses of the hyperthyroid patients treated primarily with antithyroid drug therapy.

	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Age	1.07 (1.05–1.09)	<.001[a]	1.06 (1.03–1.09)	<.001[a]
Gender (male vs. female)	2.94 (1.62–5.34)	<.001[a]	2.33 (1.03–5.28)	.042[a]
Body mass index	1.05 (1.00–1.10)	.052	1.03 (0.96–1.10)	.426
Current and ex-smoking	0.89 (0.49–1.63)	.707	0.70 (0.31–1.60)	.399
Previously diagnosed hypercholesterolaemia	4.90 (2.49–9.64)	<.001[a]	1.35 (0.57–3.16)	.494
Previously diagnosed diabetes	4.06 (1.96–8.41)	<.001[a]	1.05 (0.40–2.72)	.920
Previously diagnosed hypertension	5.06 (2.82–9.11)	<.001[a]	1.48 (0.61–3.64)	.388
Second-line RAI or surgery versus first-line ATD therapy only	1.49 (0.80–2.77)	.214	0.45 (0.20–1.03)	.058
fT4 CV	1.01 (1.00–1.02)	.227	1.02 (1.01–1.04)	.009[a]
TRAb (positive vs. negative)	0.23 (0.13–0.41)	<.001[a]	0.29 (0.14–0.61)	.001[a]

Note: The fT4 CV is included in the analyses.

Abbreviation: ATD, antithyroid drug therapy; CV, coefficient of variation; fT4, free thyroxine; RAI, radioiodine; TRAb, thyrotropin receptor antibody.

[a]Statistical association of the covariate with cardiovascular morbidity (logistic regression analyses).

and fT4-CV (OR: 1.03, 95% CI: 1.00–1.05) were associated with cardiovascular morbidity (Supporting Information: Table 3), but the fT4 median was not (OR: 1.05, 95% CI: 0.95–1.17) (data not shown). In the multivariable analyses including the whole study cohort or only the patients with positive TRAbs, the medians or CVs of the TSH or fT3 measurements were not associated with cardiovascular morbidity. When patients with hypertension ($n = 2$) or coronary artery disease ($n = 3$) as the only cardiovascular diagnosis during the follow-up were excluded, the result regarding the association of age, male gender, fT4-CV and TRAbs with cardiovascular morbidity remained unchanged.

Baseline clinical characteristics of the study cohort in relation to the follow-up fT4 median and fT4-CV are represented in Table 4. Male patients and those with diabetes had a slightly higher fT4 median than female patients and those without diabetes ($p = .048$ and .003, respectively). Patients with a family history of thyroid disease had a slightly lower fT4 median compared with patients without a family history ($p = .028$). Patients with positive TRAbs or TPOAbs had a higher fT4-CV compared with those with negative TRAbs or TPOAbs ($p = .002$ and .024, respectively).

4 | DISCUSSION

In the present study, we found that after the initiation of ATD therapy patients with autoantibody-related hyperthyroidism have a higher fT4 variability compared to patients with hyperthyroidism without autoantibodies. Age, male gender and fT4 variability are independent risk factors for cardiovascular morbidity, while TRAb positivity seems to protect from it. However, among patients with positive TRAbs, the variability of fT4 is associated with cardiovascular morbidity. Thus, fT4 variability seems to be a risk factor for cardiovascular morbidity in all hyperthyroid patients.

In previous studies, poor biochemical control of hyperthyroidism, evaluated by cumulative periods of decreased TSH or increments of 10 pmol/L in serial fT4 measurements, has been linked to increased mortality.[17,18] In 2013, Boelaert et al.[18] found that most ATD-treated patients achieved a normal fT4 value within 4 months after presentation, but 20% still had subclinical hyperthyroidism at 12 months. The severity and the duration of untreated hyperthyroidism can influence the risk of adverse outcomes of the disease,[2] but there is no previous evidence of the role of thyroid hormone variability per se. To the best of our knowledge, no studies have evaluated the visit-to-visit variability of TFTs and its association with cardiovascular morbidity among hyperthyroid patients. Besides the importance of rapid elimination of thyrotoxicosis, the ability to maintain euthyroidism is crucial to improve the outcomes of patients with hyperthyroidism.[14,15,17,18] At the same time, overtreatment with ATD therapy resulting in hypothyroidism is unfavourable, because also hypothyroidism is related to cardiovascular abnormalities, such as diastolic dysfunction, elevated blood pressure, and an increased risk of atherosclerosis.[31] Therefore, in the evaluation of thyroid hormone values and cardiovascular morbidity, the median (or mean) values of thyroid hormone measurements alone probably cannot provide sufficient information on the biochemical burden of the thyroid disease on the cardiovascular system, as thyroid hormones may fluctuate between hyperthyroidism and hypothyroidism in the course of treatments.

TABLE 4 Clinical characteristics of the hyperthyroid patients treated primarily with antithyroid drug therapy in relation to the median and the CV of all measured fT4 values during the follow-up.

		fT4 (pmol/L) Median	IQR	*p*	fT4 CV (%) Median	IQR	*p*
Gender	Female	14.5	13.4–16.0	.048[a]	22.4	14.4–35.5	.215
	Male	15.1	13.3–17.3		25.0	16.3–39.6	
Smoking	Current and ex-smokers	14.6	13.3–16.2	.913	24.8	15.3–36.7	.358
	No	14.6	13.3–16.5		22.2	14.6–34.7	
Hypercholesterolaemia	Yes	14.7	13.0–17.2	.858	19.5	13.0–33.6	.247
	No	14.6	13.4–16.4		23.2	14.9–40.0	
Diabetes	Yes	16.0	14.2–17.8	.003[a]	22.5	14.9–36.0	.805
	No	14.5	13.2–16.1		22.5	14.8–36.0	
Hypertension	Yes	14.7	13.1–17.1	.886	25.3	15.6–35.2	.631
	No	14.5	13.4–16.3		22.1	14.5–36.0	
Eye symptoms	Yes	14.4	13.4–16.5	.897	22.3	14.5–36.1	.569
	No	14.7	13.4–16.2		23.5	14.7–35.2	
Family history of thyroid disease	Yes	14.2	13.3–15.6	.028[a]	22.3	15.2–34.1	.866
	No	14.8	13.3–16.6		23.6	14.6–36.0	
TPOAb positive	Yes	14.3	13.1–15.9	.121	24.9	16.4–38.6	.024[a]
	No	14.7	13.5–16.4		22.1	13.7–33.6	
TRAb positive	Yes	14.6	13.4–16.1	.668	25.0	16.4–40.0	.002[a]
	No	14.3	13.1–15.4		19.8	12.7–30.6	

Abbreviations: CV, coefficient of variation; fT4, free thyroxine; IQR, interquartile range; TPOAb, thyroid peroxidase antibody; TRAb, thyrotropin receptor antibody.

[a]Statistical difference between the patients with and those without each baseline clinical characteristic (Mann–Whitney *U* test).

In this study, as many as 23% of the patients received a second-line treatment during a relatively short follow-up time of 1.5 years. As long-term ATD therapy is usually administrated in GD for a period of 12–24 months, this finding likely reflects difficulties in controlling hyperthyroidism during ATD therapy rather than a true relapse after a full-length ATD therapy. A high variability of thyroid hormones during ATD therapy could indicate a poor response to the ATD therapy, but also the need for various treatment options probably increases the thyroid hormone variability, as a definitive treatment with surgery or RAI commonly induces temporary hypothyroidism. Based on a previous study, hyperthyroid patients treated with surgery achieve euthyroidism faster than patients treated with RAI,[32] but the effect of different treatment options on thyroid hormone variability is not known.

The association of positive TRAbs with decreased cardiovascular morbidity probably reflects the aetiology of thyrotoxicosis reducing the risk of cardiovascular morbidity, as patients with GD are younger and develop cardiovascular complications less frequently than patients with a nodular thyroid disease.[2] Patients with a nodular disease are typically older, and have more frequently a long-lasting, less symptomatic or subclinical hyperthyroidism instead of overt hyperthyroidism, compared to patients with GD.[2,4] Nevertheless, they are more likely to develop cardiovascular complications, for example, atrial fibrillation, partly due to their higher age and prevalence of pre-existing cardiovascular risk factors and comorbidities.[2,4] The results of this study are in line with previous literature, as we found that besides fT4 variability, age and negative TRAbs were independently associated with cardiovascular morbidity. Aging and the variability of fT4 were, however, found to positively associate with cardiovascular morbidity also among TRAb positive patients. The possible confounding effect of the aetiology of hyperthyroidism may also explain, why no difference was found in the unadjusted comparison of fT4 variability between the patients with cardiovascular morbidity and those without morbidity.

In this study, the association of TFT variability with morbidity due to any CVDs and due to the subgroup of arrhythmias was analysed. Nonarrhythmia related CVDs were not evaluated separately due to the small number of events in these groups. Arrhythmias, mainly atrial fibrillation, accounted for most of the cardiovascular morbidity registered during the follow-up.

Hyperthyroidism is a well-known risk factor for atrial fibrillation and has also been linked to other CVDs, such as cerebrovascular diseases, valvular diseases, cardiomyopathies, heart failure and diseases of arteries and veins, but not inevitably to coronary artery disease.[2,9–12] Hypertension may be regarded as a risk factor, rather than being a CVD itself, although hyperthyroidism may lead to secondary systolic hypertension.[33] Therefore, the multivariable analyses were repeated excluding the patients with coronary artery disease or hypertension and the results did not change.

We found that the variability of fT4 measurements was associated with cardiovascular morbidity, whereas the variability of TSH or fT3 was not. This finding may be partly explained by the different responses of the thyroid axis hormones to the initiation of ATD therapy. After the initiation of ATD therapy, TSH may remain suppressed for several months due to delayed normalization of the pituitary-thyroid axis or continued TRAb stimulation, and fT3 may remain elevated, despite normalized fT4 levels.[34,35] Perhaps the relatively short follow-up period of this study was not optimal for evaluating the variability of TSH or fT3.

Lack of comprehensive information on pre-existing cardiovascular morbidity is a major limitation of this study, as pre-existing morbidity is a major risk factor for subsequent cardiovascular morbidity and could affect the results. Information was available on cardiovascular risk factors, which were entered as covariates in the multivariable analyses. The relatively short follow-up period and the rather small study cohort may be regarded as limitations to this study. The focus of this study was, however, on the short-term cardiovascular complications after the initiation of ATD therapy, and based on a previous study, the risk for acute cardiovascular events is highest during the first 3 months after the diagnosis of hyperthyroidism.[9] The first laboratory values measured in primary health care at the time of the diagnosis of hyperthyroidism or the doses of ATD therapy were not available in this study. Presumably, the most remarkable changes in the fT4 levels took place soon after the initiation of ATD therapy. As the initial TFT values were not available, this initial change in the TFTs was not included in the calculation of the CVs. Information on CVD-associated visits in primary health care was not available and this could underestimate morbidity, as less severe CVDs may have been treated solely in primary health care. Due to the study design, conclusions regarding the causality of the findings could not be drawn.

In conclusion, this is the first study to report that among hyperthyroid patients treated primarily with long-term ATD therapy, the variability of fT4 is associated with an increased cardiovascular morbidity. This finding emphasizes the importance of effectively controlled thyroid hormone levels during ATD therapy and early definitive treatment of hyperthyroidism if the response to ATD therapy is not optimal. Further studies are needed to verify the results of this study and to gain more insight into the clinical relevance of thyroid hormone variability and its possible associations with other adverse health outcomes, like impaired quality of life, or mortality.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. De Leo S, Lee SY, Braverman LE. Hyperthyroidism. *Lancet*. 2016;388:906-918.
2. Biondi B, Kahaly GJ. Cardiovascular involvement in patients with different causes of hyperthyroidism. *Nat Rev Endocrinol*. 2010;6:431-443.
3. Taylor PN, Albrecht D, Scholz A, et al. Global epidemiology of hyperthyroidism and hypothyroidism. *Nat Rev Endocrinol*. 2018;14:301-316.
4. Nyström HF, Jansson S, Berg G. Incidence rate and clinical features of hyperthyroidism in a long-term iodine sufficient area of Sweden (Gothenburg) 2003-2005. *Clin Endocrinol*. 2013;78:768-776.
5. Bartalena L, Burch HB, Burman KD, Kahaly GJ. A 2013 European survey of clinical practice patterns in the management of Graves' disease. *Clin Endocrinol*. 2016;84:115-120.
6. Burch HB, Burman KD, Cooper DS. A 2011 survey of clinical practice patterns in the management of Graves' disease. *J Clin Endocrinol Metab*. 2012;97:4549-4558.
7. Sundaresh V, Brito JP, Wang Z, et al. Comparative effectiveness of therapies for Graves' hyperthyroidism: a systematic review and network meta-analysis. *J Clin Endocrinol Metab*. 2013;98:3671-3677.
8. Mohlin E, Filipsson Nyström H, Eliasson M. Long-term prognosis after medical treatment of Graves' disease in a Northern Swedish population 2000-2010. *Eur J Endocrinol*. 2014;170:419-427.
9. Dekkers OM, Horváth-Puhó E, Cannegieter SC, Vandenbroucke JP, Sørensen HT, Jørgensen JOL. Acute cardiovascular events and all-cause mortality in patients with hyperthyroidism: a population-based cohort study. *Eur J Endocrinol*. 2017;176:1-9.
10. Metso S, Auvinen A, Salmi J, Huhtala H, Jaatinen P. Increased long-term cardiovascular morbidity among patients treated with radioactive iodine for hyperthyroidism. *Clin Endocrinol*. 2008;68:450-457.
11. Ryödi E, Salmi J, Jaatinen P, et al. Cardiovascular morbidity and mortality in surgically treated hyperthyroidism - a nation-wide cohort study with a long-term follow-up. *Clin Endocrinol*. 2014;80:743-750.
12. Ryödi E, Metso S, Huhtala H, Välimäki M, Auvinen A, Jaatinen P. Cardiovascular morbidity and mortality after treatment of hyperthyroidism with either radioactive iodine or thyroidectomy. *Thyroid*. 2018;28:1111-1120.
13. Nyirenda MJ, Clark DN, Finlayson AR, et al. Thyroid disease and increased cardiovascular risk. *Thyroid*. 2005;15:718-724.

14. Okosieme OE, Taylor PN, Evans C, et al. Primary therapy of graves' disease and cardiovascular morbidity and mortality: a linked-record cohort study. *Lancet Diabetes Endocrinol*. 2019;7:278-287.
15. Okosieme OE, Taylor PN, Dayan CM. Should radioiodine now be first line treatment for Graves' disease? *Thyroid Res*. 2020;13:3.
16. Vasileiou M, Gilbert J, Fishburn S, Boelaert K, Guideline Committee. Thyroid disease assessment and management: summary of NICE guidance. *BMJ*. 2020;368:m41.
17. Lillevang-Johansen M, Abrahamsen B, Jørgensen HL, Brix TH, Hegedüs L. Excess mortality in treated and untreated hyperthyroidism is related to cumulative periods of low serum TSH. *J Clin Endocrinol Metab*. 2017;102:2301-2309.
18. Boelaert K, Maisonneuve P, Torlinska B, Franklyn JA. Comparison of mortality in hyperthyroidism during periods of treatment with thionamides and after radioiodine. *J Clin Endocrinol Metab*. 2013;98:1869-1882.
19. Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F, Galofré JC. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. *J Clin Endocrinol Metab*. 2014;99:923-931.
20. Sjölin G, Holmberg M, Törring O, et al. The long-term outcome of treatment for Graves' hyperthyroidism. *Thyroid*. 2019;29:1545-1557.
21. Allahabadia A, Daykin J, Holder RL, et al. Age and gender predict the outcome of treatment for Graves' hyperthyroidism. *J Clin Endocrinol Metab*. 2000;85:1038-1042.
22. Abbara A, Clarke SA, Brewster R, et al. Pharmacodynamic response to anti-thyroid drugs in Graves' hyperthyroidism. *Front Endocrinol*. 2020;11:286.
23. Anagnostis P, Adamidou F, Polyzos SA, et al. Predictors of long-term remission in patients with Graves' disease: a single center experience. *Endocrine*. 2013;44:448-453.
24. Shi H, Sheng R, Hu Y, et al. Risk factors for the relapse of graves' disease treated with antithyroid drugs: a systematic review and meta-analysis. *Clin Ther*. 2020;42:662-675.
25. Masiello E, Veronesi G, Gallo D, et al. Antithyroid drug treatment for graves' disease: baseline predictive models of relapse after treatment for a patient-tailored management. *J Endocrinol Invest*. 2018;41:1425-1432.
26. Vos XG, Endert E, Zwinderman AH, Tijssen JGP, Wiersinga WM. Predicting the risk of recurrence before the start of antithyroid drug therapy in patients with Graves' hyperthyroidism. *J Clin Endocrinol Metab*. 2016;101:1381-1389.
27. Sotkanet Indicator Bank. National Institute of Health and Welfare*Number of inhabitants and Different age groups as a percentage of total population at year end*. Finnish Institute for Health and Welfare; 2022. https://sotkanet.fi/sotkanet/en/index
28. Ceriello A, Monnier L, Owens D. Glycaemic variability in diabetes: clinical and therapeutic implications. *Lancet Diabetes Endocrinol*. 2019;7:221-230.
29. Yang CP, Lin CC, Li CI, et al. Fasting plasma glucose variability and HbA1c are associated with peripheral artery disease risk in type 2 diabetes. *Cardiovasc Diabetol*. 2020;19:4.
30. Kilpatrick ES, Rigby AS, Atkin SL. A1C variability and the risk of microvascular complications in type 1 diabetes. *Diabetes Care*. 2008;31:2198-2202.
31. Biondi B, Klein I. Hypothyroidism as a risk factor for cardiovascular disease. *Endocrine*. 2004;24:1-14.
32. Davis JR, Dackiw AP, Holt SA, Nwariaku FE, Oltmann SC. Rapid relief: thyroidectomy is a quicker cure than radioactive iodine ablation (RAI) in patients with hyperthyroidism. *World J Surg*. 2019;43:812-817.
33. Prisant LM, Gujral JS, Mulloy AL. Hyperthyroidism: a secondary cause of isolated systolic hypertension. *J Clin Hypertens*. 2006;8:596-599.
34. Ross DS, Burch HB, Cooper DS, et al. 2016 American thyroid association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid*. 2016;26:1343-1421.
35. Chung YJ, Lee BW, Kim JY, et al. Continued suppression of serum TSH level may be attributed to TSH receptor antibody activity as well as the severity of thyrotoxicosis and the time to recovery of thyroid hormone in treated euthyroid Graves' patients. *Thyroid*. 2006;16:1251-1257.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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