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# A higher incidence of cardiovascular complications in hyperthyroid patients with Graves' disease in comparison to hyperthyroid patients with subacute thyroiditis

## Pogostejše pojavljanje srčno-žilnih zapletov pri bolnikih s hipertirozo zaradi bazedovke kot pri bolnikih s hipertirozo zaradi subakutnega tiroiditisa

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## Abstract

**Background:** Hyperthyroidism, as well as systemic inflammation, are associated with a higher incidence and complications of cardiovascular disease. Both in Graves' disease and subacute thyroiditis, patients are hyperthyroid. However, in Graves' disease, there is an autoimmune process in the thyroid, and in subacute thyroiditis, hyperthyroidism is accompanied by systemic inflammation. It is not known if the rate of cardiovascular complications is higher in the course of Graves' disease or subacute thyroiditis.

**Methods:** We performed a retrospective study of all hyperthyroid patients newly diagnosed with Graves' disease or subacute thyroiditis between January 1st 2018 and December 31st 2021 at the Department of Nuclear Medicine, University Medical Centre Ljubljana. Cardiovascular complications in the period 3 months before or after diagnosis were registered. Values are expressed as mean (SD).

**Results:** The sample analysis included 1028 patients (247 with subacute thyroiditis, 781 with Graves' disease). The two groups did not significantly differ by sex, age, and body mass index. A cardiovascular complication was registered in 78 patients; the incidence was significantly higher in Graves' disease than in subacute thyroiditis (74 vs. 4, p<0.001). Compared to patients with subacute thyroiditis, patients with Graves' disease had significantly lower TSH: 0.010 (0.006) vs. 0.024 (0.044) mIU/L (p<0.001), higher free $T_4$: 44.1 (26.6) vs. 37.0 (14.7) pmol/L (p<0.001), higher incidence of diabetes: 4.3 vs. 0.4% (p=0.001), arterial hypertension: 12.2 vs. 5.7% (p=0.004) and smoking: 26.7 vs. 8.7% (p<0.001). In a logistic regression model, a significantly higher likelihood for cardiovascular complications was found in Graves' disease vs. subacute thyroiditis (odds ratio 5.82, p=0.001), in patients with arterial hypertension (odds ratio 2.83, p=0.002), and in those with higher body mass index (odds ratio 0.92, p=0.043).

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**Key words:** hyperthyroidism; thyroiditis; cardiovascular events; inflammation

**Ključne besede:** hipertiroza; tiroiditis; srčno-žilni zapleti; vnetje

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**Conclusion:** We report a higher incidence of cardiovascular complications in hyperthyroid patients with Graves' disease in comparison to hyperthyroid patients with subacute thyroiditis. Patients with Graves' disease were more severely hyperthyroid and had more adverse cardiovascular risk factors.

## Izvleček

**Izhodišče:** Povezava med hipertirozo in večjim tveganjem za pojav in zaplete srčno-žilnih bolezni je znana, prav tako pa tudi povezava med okužbami oz. vnetjem in srčno-žilnimi dogodki. Pri subakutnem tiroiditisu se v klinični sliki prepletata tako hipertiroza kot sistemsko vnetje, pri bazedovki pa gre za avtoimunski vnetni proces, ki je omejen na ščitnico. Zaenkrat ni znano, ali se srčno-žilni dogodki pogosteje pojavljajo pri bolnikih s hipertirozo zaradi bazedovke ali zaradi subakutnega tiroiditisa.

**Metode:** V retrospektivni raziskavi smo zbrali podatke vseh bolnikov s hipertirozo in bazedovko ali subakutnim tiroiditisom, ki so bili na Kliniki za nuklearno medicino UKC Ljubljana prvič obravnavani v obdobju med januarjem 2018 in decembrom 2021, in so v obdobju 3 mesecev pred postavitvijo diagnoze ali po njej doživeli srčno-žilni dogodek. Vrednosti so izražene kot povprečje (SD).

**Rezultati:** V analizo je bilo vključenih 1.028 bolnikov (247 s subakutnim tiroiditisom, 781 z bazedovko). Skupini se po spolu, starosti in indeksu telesne mase nista statistično pomembno razlikovali. Srčno-žilni dogodek je doživelo 78 bolnikov, od tega statistično značilno več v skupini z bazedovko (4 s subakutnim tiroiditisom, 74 z bazedovko, p<0,001). Bolniki z bazedovko so imeli v primerjavi z bolniki s subakutnim tiroiditisom značilno nižji TSH: 0,010 (0,006) proti 0,024 (0,044) mIU/L (p<0,001), višji prosti $T_4$: 44,1 (26,6) proti 37,0 (14,7) pmol/L (p<0,001), večjo pojavnost sladkorne bolezni: 4,3 % proti 0,4 % (p=0,001), arterijske hipertenzije: 12,2 % proti 5,7 % (p=0,004) in kajenja: 26,7 % proti 8,7 % (p<0,001). Model logistične regresije je pokazal, da je tveganje za pojav srčno-žilnega dogodka značilno večje v skupini z bazedovko kot v skupini s subakutnim tiroiditisom (razmerje obetov 5,82, p=0,001), pri bolnikih z arterijsko hipertenzijo (razmerje obetov 2,83, p=0,002) in višjim indeksom telesne mase (razmerje obetov 0,92, p=0,043).

**Zaključek:** Srčno-žilni dogodki se pojavljajo statistično značilno pogosteje pri bolnikih s hipertirozo in bazedovko kot pri bolnikih s hipertirozo in subakutnim tiroiditisom. Bolniki z bazedovko so bolj hipertirotični in imajo več neugodnih dejavnikov tveganja za razvoj srčno-žilnih bolezni.

## 1 Introduction

Graves' disease (GD) is the most common autoimmune thyroid disease causing hyperthyroidism, with an incidence of 30–35/100,000 in Slovenia (1). Subacute thyroiditis (ST), or viral, de Quervain's subacute granulomatous thyroiditis is a self-limiting inflammatory disease of the thyroid gland that sometimes follows a viral infection. Its clinical course is usually accompanied by transient hyperthyroidism. It has an incidence of 9–10/100,000 (1,2).

Thyroid hormones thyroxine ($T_4$) and triiodothyronine ($T_3$) affect cardiac function, especially the contractility, frequency, and compliance of the heart wall, as well as peripheral blood vessels, by influencing endothelial cells and smooth muscle (3-5). Hyperthyroidism has been associated with cardiac arrhythmias, heart failure, acute myocardial infarction (AMI), stroke, and hypercoagulopathy. A large epidemiological study reported increased all-cause mortality and serious adverse cardiovascular (CV) complications in overt and subclinical hyperthyroidism compared with euthyroidism (6). A meta-analysis of 37 cohort studies reported increased CV morbidity and mortality in hyperthyroid patients (7). A large case-control study reported an increased risk of CV disease in untreated hyperthyroid patients, and the duration of decreased thyroid stimulating hormone (TSH) was associated with an increased risk of adverse CV outcomes in both treated and untreated hyperthyroid patients (8). Overt and subclinical hyperthyroidism has been associated with increased markers of thrombogenesis (fibrinogen and factor X levels) and higher von Willebrand antigen levels, leading to increased platelet plug formation, which decreased after treatment (9-12). A limited body of evidence also suggests an association between hyperthyroidism and increased risk of venous and arterial thrombosis (12,13). Whether the increased risk of stroke in hyperthyroid patients is accounted for by the increased prevalence of atrial fibrillation (AF) in this population or by hyperthyroidism itself is still debated (12).

Systemic inflammation, as encountered in ST (but not in GD, where the autoimmune inflammation process is limited to the thyroid gland and potentially to the eyes and skin), can act as a systemic stressor, leading to an excessive inflammatory response and causing harmful, systemic spread of inflammatory mediators, which can gradually lead to the worsening and progression of other diseases (14). Inflammation is one of the key triggers of non-infectious heart disease, which occurs in long-term systemic and vascular diseases (15). There is a clearly proven connection between influenza or sudden respiratory infections and a six-fold higher frequency of AMI during the narrow time period of recovery from these infections (16). The processes contributing to acute coronary syndrome (ACS) development in infection are acute inflammation, biomechanical stress, and vasoconstriction (16). The metabolism is, therefore, further accelerated, which can lead to a reduced concentration of oxygen in the arterial blood and reduced blood pressure (16). This can lead to the development of occlusion of the vessel with a clot and the resulting ACS (16).

Since there is a clear association between hyperthyroidism and complications of CV disease and also between systemic inflammation and complications of CV disease, this study was designed to compare the incidence of CV complications in hyperthyroid patients with GD (autoimmune thyroid disease) and in hyperthyroid patients with ST where systemic inflammation is present.

## 2 Methods

In a retrospective study, medical records of all hyperthyroid patients newly diagnosed with GD or ST at the Department of Nuclear Medicine, University Medical Centre Ljubljana, between January 1st 2018 and December 31st 2021, were examined. The study was approved by the Republic of Slovenia National Medical Ethics Committee (No. 0120-515/2018/7).

The following data were collected:

- patient's age, gender, date of diagnosis, date of potential CV complication;
- risk factors for CV disease: arterial hypertension, smoking, hyperlipidemia, diabetes, body mass index (BMI);
- laboratory values: TSH, free $T_4$, free $T_3$, sedimentation rate in ST patients, thyroid peroxidase antibodies (TPOAb), thyroglobulin antibodies (TgAb), TSH-receptor antibodies (TSH-R Ab).

Arterial hypertension was defined as systolic blood pressure higher than 140 mmHg or diastolic blood pressure higher than 90 mmHg, previous diagnosis I10 in the International Classification of Diseases 10 (ICD-10), or if taking antihypertensive medication. The variable smoking was defined as regular smoking at the time of diagnosis, whereas ex-smokers and occasional smokers were analysed as non-smokers. Hyperlipidemia was marked as present if the serum low density lipoprotein value was above 2.59 mmol/L, previous ICD-10 diagnosis E78, or if taking antihyperlipidemic medication. Diabetes mellitus was defined as a previous ICD-10 diagnosis of E10, E11, or O24 or taking anti-glycaemic medication. BMI was calculated based on collected weight and height data using the standard formula: dividing weight (kg) by square height ($m^2$) (2). Furthermore, BMI was noted as increased if it exceeded 25.0 kg/$m^2$.

GD and ST were diagnosed by an experienced thyroid specialist. GD was diagnosed based on the following: clinical symptoms and signs of hyperthyroidism; laboratory findings: decreased serum level of TSH, elevated serum level of free $T_4$ and/or free $T_3$, elevated TSH-R Ab; thyroid ultrasound: hypoechoic and heterogeneous thyroid structure with increased parenchymal vascularity; in selected cases, increased uptake on thyroid scan with technetium-99m pertechnetate. ST was diagnosed based on the following: swelling with pain and tenderness of the thyroid gland; laboratory findings: elevated sedimentation rate (SR), decreased serum level of TSH, elevated serum level of free $T_4$ and/or free $T_3$; thyroid ultrasound: hypoechoic lesions in the painful region of the thyroid gland; and, in selected cases, suppressed thyroid scintigraphy with technetium-99m pertechnetate (2). Only overtly hyperthyroid patients (TSH below and free $T_4$/free $T_3$ level above normal value) were included in the final analysis. A CV complication was registered according to data in the patient's paper and electronic documentation if, in the period 3 months before or 3 months after the diagnosis of ST or GD, the patient suffered one of the following: sudden cardiac death, AMI (both non-ST-elevation myocardial infarction or ST-elevation myocardial infarction), unstable angina pectoris, AF, tachycardia (except sinus tachycardia and AF), atrioventricular block, transient ischemic attack (TIA), stroke, deep vein thrombosis or pulmonary embolism. AMI, sudden cardiac death or stroke were considered major adverse CV events.

### 2.1 Laboratory measurements

All laboratory measurements were performed at the biochemical laboratory of the Department of Nuclear Medicine at the University Medical Centre Ljubljana. Serum concentrations of TSH, free $T_4$, and free $T_3$ were measured using a chemiluminescence immunoassay (Advia Centaur till January 2021, afterward Atellica, both Siemens Healthineers). Ranges of TSH 0.59–4.23 mIU/L, free $T_4$ 11.5–22.7 pmol/L, and free $T_3$ 3.5–6.5 pmol/L were considered normal. SR was measured semi-automatically (Sediko m10, Laboratorijska tehnika Burnik, Slovenia).

### 2.2 Statistical analysis

Data is expressed as mean (SD). A two-way t-test for independent samples was used for normally distributed variables, and the Mann-Whitney u-test for variables that were not normally distributed. The analysis of descriptive variables was performed with Pearson's $\chi^2$-test or Fisher's exact test, the choice of test depending on the value of the expected frequencies. Multivariate logistic regression was performed to assess the relative contribution of variables to cardiovascular complications; p-value <0.05 was considered statistically significant.

Statistical processing was performed with the GNU PSPP version 1.2.0-g0fb4db, Free Software Foundation) (PSPP). Pivot tables of the Excel program and the online tool Easy Fisher Exact Test Calculator (*Web tool 1*, Social Science Statistics, version 2022) were also used. Fisher Exact Probability Test: 2x4 was calculated by *Web Tool 2*, Vassarstats.net, Richard Lowry 2001-2022).

## 3 Results

The final analysis included 1028 hyperthyroid patients (247 with ST and 781 with GD) (Figure 1).

Baseline demographic data, risk factors for CV disease, and TSH and thyroid hormone values at the diagnosis are outlined in Table 1. The mean value of the SR in the ST group was 64 (27) mm/h.

The CV complications registered in the ST and the GD groups are depicted in Figure 2, respectively. The incidence of CV complications in the GD group was significantly higher than in the ST group (p<0.001).

As evident from Figure 2, CV complications were recorded in 78 (7.6%) patients. In the ST group, 4 (1.6%) had a CV complication, their average age was 44.8 (19.1) years, and 3 (75%) were women. In the GD group, 74 (9.5%) patients suffered a CV complication, their average age was 53.2 (17.6) years, and 43 (58.1%) were women. The groups of patients with GD and ST who suffered a CV complication did not differ statistically significantly by age (p=0.87) or gender (p=0.64). The patient's average age at the time of thyroid disease with the CV complication was 52.8 (17.7) years which was statistically significantly higher than the average age in patients without a CV complication: 45.9 (14.0) years, p=0.002.

In both groups, 37 patients (47.4% of CV complications) had AF (absolute values and proportions are shown in Figure 2). The ST and GD groups did not differ significantly in the incidence of AF (p=0.62). The ST and GD groups did not differ significantly in the occurrence of two out of three major adverse CV events (AMI and stroke while no sudden cardiac death was recorded): one event (AMI) occurred in the ST group and 17 in the GD group (14 patients suffered AMI, 3 patients stroke) (p>0.99).

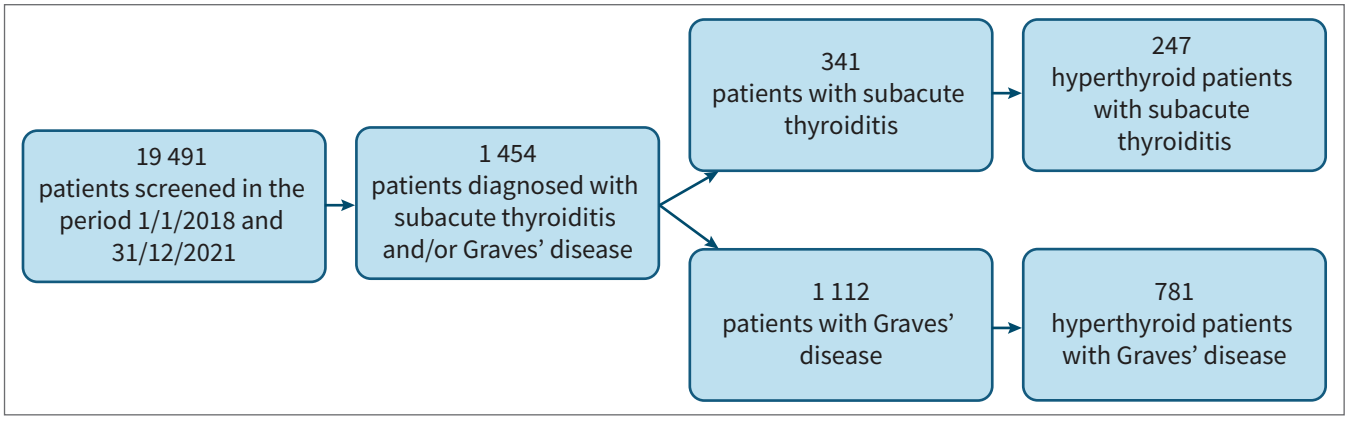


**Figure 1:** Flowchart for the study sample. One patient fulfilled the diagnostic criteria for subacute thyroiditis and Graves' disease simultaneously and was not included in further analysis.

**Table 1:** Clinical characteristics of patients with hyperthyroidism due to subacute thyroiditis or Graves' disease. Data is reported as mean (SD) or number of cases (% of whole sample).

| Parameter | Subacute thyroiditis (N=247) | Graves' disease (N=781) | p-value |
|---|---|---|---|
| **Gender (female/male; % female)** | 182/65 (73.7%) | 604/177 (77.3 %) | 0.24 |
| **Age (years)** | 46.8 (11.9) | 46.2 (15.2) | 0.61 |
| **Body mass index (kg/m²)** | 24.2 (3.8) | 24.2 (5.9) | 1.0 |
| **Hyperlipidemia (%)** | 5 (2.0%) | 33 (4.2%) | 0.12 |
| **Diabetes* (%)** | 1 (0.4%) | 34 (4.3%) | **0.001** |
| **Arterial hypertension (%)** | 14 (5.7%) | 95 (12.2%) | **0.004** |
| **Smoking (%)** | 19 (8.7%) | 188 (26.7%) | **<0.001** |
| **TSH (mIU/L)** | 0.024 (0.044) | 0.010 (0.006) | **<0.001** |
| **Free $T_4$ (pmol/L)** | 37.0 (14.7) | 44.1 (26.6) | **<0.001** |
| **Free $T_3$ (pmol/L)** | 16.85 (69.57) | 19.50 (11.33) | 0.32 |

Legend: ST – subacute thyroiditis; GD – Graves' disease.
* In the ST group, type 2 diabetes was diagnosed in 1 patient. In the GD group, type 1 diabetes was diagnosed in 5 patients, type 2 diabetes in 22 patients and gestational diabetes in 7 patients.

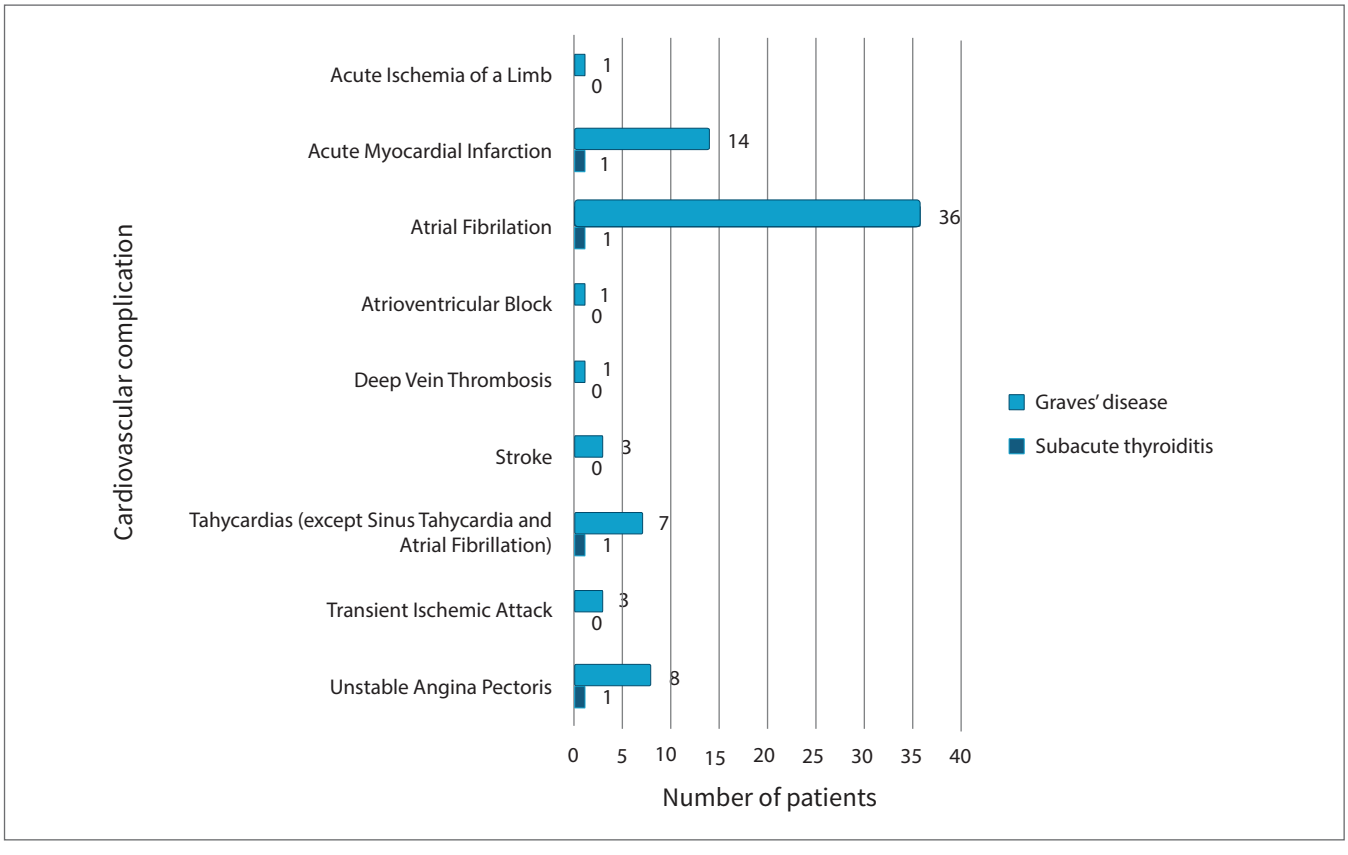


**Figure 2:** Cardiovascular complications in patients with subacute thyroiditis (N=4) and in patients with Graves' disease (N=74).

**Table 2:** Results of a logistic regression model to test the specific effect of independent variables (predictors) on cardiovascular complication ocurrence. The Nagelkerke R2 value of the model was 0.14.

| Predictor | Odds ratio (95% confidence interval) | p-value |
|---|---|---|
| **Gender (0=female, 1=male)** | 1.44 (0.85–2.44) | 0.171 |
| **Age** | 1.02 (1.00–1.04) | 0.063 |
| **Arterial hypertension (0=no, 1=yes)** | **2.83 (1.46–5.48)** | **0.002** |
| **Smoking (0=no, 1=yes)** | 1.39 (0.98–1.98) | 0.065 |
| **Hyperlipidaemia (0=no, 1=yes)** | 1.17 (0.41–3.34) | 0.763 |
| **Diabetes (0=no, 1=yes)** | 0.79 (0.44–1.42) | 0.427 |
| **Increased BMI (0=no, 1=yes)** | **2.99 (1.43–6.26)** | **0.004** |
| **TSH** | 70.61 (0.02–80.4) | 0.295 |
| **Free $T_4$** | 1.00 (0.99–1.01) | 0.442 |
| **Free $T_3$** | 1.00 (0.98–1.01) | 0.817 |
| **Thyroid disease (0=ST, 1=GD)** | **5.82 (2.07–16.3)** | **0.001** |

Legend: ST – subacute thyroiditis; GD – Graves' disease; BMI – Body Mass Index.

Table 2 shows the results of a logistic regression model to test the specific effect of independent variables on CV complication occurrence. The Nagelkerke R2 value of the model was 0.14. GD, AH, and increased BMI were found to be independently associated with CV complications.

## 4 Discussion

In our study, the incidence of CV complications in a large cohort of hyperthyroid patients with ST or GD comparable by age, sex, and BMI was analyzed. A statistically significantly higher incidence of CV complications was found in the GD group compared to the ST group, and a logistic regression model confirmed that the type of thyroid disease, AH, and increased BMI were independent predictors of CV complications. To our best knowledge, our study is the first to evaluate the incidence of CV complications in patients with ST compared to patients with GD.

In hyperthyroid patients, increased metabolism, oxidative stress, and consequent inflammation lead to structural and functional cell and tissue changes that affect cardiomyocytes and atrial fibroblasts. These changes lead to the development of arrhythmogenic zones, including inflammation-induced fibrosis, with electrical remodeled cardiomyocytes and consequently abnormal electrical conduction, ectopy and re-entry phenomenon (12). In our study, the most common CV complication in patients with GD was AF, which is consistent with data from the literature (17). Hyperthyroidism is associated with increased oxygen demand in the target organs, hyperdynamic circulation, elevated systolic blood pressure, and hypercoagulability (6). In a patient with a pre-existent non-occlusive atherosclerotic disease, the combination of adverse effects of these factors can lead to an acute complication. In our study, the incidence of adverse risk factors for CV disease – smoking, arterial hypertension, and diabetes was also statistically significantly higher in the GD group than in the ST group. This finding could explain the higher frequency of CV complications other than AF in the GD group. Smoking is a known dose-dependent risk factor for GD (18-20). Increased systolic blood pressure in hyperdynamic circulation in patients with overt hyperthyroidism was reported (9,21,22). One possible explanation for the higher incidence of arterial hypertension in the GD group in our study could be the more severe hyperthyroidism in this group. The other possible reason could be the longer duration of hyperthyroidism in the GD group; however, the exact onset of either disease could not be estimated and is not reported in the study. Type 1 diabetes and GD are both autoimmune endocrine diseases, and the association between type 1 diabetes and a higher incidence of GD is well documented (23). A higher incidence of hyperthyroidism in type 2 diabetes was also reported (24,25).

Systemic inflammation is a known risk factor for a higher incidence of sudden CV complications, such as AMI (16). The latter event was recorded in our group of patients with ST, although it was not statistically more frequent than in the GD group. However, the results of our study suggest that the severity of hyperthyroidism and clustering of adverse CV risk factors contribute to CV complications more than systemic inflammation.

In one patient in the GD group, a second-degree

atrio-ventricular (AV) block was recorded, which was not an expected finding in a hyperthyroid patient. It seems most likely that the patient had an underlying disease of the cardiac conduction system or the presence of one of the other triggers of AV block and that this complication was not related to hyperthyroidism.

Only hyperthyroid patients with GD and ST were included in our study. Other patients with ST were probably already in the second, i.e., recovery phase of the disease at the time of diagnosis (2,26,27). In the final sample, approximately a quarter of the patients had a diagnosis of ST and three-quarters a diagnosis of GD, which is also expected in terms of Slovenian population incidence – the incidence of GD is between 30–35 cases/100,000 inhabitants, and the incidence of ST between 9–10 cases/100,000 inhabitants (2,28,29). The ratio between the incidences in the population and in both samples is thus 1:3 in favor of GD.

One of the strengths of our study is the large study sample. Furthermore, the two groups of patients with GD and ST did not significantly differ with respect to gender, age and BMI. In compliance with data from the literature, the ratio between men and women in the sample was about 1:3, which is expected for thyroid disease (30). The average age of the patients was in the middle age range, which is also in agreement with other published data, as both diseases occur most often between the ages of 35 and 55 (31). Our study deepens the knowledge about the association between individual thyroid diseases that cause hyperthyroidism and CV complications (32). Although several epidemiological studies report the association between hyperthyroidism and adverse CV complications, large epidemiological studies rarely report specific thyroid diseases leading to thyroid dysfunction. However, the specific pathophysiological mechanisms are different in different thyroid diseases (e.g., autoimmune processes in GD, systemic inflammation in ST, etc).

One of the weaknesses of our study is its retrospective nature. Despite the careful review of the patients' paper and electronic documentation, there is a possibility that all the CV complications the patients suffered were not recorded. This influence is estimated to be at least partially attenuated by the large number of patients included in the study. Furthermore, hospital admissions and poorly documented outpatient treatments due to heart failure decompensation, which is also a CV complication, could not have been included. Also, for methodological reasons, only patients who were newly diagnosed with one of the investigated diseases between 2018 and 2021 were included in the research, and not all patients with GD and ST treated at our centre during that time period.

## 5 Conclusion

In conclusion, our study found a higher incidence of CV complications in hyperthyroid patients with GD in comparison to hyperthyroid patients with ST. According to the results of our study, patients with GD are more hyperthyroid and have more adverse risk factors for CV disease.

### Conflict of interest

None declared.

### Editorial comment

The article was based on Prešeren's award-winning student research paper in 2022.

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