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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

FUNCTİONAL STATUS OF THE THYROİD GLAND İN PATİENTS WİTH ATRİAL FİBRİLLATİON AND ASSOCİATED DİSEASES

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GENERAL CHARACTERISTICS OF THE STUDY

Relevance of the topic and the degree of its development.

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by uncoordinated electrical activity of the atria, resulting in their ineffective contraction. During this rhythm disorder, multiple ectopic foci arise in the atrial myocardium, which impairs effective atrial contractility, thereby reducing the functional value of atrial systole and predisposing the patient to hemodynamic disturbances and thromboembolic complications.

The clinical significance of AF lies not only in its increasing prevalence but also in the serious complications it causes. Despite significant advances in the management of AF—such as antiarrhythmic drugs, anticoagulant therapy, ablation, and other treatment methods—this arrhythmia remains one of the leading causes of stroke, heart failure (HF), and sudden cardiac death.

It should be noted that in patients with AF, the risk of stroke is increased fivefold and the risk of HF is doubled, emphasizing the importance of early diagnosis and comprehensive treatment. More than 60% of patients with AF experience significant impairments in quality of life, reduced tolerance to physical activity, and 17% exhibit symptoms of disability. Quality of life is especially lower in women, younger individuals, and those with comorbid conditions. AF patients often suffer from depressive symptoms, and in some cases, even suicidal ideation and personality disorders are observed.[1;2]

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[1] Isabelle C Van Gelder, Michiel Rienstra et al. 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): European Heart Journal, Volume 45, Issue 36, 21 September 2024, Pages 3314–3414, https://doi.org/10.1093/eurheartj/ehae176

2 Joglar, J. A., Chung, M. K., Armbruster, A. L., Benjamin, E. J., Chyou, J. Y., Cronin, E. M., … Van Wagoner, D. R. (2024). 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation. Circulation, 149(1), e1–e156. https://doi.org/10.1161/CIR.0000000000001193

The main risk factors for AF are classified as modifiable and non-modifiable. Modifiable risk factors play a significant role in the development and progression of AF; therefore, identifying individuals at high risk for developing this arrhythmia can facilitate the imple-mentation of prevention and screening programs for atrial fibrilla-tion.[3;4]

The key risk factors contributing to the onset and progression of atrial fibrillation (AF) include ischemic heart disease (IHD), obesity, heart failure, diabetes mellitus/prediabetes, arterial hypertension (AH), and thyroid dysfunction. These risk factors involve structural, metabolic, and endocrine mechanisms, leading to electrical, structural, and functional remodeling of the left atrium, thereby creating a favorable environment for the development of AF. Therefore, in modern clinical practice, the treatment strategy for AF not only focuses on managing the arrhythmia itself but also includes the early identification and control of its risk factors as an integral component of therapy. [1;2]

Any changes in the hormonal homeostasis of the body are accompanied by disturbances in its physiological and functional activity.[5] Various dysfunctions of the thyroid gland (TG), arising from different causes and of diverse types, can lead to a range of diseases, including cardiac arrhythmias.[6] Functional disorders of the

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[3] Chen LY, Sotoodehnia N, Bůžková P, et al. Atrial Fibrillation and the Risk of Sudden Cardiac Death: The Atherosclerosis Risk in Communities Study and Cardiovascular Health Study. JAMA Intern Med. 2013;173(1):29–35. doi:10.1001/2013.jamainternmed.744

[4] Odutayo A, Wong C X, Hsiao A J et al. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. BMJ 2016; 354: i4482 doi:10ş1136/bmjşi4482

[5] Killpatrick JA, Loeb M. Physiology, Homeostasis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. Available from: NCBI Bookshelf.

[6] Sadeghi SA, Yamamoto Y. Systemic Regulation of Organ Homeostasis and Implications of Hormones and Immunity, Volume II. Front Endocrinol (Lausanne). 2023;14:1235274. 5. Singh H, Shahid MZ, Harrison SL, Lane DA, Lip GYH, Logantha SJRJ. Subclinical thyroid dysfunction and the risk of incident atrial fibrillation: A systematic review and meta-analysis. PLoS One. 2024 Jan; 19(1): e0296413. doi:10.1371/journal.pone.0296413

thyroid gland (TG) play a significant role in the etiology of atrial fibrillation (AF). Studies based on thyroid function tests examining the cumula-tive incidence of AF have shown that, over time, both hyperthyroidism and hypothyroidism increase the risk of developing AF. This effect is observed not only in clinical forms but also in subclinical hypo- and hyperthyroid states. Even when TSH levels are within the normal range, slight variations in free T4 levels have been shown to contribute to atrial arrhythmogenesis.[7;8]

Negative changes in the hormonal activity of the thyroid gland (TG) can become a trigger not only for disorders within the endocrine system but also for numerous pathophysiological processes in the cardiovascular system. The impact of thyroid dysfunction on the cardiovascular system occurs through several mechanisms — including endothelial dysfunction, hypertension, increased levels of inflammatory cytokines, disturbances in lipid metabolism, athero-thrombosis, and others.[9;10;11;12]

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[7] Baumgartner C, da Costa BR et al. Thyroid Function Within the Normal Range, Subclinical Hypothyroidism, and the Risk of Atrial Fibrillation. Circulation. 2017 Nov 28;136(22):2100-2116. doi: 10.1161/CIRCULATIONAHA.117.028753.

[8] Selmer C, Olesen JB, Hansen ML, et al. Subclinical and overt thyroid dysfunction and risk of atrial fibrillation and stroke: a study of 586,460 individuals from primary care. Clin Endocrinol (Oxf). 2021;94(5):735–742.

[9] Chaker L, Heeringa J, Dehghan A, Medici M, Visser WE, Baumgartner C, Hofman A, Rodondi N, Peeters RP, Franco OH. Normal Thyroid Function and the Risk of Atrial Fibrillation: the Rotterdam Study. J Clin Endocrinol Metab. 2015 Oct;100(10):3718-24. doi: 10.1210/jc.2015-2480. Epub 2015 Aug 11. PMID: 26262438.

[10] Lourenço IM, Cavalcante M, Jesus CC, et al. Subclinical thyroid dysfunction and cardiovascular disease: impact on endothelial dysfunction, hypertension, dyslipidaemia and thrombotic risk. Rev Portug Endocrinol Diabetes Metab. 2023;12(4):537–55.

[11] Singh H, Shahid MZ, Harrison SL, Lane DA, Lip GYH, Logantha SJRJ. Subclinical thyroid dysfunction and the risk of incident atrial fibrillation: a systematic review and meta-analysis. PLoS One. 2024;19(1):e0296413. doi:10.1371/journal.pone.0296413

[12] Pereira T, Moura-Moreno JM, Baptista R, et al. Cardiovascular outcomes in subclinical thyroid disease: an updated review. Rev Port Endocrinol Diabetes Metab. 2023; ahead of print.

When it comes to the mechanism of atrial fibrillation (AF) development in hypothyroidism, it is complex and multifactorial. In subclinical hypothyroidism, myocardial relaxation and ventricular filling are consistently impaired, and ventricular diastolic dysfunction can increase intra-atrial pressure, leading to stretch-induced tachyarrhythmia. Moreover, subclinical hypothyroidism may also create a predisposition for AF by increasing the risk of coronary atherosclerosis.[13]

Abnormal changes in thyroid hormone levels in patients with acute illness and no history of thyroid pathology are known as "non-thyroidal illness" or "euthyroid sick syndrome."[14] The most commonly observed hormonal changes in these patients include decreased T3 levels with normal TSH levels. In "non-thyroidal illness syndrome," one of the possible causes of changes in thyroid hormonal status is considered to be a compensatory response to oxidative stress occurring during acute illness. This syndrome is observed in both hospitalized and outpatient patients and is associated with poor prognosis. Identifying "non-thyroidal illness syndrome" in cases of atrial fibrillation may contribute to achieving better outcomes in the management of this arrhythmia.[15;16]

Thus, hormonal imbalance of the thyroid gland disrupts atrial electrical stability both directly and indirectly, resulting in atrial

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[13] Baumgartner C, da Costa BR et al. Thyroid Function Within the Normal Range, Subclinical Hypothyroidism, and the Risk of Atrial Fibrillation. Circulation. 2017 Nov 28;136(22):2100-2116. doi: 10.1161/CIRCULATIONAHA.117.028753.

[14] Biondi B, Kahaly GJ. Cardiovascular involvement in patients with different causes of hyperthyroidism. Nat Rev Endocrinol. 2021;17(8):479–495. doi:10.1038/s41574-021-00503-6

[15] Dietrich JW, Müller P, Schiedat F, Schlömicher M, Strauch J, Chatzitomaris A, Klein HH, Mügge A, Köhrle J, Rijntjes E, Lehmphul I. Nonthyroidal Illness Syndrome in Cardiac Illness Involves Elevated Concentrations of 3,5-Diiodothyronine and Correlates with Atrial Remodeling. Eur Thyroid J. 2015 Jun;4(2):129-37. doi: 10.1159/000381543.

[16] Langouche L, Lehmphul I, Perre SV, Köhrle J, Van den Berghe G. Nonthyroidal Illness Syndrome in Cardiac Illness Involves Elevated Concentrations of 3,5-Diiodothyronine and Correlates with Atrial Fibrillation. Thyroid. 2016;26(12):1670–1677.

dilation and fibrosis, thereby creating a substrate for atrial fibrillation (AF). From this perspective, regular assessment of thyroid function in every patient with AF — including early detection of subclinical dysfunction — plays a crucial role in arrhythmia management and is considered one of the key components of modern treatment strategies.

The object ans subject of the study: For achieving the goals and objectives of the research, 134 patients with atrial fibrillation admitted to the Republican Clinical Hospital named after academician M. Mirgasimov were examined.

The subject of the study was the analysis of the structural and functional status of the thyroid gland in patients with atrial fibrillation.

The purpose of the study: The purpose of the research was to study the morphofunctional state of the thyroid gland in patients with atrial fibrillation. The following objectives were set within the framework of the study:

1. Assessment of the structure and functional status of the thyroid gland in patients with atrial fibrillation.
2. Investigation of the potential presence of "Euthyroid sick syndrome (ESS)" also known as "Non-thyroidal illness syndrome (NTIS)" in atrial fibrillation.
3. Evaluation of the prevalence of comorbid conditions in patients with atrial fibrillation and their association with morphofunctional changes in the thyroid gland.
4. Analysis of the impact of thyroid functional changes on the characteristics of atrial fibrillation.
5. Evaluation of the applicability of the Resampling statistical model for optimizing the study of the impact of thyroid hormonal changes on the characteristics of atrial fibrillation.

The methods of the study: The following methods were used in the study:

– Survey and questionnaire;
– Clinical and instrumental methods;
– Laboratory methods;
– Theoretical and comparative analysis;

– Statistical methods.

The main provisions of the dissertation submitted to the defence:

1. The impact of the morphofunctional state of the thyroid gland on the form, symptomatology, and course of atrial fibrillation.
2. Development and application of a Resampling statistical model to identify the influence of morphofunctional changes in the thyroid gland during atrial fibrillation.
3. The role of Euthyroid Sick Syndrome in assessing the severity of the underlying disease in patients with atrial fibrillation.

Scientific novelty of the research. For the first time in Azerbaijan, the prevalence of morphofunctional changes in the thyroid gland during atrial fibrillation (AF) has been evaluated. The "Euthyroid Sick Syndrome" has been described in Azerbaijan for the first time, and instead of the previously used terms "Euthyroid sick Syndrome (ESS)" or "Non-thyroidal illness syndrome," the term "Fslse dysthyroidism syndrome" has been proposed. Additionally, for the first time, a mathematical model based on the Resampling method was developed, and using this model, the prevalence of morphofunctional changes in the thyroid gland was assessed in virtual patient groups.

Theoretical and practical significance of the research. Detection of morphofunctional changes in the thyroid gland during atrial fibrillation is considered essential for the effective management of this arrhythmia.

In patients with AF, it is important to identify not only hyperthyroidism and hypothyroidism syndromes but also the presence of Pseudodysthyroidism Syndrome.

The presence of Pseudodysthyroidism Syndrome in AF patients is associated with a more severe course of the arrhythmia.

The practical findings, recommendations, and proposals obtained in this dissertation can be used in the development of preventive algorithms for atrial fibrillation in patients with both clinical and subclinical thyroid dysfunction.

Approval and ımplementation.

The main findings of the dissertation were presented and discussed at the following international conferences and congresses: IX National Congress of the Azerbaijan Cardiology Society (Azerbaijan, Baku 2020); I Azerbaijan Endocrinology and Metabolism Congress, V Azerbaijan Diabetes Congress (Azerbaijan, Baku 2022).

The preliminary discussion of the dissertation was held at an interdepartmental meeting with the participation of the staff from the Departments of "Therapy," "Family Medicine," "Cardiology," and "Clinical Laboratory Medicine" of the Azerbaijan State Advanced Training Institute for Doctors named after A. Aliyev (June 11, 2025, Protocol No. 5). The dissertation was subsequently presented and discussed at the scientific seminar under the Dissertation Council FD 2.11 operating at the same institute (September 10, 2025, Protocol No. 8).

The materials of the dissertation were published in accordance with the requirements of the Higher Attestation Commission in the form of 9 (2 in abroad) articles and 10 theses (6 in abroad). The published articles and theses correspond to the main provisions of the dissertation. The journals in which the articles were published are included in the list approved by the Higher Attestation Commission.

The results of the research have been incorporated into the educational materials of the Department of Therapy at the ASATID named after A. Aliyev and applied in clinical practice at Kraton Clinic.

The dissertation was carried out at Azerbaijan State Advanced Training Institute for Doctors named after A. Aliyev.

Structure and volume of the dissertation by sections. The dissertation was submitted as a typed manuscript and consists of the following sections: Introduction – 9817 characters; Chapter I – 63751 characters; Chapter II – 18399 characters; Chapter III – 115120 characters; Conclusions – 1776 characters; Practical recommendations – 542 characters.

The dissertation is presented on 163 printed pages and includes 32 tables and 12 figures. The bibliography contains 253 sources, 12 of which are scientific works by Azerbaijani scholars.

The total character count of the dissertation (excluding table of contents, tables, figures, diagrams, references, and abbreviations) is 209405 characters.

MATERIALS AND METHODS OF THE STUDY

General characteristics of the studied patients. In this single-center, cross-sectional clinical study, the age, gender, comorbiddities, and presence of thyroid dysfunction were taken into account for patients with atrial fibrillation (AF).

As part of the study, 134 patients diagnosed with AF who had applied either as inpatients or outpatients to the Republican Clinical Hospital named after academician M. Mirgasimov were included in the analysis. Among them, 72 were male and 62 were female. The average age of the patients was 62.8 years. This demographic composition provided a reliable basis for examining clinical and laboratory parameters in individuals with AF, including thyroid functional indicators.

Patients included in the study were selected based on the following inclusion and exclusion criteria.

Inclusion criteria:

– Inpatient and outpatient individuals with atrial fibrillation;

– Age above 18 years.

Exclusion criteria:

– Previously diagnosed clinical hypo- or hyperthyroidism;

–Previously diagnosed laboratory-confirmed hypo- or hyperthyroidism;

– Use of antithyroid or thyroid medications;

– Refusal to participate in the study.

The questionnaire served as the primary document and the main source of data for statistical analysis. The questionnaire consisted of the following sections:

– Personal (passport) information;

– Anthropometric data;

– Condition of major systems and organs, previous illnesses and surgeries, presence of chronic diseases;

– Table for biochemical analysis.

To evaluate anthropometric parameters, body weight and height were measured, and body mass index (BMI) was calculated (Quetelet index – kg/m²).

Blood pressure (BP) was measured with a standard sphygmoma-nometer on both arms of the patient in a seated position after 5 minutes of rest. All patients underwent a standard 12-lead resting electrocar-diogram (ECG) and Doppler echocardiography examination. Serum levels of free T3, free T4, TSH, and anti-TPO were determined in all patients.

Comorbid conditions were confirmed based on specialist reports recorded in patients' medical histories and outpatient records.

Statistical analysis was performed using the standard Microsoft Excel software. During the statistical evaluation of the data, minimum, maximum, and mean values of the sample, as well as standard deviation and standard error of the mean, were calculated. Student's t-test was applied. Differences between mean values were considered statistically significant at $p<0.05$.

The confidence interval (CI) for proportions was determined using the Wilson method at a 95% confidence level via an online calculator. Confidence intervals for mean values were also calculated at a 95% confidence level using the "Confidence Limits for Mean Calculator." When sample sizes were small, the significance of differences was assessed using the Mann–Whitney U test.

The significance of differences between proportions was evaluated using the Chi-square (χ^2) method and Fisher's exact test. These calculations were performed online using the MEDCALC calculator.

To improve the informativeness when working with small samples, a statistical resampling model ("Resampling") was applied.

RESULTS AND DISCUSSION

Males accounted for 53.7% of the patients, while females made up 46.3%. The majority of patients (59.7%) belonged to the 20–65 age group, while the smallest group consisted of patients aged ≥75 years (11.9%). The average age of the patients was 62.8 years.

The results showed that the most common form of atrial fibril-

lation (AF) among the examined patients was the tachysystolic type, observed in 87.3% of cases. The normosystolic type was present in 10.4%, and the bradysystolic type in 2.2% of patients. Analysis of AF form revealed the following distribution: permanent AF – 79.1%, persistent AF – 5.2%, and paroxysmal AF – 15.7%.

In analyzing the clinical status of the patients, it was found that symptoms associated with AF ranged from completely asymptomatic cases to symptoms causing significant disability. Symptomatology in AF should be classified using the European Heart Rhythm Association (EHRA) symptom scale. Among the patients included in the study, 3.7% were categorized as EHRA 1, 38.1% as EHRA 2, 42.5% as EHRA 3, and 15.7% had severe symptoms corresponding to EHRA 4.

To reduce the risk of stroke in patients with AF, it is recommended to assess thromboembolic risk using the CHA_2DS_2-VASc score before initiating anticoagulant therapy. Based on the calculations, patients were divided into three risk groups: low stroke risk – 14.9%, moderate risk –11.2 %, and high stroke risk – 73.9%. A history of ischemic stroke was present in 6.7% of the patients. Prior to the study, 23.9% of patients were receiving anticoagulant therapy, while 76.1% were not (Table 1).

Table 1. Stroke risk assessment and oral anticoagulant (OAC) use in patients with atrial fibrillation (AF)

CHA_2DS_2VASc			**History of Stroke (%)**	**Anticoagulant Therapy**	
Low risk (%)	Normal risk (%)	High risk (%)	6.7	Received (%)	Not received (%)
14.9	11.2	73.9		76.1	23.9

The presence of comorbid pathology during atrial fibrillation (AF) worsens both the course of the arrhythmia itself and that of the associated diseases, negatively affecting the overall prognosis.

Among the examined patients, arterial hypertension (AH) was found in 60.4%, type 2 diabetes mellitus (T2DM) in 19.4%, various degrees of obesity in 17.2%, ischemic heart disease (IHD) in 31.3%, and chronic heart failure (CHF) in 80.6% of cases (Table 2).

Analysis of the collected data revealed that all patients with AF had at least one form of comorbid pathology. Specifically, 18.7% of patients had one comorbid condition, 29.1% had two, 32.8% had three, 14.2% had four, and 4.5% had five comorbid diseases.

Table 2. Comorbid conditions in patients with atrial fibrillation (AF)

AH (%)			T2DM (%)	Obesity (%)	IHD (%)	CHF (%)		
60.4			19.4	17.2	31.3	80.6		
1 lev. (%)	2 lev. (%)	3 lev. (%)				II FS (%)	III FS (%)	IV FS (%)
25.9	37	2.5				26.9	54.6	18.5

In order to obtain information about the thyroid gland structure in patients with atrial fibrillation (AF) included in the study, thyroid ultrasonography was performed (Table 3).

The obtained results revealed that, based on thyroid ultrasonography (US) findings, 48.6% of patients had normal thyroid gland volume, while in 50.7% of cases the thyroid volume was enlarged. Only one patient (0.7%) was found to have a reduced thyroid volume.

Assessment of thyroid echogenicity showed that 97 patients (72.4%) had normal echogenicity, while 37 patients (27.6%) had increased echogenicity.

During the ultrasound examination, thyroid nodules were not detected in 66.4% of cases. However, in 45 patients (33.6%), nodular formations of various sizes and numbers were found. Among them, 26.9% had 1–2 nodules, and 6.7% had more than 2 nodules.

As for thyroid cystic formations, they were observed in only 7 patients (5.2%). No cystic changes were found in 127 patients, accounting for 94.8%.

Table 3. Thyroid gland structure in patients with atrial fibrillation (AF)

Indicator	Incidence rate			
	n	%	95% CI	
			Low	High
Thyroid Gland Volume				
Decreased	1	0.7	0.00	2.21
Normal	65	48.6	40.01	57.00
Increased	68	50.7	42.25	59.24
Thyroid Gland Echogenicity				
Increased	37	27.6	20.01	35.21
Normal	97	72.4	63.98	79.30
Thyroid Nodular Formations				
No nodular formations	89	66.4	58.39	74.44
Nodular formations present	45	33.6	25.56	41.61
Thyroid Cysts				
Cysts present	7	5.2	1.44	9.01
No cysts	127	94.8	90.99	98.56

Analysis of laboratory parameters of the thyroid gland showed the following mean values (with 95% confidence intervals):

– Mean anti-TPO: 25.3IU/ml (95% CI: 22.07 :100.53)

– Mean TSH: 2.79 mIU/L (95% CI: 2.22 :3.35)

– Mean free T4: 16.97 pmol/L (95% CI: 15.65 :18.28)

– Mean free T3: 4.95 pmol/L (95% CI: 4.68 :5.22)

In patients with atrial fibrillation, normal anti-TPO levels were observed in 73.9% of cases (95% CI:66.41:81.35), while elevated/ /pathological anti-TPO levels were detected in 26.1% of cases (95% CI: 18.65 :33.59).

As shown in Table 4, 76.1% of patients with atrial fibrillation had normal TSH levels (95% CI: 68.87:83.37). In 6.7% of patients (95% CI: 2.46% :10.97%), TSH levels were decreased, and in 17.2% (95% CI: 10.76%: 23.57%) TSH levels were elevated.

Table 4. Frequency of Various Hormone Levels of the Hypothalamic–Pituitary–Thyroid Axis in Patients with Atrial Fibrillation

Results		Low	Normal	High
TSH	%	6.7	76.1	17.2
	95% CI	2.46; 10.97	68.87; 83.37	10.76; 23.57
ST4	%	6.0	85.0	9.0
	95% CI	1.94; 10.00	79.02; 91.13	4.10; 13.61
ST3	%	6.0	74.6	19.4
	95% CI	1.94; 10.00	67.23; 82.02	12.68; 26.12

Analysis of free T4 (FT4) levels revealed the following distribution: normal FT4 values were observed in 85.0% of patients (95% CI: 79.02%: 91.13%), decreased FT4 levels in 6.0% (95% CI: 1.94% :10.00%), and elevated FT4 levels in 9.0% of patients (95% CI: 4.10% :13.61%).

Among the patients with atrial fibrillation included in the study, normal free T3 (FT3) levels were found in 74.6% (95% CI: 68.87%: 83.37%), decreased FT3 levels in 6.0% (95% CI: 1.94%:10.00%), while elevated FT3 values were observed in 19.4% of patients (95% CI: 12.68%:26.12%), exceeding the incidence of elevated FT4 levels.

In the first phase of the study, the examined patients were divided into two groups based on the structural and hormonal condition of the thyroid gland: the euthyroid group and the dysthyroid group. Subsequently, these groups were further subdivided into five subgroups according to hormonal status and structural changes:

Ideal Norm (IN) Group – normal thyroid structure, normal hormonal profile, and normal anti-TPO levels;

Functional Norm (FuN) Group – structural abnormalities present, normal hormonal profile, anti-TPO normal or elevated;

Hypothyroidism (HipoT) Group – structural abnormalities, abnormal hormonal profile, anti-TPO normal or elevated;

Hyperthyroidism (HiperT) Group – structural abnormalities, abnormal hormonal profile, anti-TPO normal or elevated;

Euthyroid Sick Syndrome Group – normal structure, normal anti-TPO, but abnormal hormonal profile.

The Ideal Norm group served as the classical control group. The

Functional Norm group and its subgroups were not considered in the current study; their analysis is planned for future research.

In the next stage of the study, a comparative analysis was conducted between the mentioned groups. The Ideal Norm and Hypothyroidism groups were compared across various parameters.

Comparison of indicators between the IN and HipoT groups showed that no patients with bradysystolic-type atrial fibrillation (AF) were found in either group. The incidence of the normosystolic type of AF was 10.0% in the IN group and 9.5% in the HipoT group. The incidence of the tachysystolic type was 90.0% in the IN group and 90.5% in the HipoT group. Differences between the groups were not statistically significant ($p>0.05$).

As for the form of atrial fibrillation (AF), the results were as follows: in the Ideal Norm (IN) group, the paroxysmal form of AF was observed in 25.0% of patients, while in the Hypothyroidism (HipoT) group it was found in 19.0% of cases. The persistent form of AF was diagnosed in 10.0% of patients in the IN group and in 4.8% of patients in the HipoT group. The permanent form of AF was diagnosed in 65.0% of patients in the IN group and in 76.2% of those in the HipoT group. These differences between the groups were not statistically significant ($p>0.05$).

Thus, no significant influence of hypothyroidism on the form or type of atrial fibrillation was identified.

The frequency of different severity levels of AF-related symptoms (according to the EHRA classification) in the IN and HipoT groups was as follows: in the HipoT group, EHRA 1 was observed in 9.5% of patients, compared to 5.0% in the IN group. Although the frequency of EHRA 2 was lower in the HipoT group (28.6%) compared to the IN group (50.0%), the difference between the groups was not statistically significant ($p>0.05$). EHRA 3 was found in 33.3% of patients in the HipoT group and in 40.0% of patients in the IN group. However, EHRA 4 was observed in 28.6%

of patients in the HipoT group compared to only 5.0% in the IN group — this difference was statistically significant ($p<0.05$). The next comparison was conducted between the IN and Hyperthyroidism (HiperT) groups.

In the Ideal Norm (IN) group, the frequency of the normosystolic type of atrial fibrillation (AF) was 10.0%, while in the Hyperthyroidism (HiperT) group it was 9.1%. The frequency of the tachysystolic type in the IN group was 90.0%, and in the HiperT group — 81.8%. No cases of bradysystolic AF were observed in the IN group, whereas in the HiperT group this type was found in 9.1% of patients.

Analysis using Fisher's exact test showed that differences between the groups were not statistically significant ($p>0.05$). Analysis of AF form in the IN and HiperT groups showed that the paroxysmal form was found in 25.0% of patients in the IN group and in 18.2% in the HiperT group. The persistent form was observed in 10.0% of IN patients and was not detected in the HiperT group. The permanent form was present in 65.0% of IN patients and in 81.8% of HiperT patients. These differences were also not statistically significant ($p> 0.05$).

Thus, hyperthyroidism was not found to have a statistically significant effect on the type or form of atrial fibrillation. When evaluating the severity of AF-related symptoms, it was found that the frequency of EHRA 1 was 9.1% in the HiperT group and 5.0% in the IN group. EHRA 2 was observed in 18.2% of HiperT patients, which was lower than in the IN group (50.0%). EHRA 3 occurred in 63.6% of HiperT patients and 40.0% of IN patients. EHRA 4 was noted in 9.1% of HiperT patients and in only 5.0% of those in the IN group. None of these differences between groups reached statistical significance ($p>0.05$).

Finally, a comparative analysis was conducted between the IN and Euthyroid Sick Syndrome (ESS) groups. The results showed that in the ESS group, the most common AF type was tachysystolic (78.9%), followed by normosystolic (15.8%), and the least common was bradysystolic (5.3%). The differences between groups were not statistically significant ($p>0.05$).

Analysis of the AF form in the Euthyroid sick syndrome (ESS) group revealed that permanent form AF was present in 84.2% of patients, persistent form AF in 5.3%, and paroxysmal form AF in 10.5%. The differences between groups were not statistically significant ($p>0.05$).

When evaluating the severity of AF-related symptoms in the ESS group, EHRA1 was not observed. EHRA 2 was present in 31.6% of patients, and EHRA 3 in 42.3% — slightly higher than in the IN group (40.0%). The frequency of EHRA 4 in the ESS group was 26.1%, while in the IN group it was only 5.0%. However, these differences also did not reach statistical significance ($p>0.05$).

The analysis of real patient groups with AF did not yield statistically significant results, which was attributed to the small sample sizes in each group. Therefore, it was decided to construct a medical statistical model that would allow for a deeper analysis.

The "Thyroid Gland in Atrial Fibrillation" statistical model was developed, using previously defined groups — Ideal Norm (n=20), Hypothyroidism (n=21), Hyperthyroidism (n=11), and Euthyroid Sick Syndrome (n=19) — and applying the jackknife resampling principle to expand them into virtual groups:

Virtual Ideal Norm group (n=4776)

Virtual Hypothyroidism group (n=4940)

Virtual Hyperthyroidism group (n=2646)

Virtual ESS group (n=221)

In the next phase of the study, the frequencies of various parameters in the Virtual HiperT, Virtual HipoT, and Virtual ESS groups were compared with those of the Virtual IN group.

First of all, the Virtual HyperT group was compared with the Virtual IN group.

In the Virtual IN group, the prevalence of paroxysmal atrial fibrillation (AF) was 25%, while in the Virtual HyperT group it was 17.4%. The permanent form was observed in 65.2% and 82.6% of patients, respectively.

No patients with the persistent form of atrial fibrillation were identified in the Virtual HyperT group, whereas in the Virtual IN group, this form of arrhythmia was detected in 9.8% of patients.

According to the analysis using Fisher's exact test, the differences between the groups were statistically significant ($p<0.001$).

In the Virtual Ideal Norm (IN) group, the bradysystolic type of atrial fibrillation (AF) was not observed at all. In the Virtual Hyperthyroidism (HiperT) group, this indicator was 11.0%. The tachysystolic type of AF was more frequently recorded in the Virtual İN group: 90.3% vs. 79.3%. The incidence of the normosystolic type was the same in both groups — 9.7% in the Virtual IN group and 9.7% in the Virtual HiperT group. The differences between the groups were statistically significant according to Fisher's exact test ($p<0.001$).

A comparative analysis of the severity of AF symptoms in the Virtual HiperT and Virtual IN groups revealed the following: Asymptomatic AF (EHRA 1) occurred in 4.4% of patients in the Virtual IN group and in 9.7% of patients in the Virtual HiperT group. The difference between groups was statistically significant ($p< 0.001$). EHRA 2 was present in 48.9% of patients in the Virtual IN group and in only 19.1% in the Virtual HiperT group — again, with statistically significant differences ($p<0.001$). An opposite pattern was observed for EHRA 3: 41.3% in the Virtual IN group and 60.2% in the Virtual HiperT group ($p<0.001$).

Regarding the most severe form of AF symptomatology, EHRA IV, the frequency was 5.4% in the Virtual IN group and 11.0% in the Virtual HiperT group, with statistically significant differences noted ($p<0.001$).

Figure 1 illustrates the frequency of comorbid conditions observed in the Virtual IN and Virtual HiperT groups. The obtained results showed that in the Virtual HyperT group, the prevalence of IHD (ischemic heart disease), overweight, obesity, and arterial hypertension was higher compared to the Virtual IN group. CHF (chronic heart failure) was found with very high frequency in both groups and was almost at the same level (≈80%). A different trend was observed only in diabetes mellitus: in the Virtual HyperT group, this indicator was more than twice as low as in the Virtual IN group (7.8% vs. 20.6%) (Figure 1).

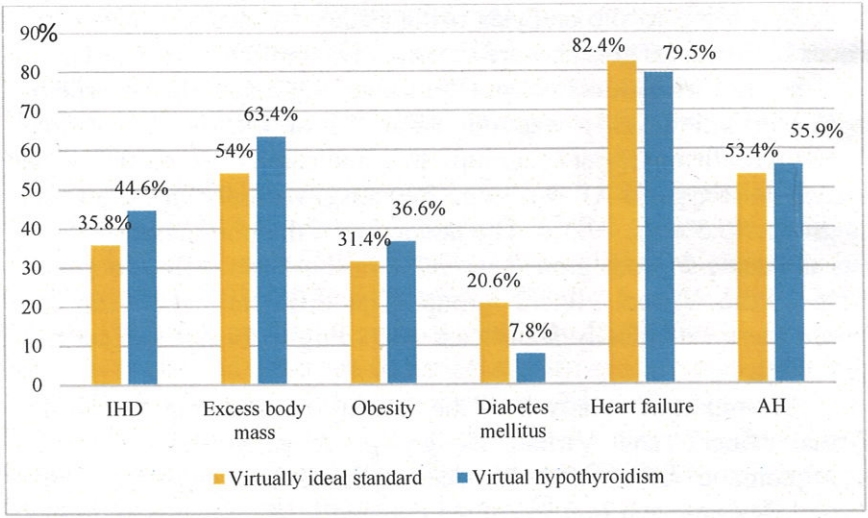

Figure 1. Comorbid diseases in the Virtual IN and Virtual HyperT groups

In the next stage of the study, a comparative analysis of the Vir tual IN and Virtual HypoT groups was conducted. In both groups, the most prevalent form of AF (atrial fibrillation) was the permanent type; however, it was more frequent in the Virtual HypoT group (76.8% vs. 65.2%), which suggests that hormone deficiency accelerates the progression to the permanent phase of arrhythmia. Conversely, the paroxysmal (18.0% vs. 25.0%) and especially the persistent forms (5.2% vs. 9.8%) were relatively less common in the Virtual HypoT group.

As for the frequency of different types of AF, the results were as follows: the tachysystolic type of AF was most frequently observed in both groups — 90.3% in the Virtual IN group and 89.6% in the Virtual HypoT group. Normosystolic AF accounted for approximately 10% in both groups (9.7% and 10.4%, respectively), while the bradysystolic type was not observed at all in either group.

In the Virtual HypoT group, the spectrum of symptoms differed somewhat from that of the Virtual IN group: the frequency of EHRA 2 was 30.3%, and EHRA 3 — 32.7%. In contrast, both the

proportion of asymptomatic patients (EHRA 1) more than doubled (reaching 9.5%), and the rate of patients with severe functional limitation (EHRA 4) increased fivefold, reaching 27.5%. Therefore, it can be concluded that the presence of hypothyroidism exacerbates the clinical burden of AF (atrial fibrillation).

Analysis of comorbidities showed that, compared to the Virtual Hypo group, the Virtual İN group had a significantly higher prevalence of overweight (54.0% vs. 13.7%), obesity (31.4% vs. 13.7%), and diabetes mellitus type 2 (20.6% vs. 4.3%) (Figure 2).

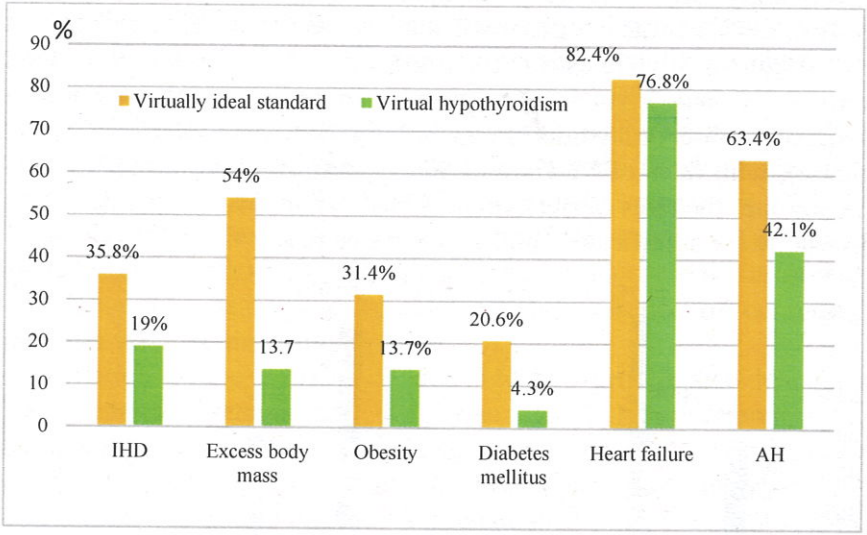

Figure 2. Comorbid diseases in the Virtual IN and Virtual HypoT groups

Finally, the indicators of the Virtual EXS group were analyzed. The results showed that, compared to the Virtual IN group, the frequency of permanent AF was also higher in the Virtual EXS group (83.8% vs. 65.2%), while the paroxysmal and persistent forms were observed less frequently — 11.3% and 4.9%, respectively.

A comparative analysis of AF types in the Virtual IN and Virtual EXS groups revealed that although the tachysystolic type of AF predominated in both groups (90.3% and 78.1%, respectively),

the Virtual EXS group showed higher rates of normosystolic and bradysystolic AF types (16.3% and 5.6%, respectively).

The following results were obtained regarding AF symptomatology in the Virtual IN and Virtual EXS groups: in the Virtual IN group, EHRA 2 was the most prevalent (48.9%), while EHRA 3 was observed at approximately the same frequency in both groups (41.3% and 41.6%, respectively).

A noteworthy point is that in the Virtual EXS group, the level of EHRA IV, which is characterized by severe symptoms, was significantly higher (26.4%) compared to the Virtual IN group (5.4%). EHRA I was not observed at all in the Virtual EXS group.

Figure 3 illustrates a comparison of comorbid diseases in the Virtual IN and Virtual EXS groups. In both groups, the most frequently observed comorbid pathology was CHF (chronic heart failure), with rates of 82.4% and 80.0%, respectively. In the Virtual EXS group, the rates of overweight (78.7%) and IHD (ischemic heart disease) were significantly higher compared to the Virtual IN group.

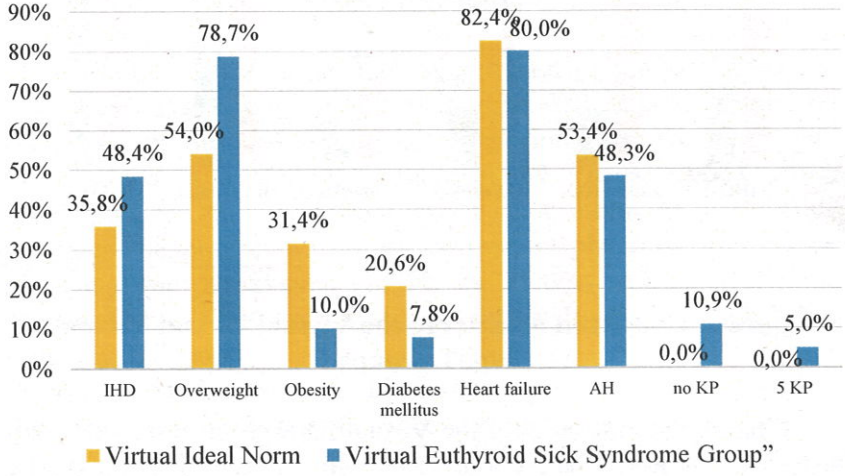

Figure 3. Comorbid diseases in the Virtual IN and Virtual EXS groups

Conversely, the prevalence of obesity and diabetes mellitus type 2 was higher in the Virtual IN group. Notably, 10.9% of patients in the Virtual EXS group had no detectable comorbid pathology,

which further supports the idea that thyroid function abnormalities are directly associated with AF.

Atrial fibrillation (AF) remains one of the most serious challenges in modern medicine and clinical cardiology. It is associated with a high risk of stroke, thromboembolism, and sudden cardiac death and is projected to become even more prevalent in the future.

Alongside classical cardio-metabolic factors, the condition of the thyroid gland plays an important role in the pathogenesis of AF: thyroxine (T4) and triiodothyronine (T3) regulate myocardial energy metabolism, diastolic function, and atrioventricular conduction. Even mild dysfunction of these hormones can accelerate atrial electrical and structural remodeling.

In this scientific study, 134 patients (72 men, 62 women, with a mean age of 62 ± 10.3 years) were examined. To document the presence of AF (atrial fibrillation), all patients underwent 12-lead ECG; to assess the structural and functional status of the heart, Doppler echocardiography was performed; and thyroid ultrasound and laboratory tests were conducted. The presence of comorbid diseases was also determined.

Patients were initially divided into two groups and then into subgroups for comparison with the "Ideal Norm" group. To compensate for the limited sample size in the subgroups, the classical bootstrap-resampling approach was used to create expanded virtual equivalents of the real cohort: "Virtual Ideal Norm," "Virtual Hypothyroidism," "Virtual Hyperthyroidism," and "Virtual EXS" models. This method enhanced the statistical reliability of results within small groups.

The conducted research confirms the widespread occurrence of various structural and functional changes in the thyroid gland in patients with AF. According to ultrasound examination results, more than half of the patients (50.7%) showed thyroid enlargement. These findings indicate structural changes that may play a significant role in the pathogenesis of AF. Increased echogenicity of the gland was noted in 27.6% of cases and is typically associated with diffuse chronic processes, particularly autoimmune thyroiditis.

The presence of nodular formations in 33.6% of patients — with multiple nodules observed in a portion of these cases — reinforces the hypothesis regarding the arrhythmogenic potential of nodular transformations in the thyroid gland. In contrast, the relatively low occurrence of cystic changes (only 5.2%) suggests that this type of structural abnormality has a weaker direct association with AF.

Laboratory test results allowed for a deeper evaluation of the thyroid gland's functional status. Elevated anti-TPO levels were found in 26.1% of patients with AF, indicating the prevalence of autoimmune processes and their possible link to atrial fibrillation. Additionally, TSH levels were elevated in 17.2% of patients and decreased in 6.7%, while deviations in free T3 and T4 hormone levels further confirm that thyroid dysfunctions associated with AF may manifest in both hyperthyroid and hypothyroid forms.

Notably, elevated free T3 levels were detected in 19.4% of cases, supporting theories regarding the arrhythmogenic potential of this hormone. The results showed that although 61.9% of patients were in a euthyroid state (TSH, free T3, and free T4 within the reference range), 38.1% had varying degrees of thyroid dysfunction: clinical or subclinical hypothyroidism in 15.7%, hyperthyroidism in 8.2%, and "euthyroid sick syndrome" in 14.2%. Thyroid gland enlargement was observed in 49% of those examined, and nodules or cysts were detected in 33–35%; however, hormonal disorders emerged as stronger clinical determinants than structural changes. In cases with elevated anti-TPO titers, no independent association was found with the form or severity of AF.

Based on the study results, it can be concluded that both structural and functional changes of the thyroid gland are frequently observed in patients with atrial fibrillation. Thyroid enlargement, the presence of nodular formations, and especially hormonal imbalances — particularly changes in TSH, free T3, and anti-TPO — may serve as significant factors involved in the pathogenesis of AF.

The influence of thyroid dysfunction on the clinical phenotype of atrial fibrillation (AF) was clearly evident. In the vast majority of patients with hypothyroidism, the permanent form of AF, EHRA 3

and IV symptomatology, and an increase in the mean CHA_2DS_2-VASc scores to 3–4 points were recorded. This association was even more pronounced in the virtual hypothyroidism model. On the background of long-standing subclinical or clinical hypothyroidism, electrical stability in the atrial myocardium is disrupted, forming a trajectory from sinus bradycardia to "atrial dilation/fibrillation. "In patients with hyperthyroidism, accelerated atrioventricular coduction, increased activity of triggering foci, and shortening of the refractory period resulted in AF manifesting more frequently as the tachysystolic type, often in the form of permanent AF. The preservation of this same trajectory in the virtual hyperthyroidism model — with a noticeable decrease in the prevalence of bradysystolic type and paroxysmal form and a sharp increase in the permanent form — serves as compelling evidence that hyperthyrotoxic metabolic overload transforms rhythm disturbances into a "sustained" condition.

EXS cases require special attention: even with normal TSH levels, free T3 and T4 may fall outside the reference range. This anomaly often arises from the metabolic effects of sepsis, decompensated CHF, trauma, or severe chronic systemic diseases. AF patients with EXS are characterized by more severe clinical symptomatology. Notably, in 10.9% of patients in this group, no comorbid pathology was identified, reinforcing the notion that this syndrome is directly associated with AF. These findings suggest that EXS is not merely a laboratory "incidental finding" in clinical practice, but rather an adaptive-metabolic response. In such patients, pharmacological correction of thyroid hormones does not provide hemodynamic benefit and may sometimes lead to adverse outcomes.

Analyses show that thyroid status modulates not only the risk of developing AF, but also its clinical form, symptom severity, and likelihood of thromboembolic complications. In this context, hypothyroidism is not a protective factor; on the contrary, it exacerbates AF against a background of prolonged diastolic stiffness and atherosclerosis. Hyperthyroidism, in turn, rapidly and destructively affects atrial electrophysiology, rendering the rhythm refractory. EXS functions as a biomarker of comorbid burden, worsening the

overall prognosis of the patient. In the context of EXS, the priority is not to superficially "normalize" thyroid hormone levels, but rather to stabilize the underlying acute illness.

In conclusion, this study has comprehensively demonstrated, from both clinical and biological perspectives, the complex interplay between AF and thyroid function. It has provided strong evidence that thyroid dysfunction significantly influences the form and severity of arrhythmia. In modern clinical practice, systematic assessment of thyroid status, individualized treatment based on dysfunction type, and active management of comorbid conditions remain essential strategies for reducing AF burden and its complications.

RESULTS

1. In patients with atrial fibrillation, a wide spectrum of thyroid gland alterations was identified: ideal normal status without structural, hormonal, or autoimmune disorders (14.9%); functional normal status with structural and autoimmune alterations (47%); primary subcli-nical, clinical, and secondary hypothyroidism syndrome (15.7%); primary subclinical, clinical, and secondary hyperthyroidism syndrome (8.2%); and euthyroid sick syndrome (14.2%) [1, 14].
2. In patients with atrial fibrillation, the euthyroid sick syndrome was described, and the spectrum of hormonal changes observed in this syndrome was presented. Instead of the previously used terms "Euthyroid Sick Syndrome (ESS)" or "Non-thyroidal Illness Syndrome (NTIS)" the term " False dysthyroidism syndrome" is proposed [15, 18].
3. During atrial fibrillation, the co-occurrence rate of 3 comorbid pathologies was 32.8%, of 4 comorbid pathologies – 14.2%, and of 5 comorbid pathologies-4.5%.
comorbid pathologies – 4.5% [6, 7, 11, 12].
4. The analysis of clinical data showed that the absence of a statistically significant effect of the thyroid gland on atrial fibrillation was attributed to the small sample sizes in some of the groups. To enhance the informativeness when working with small samples, a

statistical resampling model was applied, which enabled the creation of a virtual sample fully corresponding to the real prototype of patients with atrial fibrillation.

5. Using the virtual sample, the following data were obtained regarding the effect of thyroid gland function on atrial fibrillation:

— In the case of hypothyroidism group, compared to the virtual ideal norm group, the prevalence of EHRA 1–2 was lower — 39.8% vs. 53.4% , while the prevalence of EHRA 3–4 was higher — 60.2% vs. 46.6% ($p<0.0001$);

– In the virtual hyperthyroidism group, the prevalence of the tachysystolic type of atrial fibrillation was lower compared to the virtual ideal norm group: 79.3% vs. 90.3% 9($p<0.001$);

– In the virtual hyperthyroidism group, compared to the virtual norm group, the prevalence of EHRA 3 was higher: 60.2% vs 41.3 % ($p<0.0001$).

PRACTICAL RECOMMENDATIONS

1. In patients with atrial fibrillation, morphofunctional changes of the thyroid gland should be thoroughly evaluated.
2. The high prevalence of "False dysthyroidism syndrome" in atrial fibrillation should be interpreted as a response to the severity of the arrhythmia.
3. The possible association between the tachysystolic type of atrial fibrillation and hypothyroid syndrome should be taken into account.
4. Although symptom severity in atrial fibrillation is traditionally associated with hyperthyroidism, its frequent occurrence in patients with hypothyroid syndrome should also be considered.

LIST OF SCIENTIFIC PUBLICATIONS RELATED TO THE DISSERTATION TOPIC

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LIST OF ABBREVIATIONS AND SYMBOLS

AH – Arterial hypertension
Anti-TPO – Anti-thyroid peroxidase antibodies
ESS – Euthyroid sick syndrome
FuN – Functional norm
HiperT – Hyperthyroidism
HipoT – Hypothyroidism
IN – Ideal norm
CP – Comorbid pathology
AF – Atrial fibrillation
TG – Thyroid gland
OAC – Oral anticoagulants
FT3 – Free T3
FT4 – Free T4
TSH – Thyroid-stimulating hormone
HF – Heart failure
IHD – Ischemic heart disease

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