MEDICAL UNIVERSITY - PLEVEN
FACULTY OF MEDICINE

DEPARTMENT OF CARDIOLOGY, PULMONOLOGY AND ENDOCRINOLOGY

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COMORBIDITY AND PROGNOSIS IN PATIENTS WITH ATRIAL FIBRILATION HOSPITALIZED IN UMHAT-PLEVEN

AUTHOR'S ABSTRACT

of a dissertation for awarding the educational and scientific degree of Doctor

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Doctoral program "Cardiology"

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Пр The dissertation is written on 140 standard typewritten pages and is illustrated with 34 tables and 70 figures. The list of cited literary sources includes 139 sources, of which 22 are in Cyrillic and 117 in Latin.

The author is a doctoral student, independent form of study at the Department of Cardiology, Pulmonology and Endocrinology, Faculty of Medicine, Medical University - Pleven.

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The materials for the defense are available to those interested on the website of MU – Pleven, www.mu-pleven.bg

Contents:

USED ABBREVIATIONS:

ACC	American College of Cardiology
AHA	American Heart Association
ARB	Angiotensin II Receptor Blocker
BMI	body mass index
BNP	brain natriuretic peptide
CACS	coronary artery calcium score
CCI	Charlson comorbidity index
CI	confidence interval
CRP	C-reactive protein
eGFR	Estimated glomerular filtration rate
EHRAm	Modified European Heart Rhythm Association rhythm scale
ESC	European Society of Cardiology
IL	interleukin
IL-1	interleukin 1
IL-6	interleukin 6
IL-18R-β	interleukin -18 receptor beta
IVC	inferior vena cava
GWGHF	Get With the Guidelines Heart Failure
HFA	Heart Failure Association
MAFCCI	Modified, AF adjusted Charlson Comorbidity Index
MGP	Matrix Gla Protein
mRNA	matrix ribonucleic acid
NYHA	New York Heart Association
NTproBNP	N-terminal pro B-type Natriuretic Peptide
OR	odd ratio
PCWP	pulmonic capillary wedge pressure
SGLT2i	Sodium-Glucose Cotransporter 2 inhibitors
TAPSE	tricuspid annular plane systolic excursion
TDI	tissue dopler imaging
TNF-α	Tumor necrosis factor alpha
WRN	warfarin-related nephropathy

I. Introduction

Atrial fibrillation – THE EPIDEMIC!

Atrial fibrillation is the most common cardiac arrhythmia, representing a multifactorial disease, arising from various pathogenetic mechanisms and leading to serious consequences. According to data from various authors, it affects about 3% of the population, with its frequency varying depending on two main demographic factors - age and sex. The prevalence of AF is 0.12%–0.16% among people under 49, 3.7%–4.2% in those 60–70, and 10%–17% in individuals over 80. Men are more commonly affected, with a male-to-female ratio of 1,2:1 (Nattel et al., 2008; Kirchhof et al., 2016, Zoni-Berisso, 2014). As of 2010, this arrhythmia has affected 35 million people worldwide, of whom about 6 million were Europeans. Given the aging of the population, this number is expected to at least double in the next 50 years (Camm et al., 2010, Kirchhof et al., 2016). Atrial fibrillation is associated with a twofold increase in overall mortality in women and a 1.5-fold increase in men. According to Wolf et al. (1991), it causes 36% of strokes in adults aged 80-89 and 20% of all strokes, increasing the risk of embolic stroke five times.

Atrial fibrillation is associated with many cardiovascular diseases – arterial hypertension, diabetes mellitus, coronary artery disease, valvular diseases, HF, COPD, thyroid dysfunction, etc. Other, not so clearly defined factors, are OSA syndrome, obesity and CKD. All of these conditions are associated with electrical and structural remodelling of the atria (Zhang et al., 2015).

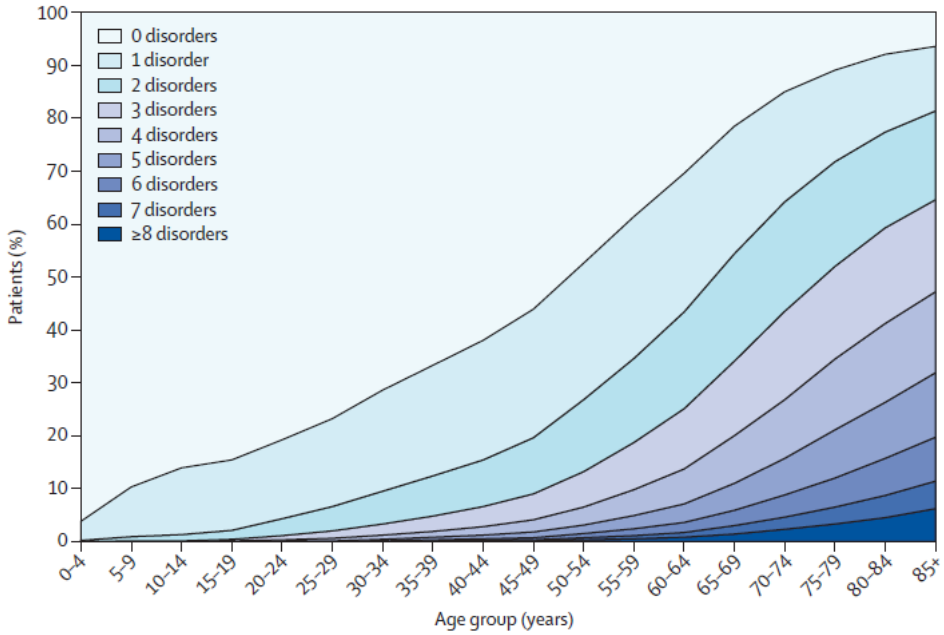
Changes in the atria are also observed with advancing age. Current evidence, however, lends merit to the idea that they are not just a result of ageing but rather a reflection of the clinical problems that frequently accompany ageing.

Comorbidity – history

Comorbidity (concomitant diseases) is the simultaneous manifestation of two or more diseases or syndromes that are pathogenetically related to each other. In literal translation from Latin comorbidity has two components: co - together and morbus - disease. The concept of comorbidity was proposed in 1970. by the American epidemiologist Prof. Alvani Feinstein. The professor's first example of a comorbidity is acute rheumatic fever, which deteriorates the prognosis of individuals who have several other illnesses.

Frequency of manifestation

It has been shown that the number of concomitant diseases varies with the patient's age: concomitant diseases are less common in young people, but they are more likely to develop in elderly patients. Just 10% of individuals had a concurrent condition at age 19, and by age 80, that number rises to 80%.



Relationship between age and number of comorbidities according to Bernett et al, Lancet 2012

II. Objectives and goals

A. Objectives of the study:

To determine the comorbidity in patients with AF hospitalized at the University Hospital of Pleven for a three-year period.

To determine the prognosis of patients with AF and concomitant diseases.

B. Goals

To achieve the first goal, we set ourselves the following tasks:

1. To develop a universal electronic registry of patients hospitalized with AF at the University Hospital "Dr. Georgi Stranski" - Pleven.
2. To characterize the group of patients hospitalized with AF at the University Hospital "Dr. Georgi Stranski" - Pleven according to demographic indicators (sex, age, place of residence).
3. To analyse the importance of risk factors (sex, age, smoking, alcohol consumption, previous and concomitant diseases) for the occurrence of AF.
4. To study the clinical picture of patients hospitalized with AF at the University Hospital - Pleven.
5. To determine the role of cardiac and extracardiac comorbidities in hospitalizations with AF.
6. To evaluate the data from instrumental studies and determine the role of the volume of the left ventricle for the occurrence, recurrence and persistence of AF.
7. To determine FI% in hospitalizations with AF and comorbidity
8. To classify patients according to the EHRA modified scale.

To achieve the second goal (to determine the prognosis of patients with moderate and severe AF and concomitant diseases), we set the following tasks:

9. To develop a modified Charlson AF scale (MAFCCI) to assess comorbidity in patients hospitalized with AF.
10. To study the cumulative burden of comorbidity according to the EHRA modified scale (EHRAm) and MAFCCI.
11. To study the role of the anticoagulant used (indirect, direct) in the occurrence and progression of CKD in patients with AF.
12. To investigate calcium accumulation in valves and large vessels in patients with CKD and anticoagulant therapy.
13. To investigate whether there is seasonality in the hospitalizations of patients with AF and comorbidity.
14. To assess the role of geomagnetic activity in worsening the condition requiring hospitalization in patients with AF and comorbidity.
15. To determine the prognosis in patients hospitalized with severe AF (EHRA modified scale) and comorbidity (MAFCCI).

III. Materials and methods

A. Patients

The present dissertation represents a retrospective, observational study over a period of over three years. The studied hospitalizations of patients with AF were divided into two groups: acute and permanent respectively. All patients included in our study had hospitalization, performed 2D echo, ECG and laboratory tests. Study group patients with AF were included based on the following criteria:

1. Inclusion criteria

Criteria for inclusion in the AF study group:

• Registered with ECG, 24HolterECG or AF monitor before and during hospitalization.

• Episode of AF in the past registered in the hospital database.

• Documentation from other medical institutions.

• Information from GP, hospital emergency department and EMC (emergency medical center).

2. Exclusion criteria

Patients without evidence of AF at the time of hospitalization or a documented history of an attack.

Patients under 18 years of age.

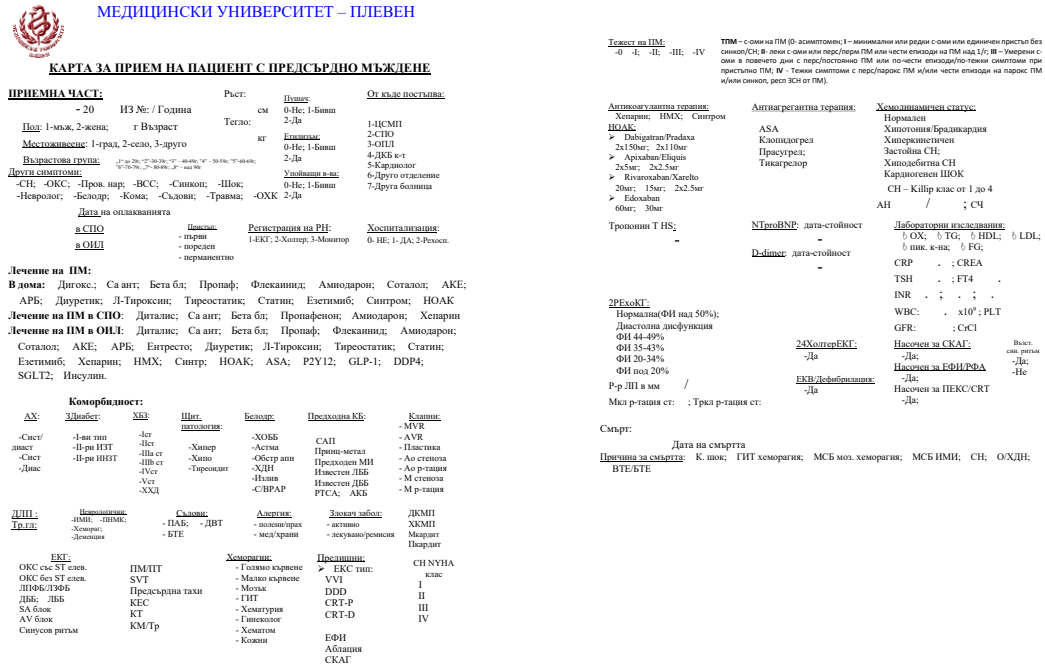
3. Clinical group

The study included over 600 hospitalizations of patients with AF and concomitant diseases. After reassessment, 500 hospitalizations of patients with AF were selected. Of these, 175 were consecutive hospitalizations for AF recurrence or due to concomitant disease in patients already diagnosed with the disease. Thus, our study includes 325 different patients. For the purposes of the study, the number of hospitalizations was used regardless of the number of

patients. The first hospitalized patient included was on 26.12.2016, and the last on 15.02.2020.

B. Methods

For the purposes of the study, a "Admission card for patients with AF" was developed, including data from the anamnesis, status, instrumental and laboratory results of hospitalized patients.



МЕДИЦИНСКИ УНИВЕРСИТЕТ – ПЛЕВЕН

КАРТА ЗА ПРИЕМ НА ПАЦИЕНТ С ПРЕДСЪРДНО МЪЖДЕНЕ

ПРИЕМНА ЧАСТ: - 20 ИЗ №: / Година

Пол: 1-мъж, 2-жена; г Възраст

Местоживеене: 1-град, 2-село, 3-друго

Възрастова група: „1" до 29г; "2"-30-39г; "3" - 40-49г; "4" - 50-59г; "5"-60-69г; "6"-70-79г; „7"- 80-89г; „8" - над 90г

Други симптоми:
-СН; -ОКС; -Пров. нар; -ВСС; -Синкоп; -Шок;
-Невролог; -Белодр; -Кома; -Съдови; -Травма; -ОХК

Ръст: см Тегло: кг

Пушач: 0-Не; 1-Бивш 2-Да

Еднакъм: 0-Не; 1-Бивш 2-Да

Уплйващи в-ва: 0-Не; 1-Бивш 2-Да

От къде постъпва: 1-ЦСМП 2-СПО 3-ОПЛ 4-ДКБ к-т 5-Кардиолог 6-Друго отделение 7-Друга болница

Дата на оплакванията

в СПО

в ОИЛ

Приказа: - първи - повторен - перманентно

Регистрация на РН: 1-ЕКГ; 2-Холтер; 3-Монитор

Хоспитализация: 0- НЕ; 1- ДА; 2-Рехосп.

Лечение на ПМ:
В дома: Дигокс.; Са ант; Бета бл; Пропаф; Флекаинид; Амиодарон; Соталол; АКЕ; АРБ; Диуретик; Л-Тироксин; Тиреостатик; Статин; Езетимиб; Синтром; НОАК
Лечение на ПМ в СПО: Диталис; Са ант; Бета бл; Пропафенон; Амиодарон; Хепарин
Лечение на ПМ в ОИЛ: Диталис; Са ант; Бета бл; Пропаф; Флекаинид; Амиодарон; Соталол; АКЕ; АРБ; Ентресто; Диуретик; Л-Тироксин; Тиреостатик; Статин; Езетимиб; Хепарин; НМХ; Синтр; НОАК; ASA; P2Y12; GLP-1; DDP4; SGLT2; Инсулин.

Коморбидност:

АХ: -Сист/диаст -Сист -Диас

ЗДиабет: -I-ви тип -II-ри ИЗТ -II-ри ИНЗТ

ХБЗ: -Ист -IIст -IIIа ст -IIIв ст -IVст -Vст -ХХД

Щит. патология: -Хипер -Хипо -Тиреоидит

Белодр: -ХОББ -Астма -Обстр апн -ХДН -Илия -С/ВРАР

Предходна КБ: САП Приц-метал Предходен МИ Известен ЛББ Известен ДББ РТСА; АКБ

Клапни: - MVR - AVR - Пластика - Ао стеноза - Ао р-тация - М стеноза - М р-тация

ДЛП : Тр.гл:

Психиатрични: -ИМИ; -ПНМК; -Хемор; -Деменция

Съдови: - ПАБ; - ДВТ - БТЕ

Алергия: - полени/прах - мед/храни

Злокач заб: - активно - лекувано/ремисия

ДКМП ХКМП Мкардит Пкардит

ЕКГ: ОКС със ST елев. ОКС без ST елев. ЛПФБ/ЛЗФБ ДББ; ЛББ SA блок AV блок Синусов ритъм

ПМ/ПТ SVT Предсърдна тахи КЕС КТ КМ/Тр

Хеморагии: - Голямо кървене - Малко кървене - Мозък - ГИТ - Хематурия - Гинеколог - Хематом - Кожни

Предписани: ➢ ЕКС тип: VVI DDD CRT-P CRT-D ЕФИ Аблация СКАГ

СН NYHA клас I II III IV

Тежест на ПМ: -0 -I; -II; -III; -IV

ТПМ – с-оми на ПМ [0- асимптомен; I – минимални или редки с-оми или единичен пристъп без синкоп/СН; **II**- леки с-оми или перс/парм ПМ или чести епизоди на ПМ над 1/г; **III** – Умерени с-оми в повечето дни с перс/постоянно ПМ или по-чести епизоди/по-тежки симптоми при пристъпно ПМ; **IV** - Тежки симптоми с перс/пароксПМ м/или чести епизоди на пароксПМ м/или синкоп, респ ЗСН от ПМ).

Антикоагулантна терапия: Хепарин; НМХ; Синтром
НОАК:
➢ Dabigatran/Pradaxa 2x150мг; 2x110мг
➢ Apixaban/Eliquis 2x5мг; 2x2.5мг
➢ Rivaroxaban/Xarelto 20мг; 15мг; 2x2.5мг
➢ Edoxaban 60мг; 30мг

Антиагрегантна терапия: ASA Клопидогрел Прасугрел; Тикагрелор

Хемодинамичен статус: Нормален Хипотония/Брадикардия Хиперкинетичен Застойна СН; Хиподебитна СН Кардиогенен ШОК
СН – Killip клас от 1 до 4
АН / ; СЧ

Тропонин T HS: -

NTproBNP: дата-стойност -

D-dimer: дата-стойност -

Лабораторни изследвания: ↓ ОХ; ↓ TG; ↓ HDL; ↓ LDL; ↓ пик. к-на; ↓ FG;
CRP . ; CREA
TSH . ; FT4 .
INR . ; . ; .
WBC: . x10⁹ ; PLT
GFR: ; CrCl

2РЕхоКГ: Нормална(ФИ над 50%); Диастолна дисфункция ФИ 44-49% ФИ 35-43% ФИ 20-34% ФИ под 20%
Р-р ЛП в мм /
Мкл р-тация ст: ; Тркл р-тация ст:

24ХолтерЕКГ: -Да

ЕКВ/Дефибрилация: -Да

Насочен за СКАГ: -Да;
Насочен за ЕФИ/РФА -Да;
Насочен за ПЕКС/CRT -Да;
Вълст. сви. ритъм -Да; -Не

Смърт:
Дата на смъртта
Причина за смъртта: К. шок; ГИТ хеморагия; МСБ моз. хеморагия; МСБ ИМИ; СН; О/ХДН; ВТЕ/БТЕ

Figure 1. Admission card for patients with AF

The admission card served to develop a software for filling in a patient database with an easy and intuitive interface.

To carry out the study, a universal electronic registry of patients with AF was developed. The project was launched in 2018, OBDC Microsoft Access 2016 was used as a platform and is a personal development of the author of the dissertation. The registry and the data entered into it are available for free use by anyone who wishes, after contacting the author. It is currently being used to work on two other projects.

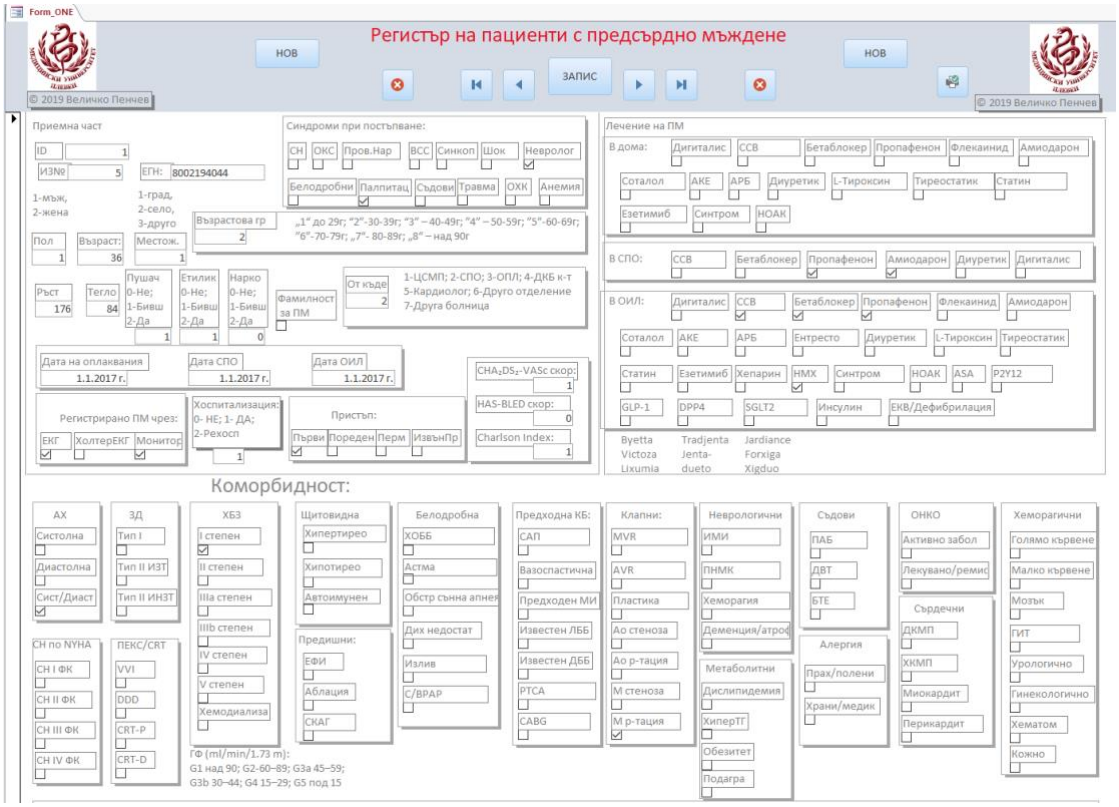


Figure 2. Database of patients with AF

The data source used was the hospital system of the University Hospital "Dr. Georgi Stranski" Pleven – Gamma Codemaster, which allows prompt and dynamic monitoring of patient hospitalizations, rehospitalizations, as well as laboratory data. The information was completed using the patient's history and current condition, together with information from the hospital system on therapy after discharge, treatment at home, and care while in the hospital.

The Riva-Rocci indirect sphygmomanometric method using Korotkoff sounds was used to measure the patients' blood pressure manually. Systolic and diastolic pressure were determined in phases 1 and 5, respectively. The higher blood pressure readings, independent of the arm on which they were taken, were used for our investigation if there was a difference between the two arms' readings.

24HolterECG was performed with Sygnalizer 2000 and CONTEC TLC 5000 devices.

All patients upon admission to the hospital had a baseline 12-lead ECG recorded with a CONTEC ECG 1200G device and 2D echo (M-mode, B-mode and Doppler) performed with a Phillips HD7 echocardiograph.

All ejection fractions used in the study were calculated using the Simpson method.

Two methods are used to estimate the volume of the left atrium (LA) without significant differences between them. These are the Simpson method and the area/length method. The measurement in both methods is performed in two planes from the apical position in four and two-chamber slices. To calculate the volume of the LA using the area/length method, the formula is used:

LA volume = (0.85 x A1 x A2)/L - Where A1 is LA area from apical 4-chamber position, A2 – LA area from apical 2-chamber position, L is the arithmetic mean of the atrial length from the 2- and 4-chamber positions.

Another much easier and more accessible method for measuring the volume of the LA, which we used in our study, is the determination of the transverse and longitudinal dimensions from the apical 4-cavity position and parasternal long-axis section (Figure 3). The volume is calculated with satisfactory accuracy by the formula:

LA ml = (D1 x D2 x D3) x (0.523).

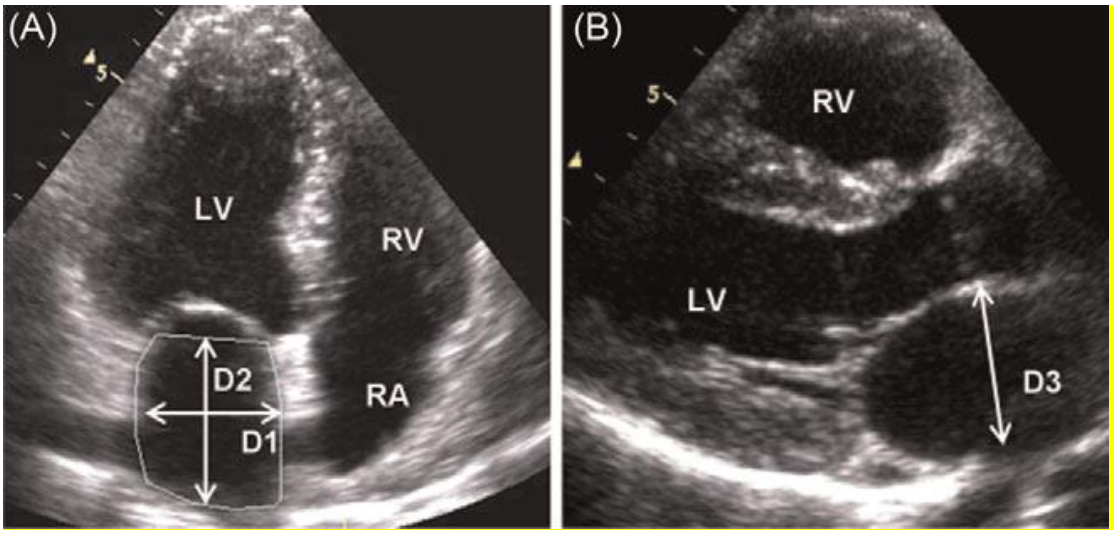


Figure 3. Calculation of the LA volume through a formula

NYHA classification of HF:

• First functional class: No symptoms during prolonged physical exertion (I);

• Second functional class: Reduced physical capacity (dyspnea, fatigue) during moderate exertion (II);

• Third functional class: Significantly reduced physical capacity (dyspnea, functional fatigue) during light physical exertion (III);

• Fourth functional class: Significantly reduced physical capacity (dyspnea, fatigue) at rest (IV).

Isolated diastolic dysfunction must meet several conditions simultaneously: symptoms of HF; EF% > 45-50%; increased left ventricular stiffness; absence of pulmonary disease.

According to the 2016 ESC guidelines, the differentiation of patients with HF based on LV EF% is important, due to the different underlying causes, demographics, comorbidities, and responses to therapy. (2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2016;37:2136-2137).

According to the ejection fraction (EF) of the left ventricle (LV), patients with HF are divided into:

- with reduced EF (HF-rEF) – (EF<40%)
- with intermediate EF (HF-mrEF) – (EF 40% - 49%)
- with preserved EF (HF-pEF) – (EF 50% and above 50%).

Laboratory markers for myocardial damage (creatinine phosphokinase, total and MB fraction, and troponin T), as well as D-Dimer, CRP, etc. were tested in the Central Laboratory of UMBAL - Pleven. In all hospitalizations (500 in total), creatinine levels were tested with calculated GFR and creatinine clearance.

The troponin T (HS) test was performed only in a part of the hospitalized patients, as it is required only for certain clinical diagnoses. The reference values for healthy individuals in this immunochromatographic test for troponin are up to 0.014 ng/ml.

Charlson comorbidity index (CCI)

Comorbidity is a condition that coexists with another underlying disease, influencing its progression, altering its symptoms, changing the therapeutic approach, and significantly influencing the prognosis in the end. Comorbidity in AF can be assessed using the Charlson comorbidity index (CCI).

It was founded by Mary Charlson in 1987. The CCI is a primary method for categorizing comorbidities. It determines the risk of death within 1 year of hospitalization for patients with specific comorbidities. The scoring system includes 19 indicators.

The CCI was developed by determining the severity of 19 chronic diseases according to their association with 1-year mortality in a cohort of 559 patients. The CCI is widely used to predict the risk of death for a variety of conditions, including malignant diseases.

Variables	Weights of the original CCI	Weights of the adjusted CCI
Age	1 point for each decade from 50 to 90 years of age.	1 point for each decade from 50 to 90 years of age.
AIDS	6	4
Cerebrovascular disease	1	0
Chronic pulmonal disease	1	1
Congestive heart failure	1	2
Connective tissue disease	1	1
Dementia	1	2
Diabetes	1	0
Diabetes with end organ damage	2	1
Hemiplegia	2	2
Leukemia	2	2
Liver disease - Mild	1	2
Liver disease - Moderate or severe	3	4
Lymphoma	2	2
Moderate or severe renal disease	2	1
Myocardial infarction	1	0
Peptic ulcer disease	1	0
Peripheral vascular disease	1	0
Tumor, local	2	2
Tumor, metastatic	6	6

Table 1. The variables and weights of the original and adjusted CCIs (Charlson et al. 1987; Quan et al. 2011)

Modified AF adjusted Charlson Comorbidity Index (MAFCCI).

For the purposes of our study, an original modified comorbidity index was developed called: Modified, AF adjusted Charlson Comorbidity Index – MAFCCI, including a total of 13 groups of cardiological and non-cardiological criteria with a maximum score of 36 points.

Modified AF adjusted Charlson Comorbidity Index	
1 point	- male sex - age 50-59y - arterial hypertension - HF II FC by NYHA - CIHD (ACS, SAP, MI) - CMP - Myocarditis/Pericarditis - Aovalve stenosis - CKD (IIIa, IIIb) - hypothyroidism - COPD, CRF - dyslipidemia - gout - obesity - PAD, DVT, PE - anemia - cancer in remission - minor bleeding
2 points	- age 60-69y - HF III FC by NYHA - Mvalve stenosis - type 2 diabetes - CKD (IV, V, HD) - hyperthyroidism - pleural effusion - IMI, TIA, Haemorrhaging - active oncological disease - major bleeding
3 points	- age 70-79y - HF IV FC by NYHA - dementia - sleep apnea
4 points	- age >80y

Table 2. Modified, AF adjusted Charlson Comorbidity Index – MAFCCI

Impact of GMA on hospitalization in patients with AF and comorbidities.

Geomagnetic activity (GMA) data is from the National Geophysical Institute at; http://www.geophys.bas.bg/kp_for/kp_mod_bg.php

According to the National Geophysical Institute, GMA is a measure of the disturbance of Earth's magnetic field on a global scale and is represented by the Kp index. Values below 4 indicate a calm state, values between 4 and 5 - active, above 5 - a magnetic storm. The planetary Kp index is a measure of the disturbance of the Earth's magnetic field. It is given in relative units, which vary from 0 to 9 depending on the disturbance of the field.

The value of the Kp index is determined from the data of 12 geomagnetic stations located in the northern and southern hemispheres of the Earth, one of which is the geomagnetic observatory - Panagyurishte.

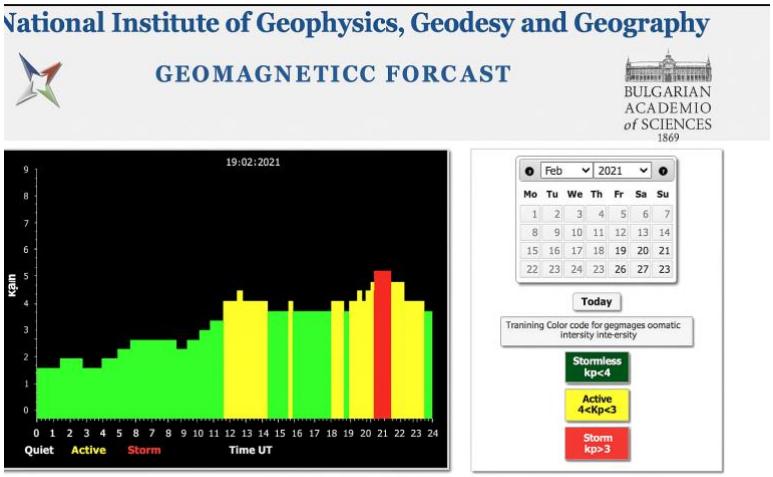


Figure 4. National Institute of Geophysics, Geodesy and Geography(NIGGG) – BAS geomagnetic forecast website

Due to the fact that the anomalies in the Earth's magnetic field are caused by the solar wind - the streams of charged particles that are ejected from the Sun, and which, entering the Earth's atmosphere, cause ionization, eddy currents and from there - variations in the Earth's magnetic field, there is a possibility to determine the degree of disturbance of the Earth's magnetic field from the parameters of the solar wind. This is possible due to the availability of current

data received from a stationary satellite outside the Earth's atmosphere Advanced Composition Explorer (ACE). The methodology developed by the team of the Geophysical Institute - BAS allows to calculate an approximate estimate of the Kp index called Kpm based on these data, which are available every 15 minutes, which is automatically published on this Internet page. The confidence interval of this value at a probability of 50% is 0.63. The forecast value for the next 6 hours from the current moment is also published. The forecast is calculated based on the behavior of geomagnetic activity over the past two days using the Wiener-Hopf method.

Statistical analysis

- Descriptive analysis: the frequency distribution of the features under investigation is broken down into study groups and shown in tabular form.
- Variance analysis: used to evaluate the data's dispersion and central tendency properties.
- Graphical analysis: used to show the results that were obtained.
- Crosstabulation – to find a relationship between categorical features.
- To test hypotheses for the existence of a relationship between categorical variables, use the Fisher's test and the c2 test.
- The Shapiro-Wilk and Kolmogorov-Smirnov tests are used to check for normality in distributions.
- Nonparametric Mann-Whitney test - to test hypotheses for a difference between two independent samples
- The Kaplan-Meier technique for calculating how long it will take for the event under study to occur.

Student's t-test was used to analyse continuous variables, which were represented as means and standard deviations. The χ-square test was used to examine differences between categorical variables, which were displayed as percentages. Regression analysis and correlation were used to look at the

relationship between the parameters. The data were also visualised using graphic analysis.

All data in the development were processed using a specialized standard statistical package for a personal computer – IBM SPSS® for Mac and Windows, version 26.0 and 27.0.

IV. Results and discussion

A. The significance of risk factors in the development of AF.

1. The role of sex in the incidence of AF

There were 218 women and 282 men among the 500 hospitalisations with AF that were part of the study group. Statistically, men were significantly more (p=0.004). Acute AF was more common in men than in women, with a statistically significant difference (p<0.05). Men outnumbered women in the group of hospitalised patients with chronic AF, although this difference was not statistically significant (p=0.326).

	Male	Female	Total	%	Statistical significance (chi square)
Acute AF	188	137	325	65%	Men predominate with p<0.05 (p = 0.005)
Chronic AF	94	81	175	35%	Men predominate with p>0.05 (p=0.326)
Total	282	218	500	100%	Men predominate with p<0.05 (p = 0.004)

Table 3. Number of hospitalizations (men and women) depending on the type of AF

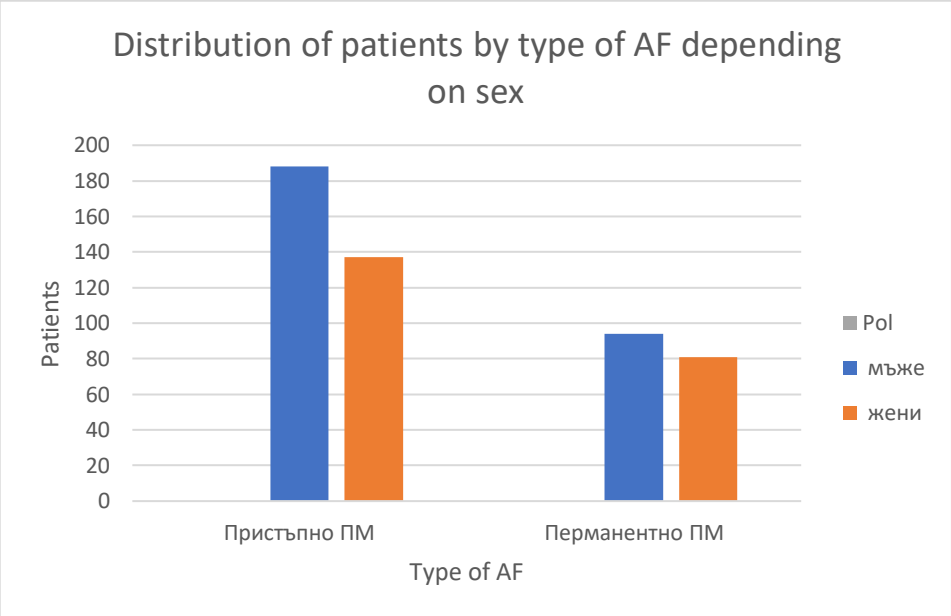


Figure 5. Sex ratio in AF groups

Men with acute AF are statistically significantly more likely to be hospitalised than those with permanent AF (p=0.005). The information gathered from our investigation aligns with the findings of other writers: With a male to female ratio of 1.2:1, men are more likely to be impacted (Nattel et al., 2008; Kirchhof et al., 2016, Zoni-Berisso, 2014).

In conclusion, both internationally and among Bulgarians, male gender is a substantial risk factor for the onset of acute AF.

2. Importance of age as a risk factor for the development of AF.

Data from literature indicates that over 70% of all AF instances, approximately equal for men and women, occur between the ages of 65 and 85. Risk factors include HF, AH, and CAD, as well as left ventricular dysfunction, are linked to an increased incidence of AF. Mortality is attributable to AF alone (Benjamin E.J., et al., 1998). In older adults, AF is far more likely to be permanent (58–67%).

The results of our study on the age of patients hospitalized with AF by group and sex are presented in Table 4, Figure 6 и Figure 7.

	Acute AF	Chronic AF
Mean age of patients (years)	68,7	73,43
Standard deviation	11,1	9,3
Median age of patients	69	74
Minimal age of patients	31	38
Maximal age of patients	92	94
Mean age of males	65,1	71,7
Standard deviation	11,5	10
Median age of males	67	72
Minimal age of males	31	44
Maximal age of males	87	89
Mean age of females	71,1	75,5
Standard deviation	9,2	8
Median age of females	72	76
Minimal age of females	44	38
Maximal age of females	92	94

Table 4. Age of patients (in years)

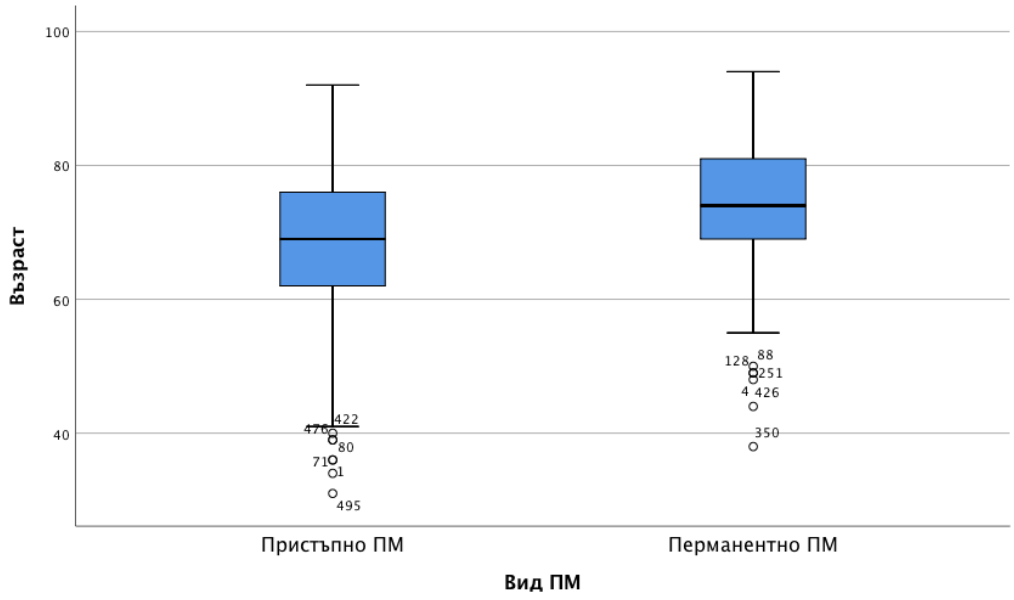


Figure 6. Age of patients (total males and females) – minimum, maximum and mean ± standard deviation (in years)

It is statistically significant ($p<0.05$) that the age of patients (both men and women) hospitalised with acute AF is lower than the age of patients with chronic AF.

For men exclusively, the age difference between patients with acute AF and those with chronic AF is statistically significant ($p<0.05$).

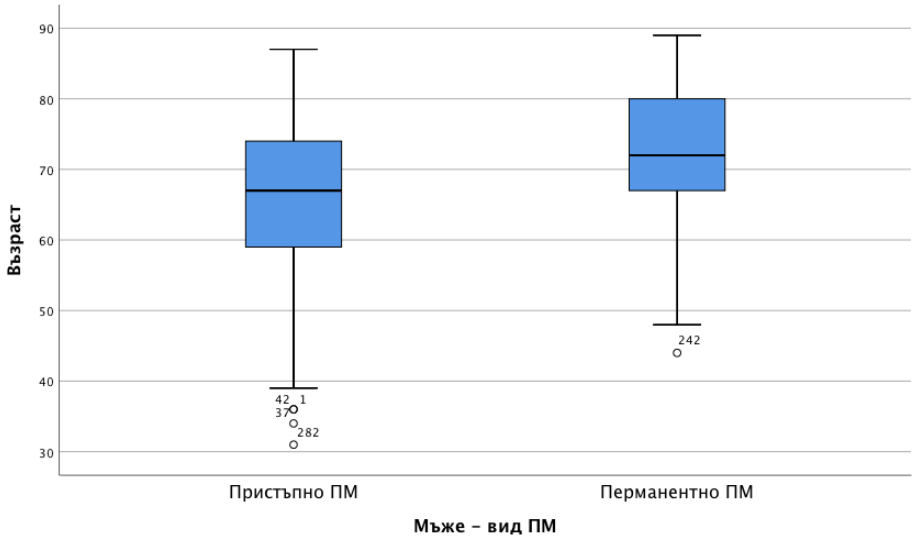


Figure 7. The average age of men with acute AF is lower than the average age of men with chronic AF

The same applies to females – those with acute AF are younger than the ones with chronic AF, but with less statistical significance.

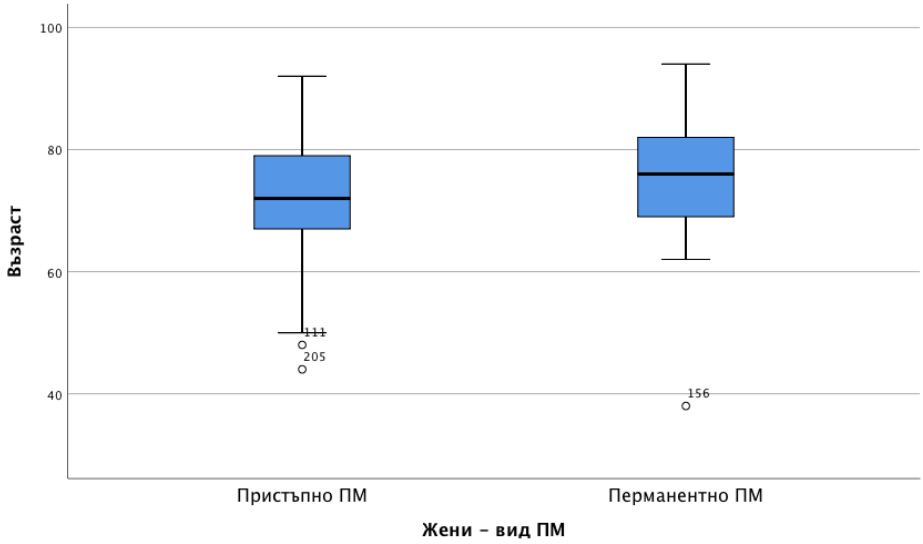


Figure 8. Females who have acute AF are typically younger than those who have chronic AF.

The distribution of patients with AF by age decade at the time of their hospitalization is presented in Table 5 and Figure 9:

Decade	Males	Females	Total
1 - 20-29 years	0	0	0
2 - 30-39	6	2	8
3 - 40-49	16	2	18
4 - 50-59	43	8	51
5 - 60-69	89	62	151
6 - 70-79	88	87	175
7 - 80-89	40	55	95
8 - over 90 years	0	2	2

Table 5. Distribution of hospitalizations with AF by sex and age groups.

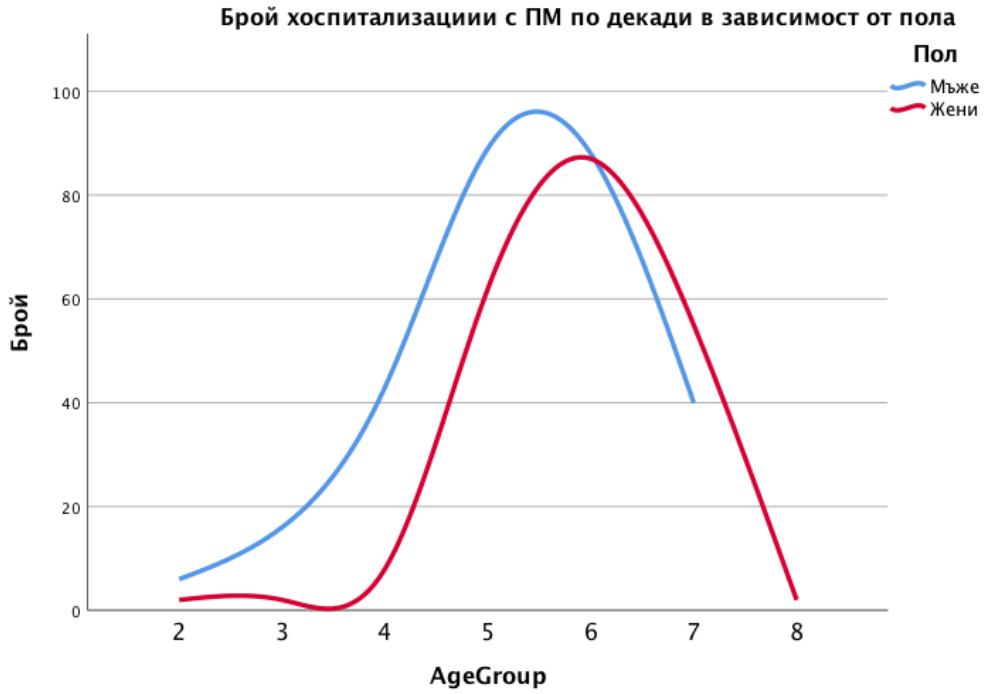


Figure 9. Distribution of patients with AF according to their age at the time of hospitalization.

There were no hospitalised patients in the first group of people aged 20 to 29. The age groups of 5 (60–69 years) and 6 (70–79 years) had the highest number of patients, confirming the idea that the frequency of AF rises with age. Men surpassed women in every group from the second to the fifth, with a highly significant statistical difference ($p<0.05$). Due to the lower life expectancy of males with AF and comorbidity, women prevailed over men in the seventh and eighth age groups, but the difference in the sixth group was not statistically significant (own results). Other authors' data indicates that AF affects 0.12% to 0.16% of those under the age of 49, 3.7% to 4.2% of those between the ages of 60 and 70, and 10% to 17% of those over 80. Our findings also support the notion that men are more frequently impacted, with a male to female ratio of 1.2:1 (Nattel et al., 2008; Kirchhof et al., 2016, Zoni-Berisso, 2014).

3. Distribution by sex and place of residence

Both male and female patients from urban areas are hospitalised with AF symptoms far more frequently than those from rural areas. Once more, the number

of men with statistical significance is higher among city dwellers. The greater awareness, the infrastructure that is accessible, and the increased stress that city dwellers experience are probably the main causes of the high rate of hospitalisations among this demographic (Marchev S, 2018).

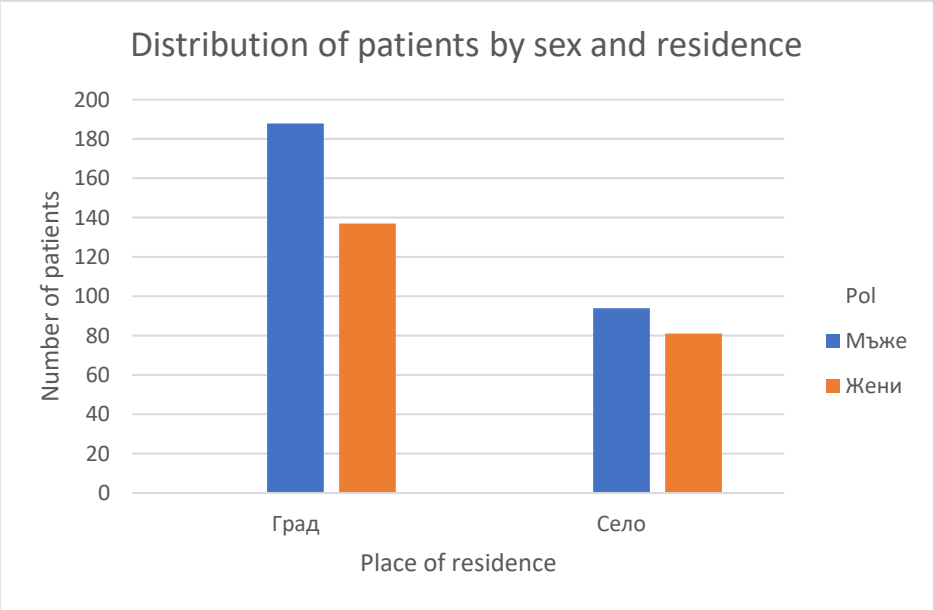


Figure 10. Distribution of patients with AF by sex and place of residence at the time of hospitalization

4. Smoking

Smokers are 259 out of 500 hospitalizations of patients with AF. Of these, 112 are current, 147 former. The number of non-smokers is 241. The total percentage of smokers (current and former) is 51.8% represented by Figure 11. Former smokers are 116 men and 31 women – a total of 147. The percentage of male smokers (current and former) with AF is 31.8%, and of female smokers – 21.7%.

	Males	Females	Total	%
Non-smoker	100	141	241	48,2%
Current smoker	66	46	112	22,4%
Former smoker	116	31	147	29,4%
Total	282	218	500	100%

Table 6. Incidence of smokers in hospitalizations with AF.

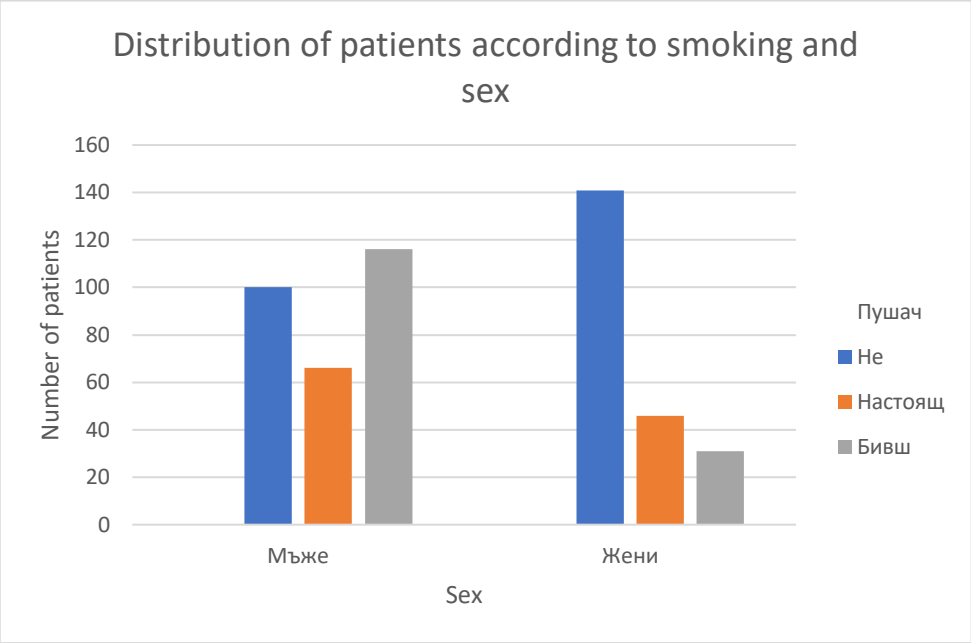


Figure 11. Distribution of smokers among hospitalizations with AF by sex.

Hospitalised male smokers – current and former – are statistically significantly more than hospitalised female patients.

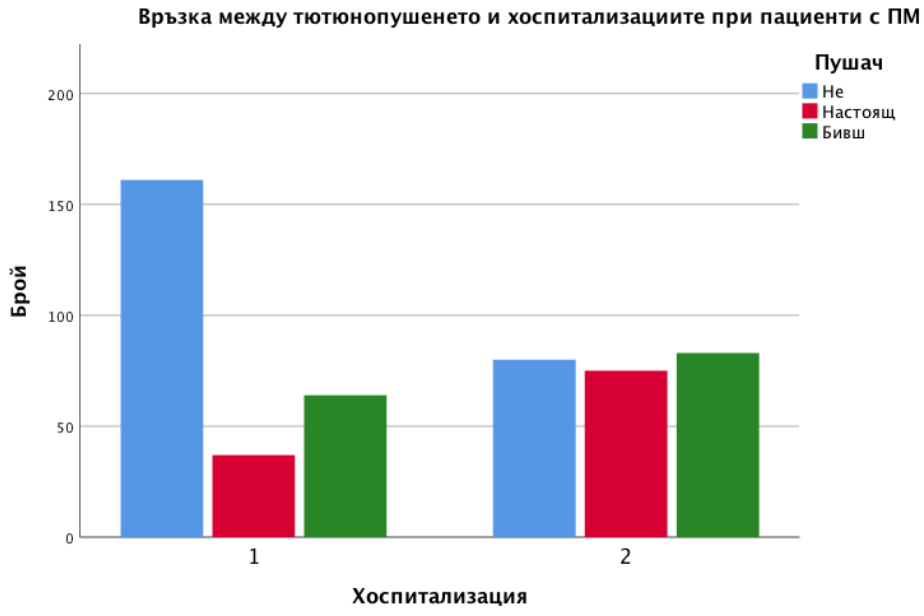


Figure 12. The association between hospitalisations (1) and rehospitalizations (2) in patients with AF and comorbidities and smokers, ex-smokers, and non-smokers.

According to our findings, nonsmokers experience the most hospitalisations, whereas former smokers experience higher rates of AF and rehospitalizations than current smokers. Subclinical hyperthyroidism was present in 0.7% of 16,533 people in the NHANES III research, which did not include patients with overt thyroid illness. According to the same study, smokers had a twofold increased likelihood of having subnormal TSH levels (0.1–0.4 mU/L).

According to Huxley RR et al.'s analysis of the ARIC data, around 10% of incident AF is caused by current smoking. Furthermore, as noted by Chamberlain AM et al., there is most likely a dose-dependent association, whereby smokers who have smoked for the longest time and consume the most cigarettes daily are at the highest risk of developing AF.

The conclusion from our results is that smoking is an important risk factor for rehospitalization of patients with AF and comorbidity, especially in former smokers who have quit for some reason. This is a result of chronic ischemia in smokers and is directly correlated with the duration of smoking.

5. Alcohol

For alcohol consumption, reliable data are available for 119 hospitalizations. Of these, 115 were male and 4 were female. The number of abstainers was 381, which is unlikely - we did not check it because it is based on history. The total percentage of alcohol consumers was 23.8%, and of abstainers 76.2% (Figure 13). The percentage of men with AF consuming alcohol was 40.7%, and of women – 1.4%.

	Males	Females	Total	%
Abstainer	167	214	381	76,2%
Current	115	4	119	23,8%
Total	282	218	500	100%

Table 7. Frequency of alcohol consumption among patient hospitalisations with AF by sex.

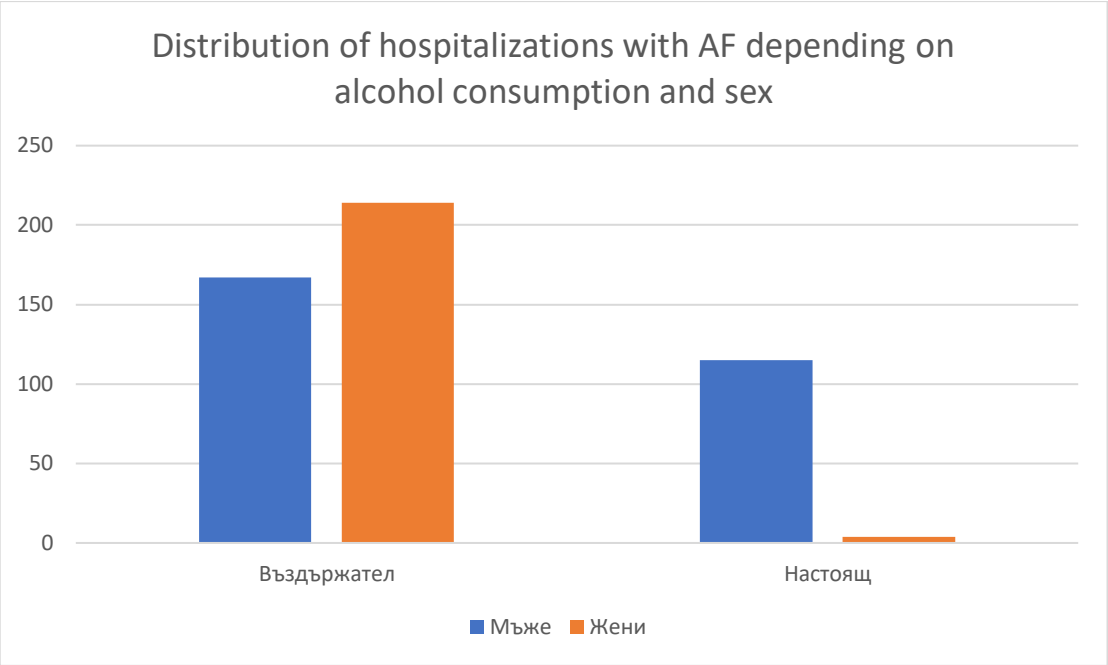


Figure 13. Distribution of hospitalisations with AF depending on alcohol consumption and sex

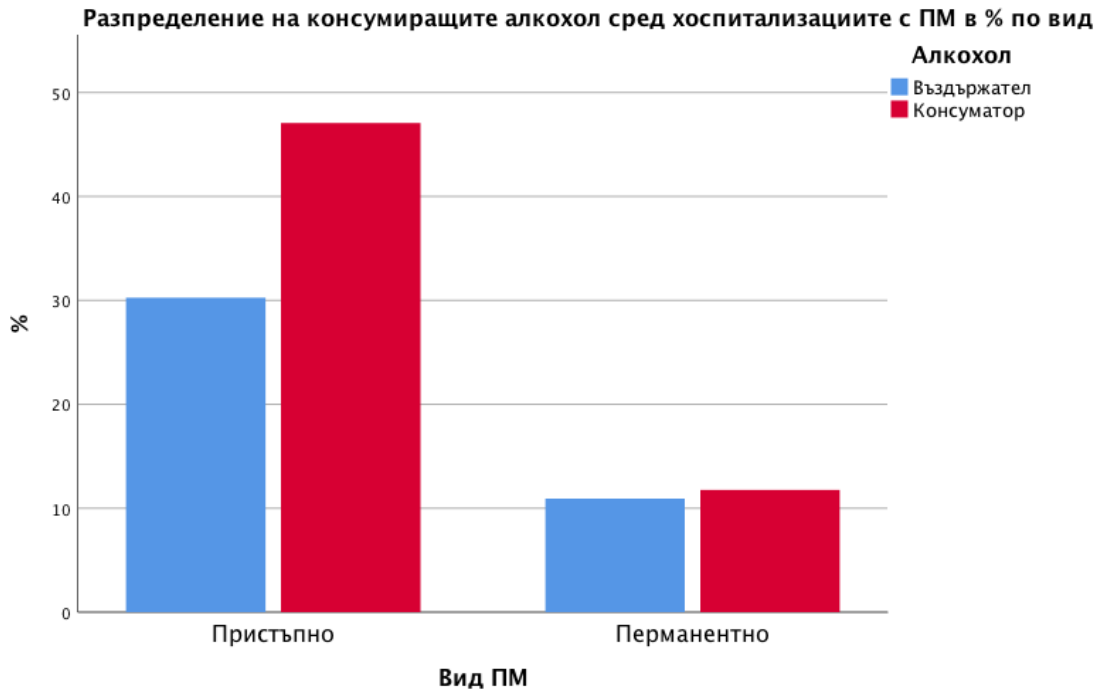


Figure 14. Distribution of alcohol consumers among hospitalisations with AF in % by type

As expected, men are significantly more likely than women to consume alcohol. Both acute and chronic AF hospitalisations have a larger proportion of drinkers. Reversible factors, such as alcohol consumption (sometimes known as "holiday heart syndrome"), are linked to secondary AF. Additionally, two meta-analyses by Larsson SC et al. demonstrated a linear dose-response association between alcohol use and the incidence of AF, with each standard drink per day significantly increasing the relative risk of incident AF by 8% when compared to not drinking at all. These findings imply that there is no safe threshold for long-term alcohol consumption in relation to the onset of AF. This correlates with the increased risk of AF with systematic alcohol consumption and is an additional risk factor of great social importance.

6. Clinical symptoms at the time of hospital admission

Upon admission to the hospital, clinical symptoms vary widely. The most common complaints are: palpitations 76.4%, manifestations of HF (orthopnea) 70%, chest tightness 51.6%, shortness of breath 36.6%, 12% have neurological symptoms, and 5.4% have syncope. Palpitations are significantly more pronounced in hospitalizations with paroxysmal AF, while orthopnea is more pronounced in those with permanent AF. The results are presented in Table 8 and Figure 15 and coincide with data from worldwide literature.

	Acute AF	Chronic AF	Total	%
HF (orthopnea)	189	161	350	70%
Chest tightness	172	86	258	51,6%
Conductive disorders	2	4	6	1,2%
Cardiac arrest	1	1	2	0,4%
Syncope	16	11	27	5,4%
Seizure	2	2	4	0,8%

Neurological	42	18	60	12%
Shortness of breath	104	79	183	36,6%
Palpitations	264	118	382	76,4%
Vascular	4	3	7	1,4%
Trauma	1	1	2	0,4%
ACS	1	1	2	0,4%

Table 8. Clinical symptoms during hospital admission

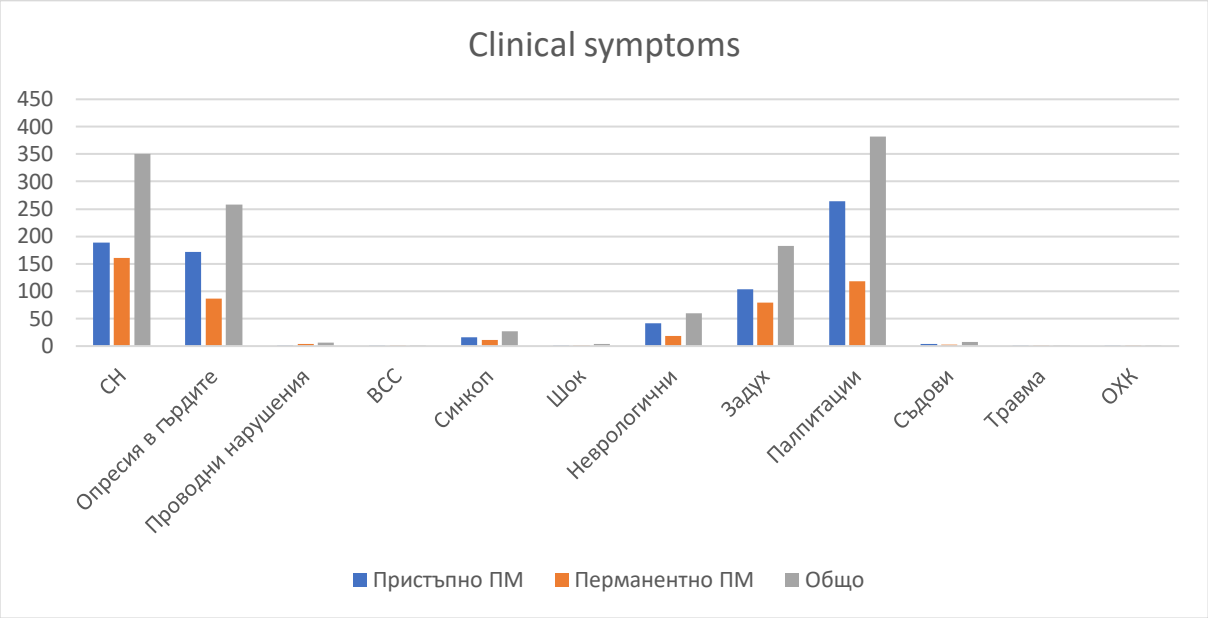


Figure 15. Clinical symptoms at the time of hospital admission

7. Hemodynamic status in hospitalisations of patients with AF

HD status	Acute AF	%	Chronic AF	%	Total
Hospitalisations	325	65%	175	35%	500
Normal	226	69,5%	118	67,3 %	344/68,8%
Hypo/brady	21	6,5%	10	5,7%	31 / 6,2%
Hyperkinetic	78	24%	47	26,9%	125 / 25%

Table 9. Hemodynamic status during hospitalisation.

The majority of patients with AF who were admitted to the hospital had normal haemodynamic condition, followed by hyperkinetic and hypotension/bradycardia. Between the two AF-type groups, there was no statistically significant difference. In hospitalised AF patients, higher blood pressure was linked to a higher risk of MI/PMIC and heart failure, while lower blood pressure was linked to a higher risk of heart failure and death from all causes (Zhaqing Sun et al., 2025).

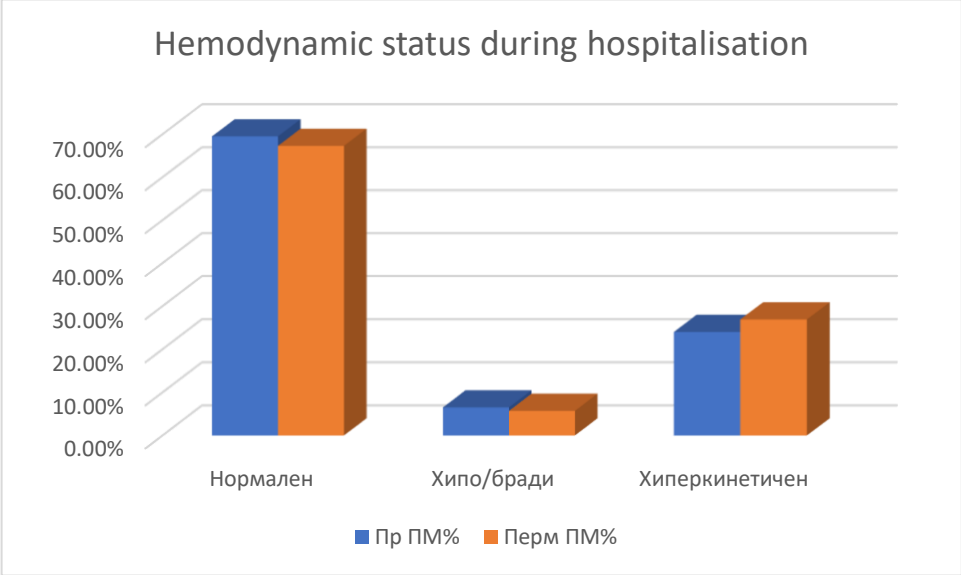


Figure 16. Hemodynamic status during hospitalisation

B. Comorbidities and AF

Comorbid conditions in patients with AF are divided into two groups: cardiological and non-cardiological.

B1. Cardiological concurrent conditions

1. Incidence of arterial hypertension (AH) in both groups

The frequency of AH is presented in the following Table 10 and Figure 17:

	Acute AF	%	Chronic AF	%	Total
Hospitalisations	325	65%	175	35%	500
Total	308	94,8%	160	91,4%	468
AH %		94,8%		91,4%	93,6%

Table 10. Incidence of AH in hospitalized patients with AF.

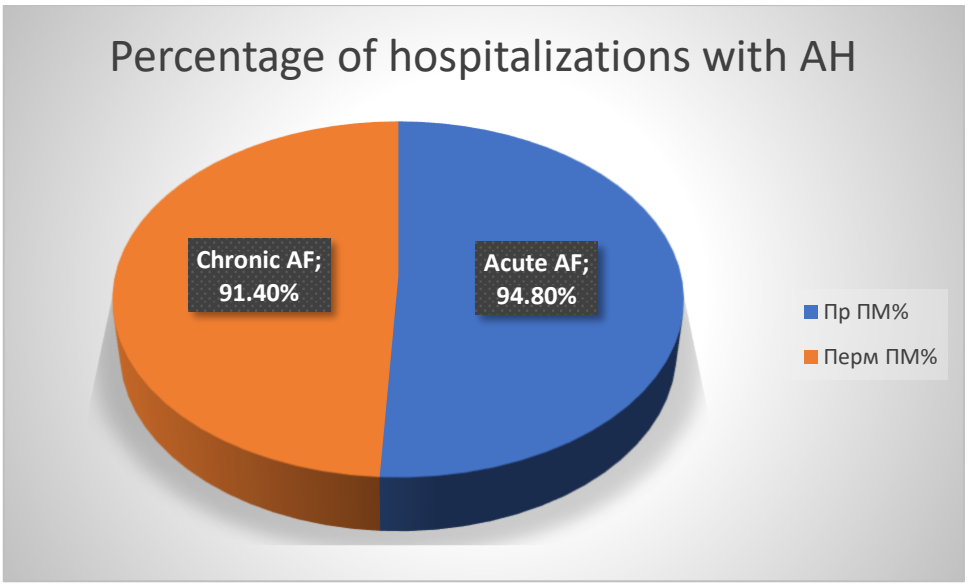


Figure 17. Frequency of AH in patients with AF

The high frequency of AH in both hospitalisation groups supports the idea that AH plays a major role in the development of AF and subsequent recurrences. The number of hospitalisations with permanent AF is decreased without statistical

significance, most likely because these patients' blood pressure is regularly controlled. AH is the most prevalent concomitant AF illness, occurring in 65–70% of AF patients, according to literature data of Nabauer M. et al. And is one highly significant risk factor for AF.

2. Heart failure in patients with AF

HF is a common concomitant syndrome in patients hospitalized with AF and occupies one of the first places as a comorbid factor in hospitalizations with AF. According to world data, patients with AF often have hypertension (62%) or coronary artery disease (43%), which in most cases are not the cause of arrhythmia (Gerald V.N. et al., 2009). Only in cases of severe dysfunction (systolic or diastolic) of the left ventricle and burden on the LA are conditions created for the development of AF. In 10-30% of patients with CHF, AF is registered, which reduces tolerance to physical exertion and worsens the prognosis (SOLVD).

According to our study, in hospitalizations with paroxysmal AF, a higher percentage of patients have NYHA class I and II HF with high statistical significance. On the other hand, compared to individuals with acute AF, those with chronic AF have a significantly higher frequency of FC III and IV ($p<0.05$). great classes of HF with great dependability are clearly correlated with the number of hospitalisations with persistent AF.

	Acute AF	%	Chronic AF	%	Total
Hospitalised	325	65%	175	35%	500
HF I by NYHA	91	28%	2	1,1%	93
HF II by NYHA	109	33,5%	27	15,4%	136
HF III by NYHA	106	32,6%	127	72,6%	233
HF IV by NYHA	12	3,7%	19	5,1%	31
Total	318		175		493
% with HF		97,8%		100%	98,6%

Table 11. NYHA HF functional class in hospitalizations with AF by type

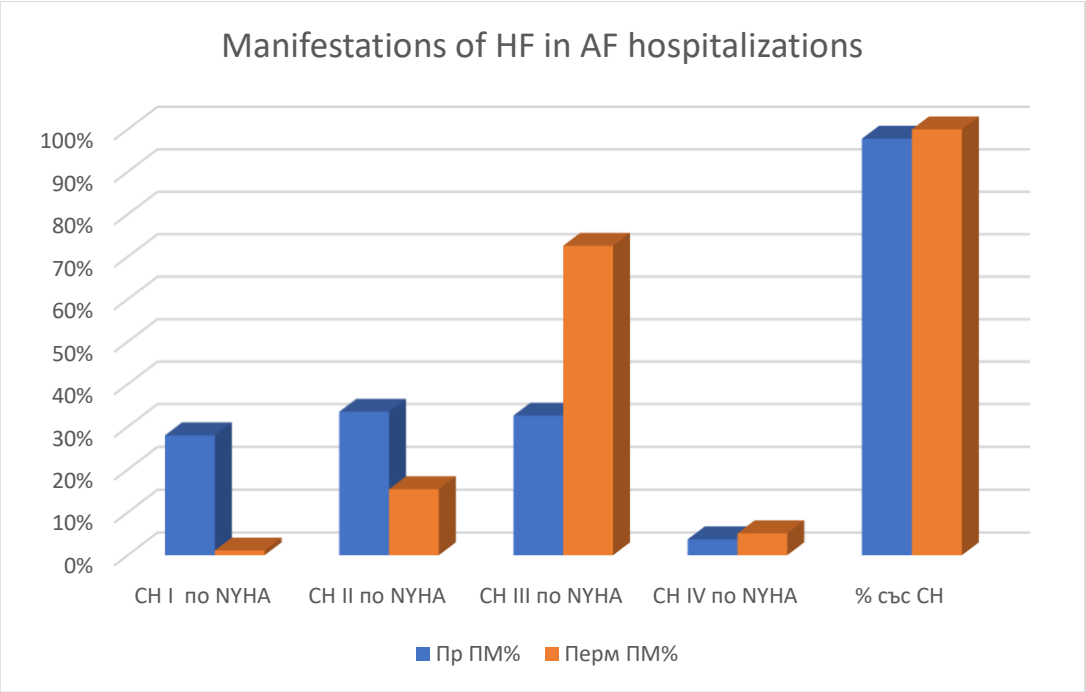


Figure 18. Hospitalization rates by NYHA HF class and AF type

3. Coronary Artery Disease (CAD) in hospitalizations with AF

Other publications claim that AF is seen in 10–20% of myocardial infarction patients, particularly in older individuals, who also have HF and LV dysfunction. Tachyarrhythmia frequently goes away on its own after the acute period of MI. Thirteen to fifteen percent of myocardial infarction patients experience AF, which is more common in older patients and those with STEMI. Acute myocardial infarction may not cause secondary AF to reoccur (Dennis H.L., et al., 2009; Saczynski, J.S., et al., 2009).

From our results, CAD in its various forms occurs in about half of hospitalizations with AF (48.2%). SAP is most often detected in both groups of hospitalizations – 35.1% in acute AF and 36% in chronic AF. Unstable angina is statistically significantly more common in patients with acute AF, while experienced AMI and SAP are more common in hospitalizations with permanent AF, but without a statistically significant difference.

	Acute AF	%	Chronic AF	%	Total
Hospitalisations	325	65%	175	35%	500
SAP	114	35,1%	63	36%	177
UAP	4	1,2%	0	0%	4
Experienced MI	19	5,8%	13	7,4%	32
Experienced MI and SAP	16	4,9%	12	6,9%	28
Total hospitalised	153		88		241
% hospitalised with CAD		47,1%		50,29%	48,2%

Table 12. Incidence of CAD in AF hospitalizations by type

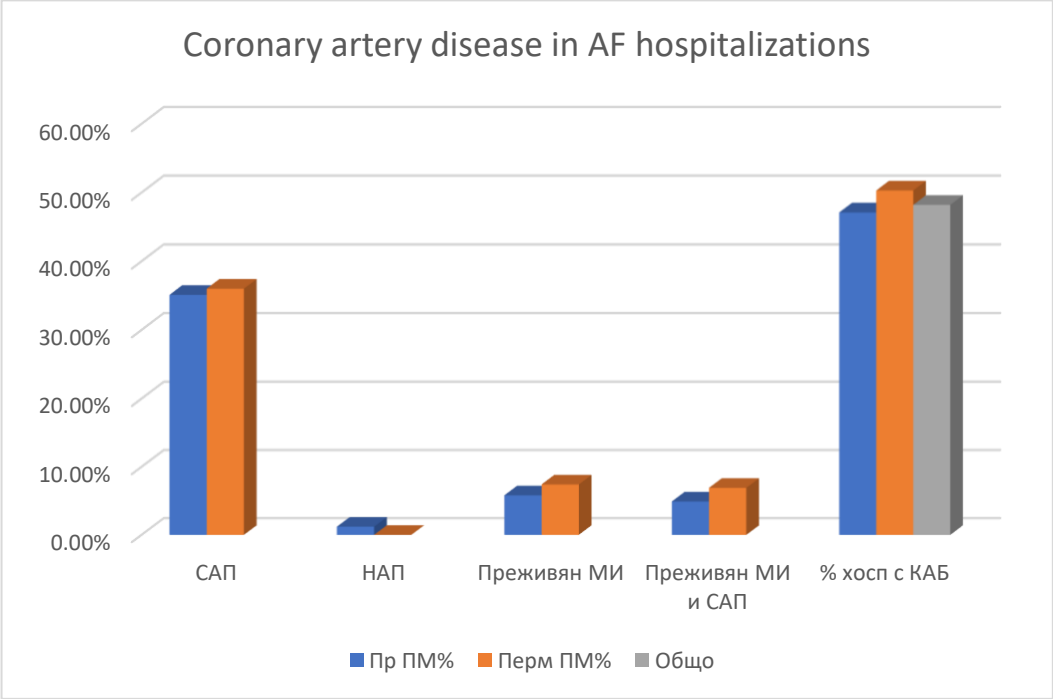


Figure 19. Frequency of hospitalisations with CAD and AF by type

4. Valve defects and AF

Valvular diseases are another major cardiac comorbid factor in hospitalizations with AF. MR is the most common, followed by AR and AS. According to the Framingham study, the risk of thromboembolism is increased 6-fold in non-valvular AF, and 18-fold in rheumatic etiology. Our findings show that there is a significant statistical difference in all valvular abnormalities between the two hospitalisation groups, particularly those with permanent AF.

	Acute AF	%	Chronic AF	%	Total
Hospitalisations	325	65%	175	35%	500
M. valve stenosis	2	0,6%	6	3,4%	8
M.valve regurg.	150	46,2%	155	88,6%	400
Ao stenosis	26	8%	23	13,1%	49
Ao regurgitation	90	27,7%	123	70,3%	213

Table 13. Incidence of valvular defects in hospitalized patients with AF.

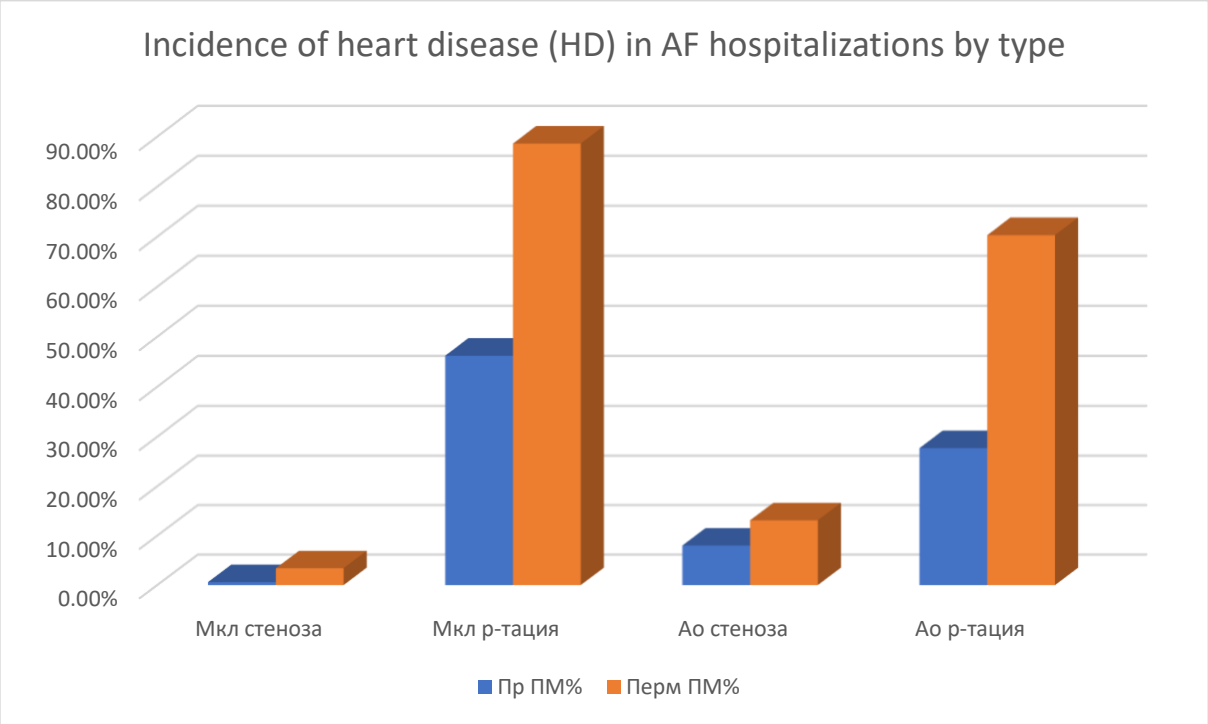


Figure 20. Frequency of hospitalizations with HD and AF by type

The formed degenerative defects are a factor comparable to HF for the hospitalizations of patients with AF.

5. Incidence of cardiomyopathy (CMP) in hospitalizations of patients with AF

According to Medi C. et al. (2009), 10% of patients with AF and high ventricular response—particularly those who have persistent or often repeated AF—develop cardiomyopathy. Our data supports the above findings by showing that 11% of patients hospitalised with AF have cardiomyopathies, including dilatative and hypertrophic cardiomyopathies. Dilatative CMP was more prevalent in hospitalisations with chronic AF, with strong statistical significance,

whereas hypertrophic CMP was only observed in hospitalisations with acute AF. Cardiomyopathies are an important risk factor for the occurrence of AF, and in turn for its development.

	Acute AF	%	Chronic AF	%	Total
Hospitalisations	325	65%	175	35%	500
D CMP	26	8%	24	13,7%	50
H CMP	5	1,53%	0	0	5
CMP %	9,5%		13,7%		11%

Table 24. Incidence of CMP in patients with AF

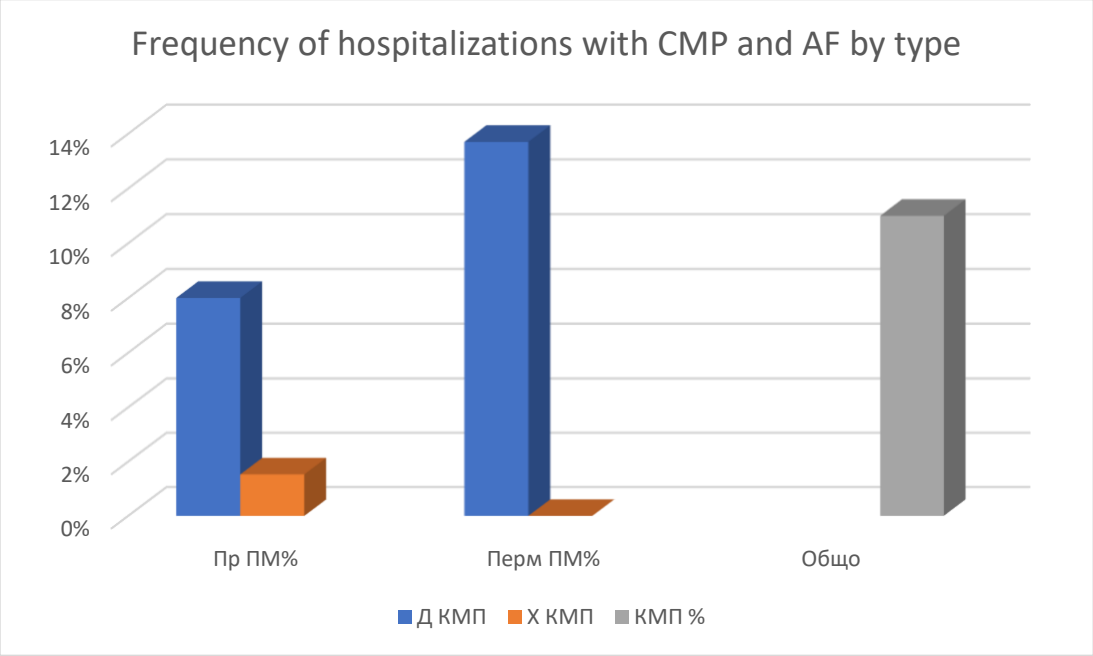


Figure 21. Frequency of hospitalizations with CMP and AF by type

From our data, dilated CMP is associated with a higher incidence of chronic AF, hypertrophic with a higher incidence of acute AF, which is also confirmed by the literature data.

6. Myocardial and pericardial diseases in hospitalizations with AF

In 10.6% of AF hospitalisations, myocardial and pericardial disorders are the cause. They are more prevalent in hospitalisations for chronic AF, with a statistically significant difference.

	Acute AF	%	Chronic AF	%	Total
Hospitalisations	325	65%	175	35%	500
Myocarditis	10	3,1%	9	5,1%	19
Pericarditis	12	3,7%	11	6,3%	23
Myopericarditis	4	1,2%	7	4%	11
MyoPeri%	8%		15,4%		10,6%

Table 15. Incidence of myocardial and pericardial diseases in AF hospitalizations

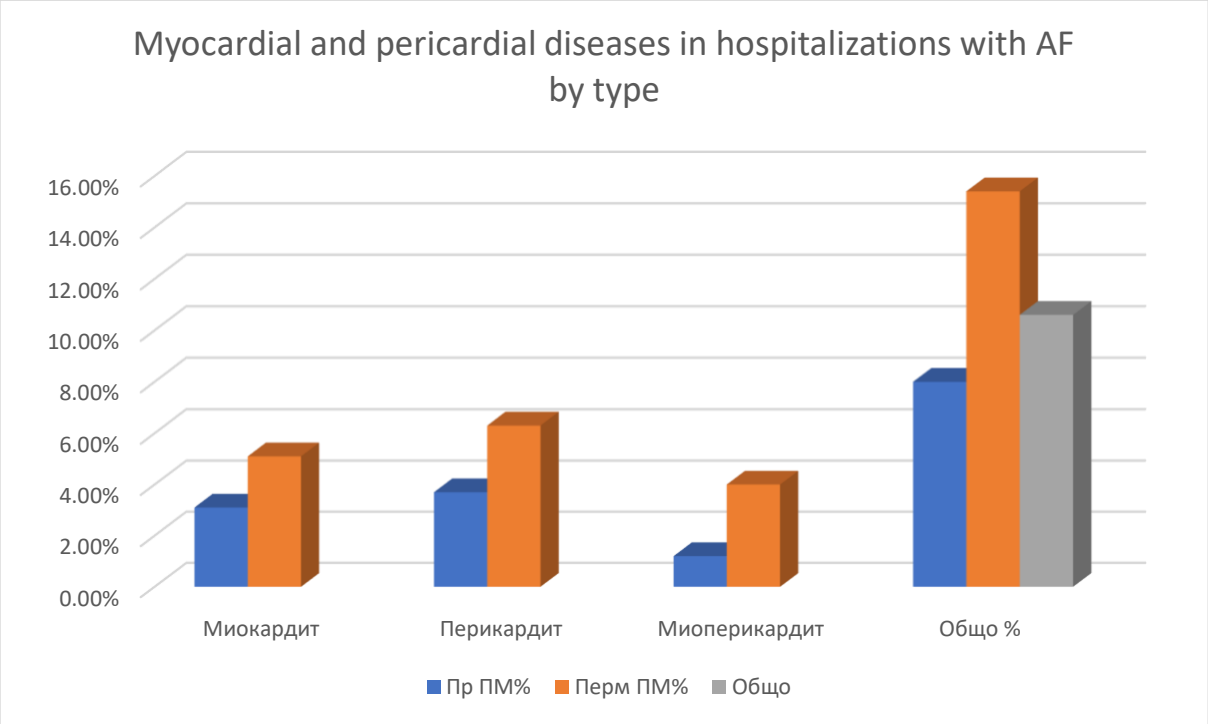


Figure 22. Incidence of myocardial and pericardial diseases in hospitalized patients with AF by type

According to our data, although a significant cause of AF, myocardial and pericardial damage has a smaller contribution to hospitalizations for AF. Some studies have shown that AF is found in 14% of patients with suspected myocarditis (Begieneman MP et al., 2016), which correlates with our results. According to other studies, myocarditis was found in 50 cases, of which (42%) were in men and 14 cases were (51.9%) in women with AF.

B2. Non-cardiological comorbid conditions

7. Incidence of diabetes mellitus (DM) in patients with AF by groups.

Of the hospitalizations included in the study, there were no patients with type I diabetes. The number of hospitalizations with type II diabetes – insulin-dependent (IDD) and non-insulin-dependent (NIDDM) in the studied groups with AF is presented in the following Table 16, and the frequency of diabetes in the groups is presented in Figure 23.

	Acute AF count	%	Chronic AF count	%	Total
Hospitalisations	325	65 %	175	35 %	500
DM type II IDD	22	6,8 %	14	8 %	36
DM type II NIDDM	99	30,5 %	71	40,6%	170
total DM type II	121	37,2 %	85	48,6%	206 / 41%

Table 16. Number of hospitalizations with type II diabetes, IDD and NIDDM in patients with AF

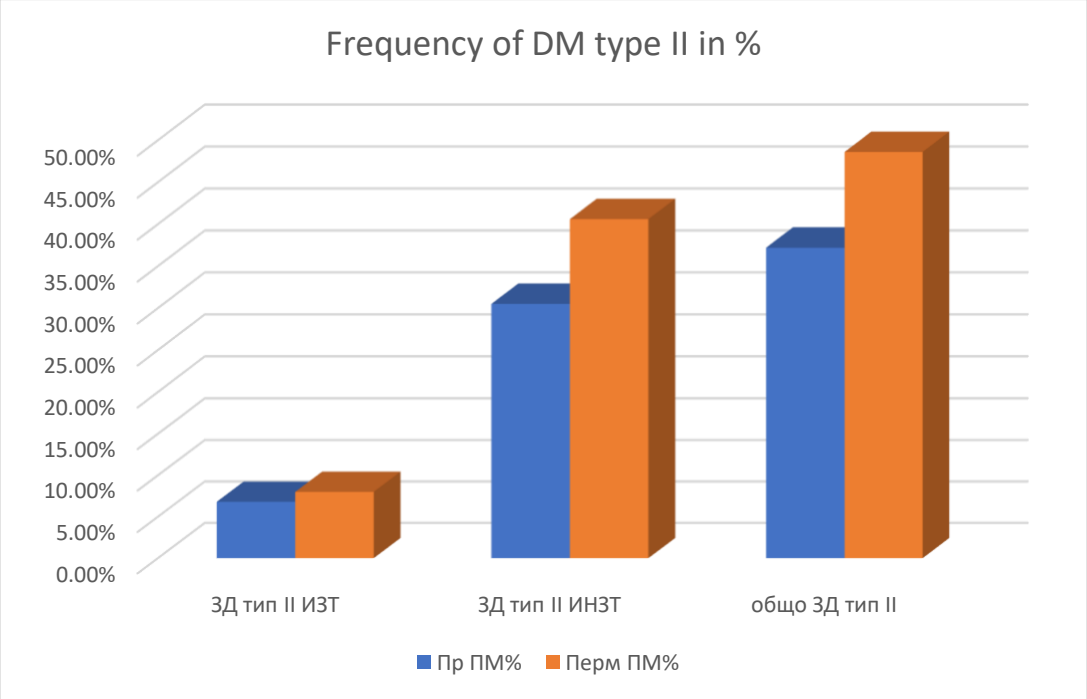


Figure 23. Incidence of DM in the studied groups with AF

According to a meta-analysis by Huxley RR et al., people with diabetes were 39% more likely than those without the disease to experience acute AF. Remarkably, Du X, Ninomiya T et al. found that AF in diabetic patients is linked to a 61% increased risk of all-cause mortality and a correspondingly higher risk of cardiovascular death, stroke, and heart failure. Regardless of the type of AF, our data showed that type II diabetes was present in nearly half (41%) of hospitalisations with AF, which is consistent with data from the literature. There was a notable frequency of type II NIDDM. The occurrence of type II IDD did not differ statistically significantly between hospitalisations with acute and chronic AF.

The results demonstrate the significant burden of type II diabetes for the manifestation of AF.

8. CKD and atrial fibrillation by type.

Wang X et al. discovered that AF is linked to a greater mortality rate and a quicker progression of CKD, while Go AS et al. discovered that CKD is an independent predictor of AF development.

Our results show that hospitalisations with AF by type have a considerable frequency of major CKD (II–Vst). In all, poor renal function accounted for 74.4% of all hospitalisations. Compared to hospitalisations for acute AF (65.8%), the percentage of hospitalisations for chronic AF (90.3%) was statistically notably greater. Table 17 and Figures 24 and 25 present the findings.

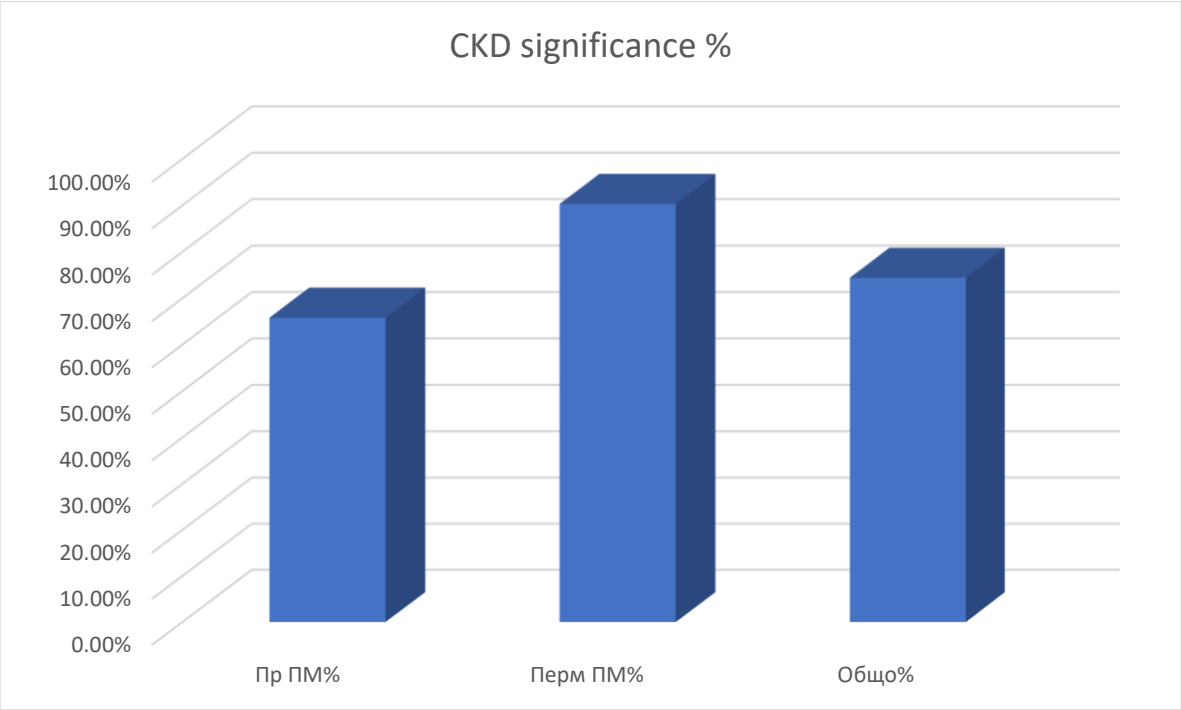


Figure 24. The incidence of significant CKD (II–Vth grade)

	Acute AF	%	Chronic AF	%	Total
Hospitalisations	325	65%	175	35%	500
CKD I stage	111	34,2%	17	9,7%	128
CKD II stage	98	30,2%	68	38,9%	166
CKD IIIa stage	55	16,9%	44	25,1%	99
CKD IIIb stage	43	13,2%	38	21,7%	81
CKD IV stage	10	3,1%	8	4,6%	18
CKD V stage	6	1,85%	0	0%	6
CKD hemodialysis	2	0,62%	0	0%	2
Hospitalizations with significant CKD	214		158		372
CKD significant %	65,8%		90,3%		74,4%

Table 17. Incidence of CKD in AF hospitalizations.

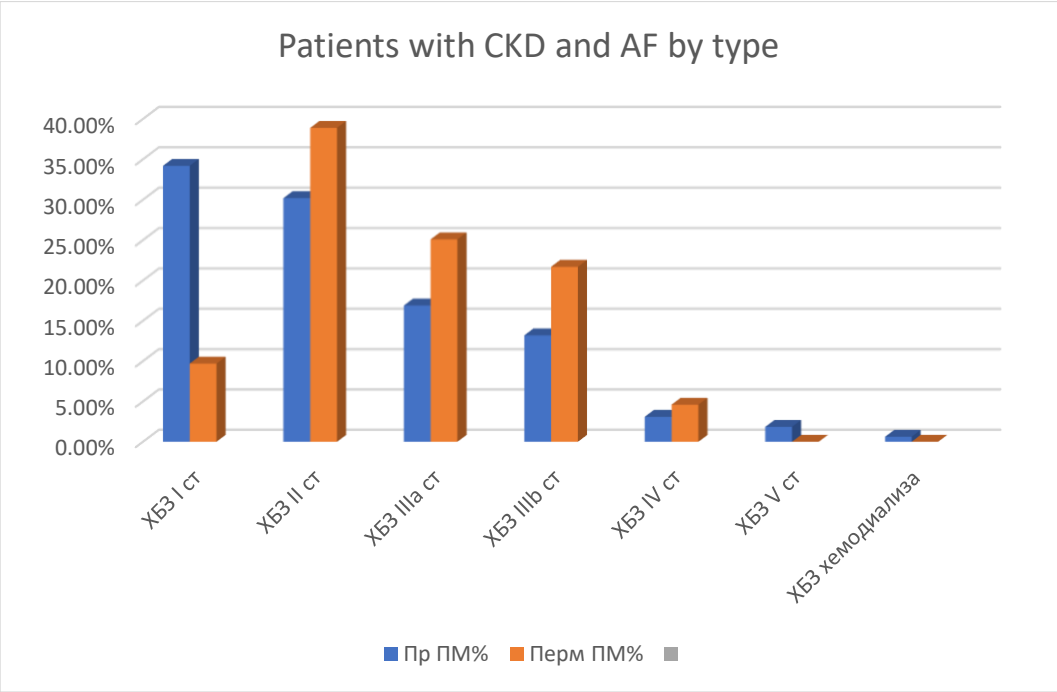


Figure 25. Incidence of patients with CKD and AF

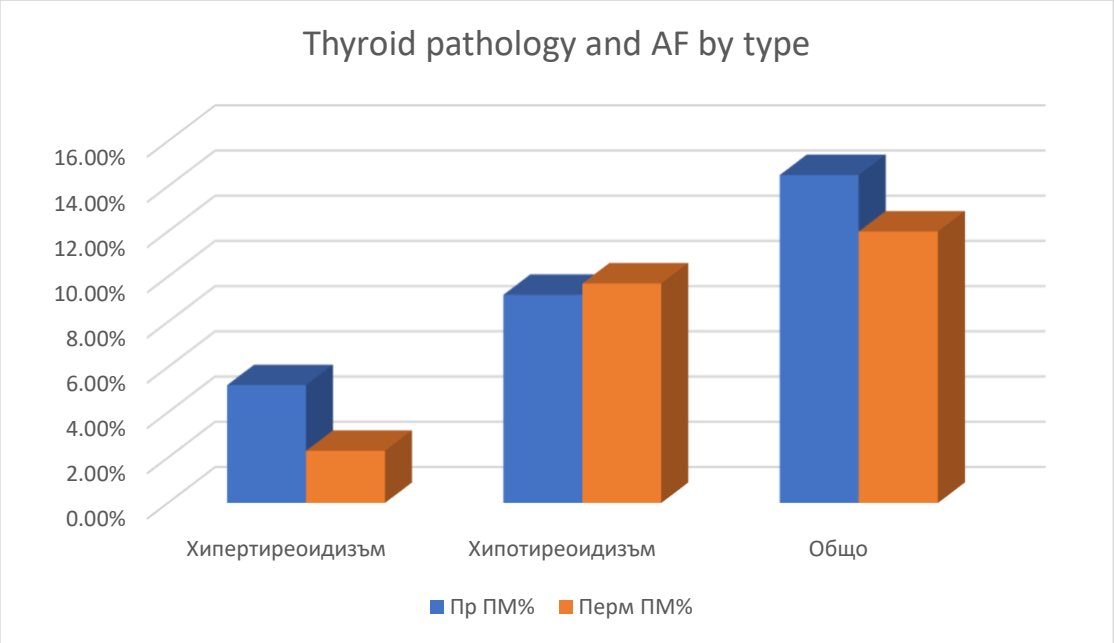
Significant impairment of glomerular filtration is more common in chronic AF, whereas milder impairment of renal function (eGFR over 60ml/min/1.73m2) is more prevalent in hospitalisations with acute AF. According to the AF-KD research (2020), patients who have both CKD and AF have a >2-fold higher overall mortality rate than those who just have one of the illnesses. In summary, there is a tight relationship between AF and CKD. Every CKD patient should have their heart rate and rhythm closely checked for arrhythmias, and if AF is present, a customised anticoagulation strategy is crucial. One significant risk factor and comorbidity for AF is CKD.

9. Thyroid pathology in AF

Thyroid pathology was found in 13.6% of hospitalizations with AF. Results are presented in Table 18 and Figure 26.

	Acute AF	%	Chronic AF	%	Total
Hospitalisations	325	65%	175	35%	500
Hyperthyroidism	17	5,2%	4	2,3%	21
Hypothyroidism	30	9,2%	17	9,7%	47
Total	47	14,5%	21	12%	68
% with th. pathology					13,6%

Table 18. Frequency of thyroid pathology in hospitalisation of patients with AF



Фигура 26. Thyroid pathology prevalence among hospitalised AF patients

Hospitalisations for acute AF are predicted to be higher in people with hyperthyroidism, whereas individuals with hypothyroidism are more likely to experience chronic AF. Global research indicates that 7–8% of middle-aged hyperthyroid patients may develop atrial fibrillation (AF). As patients age, this risk rises to 10–20%, and in patients with concomitant coronary artery disease or valvular heart disease, it rises to 20–35%. Even before other clinical cardiac signs and symptoms manifest, hypothyroidism may cause interstitial oedema and/or fibrosis of heart tissues, which can be linked to atrial fibrillation. We found that thyroid pathology was present in 13.6% of hospitalised individuals. One of the primary reasons of AF is altered thyroid function.

10. Pulmonary diseases in hospitalizations with AF by type

Coronary artery disease and COPD share several common risk factors: smoking, sedentary lifestyle and low social status. In both diseases, there is an inflammatory process and coagulation disorders. Bronchial obstruction leads to hypoxemia, and with prolonged action to the appearance of organic changes in the myocardium and the development of cor pulmonale. These factors, in combination with the arrhythmogenic effect of some bronchodilators (theophylline, beta2-agonists), and the presence of CHF predispose to arrhythmias. Patients with COPD are at increased risk for cardiovascular events, regardless of other risk factors.

According to our study's findings, 64% of patients with paroxysmal AF and 83.4% of those with persistent AF are hospitalised with COPD. Pulmonary illness coexists with AF in 85.4% of hospitalisations overall. Patients with chronic AF had a higher prevalence of pleural effusions and respiratory failure, which is statistically significant. One important concomitant factor among AF patients admitted to the hospital is pulmonary illnesses.

	Acute AF count	%	Chronic AF count	%	Total
Hospitalisations	325	65%	175	35%	500
COPD	208	64%	146	83,4%	354
Respiratory failure	12	3,7%	13	7,4%	25
Pleural effusion	20	6,2%	28	16%	48
Pulmonopathy	240	73,8%	187	>100	85,4%

Table 19. Incidence of pulmonary diseases in hospitalizations with AF

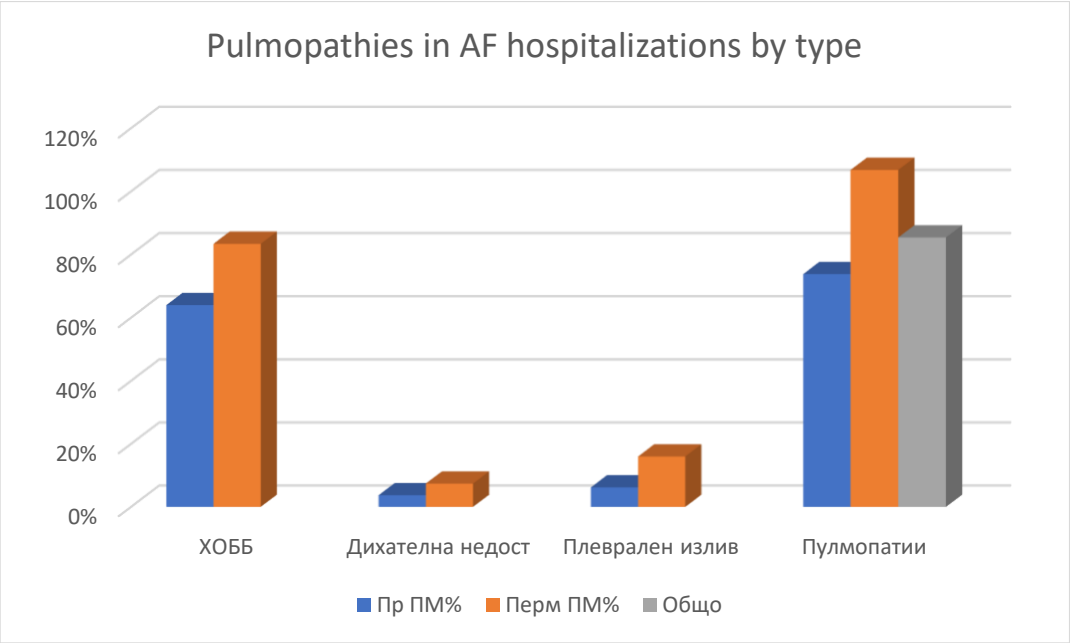


Figure 27. Frequency of pulmonary diseases in hospitalizations with AF by type

As cited in the literature, COPD, regardless of its form, makes a significant contribution to hospitalizations due to AF.

11. Neurological diseases in AF hospitalizations

According to the Framingham study, in non-valvular AF the risk of thromboembolism is increased 6 times, and in rheumatic etiology - 18 times. In patients with AF, depression was found in 38% and anxiety in 28-38% of cases (Thrall G. et al., 2007). Symptoms of affective disorders lasted 6 months in half of the patients. Along with somatic factors, depression is associated with an 8.6-fold increase in the risk of AF recurrence after successful restoration of sinus rhythm (Lange H.W et al., 2007).

Our data shows that, although it is not statistically significant, dementia is of particular importance and is more prevalent in hospitalisations with permanent AF. There is a non-significant statistical predilection for permanent AF, although the distribution of ischaemic brain stroke (IBS) and transient ischaemic attack (TIA) is nearly identical in both groups. Hospitalisations with persistent AF are

statistically substantially more likely to result in cerebral haemorrhages. One of the main risk factors for neurological problems is AF.

	Acute AF count	%	Chronic AF count	%	Total
Hospitalisations	325	65 %	175	25 %	500
IBS / TIA	14	4,3 %	8	4,6 %	22
Brain hemorrhage	2	0,6 %	2	1,2 %	4
Dementia	56	17,2 %	37	21,1%	93
Neurological	72	22,1 %	47	26,9 %	23,8 %

Table 20. Frequency of neurological diseases in hospitalizations with AF

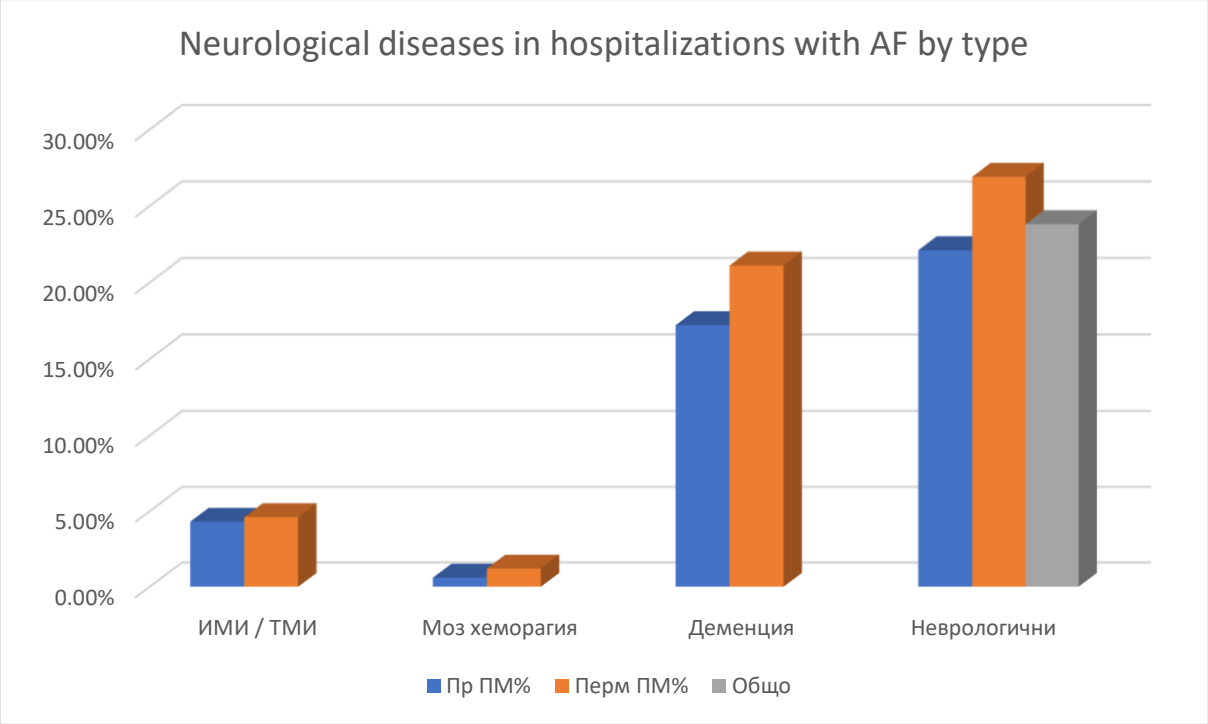


Figure 28. Neurological diseases in hospitalizations with AF by type

12. Metabolic disorders – dyslipidemia (DLP), gout, obesity

DLP, gout, and obesity were observed in 58.8% of hospitalizations with AF. Dyslipidemia and gout were more common in hospitalizations with paroxysmal AF (41.5% and 12%), in contrast to obesity, which was more common in patients with permanent AF with high statistical significance ($p<0.05$). The lower incidence in permanent AF is likely a result of systemic treatment in these patients.

	Acute AF	%	Chronic AF	%	Total
Hospitalisations	325	65%	175	35%	500
DLP	135	41,5%	56	32%	191
Gout	39	12%	18	10,3%	57
Obesity	21	6,5%	23	13,1%	46
Metabolic %		67%		33%	58,8%

Table 21. Frequency of metabolic disorders in hospitalizations with AF

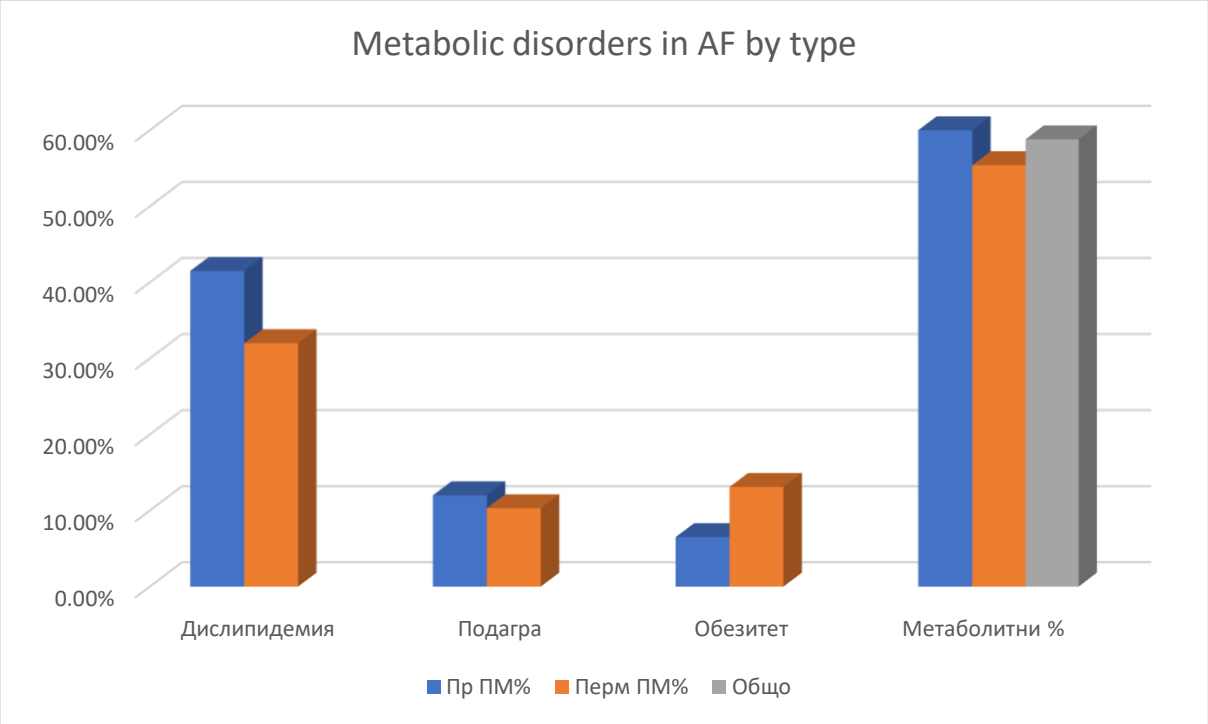


Figure 29. Frequency of metabolic disorders in hospitalization with AF by type

The high frequency of metabolic disorders in our data (58.8%) confirms the importance of DLP, gout and obesity as RFs for CV diseases and in particular for AF. Gout with a frequency of 10-12% is an independent risk factor for AF.

13. Vascular diseases – peripheral arterial disease (PAD) and DVT

Vascular diseases – PAD, DVT/PE are observed in 13.8% of hospitalizations with AF, and with high statistical significance ($p<0.05$) they are more in those with permanent AF.

	Acute AF	%	Chronic AF	%	Total
Hospitalisations	325	65%	175	35%	500
PAD	10	3,1%	13	7,4%	23
DVT/PE	26	8%	20	11,4%	46
Vascular	36	11,1%	33	18,9%	13,8%

Table 22. Incidence of vascular disease in AF hospitalizations

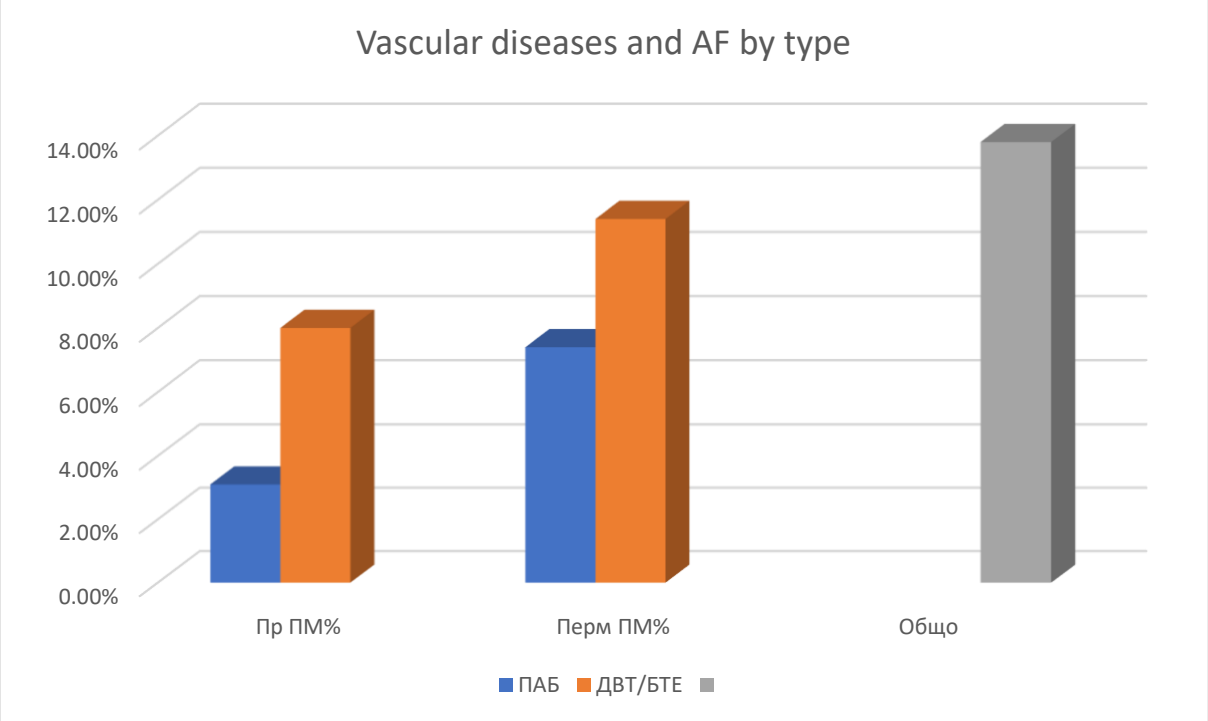


Figure 30. Incidence of vascular diseases in AF hospitalizations by type

Seventy-five percent of AF cases manifest as IBS, making it a common cause of thromboembolism (Benjamin E.J. et al., 1994). There is no discernible difference in the incidence of thromboembolism between paroxysmal, chronic, and permanent AF (ACTIVE W, EuroHeart Survey). PE typically causes AF rather than being a result of it. However, the incidence of PE in AF is increased by 8–31%, and thrombi in the right atrium are discovered at autopsy in 7.5% of patients (Frost L. et al., 2001). According to our data, vascular disorders accounted for 13.8% of hospitalisations, with DVT/PE accounting for 11.4%.

14. Anemia in AF

Hospitalisations with haemoglobin levels below 130 g/l for men and below 120 g/l for women were considered anaemia. Overall, anaemia was found in 37% of AF hospitalisations. CHF (19%), CAD or AMI (8%), AF (7%), and valvular abnormalities (2%) are the CVD symptoms that worsen the most frequently as a result of anaemic syndrome (Malcovati L et al, 2011). Hospitalisations with persistent AF are statistically substantially more likely to have anaemic syndrome. Anaemia in individuals with persistent AF is probably caused by the systemic use of anticoagulants and their increased comorbidity index.

	Acute AF	%	Chronic AF	%	Total
Hospitalisations	325	65%	175	35%	500
Anemia	60	18,5%	50	28,6%	110

Table 23. Frequency of anemia in hospitalizations with AF

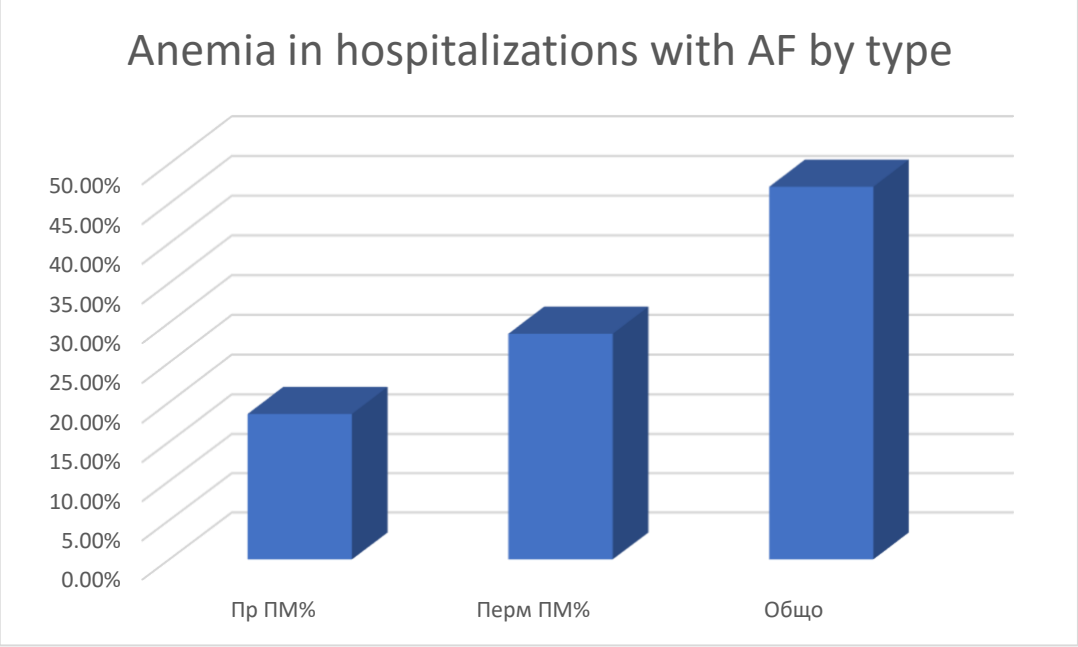


Figure 31. Frequency of anemia in hospitalizations with AF by type

15. Oncological diseases and AF

Oncological diseases are observed in 10% of hospitalizations with AF. Active and in remission – there is no statistically significant difference in patients with permanent AF. Hospitalizations with paroxysmal AF and achieved remission after treatment are significantly more with high statistical significance (p=0.004) compared to active oncological diseases in this group. Therapy for malignant diseases – radiation, chemotherapy and biological therapy is a common cause of AF.

	Acute AF	%	Chronic AF	%	Total
Hospitalisations	325	65%	175	35%	500
Active onco	9	2,8%	8	4,6%	17
Remission	24	7,4%	9	5,1%	33
Oncological	33	10,2%	17	9,7%	10%

Table 24. Incidence of oncological diseases in hospitalizations with AF

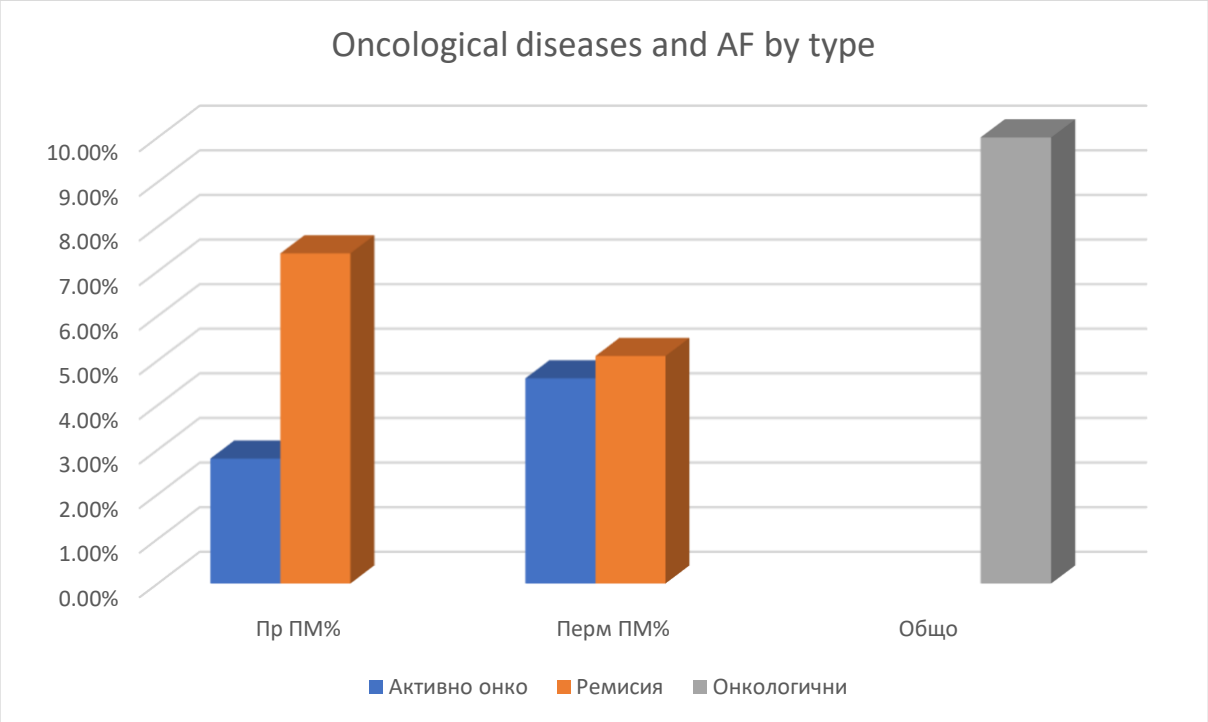


Figure 32. Incidence of oncological diseases and AF by type

C. Severity of AF

1. EHRA modified scale (EHRAm)

When determining the severity of AF according to the modified EHRA scale, a characteristic and expected feature is observed - a statistically significant predominance of hospitalizations with acute AF in low classes IIa and IIb and a statistically significant advantage for those with chronic AF in high classes III and IV. There are no hospitalizations with EHRAm class I.

	Acute AF	%	Chronic AF	%	Total
Hospitalisations	325	65%	175	35%	500
EHRA I	-	-	-	-	-
EHRA IIa	108	33,2%	1	0,6%	109
EHRA IIb	120	36,9%	15	8,6%	135
EHRA III	37	11,4%	46	26,3%	83
EHRA IV	60	18,5%	113	64,6%	173

Table 25. Severity of AF by EHRA modified scale

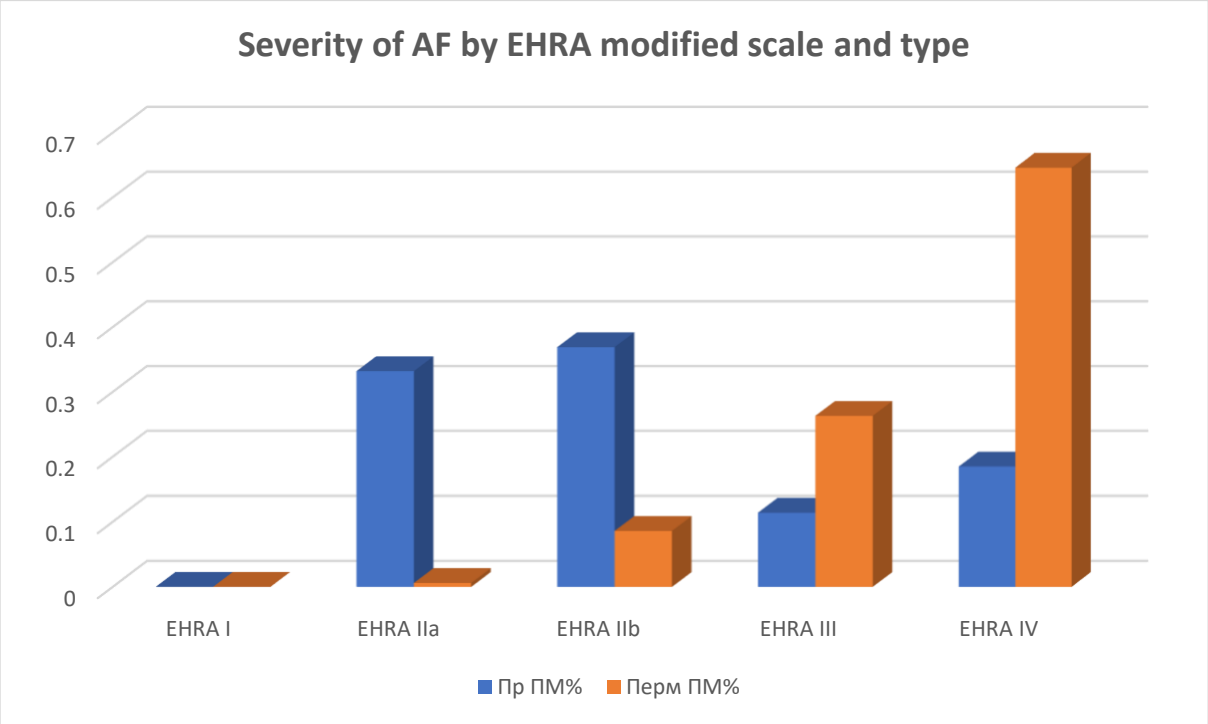


Figure 33. Severity of AF by modified EHRA scale and AF by type

2. Left atrial volume of patients hospitalized with AF by type

The time course of ventricular dysfunction in patients varies greatly. In patients without structural heart disease, it can last from a few weeks to 20 or more years. In cases of prolonged rapid atrial contractions, tachyarrhythmic atrial cardiomyopathy may occur. For example, in permanent AF, the mean volume of the left ventricle increases from 45 to 64 cm3, and in the right ventricle from 49 to 66 cm3 (Sanfilippo A.J. et al., 1990).

Our study on the role of left atrial volume in the onset, recurrence, and persistence of AF yielded the following results presented in Figures 34 to 38.

Mean pulmonary artery volume in hospitalizations with paroxysmal AF total 325 – 51.95ml, standard deviation – 22.6. In hospitalizations with chronic AF total 175, mean pulmonary artery volume – 75.47ml, standard deviation – 30.72.

The volume of the left atrium directly correlates with the type and duration of AF – paroxysmal or permanent. In acute AF, the volume of the left atrium remains the same or increases slightly, while in chronic AF the volume of the left atrium is significantly increased.

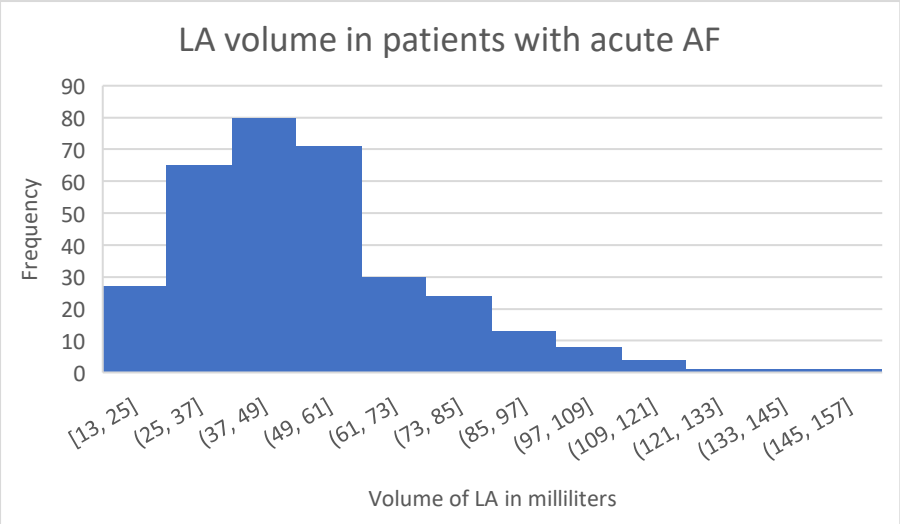


Figure 34. Left atrial volume in hospitalizations with paroxysmal AF

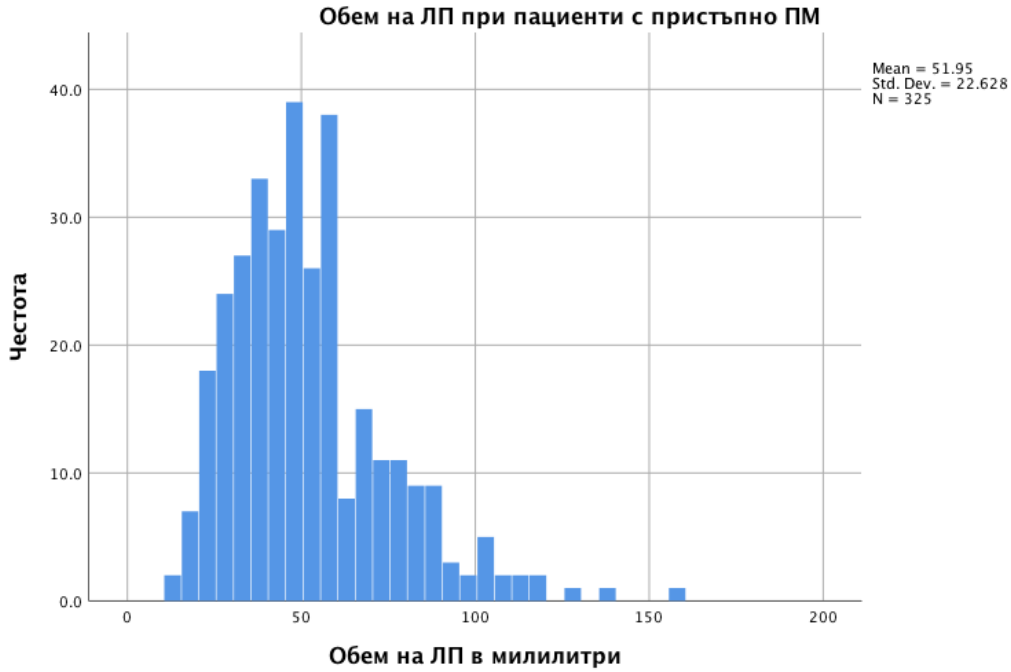


Figure 35. Left atrial volume in hospitalizations with acute AF

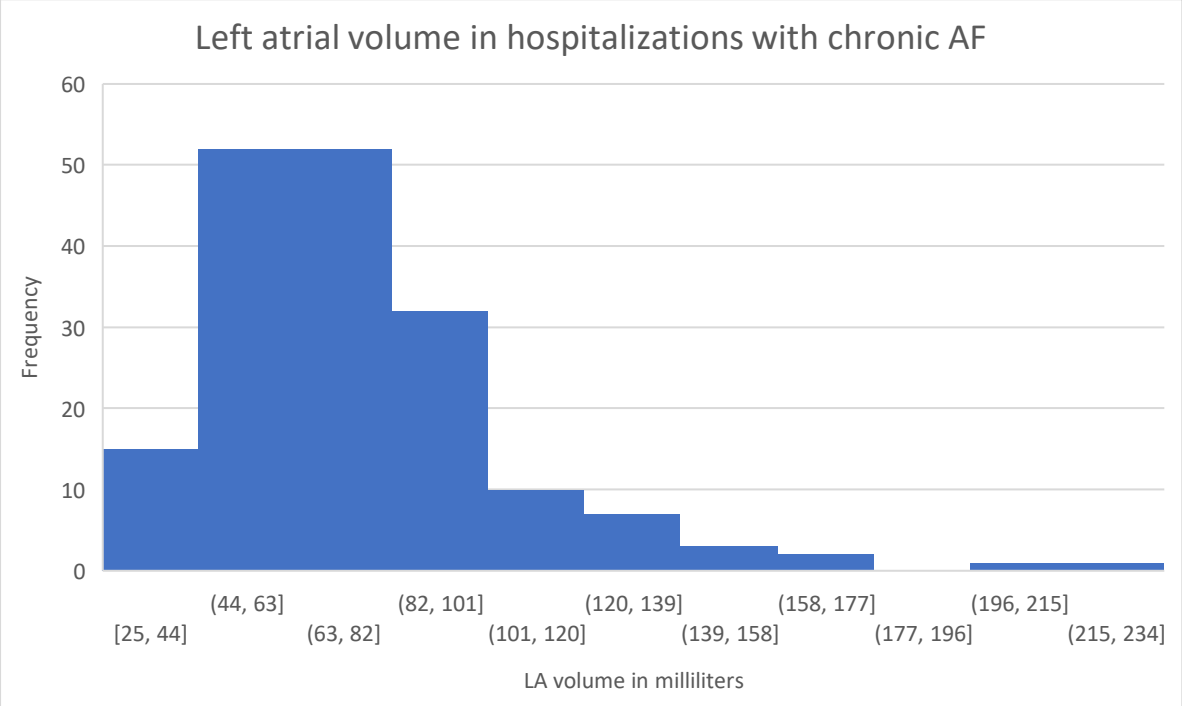


Figure 36. Left atrial volume in hospitalizations with chronic AF

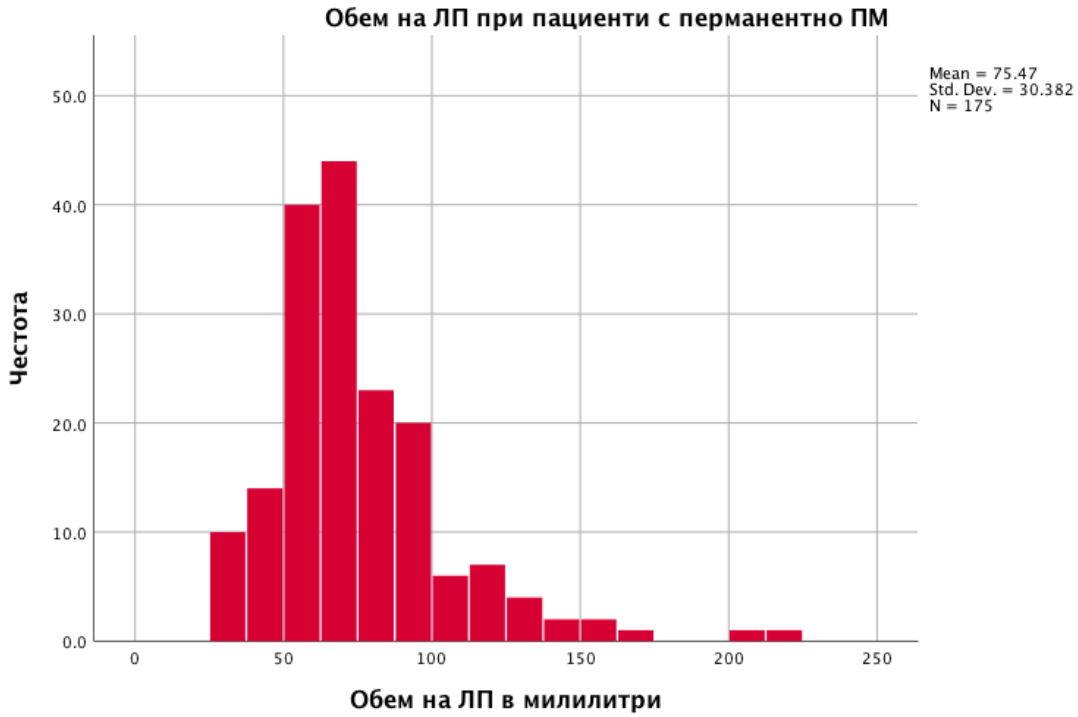


Figure 37. Left atrial volume in hospitalizations with chronic AF

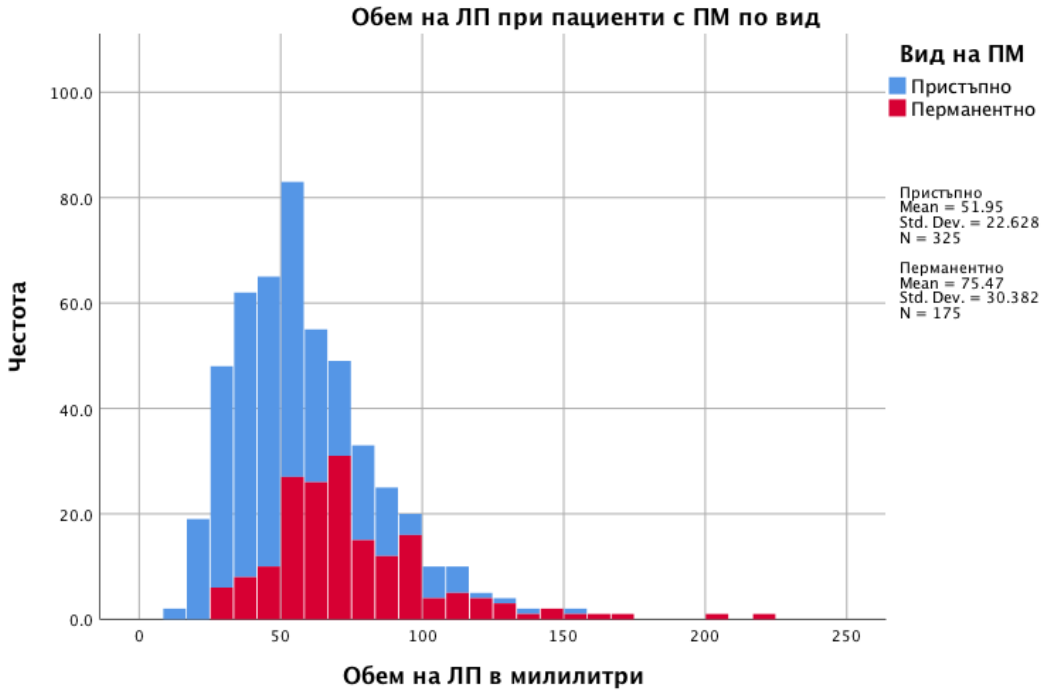


Figure 38. Left atrial volume in hospitalizations with AF by type

3. EF% in hospitalizations of patients with AF by type

	Acute AF	%	Chronic AF	%	Total
Hospitalisations	325	65%	175	35%	500
Over 50%	146	44,9%	35	20%	181
Diastolic dysf.	61	18,8%	35	20%	96
40-49%	65	20%	57	32,6%	122
Under 40%	53	16,3%	48	27,4%	101

Table 26. EF% in hospitalizations with AF by type

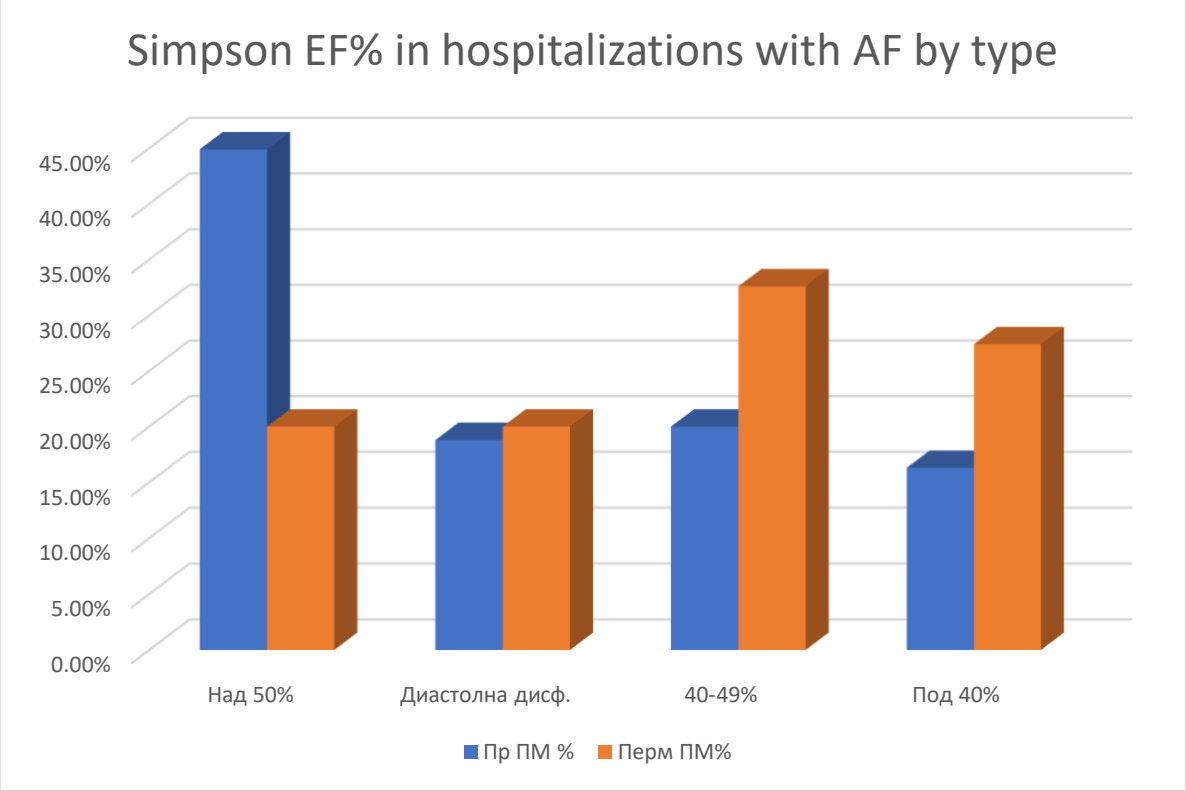


Figure 39. EF% in hospitalizations with AF by type

There was no statistically significant difference in hospitalizations with diastolic LA dysfunction in the two groups. With preserved ejection fraction, 44.9% of patients hospitalized with paroxysmal AF were with preserved ejection

fraction, while only 20% of those with permanent AF were with preserved ejection fraction. As expected, in the following categories with suppressed EF%, patients with permanent AF prevailed, and the difference was of high statistical significance. Reduced EF% is an important comorbid factor for AF.

D. Comorbidities and AF

1. Charlson modified index (MAFCCI).

For the purposes of our study, an original modified comorbidity index was developed called: Modified, AF adjusted Charlson Comorbidity Index – MAFCCI, including a total of 13 groups of cardiological and non-cardiological criteria with a maximum score of 36 points.

The results for MAFCCI in hospitalizations with AF are presented in Figure 54.

The maximum value of MAFCCI in hospitalizations with AF in our study is 16 points.

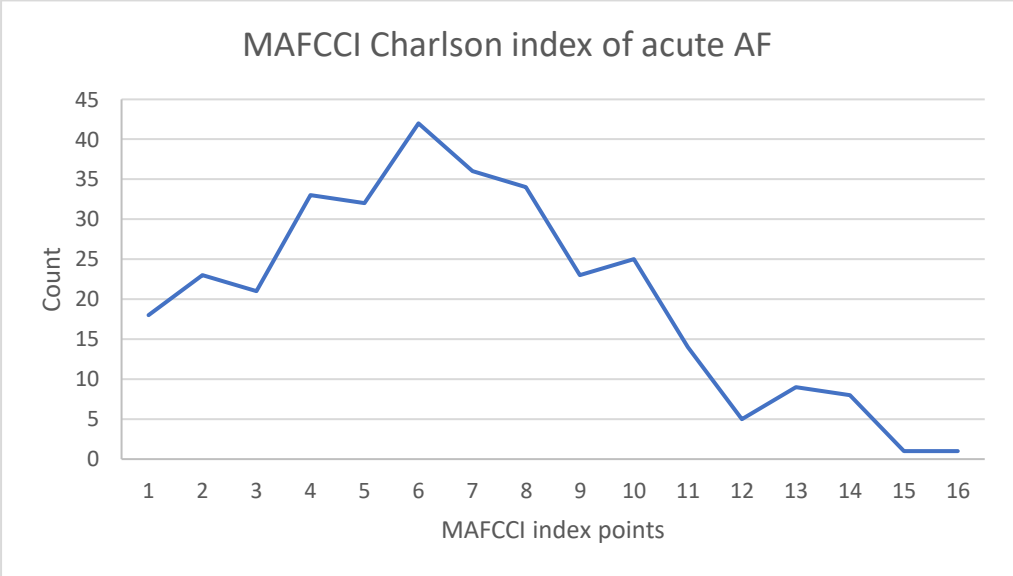


Figure 40. MAFCCI in patients hospitalised with AF

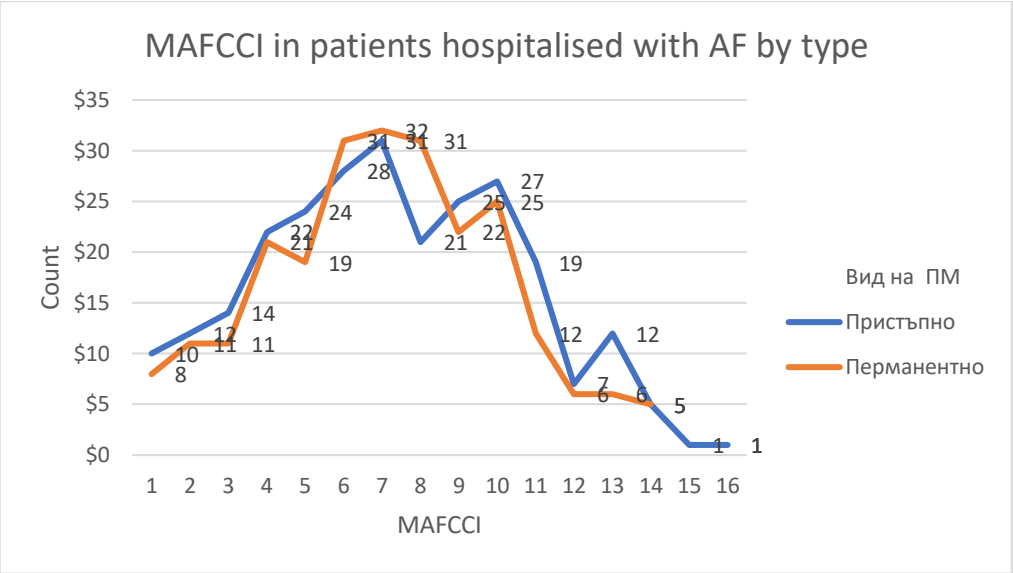


Figure 41. MAFCCI in patients hospitalised with AF by type

Hospitalizations with AF and comorbidity by type and age groups are presented in Figure 42.

As expected, the higher the value of the calculated MAFCCI, the greater the probability of hospitalizations and deterioration in patients with AF and comorbidity with a peak for paroxysmal AF – 6p (age group 6) and 4p (age group 4) in those with permanent AF. With advancing age, the number of comorbid conditions in hospitalizations with AF by type also increases.

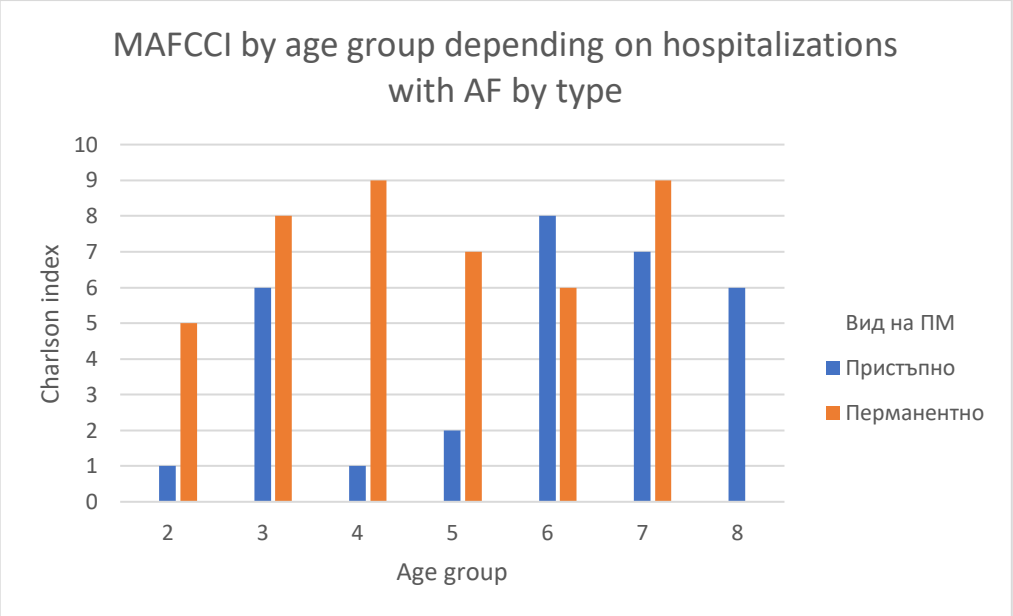


Figure 42. MAFCCI by age group and AF by type

Statistics

Charlson_index

N	Valid	175
	Missing	0
Mean		8.41
Median		9.00
Std. Deviation		2.624
Percentiles	25	7.00
	50	9.00
	75	10.00

Statistics

Charlson_index

N	Valid	325
	Missing	0
Mean		6.54
Median		6.00
Std. Deviation		3.295
Percentiles	25	4.00
	50	6.00
	75	9.00

Charlson_index

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	3	4	2.3	2.3	2.3
	4	10	5.7	5.7	8.0
	5	11	6.3	6.3	14.3
	6	17	9.7	9.7	24.0
	7	27	15.4	15.4	39.4
	8	18	10.3	10.3	49.7
	9	24	13.7	13.7	63.4
	10	27	15.4	15.4	78.9
	11	17	9.7	9.7	88.6
	12	8	4.6	4.6	93.1
	13	9	5.1	5.1	98.3
	14	2	1.1	1.1	99.4
	16	1	.6	.6	100.0
	Total	175	100.0	100.0	

Charlson_index

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	18	5.5	5.5	5.5
	2	23	7.1	7.1	12.6
	3	21	6.5	6.5	19.1
	4	33	10.2	10.2	29.2
	5	32	9.8	9.8	39.1
	6	42	12.9	12.9	52.0
	7	36	11.1	11.1	63.1
	8	34	10.5	10.5	73.5
	9	23	7.1	7.1	80.6
	10	25	7.7	7.7	88.3
	11	14	4.3	4.3	92.6
	12	5	1.5	1.5	94.2
	13	9	2.8	2.8	96.9
	14	8	2.5	2.5	99.4
	15	1	.3	.3	99.7
	16	1	.3	.3	100.0
	Total	325	100.0	100.0	

Table 27. MAFCCI Cumulative Weight Index

2. Cumulative burden of comorbidity according to EHRAm and MAFCCI.

To determine the cumulative burden of comorbidity according to EHRAm and MAFCCI, a Cox regression analysis was used, including hospitalizations with any severity of AF, as well as a sample of patients with severe AF (EHRAm grade III and IV) according to MAFCCI index (from 1 to 16).

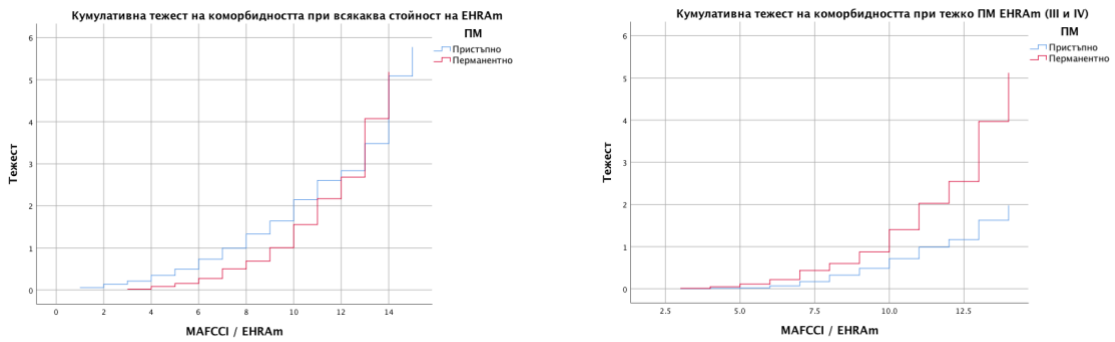


Figure 43 and 44. Cumulative burden of comorbidity

Quite naturally, in the model with any value of EHRAm, the cumulative burden of comorbidity is higher for hospitalizations with paroxysmal AF at low values of MAFCCI / EHRAm and the alignment of the curves for paroxysmal and permanent AF occurs around the value of 13p for MAFCCI. Conversely, in the

model with severe AF (EHRAm III and IV stages) the curves are separated and, as expected, the cumulative burden of comorbidity in acute AF is much lower than that in permanent AF – peak 2 versus 5.

3. CKD in patients with AF depending on the anticoagulant used (indirect, DOAC)

Brodsky SV et al. (Kidney Int, 2009) identify WAN and demonstrate tubular damage in warfarin-induced glomerular haemorrhage. According to Limdi NA et al. (JAMA, 2016), WAN is linked to a higher death rate and affects 20–25% of CKD patients using warfarin. Our results indicate that hospitalisations for AF are clearly associated with a milder impairment of renal function when taking DOAC, and vice versa—lower GFR in patients on indirect anticoagulants—depending on the kind of anticoagulant used. DOAC was also used in individuals with stage V CKD who were hospitalised with AF. Haemodialysis program patients do not take anticoagulants. Figures 45 and 46 display our findings.

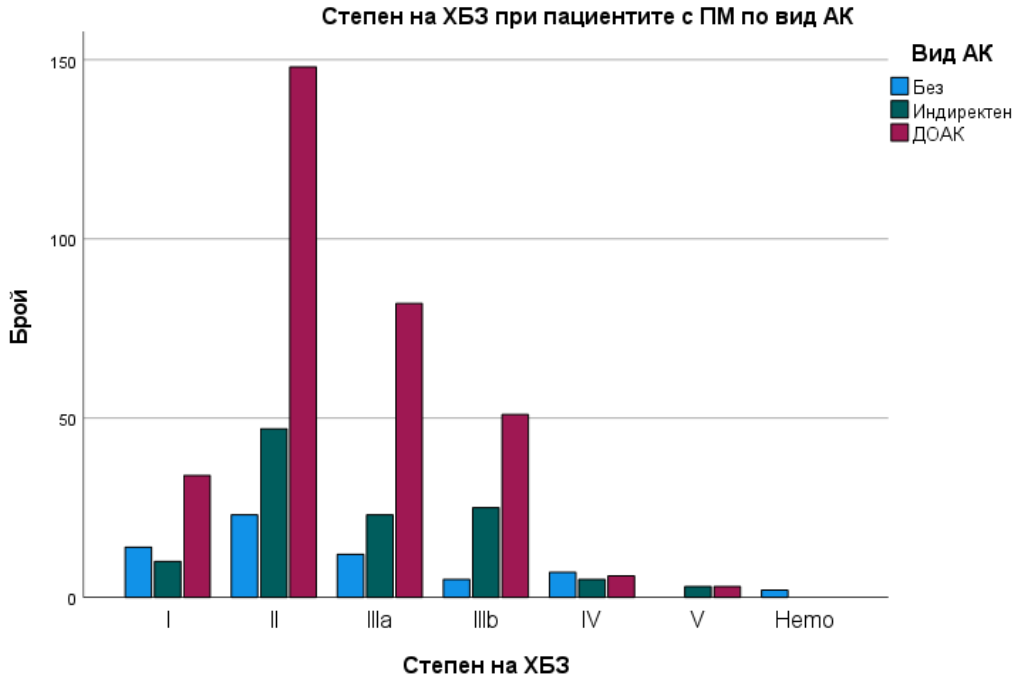


Figure 45. Frequency of patients with CKD and AF by severity and type of AC

The differences in hospitalizations of patients on DOAC and CKD grade II to III and those on indirect AC and CKD grade II to IV are of great statistical significance. Taking an indirect anticoagulant is a serious risk for reducing renal function, which is also confirmed by the literature data.

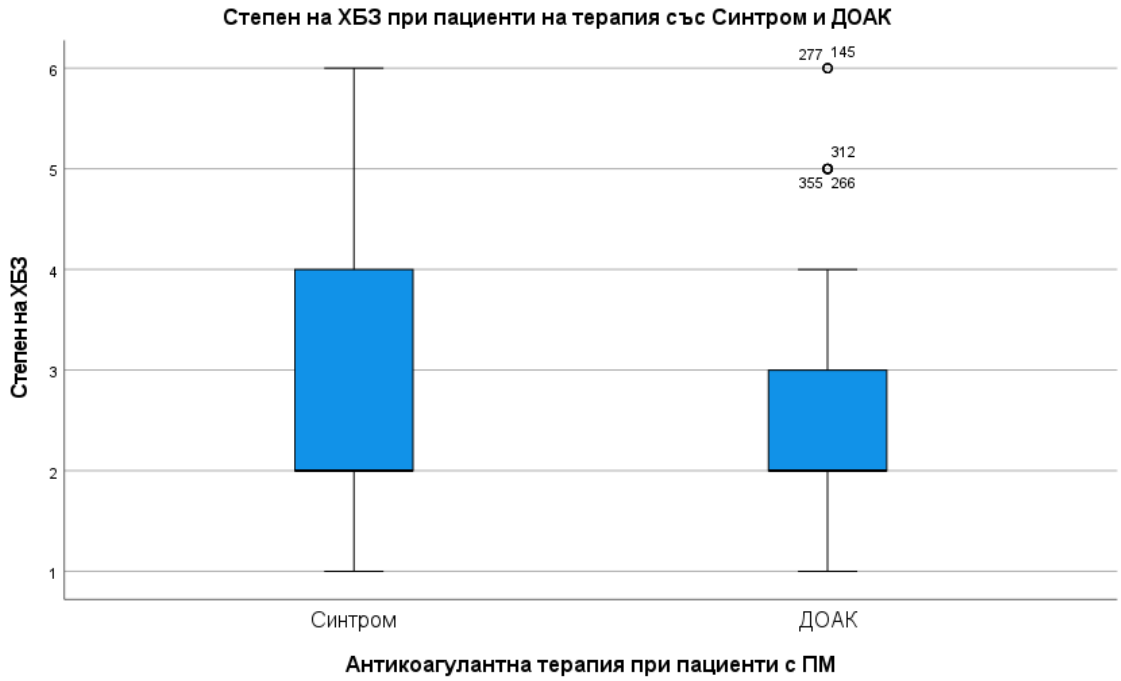


Figure 46. Comparison of the degree of CKD in hospitalizations of patients on indirect AC and DOAC therapy

4. Increased calcium accumulation in valves and large vessels in patients with CKD and anticoagulant therapy

Vascular and tissue calcification is more likely to occur in CKD patients taking indirect anticoagulants to treat AF. This results from a complicated interplay between the effects of anticoagulant medication and metabolic abnormalities in CKD. According to Koos et al. (Heart, 2005), aortic valve calcification is noticeably more common in people on warfarin.
In our investigation, a 2D echo approach was utilised to visually determine calcium deposition using a three-grade scale ranging from 1 to 4 for the aortic valve and 1 to 3 for the mitral valve in order to establish calcinosis of both valves

(Figures 47 and 48). There is a statistically significant increase in calcium deposition in the valve structure of CKD patients receiving indirect anticoagulant therapy compared to those receiving DOAC therapy.

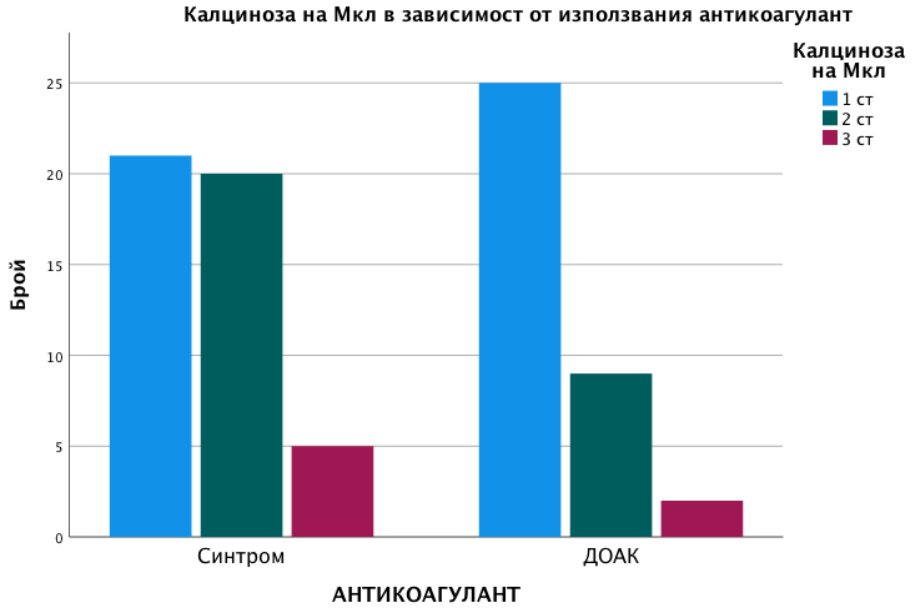


Figure 47. Degree of Mvalve calcification depending on AK

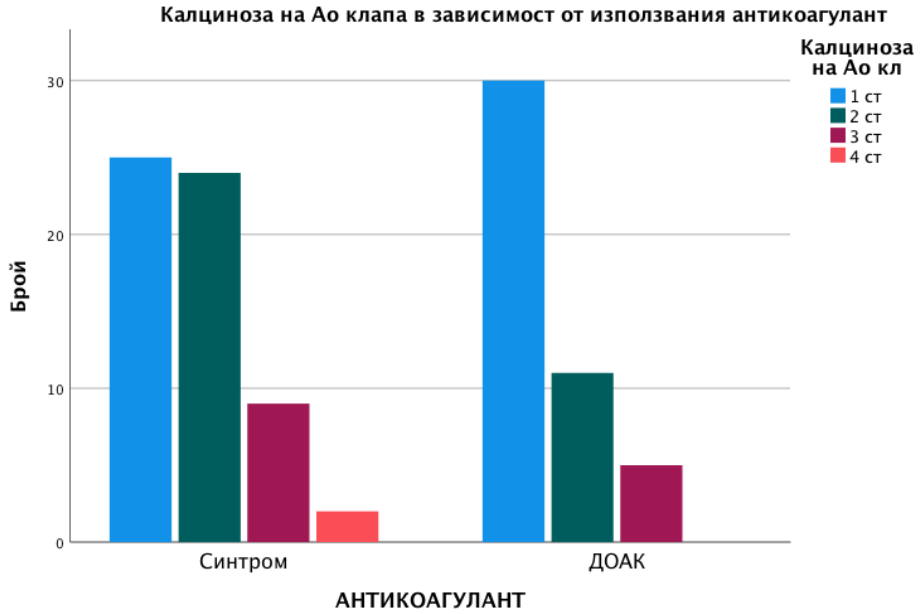


Figure 48. Degree of AOvalve calcification depending on AK

Patients with aortic calcification are similarly affected, with statistical significance (Figure 49).

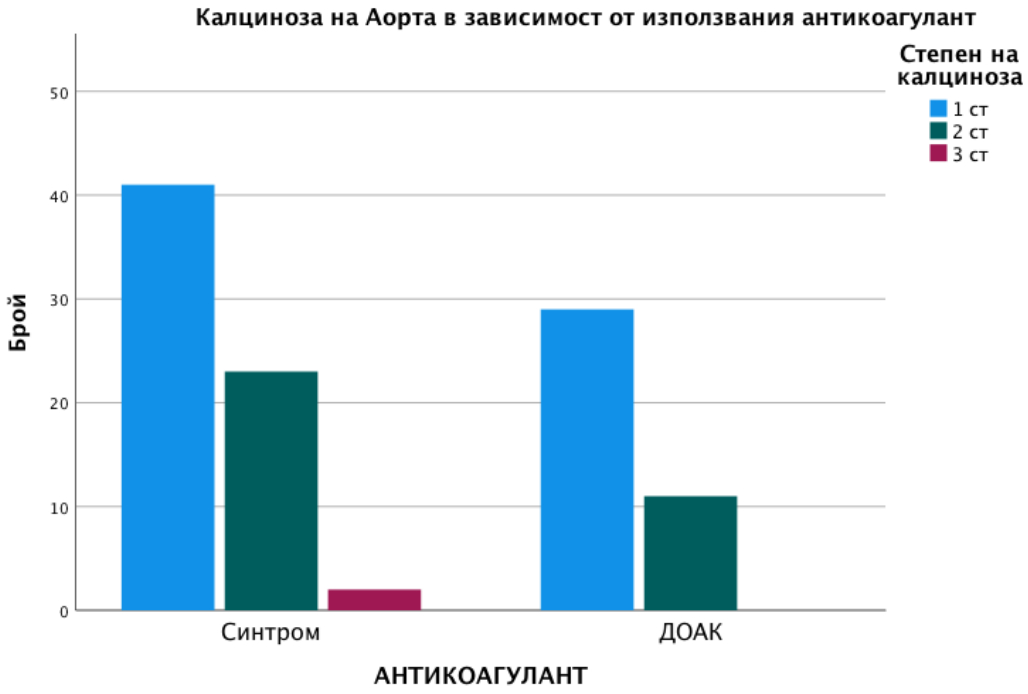


Figure 49. Calcium deposition in the aorta depending on AK

In conclusion, the use of an indirect anticoagulant carries additional risks for increased calcium deposition in valve structures and large vessels in patients with CKD, which is also confirmed by the literature data.

5. Seasonality in hospitalisations with AF and comorbidity

According to literature data, AF shows seasonality, although not as pronounced as in some other cardiovascular diseases. One of the goals we set in our study was whether there is a clearly demarcated seasonality in the hospitalizations of patients with AF and comorbidity. For this purpose, a sample was taken for one calendar year divided into 52 weeks and a graphical model of hospitalizations of patients with AF by type was made Table 28. The same setting was used for the next goal, GMA and AF, discussed below.

Week	Hospitalisations	Acute AF	Chronic AF	GEO activity
1	7	4	3	4
2	8	4	4	4,7
3	7	3	4	3,5
4	3	2	1	2,5
5	2	2	0	3
6	7	2	5	6
7	9	6	3	3,4
8	7	3	4	4
9	6	3	3	2,6
10	11	6	5	5,2
11	6	3	3	4
12	6	4	2	2
13	4	2	2	6,4
14	4	2	2	5,5
15	6	2	4	3,5
16	9	4	5	3,5
17	4	2	2	6
18	5	3	2	6,6
19	6	3	3	2,9
20	8	5	3	3,1
21	11	6	5	5,2
22	6	6	0	4,2
23	2	1	1	6,5
24	4	4	0	3
25	4	2	2	3,2
26	3	1	2	5,5
27	8	4	4	3,2
28	5	3	2	4,8
29	5	3	2	3,2
30	6	4	2	4
31	3	3	0	5,2
32	8	5	3	5,5
33	9	4	5	5,4
34	6	3	3	6
35	5	3	2	6,2
36	1	1	0	6,2
37	5	3	2	6,2
38	6	4	1	5,8
39	6	5	1	5
40	2	1	1	5,2
41	7	5	2	4,5
42	5	3	2	5
43	5	4	1	3,8
44	3	2	1	5
45	11	10	1	4,5
46	6	3	3	6
47	2	2	0	5

48	4	2	2	3,5
49	2	1	1	4
50	5	4	1	3,2
51	4	1	3	5,5
52	5	4	1	5,4

Table 28. A sample for one calendar year divided into 52 weeks including the number of hospitalizations of patients with AF by type and GEO activity.

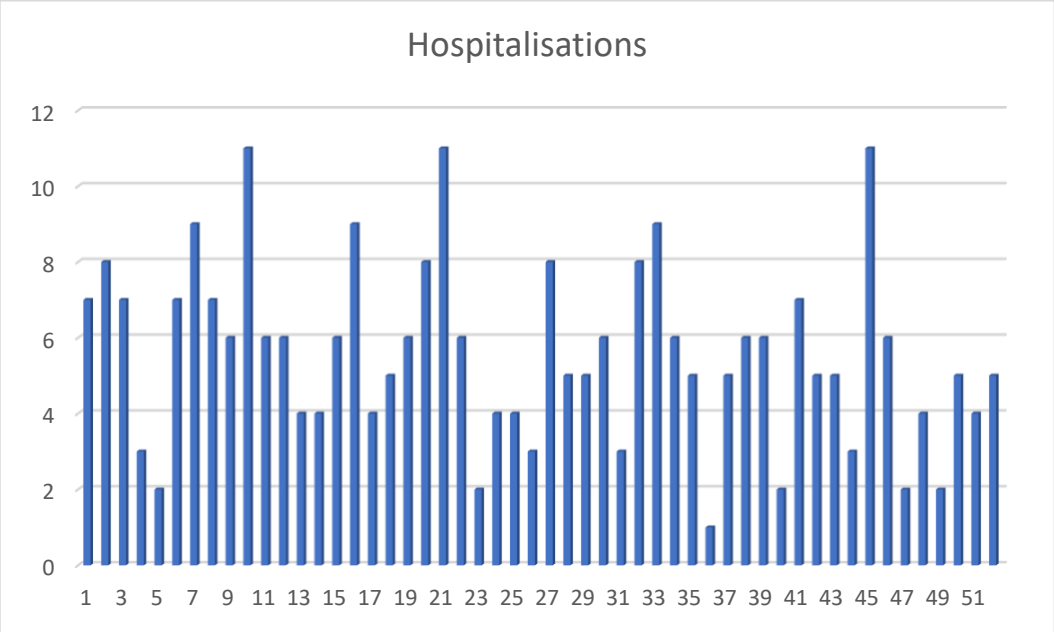


Figure 50. Frequency of hospitalizations of patients with AF per calendar year by week

Hospitalizations of patients with AF are slightly higher in number during the winter-spring season and decline in the summer months, with peaks in late summer and early autumn.

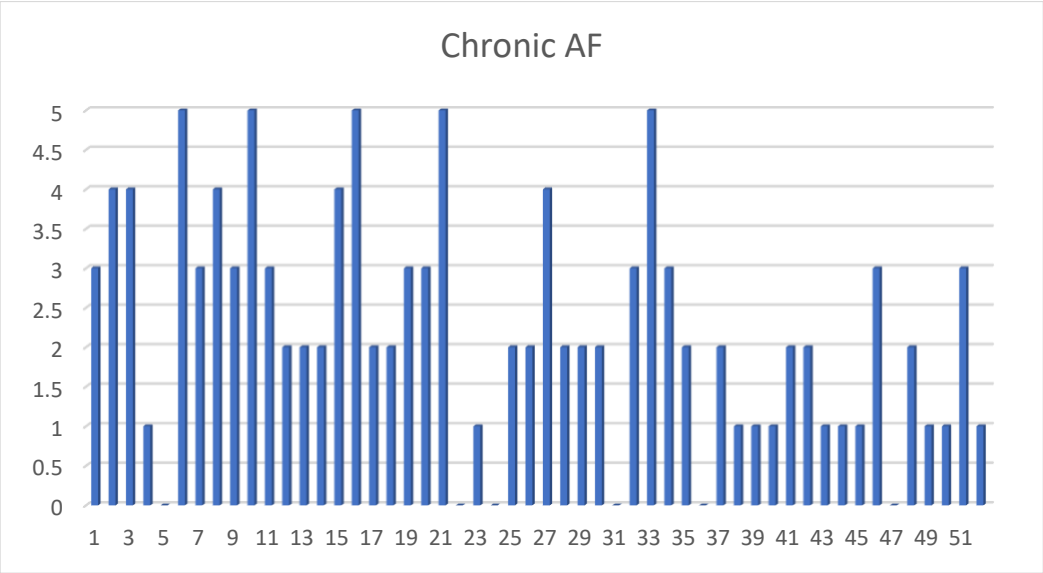


Figure 51. Frequency of hospitalizations of patients with chronic AF per calendar year by week

Hospitalizations of patients with permanent AF are significantly higher in the first 11 weeks of the year (winter-spring period), but peaks occur in all seasons.

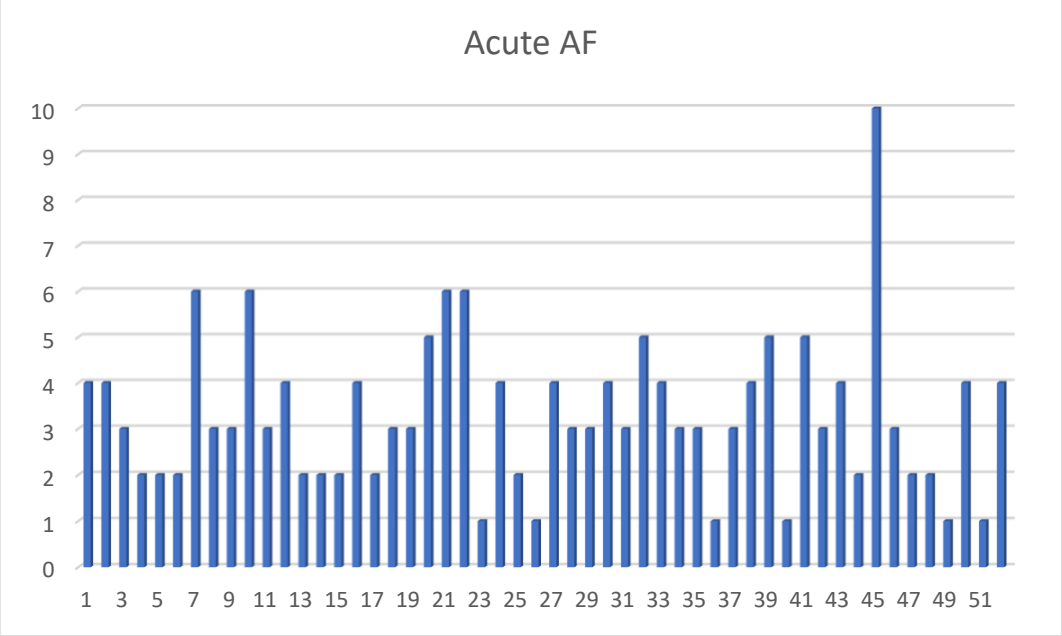


Figure 52. Frequency of hospitalizations of patients with acute AF per calendar year by week

Hospitalizations of patients with paroxysmal AF are significantly higher in the colder months of the year, as well as around public holidays and sudden changes in weather.

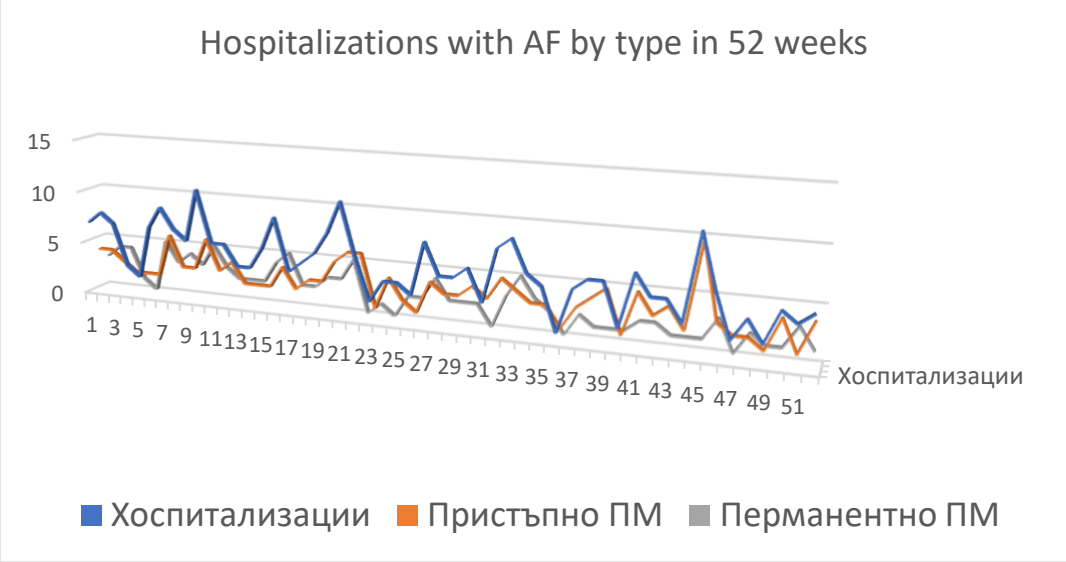


Figure 53. Frequency of hospitalizations of patients with AF by type per calendar year by week

This correlates with data from the literature on "holiday heart" associated with an increased number of AF attacks due to increased alcohol consumption, as well as lower temperatures and increased sympathetic tone in the cold months.

6. Impact of GMA on hospitalisations in patients with AF and comorbidity

Meteosensitive people may experience severe headaches, sleep disturbances, vestibular disorders, and especially changes in blood pressure during strong geomagnetic activity and solar flares. The effects of magnetic activity are also associated with a significantly increased incidence of anxiety, depression, bipolar disorder, as well as palpitations and a feeling of general malaise. In a Canadian study, Stoupel et al. observed an increased incidence of atrial arrhythmias and hospitalizations in high GMA.

Accordingly, the idea of a connection between GMA and the occurrence of rhythm disorders, in particular AF, as well as deterioration of the condition of patients with AF and comorbidity requiring hospitalization was born. For the purposes of our study, data from the NIGGG-BAS were used, calculating the average value of Kp activity for each week in a sample of one calendar year divided by 52 weeks, relative to the number of hospitalizations of patients with AF during the same period.

After the analyses, it was found that there was no significant difference in hospitalizations and rehospitalizations with AF depending on the GMA – Figure 54.

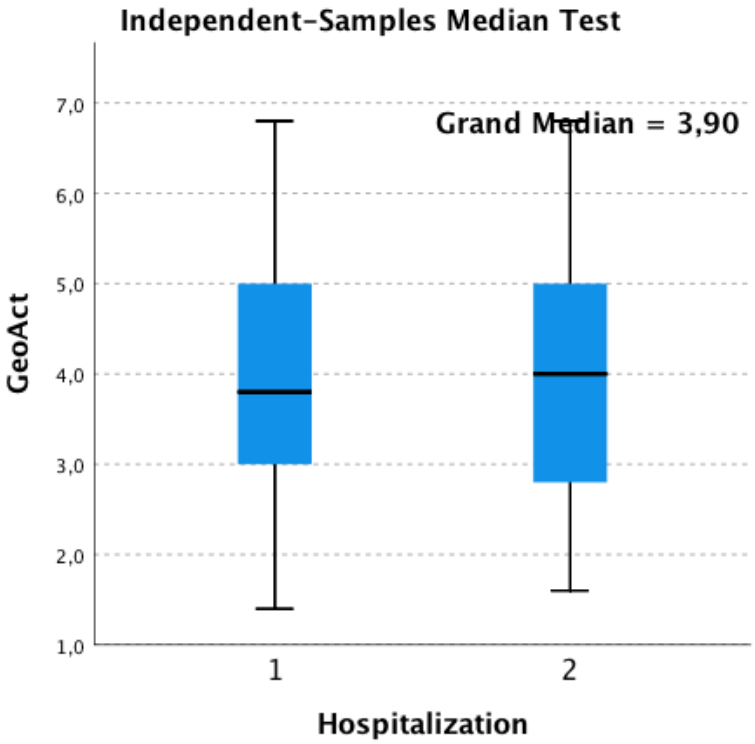


Figure 54. Hospitalizations (1) and rehospitalizations (2) depending on the GMA of patients with AF

The correlation coefficient r between hospitalizations of patients with AF and data on geomagnetic activity in the corresponding weeks is positively related

(r = 0.18), i.e. they tend to increase together and with high statistical reliability the relationship between increased GMA and hospitalizations of patients with AF and comorbidity can be assumed (table 29 and figure 69). There is no unequivocally proven cause-and-effect relationship. The data are epidemiological and correlational, i.e. they show coincidences, but do not prove a mechanism.

Correlations

		hospitalised	activity
hospitalised	Pearson Correlation	1	.101
	Sig. (2-tailed)		.477
	N	52	52
activity	Pearson Correlation	.101	1
	Sig. (2-tailed)	.477	
	N	52	52

Table 29. Correlation coefficient for hospitalizations with AF depending on GMA

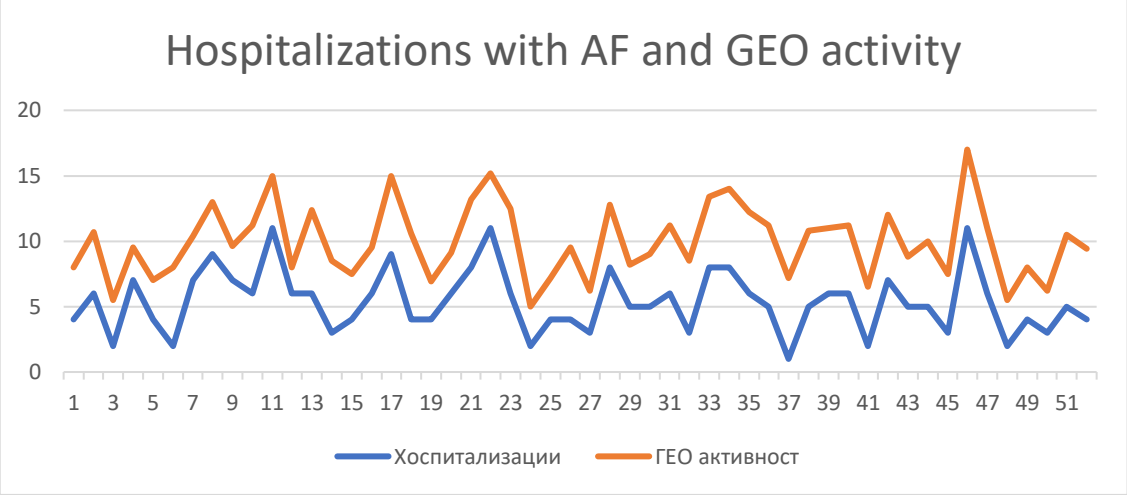


Figure 55. Hospitalizations of patients with AF and GMA dependence

7. Prediction of deterioration in hospitalisations of patients with AF according to the cumulative severity of comorbidity

Multivariable Cox analysis was used to determine the prognosis for worsening of the condition during hospitalization of patients with severe AF and comorbidities.

MAFCCI / EHRAm	Sum of individual variable score EHRAm and MAFCCI		Hazard ratio in the study group of hospitalized patients	
	Acute AF	Chronic AF	Acute AF	Chronic AF
Low risk	0 до 3	0 до 5	62/325 (19,1%)	25/175 (14,3%)
Intermediate risk	4 до 8	6 до 9	177/325 (54,5%)	86/175(49,1%)
High risk	9 and more	10 and more	86/325 (26,5%)	64/175 (36,6%)

Table 30. Scoring system for determining the risk of rehospitalization and deterioration in patients with AF and comorbidity

After statistical processing of the results of our study, a risk profile of hospitalizations with AF was defined by type, and according to the degree of risk for rehospitalization and deterioration of the condition, three groups were formed based on the cumulative severity of comorbidity - low, intermediate and high risk. Hospitalizations with a score of 0 to 3 for paroxysmal AF (19.1%) and 0 to 5 for those with permanent AF (14.3%) were assessed as low risk, intermediate 4 to 8 for paroxysmal AF (54.5%) and 6 to 9 for permanent AF (49.1%), and high 9 and above for paroxysmal AF (26.5%) and 10 and above for permanent AF (36.6%).

Risk of rehospitalization in patients with severe AF (EHRAm III-IV) and MAFCCI is shown in Figure 70.

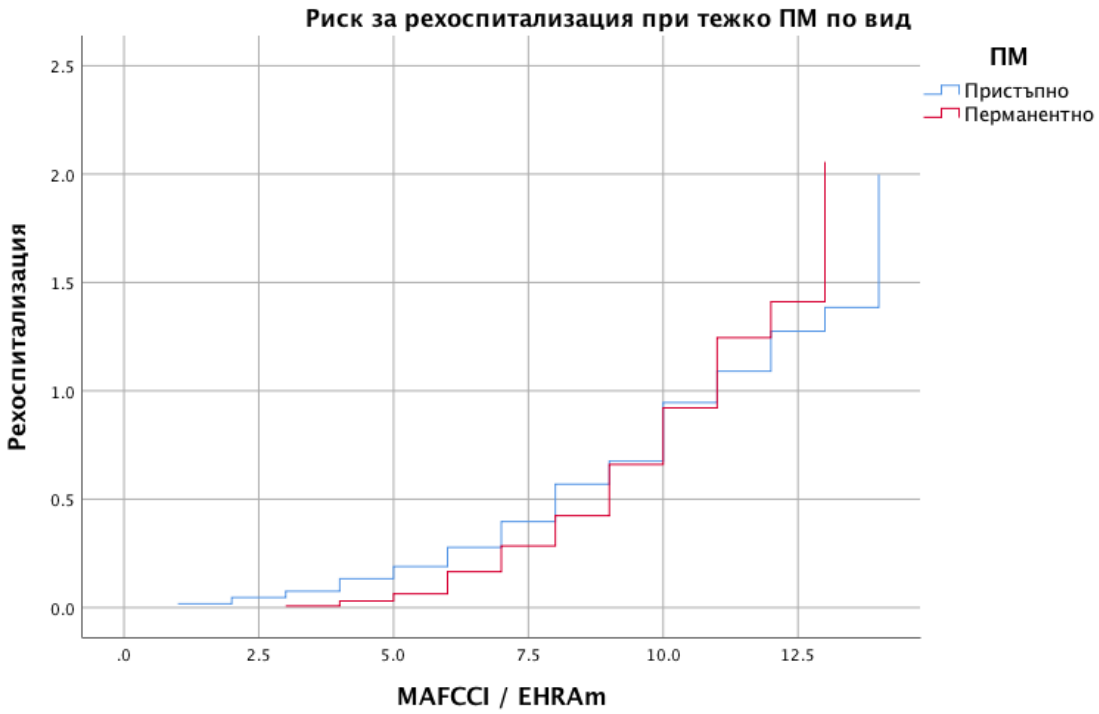


Figure 56. Risk of rehospitalization in patients with severe AF by type

Patients with a higher EHRAm score (symptomatic AF) are significantly more likely to be readmitted to the hospital than those with a lower score. Patients with comorbidities and paroxysmal AF are more likely to be readmitted to the hospital, and with a MAFCCI score of 10, the probability of rehospitalisation for patients with severe AF is the same for both groups. Hospitalised AF patients with a MAFCCI/EHRAm score of 0–8 have a good prognosis for deterioration of their illness. Those with a MAFCCI/EHRAm score more than 9 are considered to have a bad prognosis.

V. Conclusions

1. AF is more common in middle-aged and elderly men. Male gender is a significant risk factor for the occurrence of AF, both globally and among the Bulgarian population.

2. AF is more common in the hospitalizations of men from the urban population compared to those from the rural population, as well as in former smokers and alcohol drinkers.

3. AF most often manifests with palpitations 76.4%, manifestations of HF (orthopnea) 70%, chest tightness 51.6%, shortness of breath 36.6%. Palpitations are significantly more pronounced in hospitalizations with acute AF, while manifestations of LCHF in those with chronic AF.

4. Patients with AF are polymorbid (more than half of hospitalized patients have HF and more than three concomitant heart diseases). In the studied contingent, AH, DSC and CAD are leading causes of AF.

5. A larger percentage of hospitalizations with AF patients have normal hemodynamic status, followed by hyperkinetic and hypotension/bradycardia.

6. Hypertrophic CMP is registered only in hospitalizations with paroxysmal AF, while dilatative CMP is more common in hospitalizations with permanent AF - CMP are an important risk factor for the occurrence of AF, and in turn for their development.

7. Although a significant cause of AF, myocardial and pericardial damage has a smaller contribution to hospitalizations for AF.

8. Patients with AF have a high percentage of non-cardiac comorbidities (30% have two and 25% have three concomitant non-cardiac diseases). The most common non-cardiac comorbidities in patients with AF are: type 2 diabetes, COPD, CKD, hypothyroidism, metabolic disorders, anemia.

9. Gout with a frequency of 10-12% is an independent risk factor for AF.

10. AF is a major risk factor for the occurrence of neurological complications.

11. Therapy for malignant diseases - radiation, chemotherapy and biological - is a common cause of AF.

12. The volume of the left atrium directly correlates with the type and duration of AF - paroxysmal or permanent. With preserved ejection fraction, 44.9% of patients hospitalized with paroxysmal AF are with preserved ejection fraction, while only 20% of those with permanent AF are with preserved ejection fraction.

13. Indirect anticoagulant use is a serious risk for decreased renal function. Hospitalized patients with AF show a clear trend for milder impairment of renal function when using DOACs and vice versa – reduced GFR in patients on indirect anticoagulants.

14. Patients with CKD on indirect anticoagulant therapy have greater calcium deposition in the valve structures and aorta than those on DOAC therapy with high statistical significance.

15. Hospitalizations of patients with AF are slightly more common in the winter-spring season and decline in the summer months, with peaks in late summer and early autumn. Hospitalizations with chronic AF are significantly more common in the first 11 weeks of the year (winter-spring period), but there are peaks in all seasons, and those with acute AF - in the cold months of the year, as well as around public holidays and sudden changes in weather.

16. It was found that there is definitely a relationship between geomagnetic activity (GMA) and hospitalizations of patients with AF and comorbidities, but there is no significant difference in hospitalizations and rehospitalizations. The data are epidemiological and correlational, that is, they show coincidences, but do not prove a mechanism.

17. Rehospitalization is much more common in patients with a higher EHRAm score (symptomatic AF) than in hospitalizations with a lower one.

18. The prognosis for worsening of the condition in patients hospitalized with AF is:

good for those with a MAFCCI / EHRAm score from 0 to 8.

poor for those with a MAFCCI / EHRAm above 9.

VI. Contributions

Unique contributions

For the first time in Bulgaria, a proprietary program called the "Universal Registry of AF" has been created for dissertation purposes.

For the first time in Bulgaria, a MAFCCI index for the prognosis of AF has been compiled.

For the first time in Bulgaria, a cumulative burden of comorbidity MAFCCI / EHRAm has been established.

For the first time in Bulgaria, a scoring system for the prognosis of deterioration in patients hospitalized with AF has been developed.

For the first time in Bulgaria, seasonality has been established in the hospitalizations of patients with AF by type and comorbidity.

For the first time in Bulgaria, a relationship between GMA and hospitalizations for AF has been established.

Confirmatory contributions

The significance of RF for the occurrence and recurrence of AF has been established.

The higher frequency of AF in middle-aged and elderly male patients has been confirmed.

The established social significance of AF for hospitalizations and rehospitalizations in comorbid patients.

The clinical manifestations of acute and chronic AF have been established.

The major role of high-grade HF for frequent hospitalizations in patients with permanent AF.

The contribution of cardiac comorbidities to hospitalizations of patients with AF.

A high percentage of non-cardiac comorbidities has been established.

The role of type II diabetes as a factor in the manifestation and potentiation of AF.

Gout with a frequency of 10-12% is an independent risk factor for AF.

The correlation between the volume of the left atrium and the type of AF has been confirmed.

A milder impairment of renal function has been established with the use of DOAC and vice versa - reduced GFR in patients on an indirect anticoagulant.

Increased calcium deposition in vessels and valve structures in patients with CKD and AF.

VII. Publications related to the dissertation

1. Publications in refereed journals:

1.1 Petkova, M., Cekova, M., Ganeva, S., Penchev, V., Danov, Vl. Heart rate variability in patients with newly diagnosed type 2 diabetes mellitus. Endokrinologya, 2013, 18(1): 12-18; ISSN: 1310-8131; Scopus

2. Publications in non-refereed journals:

2.1 V. Tomova, M. Tzekova, V.Penchev, J. Uzunangelov. Efectiveness and safety of Tirofiban (Aggrastat) in patients with acute coronary syndrome and early manifestation of reccurent angina pectoris at rest. Heart and lung, 2004, 02, 46-54; ISSN: 1310-6341

2.2 RESISTANT HYPERTENSION: THE GUIDELINES FROM BOTH SIDES OF THE OCEAN

Penchev V., Tzekova M., "Department of Propaedeutics of Internal Diseases" Medical University – Pleven; MEDINFO 2020; 09; 26-32; ISSN 1314-0345