

RISK FACTORS, ORAL ANTICOAGULANTS-BASED THERAPEUTICAL APPROACHES AND COMORBIDITIES IN ATRIAL FIBRILLATION: 4216 PATIENTS FROM A ROMANIAN HOSPITAL

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Abstract

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia in clinical practice, is frequently correlated with risk factors and/or comorbidities, and also connected to the cardiovascular diseases. Prevention of the stroke under oral anticoagulants (OACs) therapeutical approach is one of the main goals of AF management. This research aimed to evaluate the characteristics of 4216 AF patients and to establish the risk factors, comorbidities and tendencies in using OACs. A retrospective observational study was carried out between 2017 and 2020, in the County Emergency Clinical Hospital, Oradea, Romania. It has been observed that the number of women suffering from AF is higher. The average age of the patients was 72.52 years (SD = 10.63). High blood pressure (HBP) was present in 80% of patients, followed by peripheral artery disease (76.8%), diabetes (41.88%), chronic obstructive pulmonary disease (COPD) (33.8%) and dyslipidaemia (31.8%). Heart failure (HF) had a frequency of 41.9%, coronary artery disease (CAD) 11.3% and valvular heart diseases 11.1%. 92% of the AF patients received OACs in the followed period. 41% of them (N = 1632) received acenocumarol (the only prescribed vitamin K antagonists (VKA)), 46.6% (N = 1853) direct oral anticoagulants (DOACs) and 12.4% (N = 493) OACs combinations with antiplatelet agents. Following the analysis of data on AC therapy, depending on the presence/absence of HF, CAD and valvopathies provided significant differences ($p < 0.05$). The incidence of AF is closely related to old age and increased prevalence of risk factors (i.e., HBP, dyslipidaemia, diabetes, CAD and COPD).

Rezumat

Fibrilația atrială (FA) este cea mai frecventă aritmie cardiacă susținută în practica clinică, frecvent corelată cu numeroși factori de risc și/sau comorbidități și, de asemenea, legată de bolile cardiovasculare. Prevenirea accidentului vascular cerebral sub abordarea terapeutică cu anticoagulate orale (ACO) este unul dintre obiectivele principale ale managementului FA. Această cercetare și-a propus să evalueze caracteristicile a 4216 pacienți care suferă de FA și să determine factorii de risc, comorbiditățile și tendințele în utilizarea ACO. Un studiu observațional, retrospectiv, a fost realizat în perioada 2017 - 2020, la Spitalul Clinic Județean de Urgență, Oradea, România. S-a observat că numărul de femei care suferă de FA este mai mare. Vârsta medie a pacienților a fost de 72,52 ani (SD = 10,63). Hipertensiunea arterială (HTA) a fost prezentă la 80% dintre aceștia, urmată de boală arterială periferică (76,8%), diabet (41,88%), bronhopneumopatie obstructivă cronică (BPOC) (33,8%) și dislipidemie (31,8%). Insuficiența cardiacă a avut o frecvență de 41,9%, boala arterială coronariană (BAC) 11,3%, iar bolile cardiace valvulare 11,1%. 92% dintre pacienții cu FA au primit OAC în perioada următoare. 41% dintre aceștia (N = 1632) au primit acenocumarol (singurul AVK prescris), 46,6% (N = 1853) AOD și 12,4% (N = 493) ACO combinate cu agenți antiplachetari. În urma analizei datelor privind terapia AC, în funcție de prezența/absența IC, CAD și valvulopatiilor au furnizat diferențe semnificative ($p < 0,05$). Incidența FA este strâns legată de vârsta înaintată și de prevalența crescută a factorilor de risc (HTA, dislipidemie, diabet, BAC și BPOC).

Keywords: atrial fibrillation, oral anticoagulants, risk factors, comorbidities

Introduction

Atrial fibrillation (AF) is a considerable health issue worldwide. It affects the quality of life for millions of patients and increases their incidence of morbidity

and mortality [5]. AF is causing over 20% of strokes, as well as a two times growth in mortality and morbidity attributed to cardiovascular (CV) pathology [16]. Of the European population, the individuals from countries

of Eastern Europe (including Romania) present the greatest risk of stroke [20, 22]. Recently, various conditions and risk factors connected to the occurrence and evolution of AF were revealed [11, 15, 34, 37]. Several risk factors and predisposing conditions like ethnicity, gender, genetic predisposition and age cannot be adjusted, though many risk factors can be adequately treated or are modifiable. Vascular diseases and other CVDs, like coronary artery disease (CAD) and heart failure (HF), have common risk factors with primary conditions that may determine AF. Identifying these primary conditions and risk factors before the appearance of AF may avoid or reverse atrial remodelling, therefore inhibiting or restricting AF evolution, improving the conditions, and decreasing the risk of stroke and of other CV complications [7, 33, 36, 38].

Prevention of the stroke by using oral anticoagulants is one of the main goals in AF therapeutical management. Initially, oral anticoagulants (OACs) used to prevent stroke in patients with AF were vitamin K antagonists (VKAs). Of the oral anticoagulants, VKAs (vitamin K antagonists) were the first used in AF patients for stroke prevention. For several years just VKAs oral anticoagulants, like acenocoumarol and warfarin, were available on the market. VKAs substantially reduce the risk of stroke in AF patients, yet enhance the risk of severe bleeding, particularly intracranial haemorrhage [21]. Due to a small therapeutic interval and several drug and food interactions the use of VKAs is burdensome, requiring regular observation and dose management. After 2010, various direct OACs (DOACs) were approved in AF for the prevention of stroke; the non-VKAs or DOACs are apixaban, dabigatran, edoxaban and rivaroxaban [6, 14, 29]. For AF patients, concerning stroke prevention, VKAs indicated similar or decreased safety and efficiency compared to DOACs [18]. Unlike VKAs which need regular monitoring, DOACs present anticipated pharmaco-kinetics without requiring observation and they also show decreased ability of drug and food interactions. The present research evaluated the common features of AF patients and determined the risk factors, co-morbidities and trends in using OACs. Furthermore, this research analysed the differences between AF patients with associated HF, CAD, or valvular heart disease and those without these comorbidities, to assess the prevalence of anticoagulant use in AF patients, to determine the trends in utilization of DOACs and VKAs.

Materials and Methods

Study design

To evaluate the most frequent risk factors and their incidence among patients with AF, a retrospective single centre observational research, carried out between 2017 and 2020 in the County Emergency

Clinical Hospital of Oradea, Romania, was performed in a systematic and descriptive manner. The study included 4216 subjects, with the following *defined inclusion criteria*: patients with primary discharge diagnosis code and secondary discharge diagnosis code of AF according to International Classification of Disease 10th Revision (ICD-10) codes: 148 (atrial fibrillation and atrial flutter), 148.0 (atrial fibrillation) and 148.1 (atrial flutter). The subjects with previously 148.0 diagnostic code were selected from the following departments: Cardiology, Interventional Cardiology and Advanced Cardiac Patient Surveillance and Treatment Unit. Information on the various types of AF and their individual manifestation/course were not registered, being unavailable.

Patients' data were obtained from personal medical records archived in hospital registers, as well as from the hospital's electronic database; then, all obtained information were added to an electronic form, which included comorbidities, adverse lifestyle (sedentary lifestyle, obesity, alcohol consumption, smoking, etc.), family history of CAD or AF, prescribed AOCs and demographic characteristics. Health expenditures were used to outline comorbidities. To provide diagnostic accuracy, we chose those subjects with comorbidities when there was only one diagnosis at discharge from the hospital.

Ethical statement

The study was conducted according to the WMA Declaration of Ethics in Helsinki [35], being approved by the Ethics Commission of Faculty of Medicine and Pharmacy, University of Oradea (no. 1/31.05.2021) and by the Ethics Commission of the County Emergency Clinical Hospital of Oradea (no. 11943/12.05.2021). Upon admission to the hospital, each patient signed an informed consent form.

Statistical description

IBM SPSS Statistics 20 was used to perform the statistical analysis. In the first part of the analysis, the database was described by calculating the central tendency and dispersion parameters for the numerical variables; for the ordinal and nominal variables, the frequency tables were calculated. After running the Shapiro - Wilk distribution test for the numerical data, our data shown that they are not normally distributed ($p < 0.001$), so in the analysis non-parametrical tests were used (like Mann - Whitney or Kruskal - Wallis). For the statistical significance, the Chi-Square test was applied. As threshold, an α value of 0.05 was set for the entire study.

Results and Discussion

Patients' characteristic

There were no significant differences regarding the annual number of hospitalized patients with AF in the four consecutive years of study; however, there was an increasing trend from 2017 to 2019, except for

2020, which was a pandemic year. In all the study years, a higher number of women compared to men was observed. Regarding the risk factors related to adverse lifestyle, smoking was identified as the most common (in 64.0% of patients), followed by alcohol consumption (59.7%) and sedentary lifestyle (55.08%). The mean body mass index (BMI) was 32.52 kg/m² (SD ± 3.74). Among cardiovascular diseases,

HF had an incidence of 41.9%, followed by CAD (11.3%) and valvulopathies (11.1%). High blood pressure (HBP) was present in 80% of the patients, followed by peripheral artery disease (76.8%), diabetes mellitus (41.88%), chronic obstructive pulmonary disease (COPD) (33.8%) and dyslipidaemia (31.8%); rheumatoid arthritis (RA) was present in 5.6% and obstructive sleep apnoea (OSA) in 3.8% (Table I).

Table I
Characteristics of the study cohort (N = 4216)

Parameters		Patients		Parameters		Patients	
		No.	%			No.	%
Sex	Male	1,955	46.4	Diabetes	No	2,350	55.7
	Female	2,261	53.6		Yes	1,866	44.3
Area of provenance	Urban	2,006	47.6	Sedentary lifestyle	No	1,894	44.9
	Rural	2,210	52.4		Yes	2,322	55.1
Year of study	2017	1,020	24.2	Active/passive smoking	No	1,518	36.0
	2018	1,105	26.2		Yes	2,698	64.0
	2019	1,207	28.6	Alcohol	No	1,701	40.3
	2020	884	21.0		Yes	2,515	59.7
FH-AF	No	3,420	81.1	Dyslipidaemia	No	2,876	68.2
	Yes	796	18.9		Yes	1,340	31.8
FH-CAD	No	3,569	84.7	OSA	No	4,057	96.2
	Yes	647	15.3		Yes	159	3.8
HPB	No	850	20.2	COPD	No	2,791	66.2
	Yes	3,366	79.8		Yes	1,425	33.8
Valvulopathies	No	3,750	88.9	PAD	No	977	23.2
	Yes	466	11.1		Yes	3,239	76.8
Heart failure	No	2,450	58.1	RA	No	3,979	94.4
	Yes	1,766	41.9		Yes	237	5.6
Coronary diseases	No	2,788	66.1				
	Yes	1,428	33.9				

HBP = High blood pressure; PAD = Peripheral artery disease; RA = Rheumatoid arthritis; OSA = obstructive sleep apnoea; COPD = chronic obstructive pulmonary disease; FH-AF = family history of atrial fibrillation; FH-CAD = family history of coronary diseases

92% of the AF patients received OACs in the followed period. 41% of them (N = 1632) received acenocumarol (the only prescribed VKA), 46.6% (N = 1853) DOACs and 12.4% (N = 493) OACs combinations with antiplatelet agents (AA) - clopidogrel, acetylsalicylic acid (AAS), ticagrelor (Figure 1a).

Acenocumarol consumption decreased from 46.42 in 2017 to 34.7% in 2020, at the same time as the increase in DOACs consumption, from 30.4 in 2017 to 55.1% in 2020 (Figure 1b). The most used DOAC (in 23.4% of patients) was apixaban, with a maximum prevalence in 2019, followed by rivaroxaban (15.4%) with a maximum prevalence in 2020 (Figure 1c). The most used combination of AA was clopidogrel with acenocumarol (6%) and the least used ticagrelor with acenocumarol, applied to only 0.4% of patients (Figure 1d).

Patients were divided and analysed according to the presence/absence HF, CAD and valvopathies, three heart conditions frequently associated with AF. HBP, obesity, family history of AF and of CAD, dyslipidaemia, OSA and chronic obstructive pulmonary disease (COPD) were significantly higher in HF patients (Table II). 25.9% of patients with HT also suffered

from HF; only 18.2% of those with HF also had diabetes, and in the case of BMI there were higher values in those with HF (33.02, SD = 3.89 vs. 32.17, SD = 3.60). A sedentary lifestyle was observed in only 24.5% of those with HF, and the current family history is a risk factor, being more common in those with HF than in those without. Smoking and alcohol consumption increase the incidence of HF in about a quarter of cases (28% smoking and 25.1% alcohol consumption). Dyslipidaemia and OSA are more common in those with HF; in the case of COPD, peripheral circulatory disease and RA, the presence of HF was less present. The importance of lower frequencies returns in the presence of multiple risks. Following the comparative assessment of the risk factors' prevalence in patients with CAD vs. those without CAD, the results showed that (excepting for sedentary lifestyle, BMI and smoking) all risk factors were more prevalent in the group with CAD. In patients with dyslipidaemia and diabetes, a higher percentage of patients also had CAD. In the case of BMI, no significant differences were observed between those with vs. without CAD (32.53, SD = 4.08 vs. 32.51, SD = 2.98). A significantly higher incidence in the

group with valvopathies was observed for sedentary lifestyle, family history of AF and of CAD, dyslipidaemia, smoking, alcohol consumption, obesity, OSA and RA (Table II). Valvopathies are less common

than other CVD. The parameter that indicates an impairment as a risk factor is BMI, which is significantly higher in patients with valvopathies than in those without (37.12, SD = 5.89 vs. 31.95, SD = 2.92).

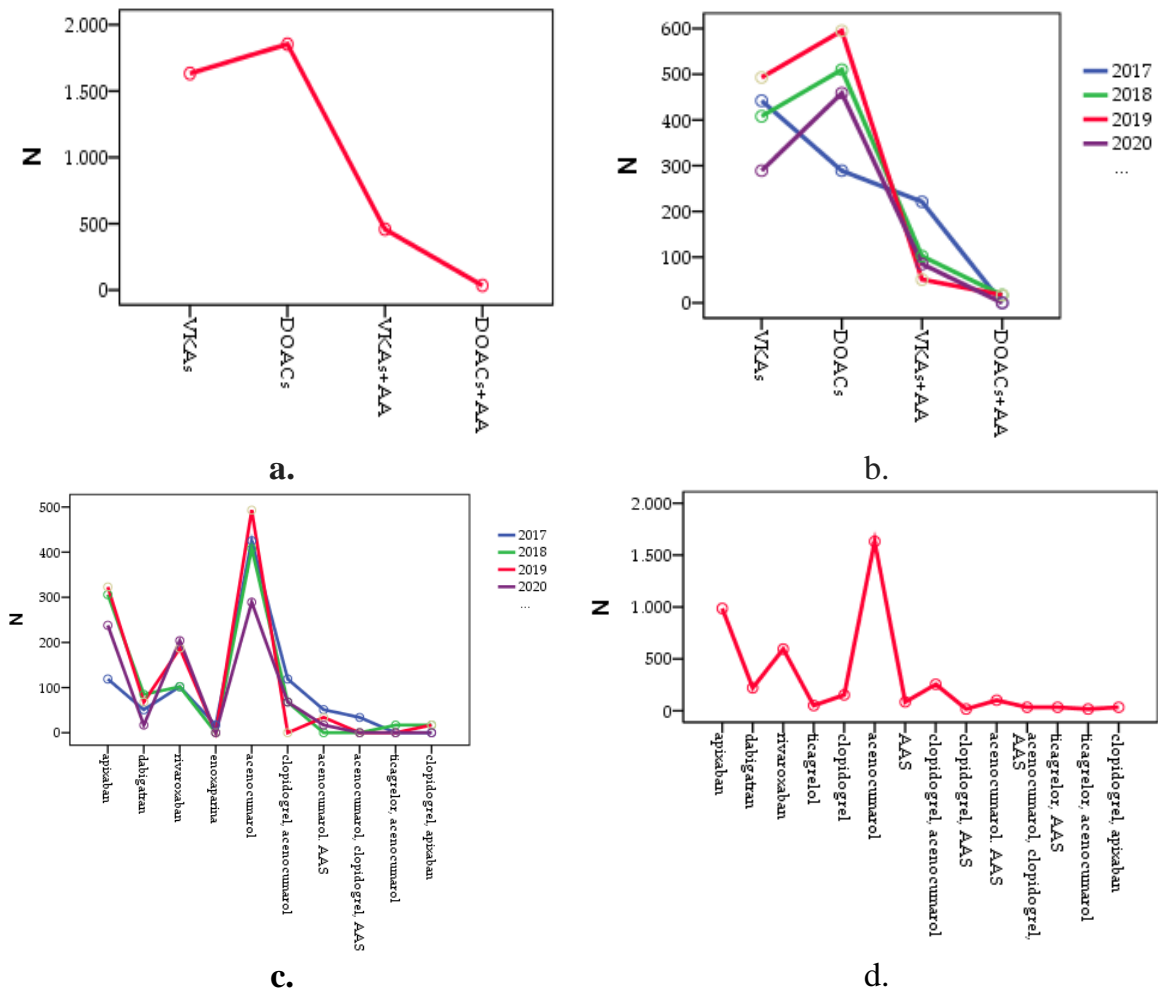


Figure 1.

Trends in OACs use, as follows: **a.** for all the categories/entire period of the study, **b.** for all the categories in every year, **c.** for individual compounds in every year, **d.** for individual compounds for entire period of study
 N = number of patients; AAS = acetylsalicylic acid, AA = antiplatelet agents; DOACs = direct oral anticoagulants; OACs = oral anticoagulants; VKAs = Vitamin K antagonists

Table II
 Frequency of risk factors in patients with/without HF, CAD and valvopathies (N = 4216)

Parameters		HF				CAD				Valvopathies			
		No		Yes		No		Yes		No		Yes	
		N	%	N	%	N	%	N	%	N	%	N	%
HBP	No	178	4.2	672	15.9	462	11.0	388	9.2	702	16.7	148	3.5
	Yes	2272	53.9	1094	25.9	2326	55.2	1040	24.7	3048	72.3	318	7.5
Diabetes	No	1350	32.0	1000	23.7	1968	46.7	382	9.1	2101	49.8	249	5.9
	Yes	1100	26.1	766	18.2	820	19.4	1046	24.8	1649	39.1	217	5.1
Sedentary lifestyle	No	1161	27.5	733	17.4	1264	30.0	630	14.9	1748	41.5	146	3.5
	Yes	1289	30.6	1033	24.5	1524	36.1	798	18.9	2002	47.5	320	7.6
FH-AF	No	2157	51.2	1263	30.0	2192	52.0	1228	29.1	3159	74.9	261	6.2
	Yes	293	6.9	503	11.9	596	14.1	200	4.7	591	14.0	205	4.9
FH-CAD	No	2213	52.5	1356	32.2	2318	55.0	1251	29.7	3242	76.9	327	7.8
	Yes	237	5.6	410	9.7	470	11.1	177	4.2	508	12.0	139	3.3
Smoking	No	934	22.2	584	13.9	993	23.6	525	12.5	1374	32.6	144	3.4
	Yes	1516	36.0	1182	28.0	1795	42.6	903	21.4	2376	56.4	322	7.6

Parameters		HF				CAD				Valvulopathies			
		No		Yes		No		Yes		No		Yes	
		N	%	N	%	N	%	N	%	N	%	N	%
Alcohol consumption	No	993	23.6	708	16.8	1105	26.2	596	14.1	1521	36.1	180	4.3
	Yes	1457	34.6	1058	25.1	1683	39.9	832	19.7	2229	52.9	286	6.8
Dyslipidaemia	No	1973	46.8	903	21.4	2166	51.4	710	16.8	2740	65.0	136	3.2
	Yes	477	11.3	863	20.5	622	14.8	718	17.0	1010	24.0	330	7.8
OSA	No	2392	56.7	1665	39.5	2658	63.0	1399	33.2	3661	86.8	396	9.4
	Yes	58	1.4	101	2.4	130	3.1	29	0.7	89	2.1	70	1.7
COPD	No	1659	39.4	1132	26.9	1819	43.1	972	23.1	2449	58.1	342	8.1
	Yes	791	18.8	634	15.0	969	23.0	456	10.8	1301	30.9	124	2.9
PAD	No	473	11.2	504	12.0	667	15.8	310	7.4	827	19.6	150	3.6
	Yes	1977	46.9	1262	29.9	2121	50.3	1118	26.5	2923	69.3	316	7.5
RA	No	2300	54.6	1679	39.8	2610	61.9	1369	32.5	3584	85.0	395	9.4
	Yes	150	3.6	87	2.1	178	4.2	59	1.4	166	3.9	71	1.7

HBP = High blood pressure; PAD = Peripheral artery disease; RA = Rheumatoid arthritis; OSA = obstructive sleep apnoea; COPD = chronic obstructive pulmonary disease; FH-AF = family history of atrial fibrillation; FH-CAD = family history of coronary diseases

Following the analysis of data on anticoagulant therapy, depending on the presence/absence of HF, CAD and valvopathies, by dividing patients into 3 groups (group I only with AF – 1,404 patients; group II with AF associated with one or two of the three cardiac conditions – 2,760 patients; and group III with AF associated with all three cardiac conditions – 52 patients) were determined significant differences. In groups I and II, most patients used DOACs (51.46% and 44.96%, respectively), and in group III, the most used AC therapy was VKAs in combination with AA (45.96%) (Table III). VKAs were significantly more used in group II than in the other two groups: group I (42.70 vs. 39.49%, $p = 0.001$) and group III (42.70 vs. 16.21%, $p = 0.001$). The use of DOACs was significantly higher in group I than in group II and III (51.36 vs. 44.96%, $p = 0.010$, respectively 51.36 vs. 37.83%, $p = 0.001$). The combination of VKAs + AA was significantly more used in group III compared to groups I and II (45.96 vs. 44.96%, $p = 0.001$, respectively 51.36 vs. 37.83, $p = 0.146$).

Table III

Data on anticoagulant therapy, depending on the presence/absence of HF, CAD and valvopathies

OACs	Groups	Count	%	p*
VKAs	I	508	39.49	0.114
	II	1118	42.70	0.010
	III	6	16.21	0.003
DOACs	I	662	51.36	0.114
	II	1177	44.96	0.001
	III	14	37.83	0.001
VKAs+AA	I	119	9,23	0.010
	II	323	12,34	0.001
	III	17	45,96	0.107
DOACs+AA	I	0	0.0	0.003
	II	34	1,30	0.001
	III	0	0.0	0.107

AA = antiplatelet agents; DOACs = direct oral anticoagulants; OACs = oral anticoagulants; VKAs = Vitamin K antagonists.

In this study, 4216 patients diagnosed with AF over a 4-year period were characterized descriptively and

analytically, to assess the prevalence of common risk factors and the differences between patients with AF suffering from HF, CAD, or valvular disease, and those without these comorbidities, based on their recorded medical data. The mean age of the patients (72.52 years, $SD \pm 10.63$) with AF included in our study is similar with that reported in the literature. The occurrence of AF is isolated among people younger than 50 years, being more frequent in the elderly population [32].

Considering subjects' sex, the data from our study were slightly different from those found in the literature. More than half of the patients enrolled in this study were females (53.8%), whereas AF is frequently reported to be more common in males [25]. The average BMI of the subjects included in our research was 32.52 kg/m^2 , with higher values in men. Several parameters like circulatory hemodynamic, cardiac structure and myocardial remodelling were negatively affected by obesity, resulting in an increased incidence of AF among obese subjects [12]. Both in women and men from the Framingham Heart Study [28], the Busselton Health Study [17] and the Malmö Diet and Cancer Study [30], higher BMI or obesity were also stronger risk factors for AF in men than in women, albeit statistically non-significant.

HF is a condition presenting characteristics of heart malfunctioning along with accurate signs of cardiogenic congestion combined with increased levels of natriuretic peptide [2]. In countries from the Western Europe, the prevalence of AF according to age is reducing, because of improved management of CV impairments, however the global impact is expanding. In Europe, the HF prevalence is 3/1000 person *per year* (regardless of age), or in case of adults, approximately 5/1000 person *per year*. The incidence of HF for adults is 1 - 2%, growing dependent of age, from about 1% in patients younger than 55 years to over 10% for patients of 70 years or older. Slightly more than half of HF subjects are female [10, 24]. In Romania, it is estimated that 4.7% of the population over the age of

35, suffer from HF (about 560,000 patients). Over 70 years, the prevalence increases by 15% [4]. The main comorbidity (60% of patients) in subjects hospitalized with HF is HT, followed by AF (35% of patients) [23]. Even though arterial HT by itself induces only a relatively low risk [1, 9, 27] of AF (relative risk 1.4 - 2.1) in contrast to congestive HF (relative risk 6.1 - 17.5) and valvular heart disease (relative risk 2.2 - 8.3), HT individually accounts for an increased number of AF cases compared to any of the other risk factors, because it has an increased incidence (one billion subjects worldwide) [13]. The general incidence of HT in case of adults is about 30 - 45%, with a general age-related prevalence of 24% in men and 20% in women, in 2015. The incidence of HT increases with age with an incidence higher than 60% for subjects over 60 years of age [19]. In 2016, the Epidemiological Study on the Prevalence of Hypertension and Cardio-vascular Risk in Romania EPHAR III was conducted, and resulting a HT prevalence of 45.1% among the adult population. Related to the Romanian population, it was estimated that, in 2016, about 7.4 million people had HT, the main risk factor for CVD, that are responsible for most deaths both globally and in this country. However, only 80.9% of hypertensive adults knew they had the disease, while the remaining 19.1% were diagnosed during the SEPHAR III study. This means that about 1 out of 5 Romanians is not aware of having HBP. Data shows that due to the CV complications, HBP causes are responsible for 62% of all deaths [3].

Regarding the risk factors, in the Framingham Heart Study, HT, diabetes mellitus, CAD and cigarette smoking were collectively responsible for an AF incidence of 58% in women and 44% in men. HT was one of the independent predictors for AF outbreak, being responsible for 14% of AF cases, both in women and men [3]. In our study, from the risk factors related to adverse lifestyle, smoking was identified as the most common, in 64.0% of patients from the cohort, followed by alcohol consumption (59.7%) and sedentary lifestyle (55.08%). Several behaviour risks factors (alcohol intake, tobacco use, inadequate diet/diabetes/obesity) [1] and reduced physical activity (totalling 62% and meaning more than the European average of 44%), determine more 50% of deaths in Romania. About 17% of deaths are determined by (direct/indirect) tobacco use and 14% (meaning more than twice the average of 6% in EU) is determined by alcohol intake. Reduced physical activity determines 4% of deaths [31].

Patients with AF frequently must handle various pre-existing conditions and risk factors. Thus, the management of AF is more and more complex, being preferred to be performed using an integrated multidisciplinary method, in which the management of underlying conditions and risk factors, as well as of invasive or medical procedures, is adapted in time, based on each

patient particularities [14, 16]. The optimal management of these patients is necessary, to improve the quality of their life.

Between the years 2017 and 2020, the percentage of anticoagulant use among the studied population was about 92%; during the 4-year study interval the use of acenocoumarol gradually decreased as highlighted by the findings of the present research. This reduction of acenocoumarol administration was correlated with a progressive growth of DOAC administration. In recent studies was suggested that more beneficial effects and safety profiles of DOACs could have determined the increase in its use compared to VKAs [8, 26].

Conclusions

Data provided by this study clearly highlight that the prevalence of AF is closely correlated with numerous risk factors (such as adverse lifestyle, HBP, diabetes), being recorded more often in cardiovascular diseases Romanian patients. The overall use of OAC in patients with AF remained constant throughout the study. Since 2017, there has been observed a gradual decrease in the use of acenocoumarol, in parallel with the increase in the use of DOACs.

Conflict of interest

The authors declare no conflict of interest.

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