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Epidemiology of atrial fibrillation in a representative sample of the European part of the Russian Federation. Analysis of EPOCH-CHF study

Aim	To study true prevalence of atrial fibrillation (AF) in a representative sample from the European part of the Russian Federation; to describe characteristics of patients with AF; and to provide the frequency of anticoagulant treatment.
Material and methods	Cross-sectional data of the EPOCH epidemiological study (2017) were used. Data were collected in 8 constituent entities of the Russian Federation; the sample size was 11453 people. The sample included all respondents who had given their consent for participation and were older than 10 years. Statistical tests were performed in the R system for statistical data analysis.
Results	The prevalence of AF in the representative sample from the European part of the Russian Federation was 2.04%. The AF prevalence increased with age and reached a maximum value of 9.6% in the age group of 80 to 89 years. The AF prevalence among females was 1.5 times higher than among men. With age standardization, the AF prevalence was 18.95 and 21.33 per 1,000 people for men and women, respectively. The AF prevalence increased in the presence of concurrent cardiovascular diseases (CVDs) or diabetes mellitus as well as with an increased number of comorbidities in the same person and reached 70.3 and 60.0% in patients with 4 and 5 comorbidities, respectively. Patients with AF had a greater number of comorbidities and higher CHA_2DS_2VASc scores (5.0 vs. 2.0, $p<0.001$) compared to patients with CVDs without AF. Only 22.6% of patients with CVD and AF took anticoagulants. Only 23.9% of patients with absolute indications for the anticoagulant treatment received anticoagulants.
Conclusion	The AF prevalence in the European part of the Russian Federation was 2.04%; it increased with age and in patients with concurrent CVDs or diabetes mellitus. Most of AF patients (93.2%) required a mandatory treatment with oral anticoagulants.

Keywords	Clinical epidemiology; atrial fibrillation; prevalence; cardiovascular diseases; thromboembolic complications; chronic heart failure; comorbidity
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Introduction

The most frequently encountered heart rhythm abnormality, atrial fibrillation (AF) is of particular clinical significance due to increased risk of ischemic stroke, cardiovascular mortality, and hospitalization [1]. The relevance of carrying out an epidemiological study of its objective prevalence in the Russian Federation based on objective data is due to the presence in existing registers of patients from previously selected groups of patients who had already applied to health facilities [2]. In this context, in order to determine the numbers of AF patients who are currently receiving adequate anticoagulant therapy and those who still require it, it is important to be able to describe patient characteristics. Although similar studies have already been conducted in the Russian Federation, determining the present number of AF patients requiring treatment correction can be helpful in developing strategies for improving the management of this category of patients.

Objective

To study the objective prevalence of AF recorded in a representative sample of residents of the European part of the Russian Federation, describe the characteristics of patients with AF and the frequency of anticoagulant therapy.

Material and methods

In this study, we used the 2017 data segment of the EPOCH epidemiological study. Data were collected in 8 regions of the European part of the Russian Federation (the Nizhny Novgorod, Kirov region, Ryazan, and Saratov Regions, the Republics of Tatarstan and Chuvashia, as well the Perm and Stavropol Krais). Information was collected from 2015 to 2017 due to organizational difficulties in finding information about respondents included in the study at the previous stages. The sample size was 11,453 people. The sample included all respondents older than 10 years residing at randomly pre-selected addresses who sign the informed consent. The EPOCH study design, methods of forming the baseline sample and the 2017 sample have been described earlier [3]. AF was diagnosed based on the survey findings, physician's examination, and the analysis of medical records.

The data were processed in the R statistical analysis system [4]. Qualitative variables were expressed as percentages, while intergroup differences were estimated using the chi-squared test or the Fischer's exact test. Quantitative variables were expressed as the median [1st quartile; 3rd quartile]; the statistical significance of intergroup differences was assessed using the Mann – Whitney test. The intergroup differences were statistically significant, having a p value less than 0.05.

Results

The prevalence of AF in the representative sample of the European part of the Russian Federation was 2.04% or 2,040 patients per 100,000 of the population. The prevalence of AF in different age groups of respondents is shown in Figure 1, while Figure 2 depicts the age-specific distribution of patients with AF. Here, the prevalence of AF among respondents from 20 to 40 years old is low (0.1%) but increases with older age and reaches the maximum value in the 80–89-year age group (9.6%).

Most patients with AF (82.9%) were 60 to 89 years old, while only 15% of patients with AF were younger than 60 years, and 2.1% of patients were older than 90 years.

The age-and sex-specific prevalence of AF is shown in Table 1. Although the prevalence of AF in women was 1.5-fold, the difference in the demographic pyramid between men and women should be taken into consideration (the survival of men becomes lower with age than that of women), which affects the prevalence of AF in the general population. The age-standardized prevalence of AF was 18.95 and 21.33 per 1,000 of population among men and women, respectively.

Since the prevalence of AF is often associated with age and/or cardiovascular diseases, we analyzed the indicator of interest depending on a history of cardiovascular diseases (CVDs) (Table 2). For example, the presence of arterial hypertension (AH) doubles the likelihood of AF. The likelihood of detecting AF is approximately the same in the presence of diabetes mellitus (DM), a history of myocardial infarction (MI), or stable angina (8.24%, 9.15%, and 9.39%, respectively). Although the prevalence of AF increased to 12.1% in peripheral atherosclerosis and intermittent claudication, it was 9.28% in patients with atherosclerosis, which is 4.5 times higher than the mean value in the general population. AF was most strongly associated with acute cerebrovascular accident (CVA) and CHF. The highest

Figures 1. Prevalence of atrial fibrillation in different age groups

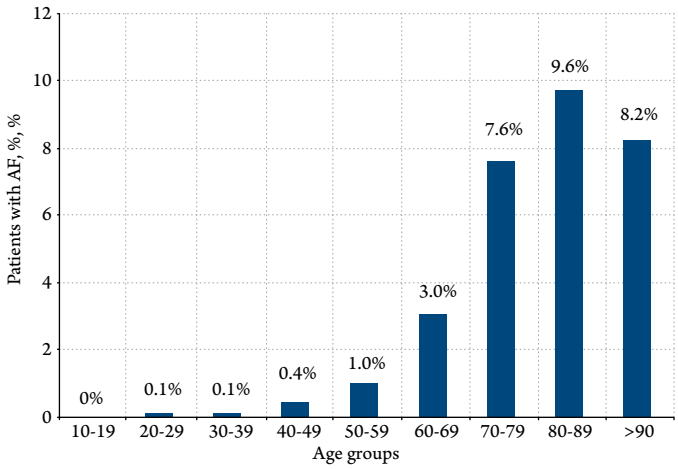


Table 1. Prevalence of atrial fibrillation depending on age and sex

Age group, years	Number of male patients with AF (all male patients)	AF in male patients, %	Number of female patients with AF (all female patients)	AF in female patients, %
10–19	0 (72)	0	0 (65)	0
20–29	0 (541)	0	1 (618)	0.16
30–39	1 (945)	0.1	1 (1051)	0.1
40–49	2 (826)	0.2	6 (1073)	0.6
50–59	10 (1030)	1.0	14 (1414)	1.0
60–69	26 (901)	2.9	40 (1308)	3.1
70–79	22 (358)	6.1	56 (670)	8.4
80–89	17 (148)	11.5	33 (372)	8.9
90 years and older	0 (11)	0	5 (50)	10.0
Total	78 (4,832)	1.6	156 (6,621)	2.4

AF – atrial fibrillation.

Table 2. Prevalence of atrial fibrillation in the study sample and subgroups of patients with various cardiovascular diseases

Patient group	Prevalence of AF, % (n)
Prevalence in the sample (n = 11,453)	2.04 (n = 234)
Arterial hypertension (n = 5,573)	4.15 (n = 231)
Stable angina (n = 1,534)	9.39 (n = 144)
History of myocardial infarction (n = 328)	9.15 (n = 30)
Diabetes mellitus, (n = 546)	8.24 (n = 45)
History of CVA (n = 288)	13.5 (n = 39)
CHF (n = 1,325)	12.3 (n = 163)
Intermittent claudication (n = 132)	12.1 (n = 16)
Structural heart defects (n = 118)	22.0 (n = 26)

CVA – cerebrovascular accident;
CHF – chronic heart failure; AF – atrial fibrillation.

prevalence of AF (22%) was observed in patients with structural heart defects; however, there were few such patients.

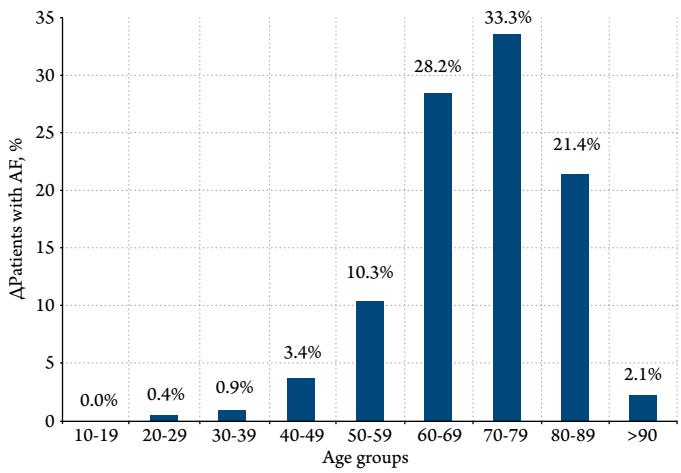
Table 2 shows the likelihood of detecting AF in an artificially isolated single diagnosis. In actual clinical practice, however, an individual patient typically has several CVDs or their combination with DM. Figure 3 shows the presence of AF depending on the number of comorbidities. There were no AF patients without comorbidities. AF was diagnosed in 4.0% of patients with one comorbidity. The prevalence of AF increased with the number of comorbidities. For example, 70% of patients with four comorbidities had AF.

A Venn diagram was used to establish the likelihood of the presence of AF in patients with the most common diagnosis combinations in the population of the European part of the Russian Federation: atherosclerosis, including ischemic artery disease (CAD), a history of MI and peripheral atherosclerosis, AH, and DM (Figure 4). Other Venn diagrams are presented online in Appendix 1.

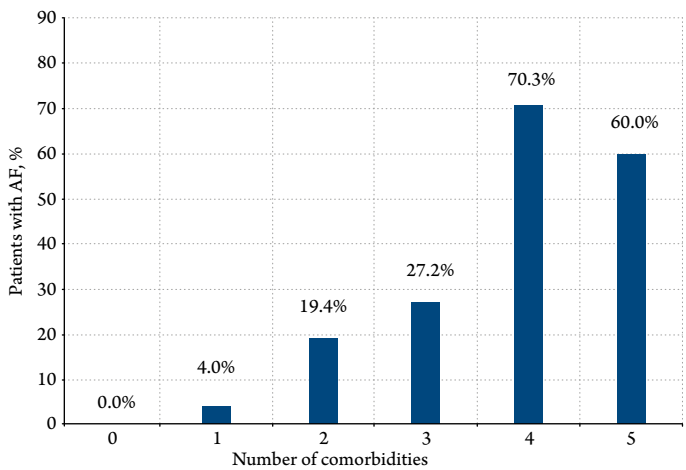
As the diagram shows, 95.3% of patients with AF had AH (32.1% isolated AH, 47.4% in combination with atherosclerosis, and 15.8% in combination with DM), while only two patients (0.85%) had no combination of AF and underlying CVDs. However, one of these patients had a structural heart defect, while the other one had CVA, which could however have been caused by a pre-existing heart rhythm disorder. Thus, only one of the 234 cases with AF (0.43%) could be classified as a «pure» AF group.

Figure 5 shows the Venn diagram of the AF combination with CHF and CVA. As can be seen, 16.7% of patients with AF had a history CVA, while in 14.0% of patients, CVA was associated with the presence of AF, confirming a bilateral

Figures 2. Age-specific distribution of patients with atrial fibrillation



Figures 3. Figure 3. Prevalence of atrial fibrillation depending on the number of comorbidities



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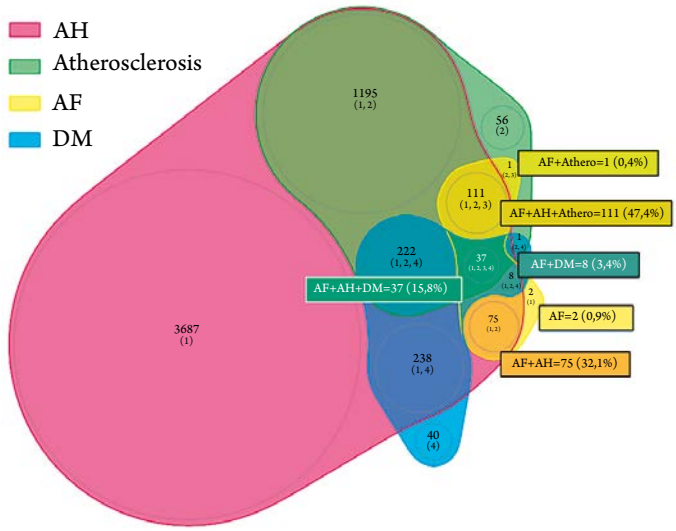
causal relationship between these diseases. At the same time, almost 70% of AH patients had CHF.

Next, we compared the groups of CVD patients depending on the presence of AF (Table 3). Patients with CVDs and AF were statistically significantly older (74 vs 61 years, p < 0.001). Most CVDs (atherosclerosis of various localizations, history of MI, structural heart defects, DM) were significantly more frequent in the group of patients with AF. Thus, patients with AF have more comorbidities (3 versus 1) and higher CHA_2DS_2-VASc score (5.0 versus 2.0) compared to CVD patients without AF. It should be noted that patients with CVDs and AF had CHF and severe CHF FC III–IV 3.3 and 5.1 times more often, respectively, than patients without AF. Moreover, a history of CVA was 3.7 times more frequent in patients with AF.

Figure 6 shows the distribution of patients with AF depending on a CHA_2DS_2-VASc score, which determines the risk of adverse thromboembolic events and the need for anticoagulant therapy. As Figure 6 and Table 3 show, the number of patients to whom anticoagulants were indicated (class of recommendations I, [1]; CHA_2DS_2-VASc >1 in male patients and CHA_2DS_2-VASc >2 in female patients) was 218 of 234 (93.2% of all patients with AF).

Figures 4. Number of patients with atrial fibrillation combined with atherosclerosis, hypertension, and diabetes mellitus



Absolute values (n) and percentages (%) are given concerning AF patients with diseases associated with atherosclerosis, AH, DM, their combinations, and the percentage of patients without these three diagnoses. The proportions are observed on the diagram. AF – atrial fibrillation; AH – arterial hypertension; DM – diabetes mellitus; Athero – atherosclerosis (CAD and/or intermittent claudication). CAD was established by the presence of stable angina and/or a history of MI.

Table 3. Analysis of groups of patients with cardiovascular diseases depending on the presence of atrial fibrillation

Parameters	CVD patients without AF, n=5,469	CVD patients with AF, n=234	p
Age, years	61.0 [54.0; 70.0]	74.0 [64.0; 79.0]	< 0.001
Female, %	61.7%	66.7%	0.140
Arterial hypertension, %	97.7%	98.7%	0.412
Stable angina, %	25.4%	61.5%	< 0.001
Myocardial infarction, %	5.45%	12.8%	< 0.001
Intermittent claudication, %	2.12%	6.84%	< 0.001
Structural heart defects, %	1.68%	11.1%	< 0.001
Diabetes mellitus, %	9.16%	19.2%	< 0.001
CVA, %	4.55%	16.7%	< 0.001
Any CHF, %	21.2%	69.7%	< 0.001
CHF NYHA FC III-IV, %	5.70%	29.1%	< 0.001
Number of comorbidities	1.00 [1.00; 2.00]	3.00 [3.00; 4.00]	< 0.001
CHA_2DS_2-VASc, score	2.00 [2.00; 4.00]	5.00 [4.00; 6.00]	< 0.001

CVA – cerebrovascular accident – CHF – chronic heart failure; FC – functional class; CVD – cardiovascular disease; CHA_2DS_2-VASc – estimation of the risk of stroke and systemic thromboembolism in atrial fibrillation.

Table 4. Drugs administered in patients with cardiovascular diseases depending on the presence of atrial fibrillation

Drugs	CVD patients without AF, n=5,469	CVD patients with AF, n=234	p
ACE inhibitors	42.4%	59.8%	< 0.001
ARBs	17.8%	25.2%	0.005
ACE inhibitors or ARBs	59.3%	82.9%	< 0.001
Beta-blockers	26.4%	65.8%	< 0.001
MRAs	3.40%	28.6%	< 0.001
Digoxin	0.27%	15.4%	< 0.001
Verapamil	0.60%	2.14%	0.019
Antiarrhythmic drugs	0.11%	6.84%	< 0.001
Anticoagulant drugs	0.15%	22.6%	< 0.001
Antiplatelet drugs	29.2%	58.5%	< 0.001

ACE – angiotensin-converting enzyme – ARB – angiotensin II receptor blocker; MRA – mineralocorticoid receptor antagonist – CVD – cardiovascular disease; AF – atrial fibrillation.

We analyzed the treatments received by patients with CVDs depending on the presence of AF (Table 4). The main drugs used to treat CHF that inhibit/delay cardiac remodeling (renin-angiotensin-aldosterone system blockers (angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers), beta-blockers, and mineralocorticoid receptor antagonists) were administered significantly more often in the presence of AF. Digoxin was rarely used in AF

(15.4%); antiarrhythmic therapy, including verapamil, was administered to 9% of patients. Such differences may be due to older age, comorbidities, as well as the type of heart rhythm and the severity of the disease. Interestingly, antiplatelet agents were often used (58.8%) to treat patients with AF. Only 22.6% of patients with CVDs and AF took anticoagulants, while 18% of patients did not receive antiplatelet or anticoagulant therapy.

Under the primary assumption that not all patients with AF have absolute indications for anticoagulants [1], we performed an analysis in the group of 218 patients with CVDs and AF, in which CHA_2DS_2-VASc was >1.0 and >2.0 in male and female patients, respectively, i.e., they required anticoagulant therapy (Figure 6B). In this group, 19.2% of patients with CVD and AF received neither antiplatelet drugs nor anticoagulants, while 56.9% of patients received only antiplatelet agents that did not provide adequate prevention of adverse thromboembolic events in AF [5, 6]. 23.9% of respondents received anticoagulants; 3.7% of patients with AF received a combination of antiplatelet drugs with oral anticoagulants. Since the study design did not allow us to distinguish patients with AF immediately following MI or recent percutaneous coronary intervention, to whom dual antithrombotic therapy with an antiplatelet and anticoagulant drug combination had been provided, we were not able to assess the advisability and safety of this combination treatment in the study population.

In the analyzed sample, 15 patients had indication class IIa (CHA_2DS_2-VASc = 1 in male patients and CHA_2DS_2-VASc = 2 in female patients) for anticoagulants, while only one patient received anticoagulants.

An additional analysis included patients at increased risk of adverse thromboembolic events (male patients with CHA_2DS_2-VASc >2 and female patients with CHA_2DS_2-VASc >3). Only 23.2% of patients (45 of 194 patients) in this group received anticoagulants.

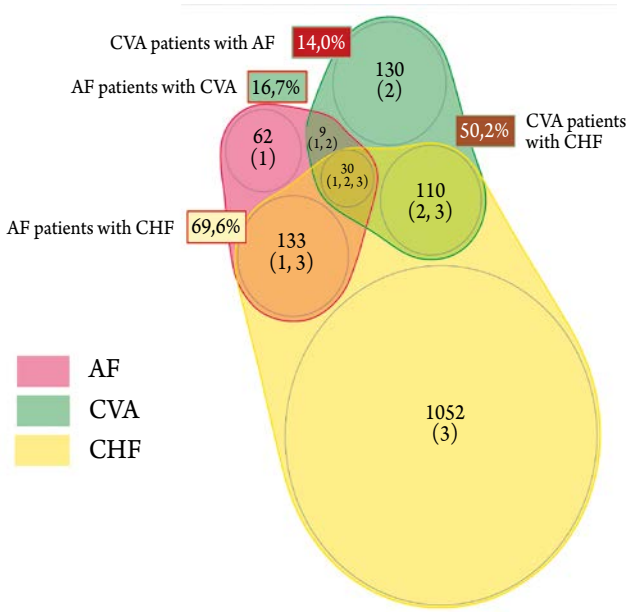
Discussion

Our study showed that AF is present in 2% of patients in the population of respondents older than 10 years in the European part of the Russian Federation; moreover, that its prevalence increases with age.

Analysis of the incidence of AF outside Europe and North America shows an extremely wide variation in this indicator (from 0.1% in India to 4% in Australia) [7]; this can be ascribed to differences in the age composition of the populations and the incidence of risk factors for AF, as well as differences in the examinations and screening of AF in different countries.

At the same time, the analysis of papers by European and US authors shows a prevalence of AF similar to our findings. In the US population over 20 years old, 2.21% of patients have AF [8]. In the Rotterdam study, which included people older

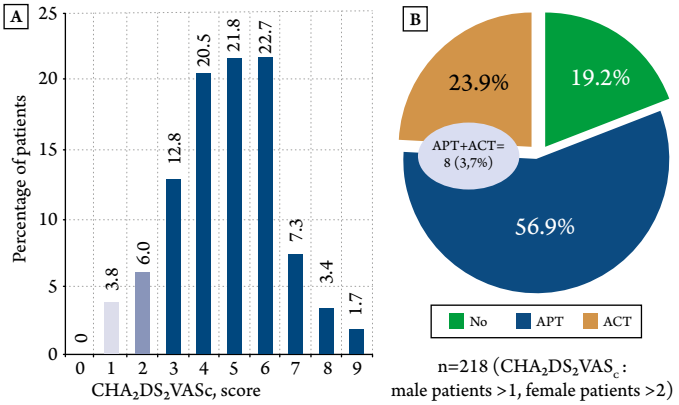
Figures 5. Number of patients with atrial fibrillation combined with chronic heart failure and cerebrovascular accident



Absolute values (n) and percentages (%) are given for patients with AF who had CHF and CVA, and their combinations. Proportions are observed on the diagram. AF – atrial fibrillation; CHF – chronic heart failure; CVA – cerebrovascular accident.

than 55 years, the prevalence of AF was 5.5%, increasing with age from 0.7% in 55–59-year-old patients to 17.8% in patients older than 85 years [9]. In the ATRIA study, the prevalence of AF in patients older than 20 years was 0.95%; this also increased with age (from 0.1% in patients younger than 55 years to 9.0% in ≥80-year-old patients) [10]. Interestingly, the prevalence of AF in the 50-60-year age group in the European part of the Russian Federation is similar to that in the European and North American populations. The lower

Figures 6. Distribution of patients with atrial fibrillation by CHA_2DS_2-VASc score (A) and percentage of antithrombotic therapy in male patients with CHA_2DS_2-VASc >1 and female patients with CHA_2DS_2-VASc >2 (B)



No = did not take antiplatelet drugs and anticoagulants; APT, antiplatelet therapy; ACT, anticoagulant therapy.

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prevalence of AF in Russian patients over 80 years old as compared to the Rotterdam study may be associated with the survival factor and insufficiently active detection of this type of arrhythmia among respondents from older age groups in the Russian Federation.

The increased prevalence of AF worldwide every year is due to population aging and increased incidence of AF risk factors, as well as growing AF detection frequency [11]. According to the analyses conducted in Europe and the US, further increases in the number of patients with AF are to be expected, primarily due to the aging of the population [8, 12].

The almost complete absence of patients with idiopathic AF is an interesting finding of our study. Here, it should be noted that the number of patients with idiopathic AF varies greatly from 0.2% to 68% depending on the population of interest and the diagnostic criteria used [13]. A principal factor determining the number of identified cases of idiopathic AF is the consideration of mild AH. For example, in the Framingham study, in which AH was diagnosed at blood pressure > 160/90 mm Hg, 11% of patients with AF had arrhythmia considered to be idiopathic. At the same time, the percentage of patients with idiopathic AF was much lower in those studies where mild AH was taken into consideration. For example, the relevant figure was 2% according to the Olmsted County study [14], in which age less than 60 years was the additional criterion for diagnosing idiopathic AF, while, according to the Euro Heart Survey, in which patients of any age were taken into consideration [15], it was 3%.

In our study, only 1 (0.43%) patient had idiopathic AF. The small number of patients with idiomatic AF could be due to «arrhythmic CAD» only being diagnosed in patients with AF in some cases in the Russian Federation, which leads to overdiagnosis of this cause of AF.

It should be noted that the 2020 ESC guidelines suggested that the term «idiopathic AF» be abandoned [1], since recent data demonstrate a reason for the development of AF in most patients with this condition, while, from the point of view of AF pathophysiology, a small number of patients without identified reasons form a heterogeneous group [13, 16].

Another interesting finding of our study is the comparable age-standardized prevalence of AF in male and female patients. According to the literature, this indicator is higher in male patients [17]. Nevertheless, the comparable number of male and female patients with AF may be explained, according to studies, by the fact that female patients with AF have more symptoms and are more likely to seek medical attention due to more distinct arrhythmia. Therefore, in the absence of systemic screening of AF in the Russian Federation, it is possible that women are diagnosed with AF more often than men. According to the Framingham and Rotterdam studies, a higher risk of developing AF was established in male patients during the prospective observation, but the differences were not pronounced (25.9% versus 23.2% for 50-year-old patients in the Framingham study [18] and 23.8% versus 22.2% for 55-year-old subjects in the Rotterdam study [9]). Our sample size could prevent the reliable detection of differences of 1–2.5% in the prevalence of AF between male and female patients.

The higher prevalence of AF in patients with CVDs is particularly striking when combined with AH, CAD, structural heart defects, and CHF [1, 11]. Increased prevalence of AF in patients with CVDs may also be due to the possibility of the same risk factors (e.g., obesity [19], smoking [20], alcohol misuse [21]) leading to AF and other CVDs [22]. Here, it should also be taken into consideration that the risk of AF and other CVDs increase with age.

The correlation of AF with CHF and CVA is of utmost interest. The majority (69.7%) of patients with AF had signs of CHF. At the same time, there was a distinct bidirectional relationship between AF and CVA, which confirms the role of this type of irregular heart rhythm in the development of adverse thromboembolic events. In other words, the following chain of events is most likely: the onset of CHF, cardiac remodeling accompanied by the development of AF, which increases the risk of CVA almost fourfold. Therefore, timely anticoagulant therapy could be a reliable way to prevent adverse thromboembolic events and strokes.

According to our data, 93.2% of patients with AF have an elevated risk of adverse thromboembolic events and indications for anticoagulants. However, only 23.9% of patients with indications actually receive anticoagulants.

The REKVAZA and REKVAZA FP registers confirm the low rate of using anticoagulants (22.6% of all patients with AF and 23.9% of patients with absolute indications for AF): 13.5% in the outpatient setting and 54.1% in hospitalized patients, according to the data collected in five regions of the Russian Federation [23]. Although the corresponding rates were higher in the RIF-KhSN register, in which specialized centers take active part, even here it was not high enough (58% in patients with CHA_2DS_2-VASc >3) [24].

Thus, active work with physicians working in outpatient clinics and the general population is required to develop an information resource concerning the substantial risk of AF complications. For example, Stepina et al. showed that 40.4% of patients received anticoagulants when admitted to hospital; the anticoagulant therapy was administered in 88% of patients at the time of discharge, with 82% of patients still taking anticoagulants a year later [25].

Our work has some limitations due to that the data were collected by patient survey and analysis of medical records. Diagnoses were not validated. CHF was diagnosed according to the epidemiological criteria, which overestimates the objective prevalence of CHF [26]. Given these limitations, the obtained CHA_2DS_2-VASc scores may be slightly overestimated compared to the objective scores.

Conclusions

1) The prevalence of AF in the European part of the Russian Federation is 2.04% and increases in patients with CVDs (4.2% in patients with AH, 9.4% in the presence of stable angina, 8.2% in patients with DM, and 12.3% in patients with CHF).
2) The prevalence of AF increases with age from 0.1% at the age from 20 to 29 years to 9.6% in the 80–89-year age group.
3) Comorbidities increase the risk of AF, particularly, in the presence of four and five comorbidities.
4) Most patients with AF (93.2%) require the mandatory use of oral anticoagulants.
5) Only 22.6% of patients with AF and 23.9% of patients with absolute (class of recommendations I) indications for the prevention of adverse thromboembolic events took anticoagulants.

No conflict of interest is reported.

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