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ORIGINAL PAPER

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The Impact of Risk Factors and Comorbidities on The Incidence of Atrial Fibrillation

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ABSTRACT

Introduction: Atrial fibrillation (AF) is the most common form of cardiac arrhythmia in clinical practice and its prevalence increases with age. Patients who develop AF also have cardiovascular risk factors, structural heart disease, and comorbidities, all of which can increase mortality. AF causes a significant economic burden with the increasing trend in AF prevalence and hospitalizations. **Research Objectives:** The objective of our study is to evaluate the impact of the most common known risk factors on the incidence of atrial fibrillation as an important precursor of cardiac and cerebrovascular morbidity and mortality among our patients in Bosnia and Herzegovina during median follow up period (September 2006 - September 2016). The other objective is to estimate the CHA₂DS₂-VASc score among our patients based on clinical parameters. **Patients and methods:** This study includes 2352 ambulant and hospitalized patients with atrial fibrillation. All patients underwent clinical evaluation which includes thorough assessment for potential risk factors and concomitant conditions in order to determine which of them represent the most common among examinees with atrial fibrillation. **Results:** The results show that male gender has slightly more incidence of AF. Obesity and overweight with BMI ≥ 27 , cigarettes smoking and sedentary life style are almost present in patients with AF. Arterial hypertension, coronary artery disease, diabetes mellitus, chronic obstructive pulmonary disease, chronic renal dysfunction, structural and valvular heart disease and peripheral vascular disease are the most common comorbidities among our patients. The mean CHA₂DS₂-VASc score was 3.2 \pm 1.4 and the mean HAS-BLED score was 2.1 \pm 1.2. **Conclusion:** Atrial fibrillation is the most common sustained cardiac rhythm disorder. The study

shows that obesity, alcohol consumption, smoking cigarettes and dyslipidemia can be considered as triggers and predisposing factors for appearance of AF. Arterial hypertension, coronary artery disease, chronic obstructive pulmonary disease, diabetes mellitus, Peripheral vascular disease and chronic kidney disease are playing important role in developing of AF.

Keywords: Atrial fibrillation, Risk factors, Stroke, Myocardial infarction, Sudden death, Heart failure.

1. INTRODUCTION

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia in clinical practice and its prevalence increases with age. By year 2030, 14–17 million AF patients are anticipated in the European Union. Patients who develop AF also have cardiovascular risk factors, structural heart disease, and comorbidities, all of which can increase mortality. Atrial fibrillation is a major medical and public health problem owing to its increasing prevalence and strong association with morbidity and mortality. AF causes a significant economic burden which has grown in the past decades and is expected to grow even further in the upcoming period with the increasing trend in AF prevalence and hospitalizations. Therefore, an adequate treatment strategy is warranted.

2. RESEARCH OBJECTIVES

The first objective of our study is to evaluate the impact of the most common known risk factors and other comorbidities on the incidence of atrial fibrillation as an important precursor of cardiac and cerebrovascular morbidity and mortality among our patients in Bosnia and Herzegovina. The second objective is to estimate the CHA₂DS₂-VASc and HAS-BLED score among our patients.

3. PATIENTS AND METHODS

This study includes 2352 ambulant and hospitalized patients with atrial fibrillation (AF) who were enrolled during median 9.7 ± 1.8 follow up period (September 2006 until September 2016). A complete medical history was taken, all patients underwent clinical evaluation which includes thorough assessment for concomitant conditions. The AF was documented by 12-lead ECG or ambulatory ECG Holter recording in order to establish the diagnosis of AF. TTE or TEE Echocardiography was performed to assess left atrial diameter and volume, as well as quantitative and qualitative evaluation of left ventricle parameters, heart structure and hemodynamic relevant parameters. In this study we evaluate the potential risk factors for atrial in order to determine which of the mentioned risk factors are the most common among examinees with atrial fibrillation. Individualized risk stratification was performed using the CHA₂DS₂-VASc. In our study we estimate CHA₂DS₂-VASc and HAS-BLED score among our patients in order to evaluate the use of oral anticoagulation therapy among our patients and the risk of bleeding.

4. RESULTS

During the follow up period, we analyzed and follow up 2352 patients with ECG documented different type of atrial fibrillation in order to assess the impact of common risk factors and comorbidities on appearance of atrial fibrillation. The demographic data, risk factors, clinical and comorbidity characteristics for all patients are shown on Table 1. The echocardiographic data and characteristics for all patients are shown on Table 2. The pattern of atrial fibrillation is shown on Table 3. The pharmacological therapy and antiarrhythmic drugs are shown on Table 4.

In our study among 2352 patients, AF was reported to be

	overall	Hazard Ratio (± 95% CI)
Left atrial diameter, mm	47 ± 8	1.058 (1.034–1.085)
Left atrial volume, mL/m ²	37 ± 13	1.006 (1.002–1.008)
LV diastolic diameter – LVEDD (mm)	4.7 ± 0.9	1.056 (1.039 – 1.064)
LV Systolic diameter–LVESD (mm)	3.3 ± 0.7	1.512 (1.508 – 1.522)
Left ventricular ejection fraction %	54 ± 14	1.003 (0.984 – 1.007)
Normal (≥50%), n (%)	1.025 (44%)	
Mildly reduced (40-49%), n (%)	652 (28%)	
Preserved (≥40%), n (%)	286 (12%)	
Moderately reduced (30-39%), n (%)	221 (9%)	
Severely reduced (<30%), n (%)	168 (7%)	

Table 2. Echocardiographic parameters

Variable	Overall	Cox and sex adjusted P-value	Hazard Ratio (± 95% CI)
No. of patients (n = 2352)			
Age, years	68 ± 13	< 0.001	1.028 (1.021–1.035)
Male, n (%)	1223 (52)	0.3562	1.074 (0.902–1.253)
BMI, kg/m ²	26 ± 7	0.0266	1.009 (1.004–1.014)
Normal BMI, n (%)	729 (31)	0.0031	0.764 (0.637–0.894)
Overweight, n (%)	1035 (44)	0.2253	0.847 (0.702–0.990)
Obesity, n (%)	588 (25)	0.0054	1.314 (1.071–1.561)
Sedentary lifestyle	1082 (46)	0.2184	1.503 (1.252–1.754)
Family history of AF	643 (27)	< 0.001	1.465 (1.287–1.682)
Family history of CAD	729 (31)	< 0.001	1.543 (1.359–1.746)
Current or past smoker, n (%)	1341 (57)	0.1464	1.240 (1.188–1.296)
Alcohol consumption acute/chronic, n (%)	635 (27)	0.1546	1.206 (1.094–1.319)
Hypertension, n (%)	1788 (76)	0.0027	1.352 (1.151–1.553)
Angina/CAD, n (%)	917 (39)	0.6842	0.916 (0.763–1.069)
Heart Failure	641 (27)	0.1603	1.425 (1.293–1.557)
Valvular heart disease, n (%)	258 (11)	< 0.001	1.280 (1.057–1.505)
Diabetes mellitus, n (%)	517 (22)	0.1761	1.170 (0.898–1.379)
Dyslipidemia, n (%)	1388 (59)	0.4892	1.082 (0.862–1.304)
Chronic obstructive pulmonary disease, n (%)	612 (26)	0.0468	1.194 (0.586–1.857)
Peripheral vascular disease, n (%)	376 (16)	0.6852	1.054 (0.792 -1.312)
Thyroid disease, n (%)	78 (3)	0.1583	1.206 (0.995–1.417)
Open heart surgery, n (%)	282 (12)	0.5124	1.240 (1.045–1.435)
Chronic kidney disease, n (%)	240 (10)	0.4981	1.165 (0.917–1.410)
Obstructive sleep apnea, n (%)	47 (2)	0.1573	1.521 (0.861–2.181)

Table1. Baseline demographics and clinical characteristics

first detected in 352, paroxysmal in 194, persistent in 728, and permanent in 1078 patients. Concomitant diseases were present in 84% of all patients. As many as 79% of patients were symptomatic during the follow up period. Oral anticoagulation drugs (VKAs and NOACs) were prescribed to 44.2% of the patients with AF. Antiplatelet agents were prescribed in 22% of patients. A rhythm control strategy was applied in 63% of currently symptomatic patients and in 47% of patients who never experienced symptoms according to the ESC guidelines. In this study, the baseline age of patients was (68 ± 13). The results show that male gender has slightly more incidence of AF. Obesity and overweight with BMI ≥ 27, cigarettes smoking and sedentary life style are almost present in patients with AF. Arterial hypertension, coronary artery disease, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, valvular heart disease and peripheral vascular disease are the most common comorbidities among our patients and they are playing important role in developing of AF.

The number of used drugs in our patient population indicates that patients with AF should receive intensified treatment to reduce their risk of cardiovascular complications. The mean CHA₂DS₂-VASc score was 3.2±1.4 with adjusted stroke rate 2.7% per year, the mean HAS-BLED score was 2.1±1.2. Our study shows that the majority of patients with atrial fibrilla-

First diagnosed AF	352 (15)
Paroxysmal AF	194 (8)
Persistent AF	728 (31)
Permanent AF	1078 (46)
Clinical presentation n (%)	
Symptomatic AF	1859 (79)
Silent AF	493 (21)

Table 3. Patterns of atrial fibrillation n (%)

Amiodarone	1324 (56)
Beta blockers	631 (27)
Calcium channel blockers	511 (22)
Digoxin	725 (31)
ACE-I/ARB	1084 (46)
Diuretics	1284 (55)
Alpha blockers	420 (18)
Nitrates	752 (32)
Statins	1657 (70)
Antiplatelet agents (Aspirin/Clopidogrel)	514 (22)
Anticoagulants (VKAs)	588 (25)
NOACs	447 (19)
Antidiabetics – oral	346 (15)
Insulin	171 (7)
Number of cardiovascular drugs (mean)	2.62 ± 1.84

Table 4. Pharmacological therapy n (%)

tion have mild to moderate enlargement of left atrium, 47% have mitral valve annulus calcification and more than half of patients have mildly-moderately reduced LV EF. The quality of patients life with AF is clear impaired in more than 67%.

5. DISCUSSION

Atrial fibrillation is the most common arrhythmia in the general population, with a prevalence of 1.5-2%, which increases with age. In addition, it occurs more frequently in males, with a male to female ratio of 1.2:1. By 2030, 14-17 million AF patients are anticipated in the European Union, with 120 000–215 000 newly diagnosed patients per year. Given that AF is associated with significant morbidity and mortality, this increasing number of individuals with AF will have major public health implications (1-6). AF is frequently associated with cardiac disease and comorbidities. The most common comorbidities are hypertension (67–76%), heart failure (22–42%), diabetes (20–24%), obesity (20–35%), chronic pulmonary disease (10–18%), thyroid dysfunction (8–11%), renal failure (11–22%) stroke/transient ischemic attack (9–16%), and neuropsychiatric disturbances (19%).(5, 6). In our study, the mean age of the patients was 68 ± 13 years, the males represent 52% of patients with AF. The published studies also have reported a predominance of males (generally around 60%), the mean age of the patients in most reports is between 65 and 70 years, which is comparable to the mean age of our population (7, 8).

Obesity is a growing epidemic with its global prevalence doubling over the past 34 years. Based on World Health Organization global estimates, in 2014 >1.9 billion adults were overweight. In Europe and North America, >60% of adults are overweight. A recent meta-analysis estimates a 3.5–5.3% excess risk of AF for every one unit of BMI increase. Our study

shows that overweight and obesity has become a major risk factors for AF. Body mass index (BMI) is the most commonly used parameter to determine categories of ‘overweight’ and ‘obese’. Overweight was detected in 44% of patients [HR 0.847 (CI 0.702–0.990)], and Obesity in 25% [HR 1.314 (CI 1.071–1.561)]. Population studies by Want et al, Frost et al, Tedrow et al, Huxley et al, Karasoy et al, Knuiman et al, Tsang et al and Sandhu et al. shows an association of obesity with mitral fibrillation (9,10).

In our study 59% of patients had dyslipidemia, the majority with high triglycerides and low HDLc [HR 1.082 (CI 0.862 - 1.3049)], which means that dyslipidemia was associated with a higher risk of AF. Alvaro Alonso et al. found in 2 large community-based cohorts, high triglycerides and low HDLc were associated with a higher risk of AF after accounting for relevant clinical risk factors and biomarkers. Results were similar in both MESA and FHS data and robust in several sensitivity analyses. In these 2 community-based cohorts, high-density lipoprotein cholesterol and triglycerides but not low-density lipoprotein cholesterol or total cholesterol were associated with the risk of AF, accounting for other cardio metabolic risk factors. Dyslipidemia is a major contributor to development of atherosclerosis and coronary disease (11,12).

Hypertension has been recognized as the principal and most common risk factor responsible for death and disability of non-communicable diseases worldwide. In our study 1788 (76%) of patients (177 had hypertension [HR 1.352 (CI 1.151–1.553)]). This is in line with the literature which shows prevalence’s ranging from 52 to 90% (13). Hypertension is a main contributor to AF risk and has been identified as such by multiple investigators (15). In the Multi-Ethnic Study of Atherosclerosis, sustained pre-hypertension (SBP 120–129 mmHg) and hypertension (SBP ≥130 mmHg) conferred a 1.8- and 2.6-fold increase in the risk of AF, respectively (14, 15). In our study 47 patients (2%) had obstructive sleep apnea all of them with BMI ≥ 29.4 [HR 1.521 (CI 0.861 – 2.181)]. As published earlier, obstructive sleep apnea is commonly associated with obesity and has a prevalence of 40-50% in the AF population (16).

Pallisgaard JL et al. found in their study that diabetes is an independent risk factor for developing atrial fibrillation/flutter, most pronounced in young diabetes patients (17). In our study the prevalence of diabetic patients was 22%, [HR 1.170 (CI 0.898 – 1.379)]. In the early 1990s, the Framingham study indicated DM to be an independent risk factor for AF with OR of 1.4 for men and 1.6 for women after 38 years follow up. In the analysis of 41436 residents in Japan, the prevalence of DM in AF patients is higher than in controls (20% vs 12%). In conclusion, the association between AF and DM has been proved both in epidemiology and experimental studies (18). Atrial fibrillation is also common in the diabetic population, with AF risk linked to diabetes duration and glycemic control (19, 20).

In our study 46% patients had sedentary life style [HR 1.503 (CI 1.252–1.754)]. The prospective cohort study of Morseth B et al. Conclude that leisure time physical activity was associated with AF in a J-shaped pattern. Moderate physical activity was associated with a reduced risk of AF. Low RHR was a risk factor for AF. The results support the hypothesis that moderate and vigorous physical activity may affect AF

risk via different pathophysiological mechanisms (21, 22).

Heeringa J et al. (23) examined the association between cigarette smoking and risk of atrial fibrillation. The results shows that current and former smoking of cigarettes are associated with increased risk of atrial fibrillation. No differences were found between men and women (22). In our study 57% of patients with AF were past or current smokers, [HR 1.240 (CI 1.188–1.296)], which support the results that smoking was associated with the incidence of AF (23), with more than a two-fold increased risk of AF attributed to current smoking (Chamberlain AM et al. - ARIC) study (24).

In our study 27% patients with AF were acute/chronic alcohol consumers, [HR 1.206 (CI 1.094–1.319)] (25). In a prospective cohort study, they studied the association between self-reported alcohol use and incident atrial fibrillation among 16 415 women and men enrolled in the Copenhagen City Heart Study. The conclusion was that heavy alcohol consumption is associated with a higher risk of atrial fibrillation (24). Kodama S et al. had published the meta-analysis of fourteen eligible studies in order to summarize the estimated risk of atrial fibrillation (AF) related to alcohol consumption. The results of meta-analysis suggest that not consuming alcohol is most favorable in terms of AF risk reduction (25).

In our study, family history of CAD was present in 31% of patients with AF, [HR 1.543 (CI 1.359–1.746)], also CAD was found in 39% of patients [HR 0.916 (CI 0.763–1.069)], which is in consistent with the results of published studies. Violi F et al. searched MEDLINE via PubMed and Cochrane database between 1965 and 2015. The main conclusion was that AF patients had a significant residual risk of MI despite anticoagulant treatment (26).

In our study, family history of atrial fibrillation was noted in 27% of patients had family history of AF, [HR 1.465 (CI 1.287–1.682)]. The Framingham Heart Study has indicated that besides hypertension and diabetes, familial history of AF was also an independent risk factor in an individual. More recently - GWAS meta-analysis for atrial fibrillation has identified six new risk loci. Overall, it is increasingly clear that a genetic predisposition contributes to the risk of developing AF (27-32).

In our study, 26% of patients with AF had COPD, [HR 1.194 (CI 0.586–1.857)]. Chronic obstructive pulmonary disease (COPD) is independently associated with atrial fibrillation (AF). Decreased oxygenation, hypercapnia, pulmonary hypertension, diastolic dysfunction, oxidative stress, inflammation, changes in atrial size by altered respiratory physiology, increased arrhythmogenicity (33, 34). In a large-scale, retrospective, case-control studies, patients with COPD had a 4.41 times higher risk of AF (95% CI 4.00-4.87) and COPD is present in 10-15% of patients with AF (27-29).

In our study, 16% of patients with AF had peripheral arterial disease (PAD), [HR 1.054 (CI 0.792–1.312)]. PAD shares several risk factors with atrial fibrillation (AF), and persons with PAD have an increased risk of stroke (30). Griffin WF et al. examined the relationship between PAD and AF in 5143 participants (85% white, 43% male) in the Cardiovascular Health Study (CHS), a longitudinal, observational study of adults aged 65 years and older and conclude that the presence of PAD should alert practitioners to the increased risk of AF (31).

In our study, 10% of patients with AF had chronic kidney

disease (CKD), [HR 0.4981 (CI 0.917–1.410)]. Chronic kidney disease (CKD) is associated with the risk of multiple life-threatening complications. Also, atrial fibrillation (AF) is common in this group of patients (32). Alonso et al. conclude that in the large population-based study (ARIC), reduced kidney function and presence of albuminuria were strongly associated with the incidence of AF independently of other risk factors (33). Oduyayo A et al. made systematic review and meta-analysis for 104 eligible cohort studies, and the results shows that atrial fibrillation is associated with an increased risk of death and an increased risk of cardiovascular and renal disease (34).

The assessment of cardiac chamber sizes and function, the atrial contribution to left ventricular filling, the pericardium, and valvular function by echocardiography may be helpful in determining the conditions associated with AF, the risk for recurrent AF following cardioversion, and the hemodynamic benefit of maintaining sinus rhythm. Also, identification of patients at increased risk for thromboembolic complications of AF before cardioversion and in patients with chronic AF (35, 36).

In our study, the most prescribed and used drugs for rhythm control were Amiodarone 56%, followed by digitalis 31% and beta-blockers 27%. The same drugs were used in other published studies (37). Lafuente C et al. performed a systematic review to determine the effect of long-term treatment with those drugs on death, embolisms, adverse effects, and atrial fibrillation recurrence. Forty-four trials were included, with a total of 11 322 patients. They conclude that Class IA, IC, and III drugs are effective in maintaining sinus rhythm but increase adverse effects, and class IA drugs may increase mortality (38).

In our study oral anticoagulation drugs (VKAs and NOACs) were prescribed to 44.2% of the patients with AF. Antiplatelet agents were prescribed in 22% of patients. In our study the mean CHA₂DS₂-VASc score was 3.2±1.4 with adjusted stroke rate 2.7% per year, the mean HAS-BLED score was 2.1±1.2. In our population, prescription of anticoagulants was low both in patients without an indication of receiving them for AF (10%) and in higher-risk patients with a CHA₂DS₂-VASc score ≥ 2. In the reviewed literature, the prescription of oral anticoagulation on hospital discharge was also lower in patients with paroxysmal vs. permanent AF (51 vs. 80%, 55 vs. 74%, 78 vs. 91%) (39-42).

Wodchis WP et al. after systematic review and for previously published studies reporting the costs for AF patients, and the study conclude AF-related medical costs are high, reflecting resource-intensive and long-term treatments including anticoagulation treatment. These costs, accompanied with increasing prevalence, justify increased attention to the management of patients with AF (43). In other systematic review by Wolowacz S.E. et al. for the economic burden of AF, hospitalizations consistently represented the major cost driver. In the USA, AF hospitalizations alone cost \$6.65 billion in 2005. Costs and hospitalizations attributable to AF have increased markedly over recent decades and are expected to increase in future due to ageing populations (44,45).

6. CONCLUSION

The incidence of AF has increased progressively in the last decades, relating closely to the aging of the population and increasing prevalence of risk factors such as hypertension, obesity, dyslipidemia, cigarettes smoking, diabetes mellitus, heart disease, chronic obstructive pulmonary disease and sleep apnea. Atrial fibrillation should be considered as a manifestation of hypertensive heart disease. AF is known to have a significant impact on healthcare costs and loss of productivity. Effective treatment of patients with atrial fibrillation includes not only rate control, rhythm control, and prevention of stroke, but also management of cardiovascular risk factors and concomitant diseases. OAC therapy can prevent the majority of ischemic strokes in AF patients and can prolong life. A multidisciplinary AF team approach is highly recommended.

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