



# Patients with atrial fibrillation in Cantonal Hospital Zenica: hypertension as the most common modifiable risk factor

ENES ABDOVIĆ  
SLAVEN ABDOVIĆ  
VELIBOR BLAŽEVIĆ

Cantonal Hospital Zenica,  
Zenica, Bosnia and Herzegovina

**Correspondence:**

Enes Abdović  
Cantonal Hospital Zenica,  
Zenica, Bosnia and Herzegovina  
E-mail: enes.abdovic@telekabel.ba

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## Abstract

**Background:** Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia in developed countries. It is a disease of the elderly and it is common in patients (pts) with structural heart disease. Hypertension, heart failure and valvular heart disease are predisposing factors to AF. **Objectives:** To evaluate predisposing factors for development of AF.

**Methods:** From June 2000 to January 2011, 2965 consecutive pts with AF were studied during echocardiographic check-up in Cantonal Hospital Zenica, Bosnia and Herzegovina. According to the 2-D transthoracic echocardiography, pts were divided into groups based on dominative underlying heart diseases. Electrocardiographically documented AF was subdivided into two groups: transitory and chronic. Binary logistic regression was used to investigate relationship of gender, age, hypertension, diabetes and underlying heart diseases with the type of AF.

**Results:** The median age was 72 years, age range between 16 and 96 years. Chronic AF was observed in 69.9% pts. There were 48.3% of males. Hypertensive heart disease (HHD) was the most common underlying heart disease (38.5%) followed by dilated cardiomyopathy (DCM), 25.3%, coronary artery disease (CAD), 14.7% and valvular heart disease (VHD), 11.2%. Lone AF was diagnosed in only 28 pts, mostly in younger males (median age 49 years, range 29–60, men 71%). Hypertension and diabetes were found in 72.5% and 17.8% pts, respectively, and primary in females.

**Conclusion:** The aim of this paper was to elucidate cardiopulmonary and circulatory comorbidities associated with AF in the largest sample of patients in Central Bosnia. HHD was by far the most prevalent associated medical condition in pts with AF. AF without underlying heart disease was present in only 1%, mostly in younger pts with transitory AF. Chronic AF was predominant in groups with advanced cardiac remodeling such as DCM and VHD, in mostly elderly patients.

## INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia in developed countries with prevalence rate reaching 8–10% in patients aged over 80 years. As a disease of the elderly it is prevalent in patients with circulatory and structural heart diseases that usually develop due to aging. Presence of lone AF, when concomitant cardiopulmonary diseases are absent, is fairly uncommon and found primarily in

younger patients (1-3). Of all comorbidities associated with development of AF, hypertension is reported as the most common (4). It has been documented that aggressive treatment of hypertension may result in clinical improvement of AF (5). Structural heart disease, such as valvular heart disease, is also strongly associated with AF. Regardless of whether it is rheumatic or degenerative in origin, disease of the heart valves has long been recognized as a risk factor for AF (6, 7). Besides, development of AF is considered a marker of disease progression and an indicator for timing of the valve surgery (8). Lastly, AF is frequent among patients with coronary artery disease. Development of AF is rarely a direct correlate of atrium ischemia. In these patients etiology of AF is considered secondary because patients with coronary heart disease often exhibit hypertension and left ventricular dysfunction which lead to atrial abnormalities (9). AF is therefore best considered to be a symptom of a more widespread process that eventually resulted in electrophysiological and structural abnormalities of atrium (10).

The aim of this paper was to elucidate circulatory and cardiac comorbidities in, hitherto, the largest sample of patients with AF in Central Bosnia, as well as in Western Balkan, and to match it up to data in published studies.

## METHODS

### Study population

This study comprised 2965 consecutive patients with AF who were examined during echocardiographic work-up at Cantonal Hospital Zenica, Bosnia and Herzegovina, between June 2000 and January 2011. The diagnosis of AF was made when characteristic irregular fibrillatory waves in the atrium in conjunction with irregular QRS complexes were evident on all 12 leads of the surface electrocardiogram (ECG). Patients with electrocardiographically confirmed presence of atrial flutter, which produces more regular sawtooth-type flutter waves, alone or in combination with atrial fibrillation were excluded. Electrocardiographically documented AF was classified into transitory or chronic based on its persistence and duration. Our classification scheme is based on that of the American College of Cardiology/American Heart Association/European Society of Cardiology (1) with minor modifications required because of the available data at the time of work-up. Transitory AF fulfilled the criteria for paroxysmal or persistent arrhythmia, while chronic AF comprised cases of long-standing persistent or permanent AF.

### Patient groups and comorbidity conditions

ECG was used to detect cardiac conduction diseases such as left bundle branch block. Hypertension was defined as systolic blood pressure above 140 mmHg, and/or diastolic blood pressure above 90 mmHg, or implied receiving blood-pressure-lowering drugs. We defined diabetes as the physician is diagnosis of diabetes, or fasting

blood sugar  $\geq 7$  mmol/L. Thyroid dysfunction was defined as hypothyroidism or hyperthyroidism according to described criteria (11).

According to the 2-D transthoracic echocardiography, patients were divided into groups based on dominant underlying heart disease. Systolic dysfunction was considered when left ventricular ejection fraction (LVEF) was  $< 50\%$ . If left ventricular (LV) diameter at end-systole/height was  $\geq 3.3$  cm/m than left ventricular dilatation was present. Pulsed-wave Doppler at the apical position was used to record mitral inflow between the tips of the mitral leaflets. Peak velocities of early (E) and atrial (A) diastolic filling and deceleration time of the E-wave (DT) were measured and the E/A ratio was calculated. Mild diastolic dysfunction was defined as  $E/A < 1$  and  $DT > 240$  ms. Severe diastolic dysfunction was defined as  $DT < 140$  ms and  $E/A_{<50 \text{ years}} > 2.5$ ,  $E/A_{50-70 \text{ years}} > 2$ , or  $E/A_{>70 \text{ years}} > 1.5$  (12). An abnormal echocardiography examination identified subjects with LV hypertrophy, dilatation, ejection fraction  $< 50\%$ , or mild or severe diastolic dysfunction. Diagnosis of valvular heart diseases (13) or dilated cardiomyopathy (12) was made according to the established guidelines or relevant echocardiographic criteria. Hypertensive heart disease was diagnosed in patients with hypertension and echocardiographic criteria of diastolic dysfunction (12). Patients with hypertension and concomitant coronary artery disease or dilated cardiomyopathy or thyroid dysfunction were classified in appropriate group based on predominant comorbid disease. Coronary artery disease (CAD) was defined in patients with myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, or angina according to described criteria (14). The CAD group excluded patients with echocardiographic signs of dilated cardiomyopathy. Lone AF was defined as AF presenting in individuals younger than 60 years without clinical or echocardiographic evidence of cardiopulmonary disease, including hypertension, or other identifiable cause for the arrhythmia such as hyperthyroidism or alcohol abuse (1).

### Statistical analysis

Normal continuous variables are presented as mean  $\pm$  standard deviations. Categorical variables are presented as number and percentage of total. Mann-Whitney *U* test and Student *t* test were used to compare the means of continuous variables. Differences among groups of continuous variables were determined by analysis of variance. Comparison of percentages was performed with the  $\chi^2$  test. Binary logistic regression was used to investigate relationship between gender, age, hypertension, diabetes and underlying heart diseases with the type of atrial fibrillation. Differences were considered significant at *P* value of  $< .05$ .

## RESULTS

The population reported here included 2965 patients (48.3% male; mean age  $71.0 \pm 10.9$  years). Twenty-eight

patients met criteria for lone AF (22 male; 48±9.4 years), whereas the remainder of patients presented with comorb diseases (Table 1). Four major concomitant diseases (hypertensive heart disease, dilated cardiomyopathy, CAD, valvular heart disease) included almost 90% of investigated sample population. In the remaining sample, excluding patients with lone AF, thyroid dysfunction was prevailing, affecting almost 40%, without significant difference in distribution of hyper- or hypothyroidism. Other rare causes of AF were pulmonary diseases, such as chronic obstructive pulmonary disease, followed by alcohol abuse, and congenital heart diseases, of which atrial septal defect was predominant.

Hypertension was the most prevalent condition, affecting 72.5% of patients. This largest group of patients, that included only cases with hypertension, had frequency of diastolic dysfunction of 70.7%, regardless of the type. Patients with dilated cardiomyopathy had CAD in 29.7% of cases (223 patients). Intraventricular block was dominant cardiac conduction disease with dilated cardiomyopathy, affecting 49.9% (374 patients); almost half of cases presented as left bundle branch block (171 patients, 45.7%). Among patients with valvular heart disease, 87.8% had primary mitral regurgitation and/or mitral stenosis; the remaining patients manifested aortic valve disease with structurally remodeled heart (Table 2).

A significant frequency of transitory AF was observed in younger patients, lone AF (OR=2.28, 95% CI=2.13–8.62) and in patients with hypertension regardless of the pres-

ence of other concomitant heart diseases (OR=1.7, 95% CI=1.36–2.14). Chronic AF was noted in 69.9%. Chronic AF was more usual in older (OR=1.04, 95% CI=1.03–1.05), dilated cardiomyopathy group (OR=2.04, 95% CI=1.31–3.18) and valvular heart disease group (OR=3.23, 95% CI=1.97–5.32). Binary logistic regression of analyzed data is shown in Figure 1.

**DISCUSSION**

To our knowledge, this is the largest observational study reporting cardiopulmonary as well as other comorbidities, including hypertension, associated with AF for the region of Central Bosnia. Reports evaluating such distribution are lacking even for Western Balkan.

In our study hypertension was the most prevalent concomitant disease, affecting more than 70% of patients with AF. Furthermore, 38.5% of our cases fulfilled the criteria for hypertensive heart disease. Prior observational studies found arterial hypertension in 65–70% of AF patients (15-17) but only in 25–50% of the general population (18). The Euro Heart Survey on Atrial Fibrillation, which included 5333 patients from 35 European countries, demonstrated hypertension as the most frequent risk factor (up to 66%) (16). Hypertension was only more common (84%) in ATRIUM registry, which enrolled 3667 patients in Germany (19).

It has been reported that, in the presence of hypertension, the risk of AF increases up to 1.5 fold, making it one

**TABLE 1**

Etiological distribution of patients with atrial fibrillation.

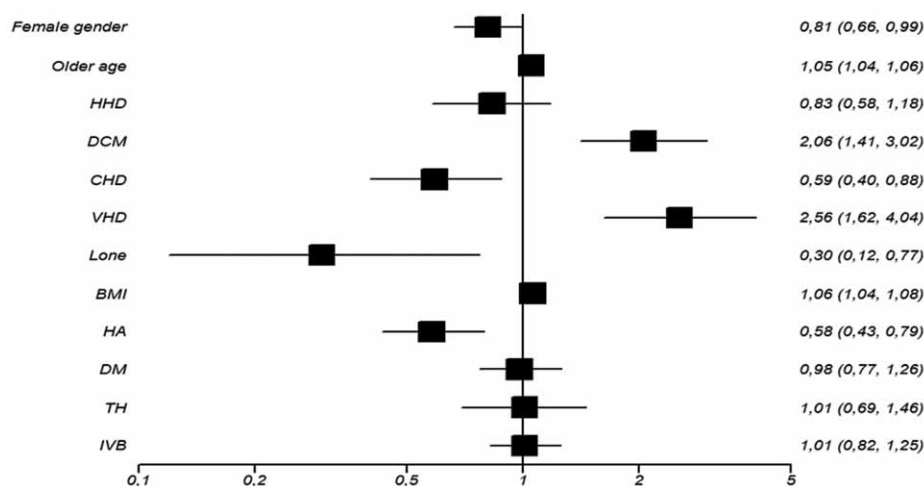
	HHD	DCM	CAD	VHD	Lone AF	Other	Total
No of pts (%)	1141 (38.5)	749 (25.3)	437 (14.7)	333 (11.2)	28 (0.95)	277 (9.3)	2965
Males (%)	494 (41.2)	436 (58.2)	248 (56.8)	135 (40.5)	22 (79.0)	103 (46.8)	1438 (48.3)
Median age (yrs)	71	72	72	68	48	69	72
Age, range (yrs)	24–96	37–95	44–94	33–90	29–59	16–93	16–96
Transitory AF (%)	414 (34.7)	150 (20.0)	179 (40.9)	54 (16.2)	21 (75.0)	74 (33.5)	892 (30.1)
Hypertension (%)	100.0	65.2	60.4	43.8	0	46.9	72.5
Diabetes (%)	18.8	17.8	27.7	6.6	0	11.8	17.8
Thyroid diseases (%)	0	5,1	4.8	3.9	0	39.7	6.1

Abbreviations: pts, patients; AF, atrial fibrillation; HHD, Hypertensive heart disease; DCM, Dilated cardiomyopathy; CAD, Coronary artery disease, VHD, Valvular heart disease; Lone AF, Lone atrial fibrillation.

**TABLE 2**

Concomitant diseases in patients with AF.

Concomitant disease	Frequency (%)	Males (%)	Age means and SD, years (range)
Hypertension	2150 (72.5)	43.9	71 ± 9.3 (24–96)
Coronary artery disease	661 (22.3)	60.2	72 ± 9.0 (37–94)
Diabetes	528 (17.8)	34.6	72 ± 8.3 (19–96)
Left bundle branch block	301 (10.2)	49.2	72 ± 8.9 (40–95)
Thyroid dysfunction	180 (6.1%)	19.4	68 ± 8.5 (38–88)



**Figure 1.** Risk of chronic atrial fibrillation, binary logistic regression model. HHD, hypertensive heart disease; DCM, dilated cardiomyopathy; CHD, coronary artery disease; VHD, valvular heart disease; Lone, lone atrial fibrillation; BMI, body mass index; HA, hypertension; DM, diabetes mellitus; TH, diseases of thyroid gland; IVB, intraventricular block.

of the most frequent supraventricular arrhythmias in these patients (20, 21). Because of its high prevalence in the population, hypertension independently accounts for more AF cases than any other risk factor (22). Furthermore, when left ventricular hypertrophy developed due to arterial hypertension, supraventricular tachycardia was present in 27.3% compared to 12.9% in controls (23). Pathophysiological mechanisms for development and sustainment of AF in hypertension include structural and electrical remodeling induced after distension of left atrium and pulmonary veins due to pressure overload. Moreover, action of renin-angiotensin-aldosterone system generates local atrial inflammation and fibrosis inducing structural atrial changes which are responsible for persistence of arrhythmia (4). To affirm proposed mechanisms, Medi *et al.* reported electrophysiological changes of atria associated with longstanding hypertension in a controlled study on 20 patients with systemic hypertension and with evidence of ventricular hypertrophy (24). Atrial remodeling was characterized by global conduction slowing, regional conduction delay, particularly at the crista terminalis, and increased AF inducibility. Authors concluded that these changes might be in part responsible for the increased propensity to AF associated with systemic arterial hypertension. Hennersdorf *et al.* were first to demonstrate association among the decrease of left ventricular hypertrophy, the reduction of left atrial diameter and the decrease in the prevalence of paroxysmal AF in patients receiving antihypertensive therapy (5).

However, despite its leading importance as a highly prevalent and modifiable risk factor, only some data are available regarding predictors and outcome of AF in large populations of subjects with essential hypertension free of coexisting valvular or coronary heart disease, congestive heart failure, hyperthyroidism, or other predisposing conditions (22). In our study, hypertension, regardless of other comorbidities, was by far the most prevalent associated medical condition (Table 2). CAD was

present in one out of five patients. Every second patient had heart failure, asymptomatic or symptomatic, with diastolic and/or systolic dysfunction. Atrial fibrillation in patients with valvular heart disease presented early in mitral stenosis and/or regurgitation and while affliction of aortic valve was fairly uncommon, fibrillation was more evident in later stages<sup>1</sup>. While 'rheumatic AF' was a frequent finding in the past, nowadays there is a clear shift to non-valvular AF.

In our sample, chronic AF was predominant in mostly elderly groups with advanced cardiac remodeling such as dilative cardiomyopathy and valvular heart disease. Aforementioned Euro Heart Survey and ATRIUM registry had comparable frequency of associated comorbidities, with CAD present in up to 36% and 34%, and heart failure in up to 49% and 43% of cases, respectively. Frequency of valvular heart disease was reported only for Euro Heart Survey and was present in up to 40% of patients. In both studies, permanent AF was associated with more concomitant conditions, especially structural heart diseases (16, 19, 25). Finally, our patients had a high degree of comorbidity and only very few presented with lone AF (0.95%), which was mostly transitory. This finding is comparable with other clinical settings, such as the FALP observational study where only 1.3% (12/903) of patients were classified as lone AF (26).

We report 17.8% cases of diabetes mellitus among our patients with AF; we found these cases mostly in women (64.5%). Similar reports of diabetes have been found in other population-based case-control studies with odds ratio in the range of 1.4 to 1.6 (27-30). The reported risk is higher in long standing treated diabetes and with poor glycemic control (28). These findings suggest that diabetes represents an independent risk factor for AF and it is one of the most concomitant diseases in patients with AF. Diabetes and AF share common antecedents such as hypertension, atherosclerosis and obesity (27, 31). Physiologic changes associated with diabetes include increased

left atrial size and elevated C-reactive protein and both findings are associated with heightened risk of AF (32–34). People with diabetes are at increased risk of CAD and congestive heart disease, which all may contribute to the development of AF. Concordantly, the number of diabetes cases in our study was the highest in patients with concomitant CAD, with the frequency of 27.7%.

### Limitations of the study

This study has several limitations. We identified only AF that came to clinical attention, so some transitory or asymptomatic cases may have been missed. Moreover, outpatient 24-hour ECG recording was not part of the systematical work-up. There was no control sample as well as randomization. At the time of work-up, data on duration and pharmacological treatment of diabetes was not available to us and therefore not included in analysis.

### CONCLUSION

Hypertensive heart disease was by far the most prevalent associated medical condition in our patient sample. Aggressive treatment of hypertension may reduce the risk and postpone the development of AF. Therefore, clinicians should have heightened suspicion for AF in patients with concomitant cardiovascular diseases, especially hypertension.

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