

ATRIAL FIBRILLATION IN YOUNG PATIENTS: ANALYSIS FROM THE JORDAN ATRIAL FIBRILLATION REGISTRY

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Abstract

Introduction: Atrial fibrillation (AF) is the most common sustained arrhythmia with an increasing incidence and prevalence in older age groups compared to younger individuals and the general population. Younger patients with AF often have different clinical characteristics, risk factors, and outcomes. Because AF among the young has not been studied in Middle Eastern populations, we conducted this study to provide valuable insights into the differences in the baseline clinical characteristics and the one-year adverse events between young and older AF patients, and thus contribute to formulate future treatment strategies and improve health outcomes. **Methods:** Consecutive adult patients previously or newly diagnosed with AF in 30 hospitals and out-patient cardiology clinics were enrolled in the Jordan AF study from May 2019 to October 2020. All patients were followed-up for one year. Baseline clinical characteristics and the one-year adverse events were assessed in young (<50 years) and older ([?] 50 years) adult patients with AF. **Results:** Of the 2020 AF patients enrolled in the study, 201 (10%) were young. Young patients were more likely to be men (75.6% vs. 43.8%, $p<0.001$), and had a lower prevalence of hypertension (31.3% vs. 79.3%, $p<0.001$), diabetes mellitus (10.4% vs. 47.2%, $p<0.001$), and previous stroke (9.0% vs. 16.1%, $p=0.027$) compared to older patients. Furthermore, young patients had a lower mean CHA₂DS₂-VASc score (1.1 ± 1.4 vs. 3.9 ± 1.7 , $p<0.001$) and mean HAS-BLED score (0.6 ± 0.7 vs. 1.8 ± 1.1 , $p<0.001$). The use of oral anticoagulant agents was significantly lower in young patients (39.3% vs. 75.0%, $p<0.001$). Young patients also had lower one-year all-cause mortality (1.1% vs. 13.7%, $p=0.001$), cardiovascular mortality (1.1% vs. 7.7%, $p=0.04$) and major bleeding (0% vs. 2.7%, $p=0.021$) compared to older patients. The rate of stroke and systemic embolization was similar in both groups (3.4% vs. 4.4%) **Conclusion:** The findings of the Jordan AF study suggest that young patients (<50 years of age) comprise a small proportion (10%) of the overall AF patient population. They had more favorable baseline clinical characteristics and risk scores compared to older patients. The one-year mortality and major bleeding rates in young patients were also lower than that in older patients.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with significant morbidity and mortality^[1,2]. The prevalence of AF increases with advancing age and is estimated to affect up to 0.5%

of individuals under the age of 45 years [3,4].

Previous studies suggest that paroxysmal AF is the most common type of AF in young adults, accounting for up to half of all AF diagnoses in this population [5,6]. Several predisposing risk factors for AF in young adults have been identified, including hypertension (HTN), diabetes mellitus (DM), obesity, smoking, vigorous or high-intensity exercise, obstructive sleep apnea (OSA), family history of AF, alcohol use, and hyperthyroidism [6-7].

Despite the high prevalence of AF and its resultant significant morbidity and mortality, there is scarcity of studies that investigated AF in Middle Eastern populations [8-12]. Additionally, special populations such as young individuals with AF have not been thoroughly investigated previously, and studies comparing these individuals to their older counterparts are relatively nonexistent. Comprehensive and well-structured studies of AF in Middle Eastern populations are needed due to their distinctive demographics and higher prevalence of certain AF risk factors such as smoking, HTN, DM, and obesity even among younger age groups [13-15]. Such studies can also help developing evidence-based guidelines, optimizing the care and treatment of AF in this population. Additionally, such studies can guide healthcare providers to better diagnostic and therapeutic schemes, improve patient outcomes, and reduce the impact of AF on patients' health and well-being.

Our present analysis pertains to young patients with AF included in the Jordan Atrial Fibrillation (JoFib) registry patients followed up for one year. We aimed to compare their clinical characteristics and one-year outcomes to those of older AF patients.

Methods:

The JoFib registry is a prospective, observational, multicenter registry of consecutive patients aged [?]18 years who were diagnosed to have AF in 30 hospitals and out-patient cardiology clinics in Jordan and one hospital in the Palestinian Territories from May 2019 to October 2020. Baseline data, including demographic and clinical characteristics, were collected using a standardized clinical study form at the time of enrollment. Patients were followed up at 1, 6, and 12 months after enrollment. Baseline data included clinical profiles, cardiovascular risk factors, laboratory data, electrocardiographic (EKG), and echocardiographic features. CHA₂DS₂-VASc and HAS-BLED scores were calculated for each patient. Utilization of pharmacotherapy including oral anticoagulant medications (OAC) was evaluated at the time of enrollment in the study. One-year follow-up data included incidence of stroke and systemic embolism, acute coronary syndrome, major and minor bleeding, and utilization of anticoagulant therapy. The present report compares the clinical characteristics and outcomes of young AF patients (<50 years of age) and older AF patients ([?]50 years of age).

Diagnosis of AF was confirmed by (1) a 12-lead EKG, (2) a rhythm strip lasting >30 seconds, (3) one or more episodes of AF on a Holter monitor, or (4) a diagnosis by a treating cardiologist. AF types, namely the first attack of AF, paroxysmal AF, persistent AF, and permanent AF, were defined according to the American College of Cardiology/American Heart Association/Heart Rhythm Society 2019 update on guidelines for the Treatment of patients with AF⁽¹⁶⁾.

CHA₂DS₂-VASc score, and HAS-BLED score were calculated for each patient according to the 2014 AHA/ACC/HRS Guideline on the management of AF⁽¹⁷⁾.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the Institutional Review Board of each of the participating hospitals. Every patient signed a written informed consent. The study is registered in ClinicalTrials.gov, unique identifier number NCT03917992. The privacy and confidentiality of the patients were maintained throughout the study and patients had the right to withdraw from the study at any time without having to provide an excuse for their decision.

Continuous data were described using mean and standard deviation. Categorical data, such as age group, gender, and other factors were presented as counts and percentages. Chi-square tests were performed to compare percentages between the two age groups. Independent t test was used to compare means between

the two groups. IBM SPSS Statistics for Windows (Version 25.0. Armonk, NY) was used for the analysis. A p-value of $[?]0.05$ was considered statistically significant.

Results:

Of the 2,020 patients included in this registry, 201 (10.0%) were young. The majority of patients were enrolled in the outpatient setting (72.8%). The baseline characteristics for both groups are summarized in Table 1. There was a lower prevalence of HTN, DM, and dyslipidemia in the young group compared to the older patients (31.3% vs. 79.3%, 10.4% vs. 47.2%, and 23.9% vs. 47.3%, respectively, all with a p-value <0.001). Cigarette smoking was significantly more prevalent in the young group compared to the older group (38.3% vs. 11.2%, $P<0.001$). Additionally, heart failure (HF), left ventricular ejection fraction (LVEF) $<40\%$, left ventricular hypertrophy (LVH), pulmonary HTN, OSA, chronic kidney disease (CKD), and co-existing thyroid diseases were all significantly higher in the older group.

Paroxysmal AF was the most common initial presentation in both groups, but it was more common in the young group compared to the older group. Valvular AF (AF in a patient with moderate to severe rheumatic mitral stenosis or prosthetic mitral valve) was uncommon in both groups.

Prior stroke (hemorrhagic, embolic, or thrombotic) was more common in the older group. However, a history of previous systemic embolism was rare in both groups.

Symptoms at presentation varied between the two groups (Table 2). Palpitations were more common as a presenting symptom in the young, while fatigue and dyspnea were more common at presentation in the older group.

The mean CHA₂DS₂VASC score was significantly lower in the younger population, and a higher percentage of patients in the older population had a score of $[?]2$ (Table 2). Women had higher scores in both populations as shown in Figure 1. The mean HAS-BLED score was significantly higher in the older population (1.81 ± 1.1 vs. 0.6 ± 0.7 , $p<0.001$), as shown in Table 3 and Figure 2.

In patients with valvular AF (VAF), OACs were used by most patients in both groups, with vitamin K antagonists (VKAs) being the mainstay of therapy. In patients with non-valvular AF (NVAF), the rate of utilization of OAC therapy varied according to the CHA₂DS₂-VASC risk category and was higher in the older population in all risk categories. Overall, 44.3% of the younger population with NVAF were not taking any anticoagulant therapy compared to 14.9% of the older population.

There were 28 (13.9%) and 1479 (81.3%) young and older patients with a high CHA₂DS₂-VASC score ($[?]3$ in females and $[?]2$ in males), respectively. Of those, 75% of the young and 83.2% of the older group were prescribed OACs ($p<0.001$). DOACs were prescribed more frequently than VKA in the young (53.6% vs. 21.4%) and in the older patients (53.1% vs. 30.1%). OACs which are typically not indicated for patients with low risk CHA₂DS₂-VASC scores, were prescribed in 27.2% of young and in 49% of older patients.

At 1 year from enrollment, 116 patients were lost to follow-up: 14 from the young age group and 102 from the older age group. Follow-up data were available for 1904 patients. All-cause mortality rate was 1.1% of the young group and 13.7% in the older group ($p=0.001$). Cardiovascular death was less frequent in the younger group (1.1% vs 7.7%, $P=0.04$), and so was major bleeding (0% vs 2.7%, $P=0.02$). However, there was no significant difference between the two age groups in the incidence of stroke or systemic embolism (3.4% vs 4.4%) (Figure 3).

Discussion

The major findings of the JoFib study are: (i) One in 10 AF patients was younger than 50 years of age, (ii) Young patients have more favorable baseline clinical profiles and one year outcome compared with older patients. All published clinical evidence clearly confirms major differences in demographics, risk factor prevalence, and outcomes between younger patients with AF and their older counterparts^[3,18]. The definition of young differs between the different studies and ranges from 40-60 years. The age cutoff of 50 years was chosen to ensure a sufficient number of patients in the young group and to exclude the potential confounding

effect of the 50–60 year age group, a population that may exhibit an increased prevalence of risk factors. This information is crucial in understanding the unique characteristics and needs of AF patients in different age groups and populations, which can inform the development of more effective prevention and treatment strategies.

The majority (65.7%) of the young population in this study were males. This is in contrast to the older age group, where females accounted for 56.3% of the whole group. This male preponderance in young patients with AF has also been reported in a study by A. Wutzler et al. on 124 patients with AF and younger than 35, of whom 97.5% were males^[5]. The reasons for the underrepresentation of females in the young AF population are not clear. Possible explanations include the tendency of females to delay reporting symptoms, their complaints not being taken seriously^[21], and a higher prevalence of AF-related risk factors such as smoking in men compared to women^[22].

The higher prevalence of risk factors such as HTN, DM, dyslipidemia, HF, and CKD in the older population suggests that these medical conditions also play a significant role in the development of AF in older individuals. Previous studies have also documented a higher prevalence of DM, HTN and dyslipidemia in Middle Eastern populations compared with populations in the West^[19]. The prevalence of HTN, DM, and dyslipidemia was 17.7%, 1.6%, and 4% respectively in young German patients with AF, compared to a prevalence of 31.3%, 10.4%, and 23.9% in our young cohort^[5]. Moreover, the prevalence of tobacco smoking (38%) was much higher in our young group when compared to the older group (11%) or to young patients with AF reported in studies from the West^[5]. These findings emphasize the importance of early detection and management of risk factors for AF in both young and older populations. Effective strategies to reduce the risk of developing AF, such as maintaining a healthy lifestyle, regular physical activity, and effective management of underlying medical conditions, should be encouraged in both populations.

Palpitations were the most common symptom in young patients with AF and was present in over 65% of such patients. This finding highlights the importance of taking symptoms such as palpitations seriously, especially in young individuals who are otherwise healthy. In addition, paroxysmal AF was the most common type of AF in both the young and old age groups. It is important for healthcare providers to consider the possibility of AF in such patients and to perform appropriate diagnostic tests to confirm or rule out the diagnosis, especially in those with risk factors and an increased CHA₂DS₂-VASc score. An EKG, echocardiogram, extended Holter monitor, or even an implantable loop recorder should be part of the routine workup for such patients since a diagnosis of paroxysmal AF may necessitate the use of oral anticoagulants to prevent thromboembolic complications^[20].

In general, younger patients had lower mean CHA₂DS₂-VASc scores than the older population, as older patients get one or two points for their age, and they tend to aggregate more risk factors. Quite concerning, however, was the fact that younger patients with AF and high CHA₂DS₂-VASc scores were less likely to be on OAC therapy than older patients with the same scores. These findings suggest that younger patients with AF may not be receiving appropriate anticoagulant therapy based on their risk for stroke and other thromboembolic complications. This disparity in treatment between young and older populations with similar CHA₂DS₂-VASc scores is concerning and highlights the need for improved awareness and understanding of the importance of anticoagulant therapy in preventing stroke and other complications in young individuals with AF. On the other hand, when younger populations are eligible to be anti-coagulated, they tend to be on new direct-acting OACs (DOACs), rather than warfarin. The higher use of DOACs in younger populations is in line with recent guidelines, which recommend the use of DOACs as the preferred anticoagulant therapy for AF.

Limitations

Few limitations of the study are worth mentioning. Observational, non-interventional studies have inherently potential bias of residual confounding, incomplete data collection and potentially limited patient's recall of events and complications. Recruiting consecutive patients could have overcome bias in enrollment. Furthermore, the fact that the major cardiovascular events evaluated in this study were hard endpoints, such

as death, stroke, ACS, coronary revascularization, and major bleeding, makes recall issues by patients very unlikely. Generalizability of the results of this to all countries in the region might be limited because our cohort was recruited from tertiary care centers and cardiology clinics in one country. Other limitations are the relatively short follow up period and the arbitrary choice of the cutoff value for age. These values differ between studies which may result in difficulty in comparing results between studies. Larger, multicenter studies involving several countries with larger sample sizes and longer follow-up may provide a more comprehensive understanding of the prevalence, risk factors, and outcomes of AF in the Middle Eastern region. Despite these limitations, this study contributes to the contemporary knowledge concerning young patients with AF who have not been studied previously in the Middle East and provides important insights into the burden of AF in the Middle Eastern region and the need for increased attention and resources towards its prevention, early detection, and management in young individuals.

Conclusion

The findings of the Jordan AF study suggest that young patients (<50 years of age) with AF tend to have better baseline clinical characteristics, lower risk scores, and lower one-year mortality and major bleeding rates compared to older patients. Further studies are needed to confirm these findings and to determine the best management strategies for young AF patients.

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Table 1: Baseline clinical and demographic features in young and older patients with atrial fibrillation

Variable	Age		P-value
	< 50 year N=201 (10.0%)	[?]50 year N=1819 (90.0%)	
Mean age, \pm SD, years	40.6 \pm 7.9	70.9 \pm 9.4	<0.001
Females	34.3%	56.3%	<0.001
Hypertension	31.3%	79.3%	<0.001
Diabetes Mellitus	10.4%	47.2%	<0.001
Dyslipidemia	23.9%	47.3%	<0.001
Current tobacco use	38.3%	11.2%	<0.001
Paroxysmal AF	64.2%	32.8%	<0.001
Valvular AF	15.4%	7.6%	0.001
Pulmonary hypertension	11.4%	26.8%	0.001
Previous stroke	9.0%	16.1%	0.027
LVEF <40%	11.9%	23.7%	<0.001
Left atrial size (cm)	3.4 \pm 1.5	3.7 \pm 1.9	0.028
Left ventricular hypertrophy	13.4%	37.5%	0.001
Previous systemic embolism	0.5%	1.6%	0.427
Obstructive sleep apnea	1%	4.5%	0.019
Respiratory comorbidity	1.0%	4.2%	0.088
Heart failure	10.4%	25.6%	<0.001
Coronary artery disease	7.5%	11.3%	0.107
Chronic kidney disease	1.0%	9.7%	<0.001
Thyroid comorbidity	5%	10.8%	0.01

AF: Atrial Fibrillation; LVEF: Left Ventricular Ejection Fraction

Table 2: Symptoms at presentation for patients with atrial fibrillation according to age

Variable	Age		P-value
	<50 year N=201	[?]50 year N=1819	
Palpitations	65.1 %	41.2 %	<0.001
Fatigue	14.4 %	23.6 %	0.003
Dizziness	10.4 %	12 %	0.52
Syncope	2.5 %	2.1 %	0.75
Chest pain	1.5 %	2.1 %	0.96
Dyspnea	27.9 %	35.2 %	0.04
Asymptomatic	17.4%	30.3%	<0.001

Table 3: CHA₂DS₂-VASc and HAS-BLED scores according to age

Variable	Age		P-value
	<50 year N=201	[?]50 year N=1819	
CHA ₂ DS ₂ -VASc Mean	1.1 ± 1.4	3.9 ± 1.7	<0.001
CHA ₂ DS ₂ -VASc score [?]2	29.4 %	92.5%	<0.001
HAS-BLED score	0.6 ± 0.7	1.81 ± 1.1	<0.001

Figure 1: Gender distribution of CHA₂DS₂VASc score in the young and older AF patients.

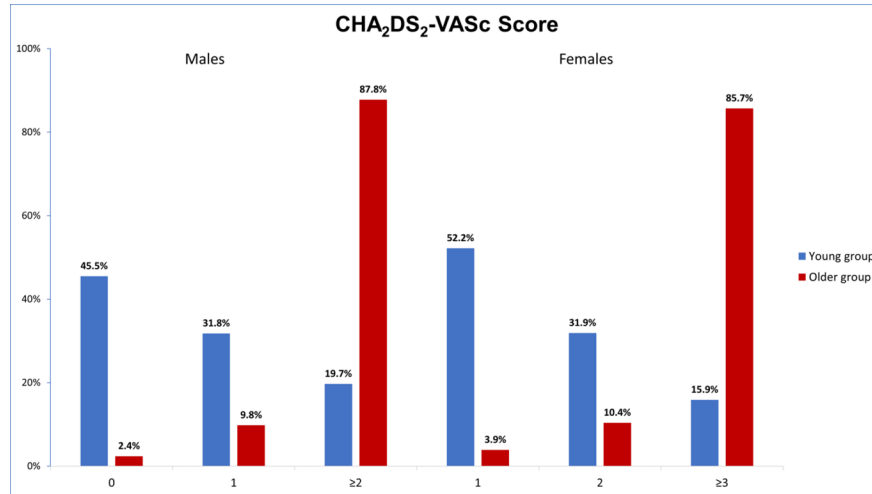


Figure 2: Gender distribution of HAS-BLED score in the young and older AF patients.

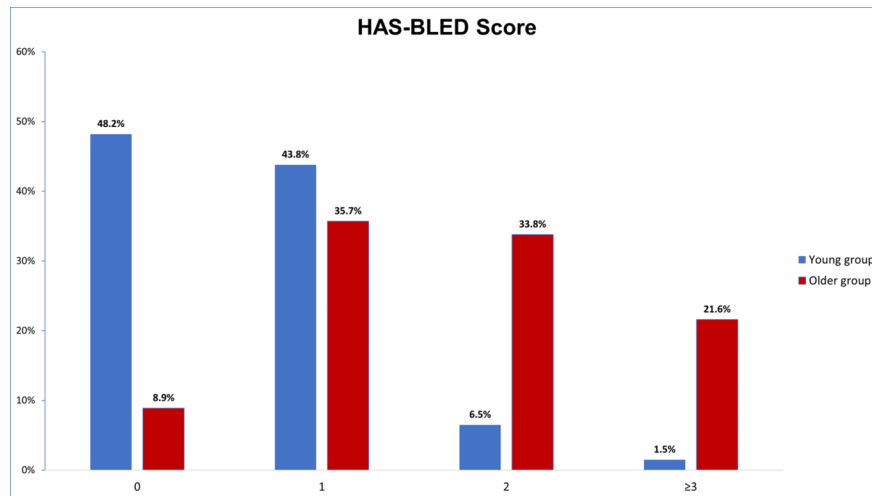


Figure 3: Major cardiovascular events at one year in the young and older patients

