Predictive factors of adverse outcomes of atrial fibrillation in elderly patients: Results of the National Tunisian Registry of Atrial Fibrillation (NATURE-AF)

Les facteurs prédictifs de mauvais pronostic de la fibrillation atriale chez les sujets agés: Résulats du Registre National Tunisien de la Fibrillation Atriale (NATURE-AF)

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Abstract

Introduction: Atrial fibrillation (AF) is the most frequent sustained cardiac arrhythmia. Data related to its clinical characteristics, management, and predictive factors of poor outcomes in elderly in Tunisia remain scarce. We aimed to evaluate the predictive factors of adverse outcomes in the elderly at 12 months follow-up among AF patients in Tunisia including thromboembolic (TE) events, hemorrhagic events, and all-cause death.
Methods: We conducted a national, prospective, and analytic multicentric study based on NATURE-AF with a 12-month follow-up period between March 1, 2017, and May 31, 2017. We evaluated the predictive factors of adverse outcomes of AF in the elderly (≥ 75 years old).
Results: We included 915 patients with AF. We studied the elderly who represented 24% of the population. Females represented 52% of the elderly. Hypertension was present in 57% of the elderly, diabetes mellitus in 22.4%, dyslipidemia in 16%, obesity in 75.8%, chronic kidney disease in 22.8% and smoking in 13.2%. Prior TE accidents and hemorrhagic accidents happened in 12.8% and 3.7% respectively. The mean CHA2DS2-VASc score was 3.92±1.28. Vitamin-K-Antagonist was used in 59.8%. The mean TTR was 47.53±26.78. The rate control strategy was adopted in 68% of patients and beta-blockers were used in 37.9%. Hospitalization during the follow-up for adverse causes occurred in 13.4%. Adverse outcomes occurred in 19.6% including 3.2% TE events, 5% hemorrhagic events, and 11.4% deaths. After multivariate analyses, prior TE accidents (ORa=3.218; p=0.025; 95%CI [1.157-8.946]) and hospitalization during the follow-up (ORa=6.489; p=0.002; 95%CI [2.035-20.697]) were independent prognostic factors associated with adverse outcomes.
Conclusion: Prior TE accidents and hospitalization during the follow-up are predictive factors of adverse outcomes in elderly with AF. Identifying them is crucial to enhancing public health strategies and lowering healthcare costs.

Key words: Atrial fibrillation, Elderly, Comorbidities, Management, Outcome, Tunisia, North Africa

Résumé

Introduction: La fibrillation atriale (FA) est l'arythmie cardiaque soutenue la plus fréquente. Les données relatives à ses caractéristiques cliniques, sa gestion et les facteurs de mauvais pronostic chez les personnes âgées en Tunisie restent limitées. Notre objectif était d'évaluer les facteurs prédictifs de mauvais pronostic de la FA chez les sujets âgés incluant les événements thromboemboliques (TE) et hémorragiques et le décès.
Méthodes: Il s'agissait d'une étude nationale, prospective et analytique multicentrique basée sur NATURE-AF entre le 1er mars 2017 et le 31 mai 2017 avec une période de suivi de 12 mois. Nous avons identifié les facteurs prédictifs de mauvais pronostic de la FA chez les sujets âgés (≥75 ans).
Résultats: Nous avons inclus 915 patients atteints de FA. Les sujets âgés représentaient 24 % de notre population. Les femmes représentaient 52% des sujets âgés. L'HTA était présente chez 57% des sujets âgés, le diabète chez 22.4%, la dyslipidémie chez 16%, l'obésité chez 75.8%, l'insuffisance rénale chronique chez 22.8% et le tabac chez 13.2%. Les antécédents d'accident TE ou hémorragiques étaient notés chez 12.8% et 3.7% respectivement. Le score CHA2DS2-VASc moyen était de 3.92±1.28. Les AVK étaient utilisés chez 59.8%. Le TTR moyen était de 47.53±26.78. Le contrôle de la fréquence était la stratégie rythmique la plus tentée (68%), utilisant principalement des bêtabloquants (37,9%). L'hospitalisation pendant le suivi a été notée chez 13.4%. La mortalité, les complications hémorragiques et les complications TE ont été observées chez respectivement 11,4 %, 5 % et 3,2 %. Les antécédents d'accidents TE (ORa=3,218; p=0,025; 95%CI [1,157-8,946]) et l'hospitalisation pendant le suivi (ORa=6,489; p=0,002; 95%CI [2,035-20,697]) étaient les facteurs prédictifs indépendants de mauvais pronostic chez le sujet âgé.
Conclusion: Les antécédents d'accidents TE et l'hospitalisation pendant le suivi étaient les facteurs prédictifs indépendants de mauvais pronostic chez le sujet âgé. Leur identification est cruciale pour l'amélioration des stratégies de santé publique.

Mots clés: Fibrillation atriale, Sujet âgé, Comorbidités, Prise en charge, Pronostic

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INTRODUCTION

Atrial fibrillation (AF) is recognized as the most frequent common sustained cardiac arrhythmia. Its incidence and prevalence are constantly increasing on a global scale. In 2020, the global prevalence of AF was estimated to be around 50 million (1), reaching 10% in patients over 80 years (2). AF is associated with significant morbidity and mortality, particularly due to the risk of cardioembolic stroke. Indeed, it increases the risk of stroke by five times (3). The importance of AF in elderly patients extends past its epidemiological consequences. It is intimately correlated to high mortality rates (4,5) and a greater burden of comorbidities associated with advanced age such as stroke (6). Awareness of this condition remains limited among the general public, caregivers, and even some healthcare professionals. Exact prognosis data regarding this disease in elderly are scarce in developing nations, including Tunisia. Our study was based on the NATURE-AF (7), a registry designed to obtain real-world information on patients with AF in Tunisia. We aimed to evaluate the predictive factors of adverse outcomes in the elderly at 12 months follow-up among AF patients in Tunisia including thromboembolic (TE) events, hemorrhagic events, and all-cause death.

METHODS

Patients and design

This was a prospective, observational, comparative, and analytic multicentric study with a 1-year follow-up period based on the NATURE-AF. NATURE-AF is a register established to address the demographic and prognostic attributes of AF in Tunisia. The primary objective of this registry was to provide an extensive account of the epidemiological attributes, the quality of patient management, and the outcomes observed during a 12-month follow-up period. The enrollment occurred in 20 governorates, all over Tunisia. Consecutive patients with AF were enrolled between March 1, 2017, and May 31, 2017. The inclusion period was estimated to be up to 3 months. The population comprised in- and outpatients with AF presenting to cardiologists. Patients were enrolled only if they were 20 years and older with at least one episode of AF recorded on a standard 12-lead electrocardiogram or a 24-hour Holter monitor wihin the last year. Patients having AF due to reversible causes (e.g. thyroid disease and pulmonary embolism) including postoperative AF (≤3 months), patients having life expectancy less than 12 months, acute coronary syndrome at the time of enrollment, isolated atrial flutter, mental disorders and ongoing anticoagulation for reasons other than AF were not included. We studied elderly patients defined as patients aged 75 years and older.

Patient's demographic and anthropometric data, cardiovascular risk factors, comorbidities were collected. Initial symptoms such as dyspnea, palpitations, and syncope were noted. We used the EHRA classification as a measure of AF-related symptoms. For every patient, we precised the classification of AF (paroxysmal, persistent, permanent), the type of AF (valvular or non-valvular), the CHA2DS2-VASc and the HAS-BLED scores, the rhythmic strategy, the antiarrhythmic drugs (AADs), the oral anticoagulation (OAC) therapy, and the time in the therapeutic range (TTR) in patients under vitamin K antagonist (VKA).

Outcomes

We aimed to evaluate the predictive factors of adverse outcomes in the elderly at 12 months follow-up among AF patients in Tunisia including TE events, hemorrhagic events, and all-cause death.

Statistics

Data were analyzed using IBM SPSS for Windows (version 25.0, SPSS Inc., Chicago, Illinois).

Quantitative variables were summarized using mean ± standard deviation (SD) for normally distributed variables otherwise median with interquartile range (p25-p75) was used and both were counted with percentages for categorical data. We evaluated the association between the patient's parameters and the adverse outcomes using univariate and multivariate logistic regression analysis. For univariate analysis, we used the Chi-Squared test and Fisher's exact test to compare categorical variables. We used an independent Student T-test to compare two means. We used logistic regression models in multivariate analysis. We sought for interactions between all the included variables. We calculated the adjusted Odds-Ratio (ORa) and its 95% CI. In all statistical tests, the significance level was set at 0.05.

RESULTS

General characteristics

A total of 219 elderly patients were studied. The patient's characteristics are summarized in Table 1. Females represented 52%. Hypertension was present in 57% of elderly, diabetes mellitus in 22.4%, dyslipidemia in 16%, obesity in 75.8%, chronic kidney disease in 22.8% and smoking in 13.2%. Prior TE accidents and hemorrhagic accidents happened in 12.8% and 3.7% respectively. The mean CHA2DS2-VASc score was 3.92±1.28. Vitamin-K-Antagonist was used in 59.8%. The mean TTR was 47.53±26.78. The rate control strategy was adopted in 68% of patients and beta-blockers were used in 37.9%.

Outcomes

During the 12-month follow-up, hospitalization for adverse causes occurred in 13.4% and an episode of acute heart failure in 8.2%. Adverse outcomes occurred in 19.6% including 3.2% TE events, 5% hemorrhagic events, and 11.4% deaths

Table 1. General population characteristics	
Variable	**Elderly patients (n=219)**
Demographic characteristics	
- Mean age (years)	84±8
- Female gender	114 (52%)
Mean BMI value	27.46±5.1
Cardiovascular risk factors	
- HTN	125 (57%)
- Diabetes mellitus	49 (22.4%)
- Dyslipidemia	35 (16%)
- Smoking	29 (13.2%)
- Obesity	166 (75.8%)
Comorbidities	
- CHF	40 (18.3%)
- Ischemic heart disease	30 (13.7%)
- Prior ACS	28 (12.8%)
- Prior TE accident	28 (12.8%)
- Prior CVA	23 (10.5%)
- Prior hemorrhagic accident	8 (3.7%)
- Respiratory disease	20 (9.1%)
- Chronic kidney disease	50 (22.8%)
Symptoms	
- Palpitation	91 (41.6%)
- Dyspnea	102 (46.6%)
- Syncope	8 (3.7%)
EHRA classification	
- Class I	54 (51.4%)
- Class II	41 (39%)
- Class III	9 (8.6%)
- Class IV	1 (1%)
Classification of AF	
- Paroxysmal	50 (27%)
- Persistent	68 (36.8%)
- Permanent	67 (36.2%)
Etiology of AF	
- Valvular	54 (24.7%)
- Non-valvular	165 (75.3%)
Antithrombotic strategy	
- VKA	131 (59.8%)
- Platelet antiaggregant	23 (10.5%)
- VKA + Platelet antiaggregants	16 (7.3%)
- No antithrombotics	49 (22.4%)
Mean CHA2DS2-VASc score	3.92±1.28
Mean HAS-BLED score	2±1
Mean INR level	5.56±4.8
Mean TTR (%)	47.53±26.78
Rhythmic strategy	
- Rate control	121 (68%)
- Rhythm control	57 (32%)
Rate control drugs	
- Beta-blockers	83 (37.9%)
- Digoxin	43 (19.6%)
- Calcium blockers'	50 (22.8%)
Rhythm control drugs	
- Amiodarone	150 (68.5%)
- Flecainide	3 (1.4%)
- Sotalol	3 (1.4%)
Mean LVEF %	56±13
eGFR (ml/min)	61±24

BMI= Body Mass Index; HTN= Hypertension; CHF = Chronic Heart Failure; ; ACS = acute coronary syndrome; TE = thromboembolic; CVA = cerebrovascular accident; EHRA= European Heart Rhythm; AF= Atrial Fibrillation; VKA= Vitamin K antagonist; INR= international normalized ratio; TTR= Time in therapeutic range; LVEF= left ventricular ejection fraction; eGFR= estimated glomerular filtration rate

Predictive factors of adverse outcomes

In univariate analysis, CHF (p=0.048), prior TE accidents (p=0.03), and prior CVA (p=0.033), all-causes AHF (<0.001), and all-cause hospitalization during the follow-up (p<0.001) were identified as significant prognostic factors of adverse outcomes. Table 2 sums up the univariate analysis.

Table 2. Predictive factors of adverse outcomes in univariate analysis				
Variable	**Elderly (n=219)**	**Adverse outcomes - (n=176)**	**Adverse outcomes + (n=43)**	**P-value**
Demographic characteristics				
- Female gender	114	95(54%)	19(44%)	0.925
Cardiovascular risk factors				
- Hypertension	125	104(59%)	21(48.8%)	0.965
- Diabetes mellitus	49	41(23.3%)	8(18.6%)	0.904
- Dyslipidemia	35	28(15.9%)	7(16.3%)	0.593
- Smoking	29	24(13.6%)	5(11.6%)	0.957
- Obesity	166	139(79%)	27(63%)	0.66
Comorbidities				
- CHF	40	29(16.5%)	11(25.6%)	**0.048**
- Ischemic heart disease	30	23(13%)	7(16.3%)	0.288
- Prior ACS	28	22(12.5%)	6(14%)	0.588
- Prior TE accident	28	19(10.8%)	9(20.9%)	**0.03**
- Prior CVA	23	15(8.5%)	8(18.6%)	**0.033**
- Prior hemorrhagic accident	8	6(3.4%)	2(4.7%)	0.621
- Respiratory disease	20	18(10.2%)	2(4.6%)	0.539
- CKD	50	41(23.3%)	9(20.9%)	0.812
Classification of AF				
- Paroxysmal	50	43(24.4%)	7(16.3%)	0.563
- Persistent	68	54(30.7%)	14(32.6%)	0.578
- Permanent	67	57(32.4%)	10(23.2%)	0.588
Etiology of AF (Valvular)	54	43(24.4%)	11(25.6%)	0.432
Antithrombotic strategy				
- VKA	131	112(63.6%)	19(44%)	0.21
- Platelet antiaggregant	23	19(10.8%)	4(9.3%)	0.531
- VKA + Platelet antiaggregants	16	12(6.8%)	4(9.3%)	0.321
- No antithrombotics	49	39(22.2%)	10(23.3%)	0.821
Rhythmic strategy				
- Rhythm control	57	48(27.27%)	9(20.9%)	0.901
- Rate control	121	101(57.4%)	20(46.5%)	0.901
The use of beta-blockers	83	67(38%)	16(37%)	0.462
Mean CHA2DS2-VASc score	3.92±1.28	3.8±1.2	4.2±1.4	0.129
Mean HAS-BLED score	2±1	1.97±0.9	2.16±1	0.249
Mean TTR (%)	48±27	46±26	52±30	0.614
Mean LVEF (%)	56±13	56±13	56±13	0.773
Hospitalization	29	12(6.8%)	17(39.5%)	**<0.001**
All-causes AHF	18	9(5.1%)	9(20.9%)	**<0.001**

ACS = acute coronary syndrome; AF = atrial fibrillation; AHF = acute heart failure; CHF = chronic heart failure; CKD = chronic kidney disease; CVA = cerebrovascular accident; INR = international normalized ratio; LVEF = left ventricular ejection fraction; TE = thromboembolic; TIA = transient ischemic attack; TTR = time in therapeutic range; VKA = Vitamin K antagonist

In multivariate analysis, prior TE accidents (ORa=3.218; p=0.025; 95%CI [1.157-8.946]) and hospitalization during the follow-up (ORa=6.489; p=0.002; 95%CI [2.035-20.697]) were independent prognostic factors associated

with adverse outcomes. Table 3 sums up the multivariate analysis.

Table 3. Predictive factors of adverse outcomes in multivariate analysis

Variable	ORa	95% CI	P-value
Prior TE accident	3.218	1.157 − 8.946	**0.025**
Hospitalization	6.489	2.035 − 20.697	**0.002**

CI= Confidence Interval; ORa= Adjusted Ods Ratio; TE= thromboembolic

DISCUSSION

This study demonstrates that prior TE accidents and hospitalization during the follow-up were independent prognostic factors associated with adverse outcomes including TE accidents, hemorrhagic events and death in elderly patients with AF after 12 months follow-up.

It was well established that hospitalization for cardiovascular causes including AHF, turned out to be predictive of mortality which is the main component of adverse outcomes in our study. Tsuda et al confirmed, that hospitalizations are known to correlate with an increased incidence of adverse outcomes in the elderly population with AF related to the prevalence of complex clinical issues like polypharmacy, frailty, and multimorbidity (8). Oba et al and Marijon et al also found that AHF was strongly related to higher mortality in the elderly with AF (9,10).

It has been a long time since the American College of Cardiology, the American Heart Association, and the European Society of Cardiology guidelines (1,11,12) had included prior TE events in the CHA2DS2-VASc and HASBLED scores to predict either TE or bleeding events occurrence (13) that are themselves associated with higher overall mortality.

Few surveys have studied the predictive factors of the composite of poor outcomes in the AF elderly. ANAFIE was among the few registries that identified the independent risk factors of mortality in these patients. Female sex, obesity, persistent and permanent AF, severe liver function disorder, HF, myocardial infarction, active cancer, dementia, dyslipidemia, CKD, CVA, history of TE events, digestive disease, and polypharmacy were factors associated with higher mortality (14). Our study met these results at some point, sharing the prior TE events as an independent risk factor of either mortality or adverse outcomes underlining the importance of this variable's prognosis value.

It is important to specify the predictive factors of adverse outcomes to formulate effective management plans for AF in the elderly. While few surveys persisted in identifying them, our registry concluded that prior TE accidents and hospitalization during the follow-up were independent prognostic factors of adverse outcomes.

Our analysis of the NATURE-AF registry provides insights into the AF patient profile in Tunisia. It underscores the escalating public health challenge posed by AF and offers a more detailed understanding of predictors of poor outcomes in the elderly. Our study emphasizes the importance of leveraging local data from registries like NATURE-AF to inform and adapt AF management strategies that are specifically suited to the Tunisian context.

Limitations

Our study population was relatively small compared to many large-scale studies found in the literature. It had a relatively low number of adverse outcome events (related to the short follow-up and the small sample size). A longer observation period and a larger study population could change the prognostic significance of certain parameters. We arbitrarily selected an age ≥75 years to identify our "elderly" group. We cannot exclude that our results could have differed if we had chosen a more advanced age for stratification purposes. Our study was held before the generalization of the use of the NOACs in Tunisia. This could interfere with our results regarding the outcomes of AF. An update of the NATURE-AF is nowadays necessary.

CONCLUSION

It is important to specify the predictive factors of adverse outcomes to formulate effective management plans for AF in the elderly. While few surveys persisted in identifying them, our registry concluded that prior TE accidents and hospitalization during the follow-up were independent prognostic factors of adverse outcomes including TE events, hemorrhagic events, and death in the elderly.

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