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ORIGINAL RESEARCH

The Atrial FibriLlatiOn Registry (FLOW-AF): Patient Characteristics, Treatment Patterns, and Outcomes in Egypt

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ABSTRACT

Introduction: Real-world data on atrial fibrillation (AF) in the Middle East and North Africa (MENA) region, including Egypt, are sparse. The aim of the FLOW-AF registry was to evaluate the characteristics, treatment patterns, and clinical and economic outcomes of newly diagnosed non-valvular atrial fibrillation (NVAF) patients within the MENA region, including Egypt.

Methods: This multicenter, prospective, observational registry enrolled newly diagnosed patients with NVAF from January 2020 to December 2022 at eight private-sector healthcare centers in Egypt. Data were collected at enrollment (baseline), and then at 6-month and 12-month follow-up. Baseline data included demographics, AF characteristics, medical history, and antithrombotic treatment patterns. Follow-up data included clinical events, healthcare resource utilization, and related costs.

Results: A total of 723 patients were enrolled. Overall, 51.87% were females, and the mean age was 61.9 years. All patients attended the private health sector. The mean (standard

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deviation) CHA_2DS_2-VASc and HAS-BLED risk scores were 2.37 (1.55) and 1.46 (1.18), respectively. Non-vitamin K antagonist oral anticoagulants (62.52%), vitamin K antagonists (22.28%), and antiplatelet therapy (9.85%) were among the prescribed treatments. Rates of transient ischemic attack and all-cause mortality were 2.64% and 0.83%, respectively; all other outcomes (stroke, bleeding, myocardial infarction, systemic embolism) occurred at a rate of ≤ 0.41%. Antithrombotic medications were the major contributors to per-patient total yearly cost (USD 381.2).

Conclusions: The FLOW-AF study showed that patients with NVAF in Egypt are younger and exhibit lower mean baseline CHA_2DS_2-VASc and HAS-BLED scores compared to Western and other Eastern regions. Additional research, including a broader study population with a longer follow-up, is essential to comprehensively assess the characteristics and outcomes of the NVAF population in Egypt.

Keywords: Atrial fibrillation; Clinical outcomes; Egypt; Healthcare resource utilization; Oral anticoagulants

Key Summary Points

Data on non-valvular atrial fibrillation (NVAF) are sparse in Egypt.
This study evaluated the characteristics, treatment patterns, and clinical and economic outcomes of newly diagnosed patients with NVAF in Egypt.
Patients with NVAF in Egypt were found to be younger and exhibit lower mean baseline CHA_2DS_2-VASc and HAS-BLED scores compared to patients in the Western and other Eastern regions.
Studies of longer follow-up and broader population can improve the knowledge of the characteristics and outcomes of patients with NVAF in Egypt.

INTRODUCTION

Atrial fibrillation (AF), the most encountered type of irregular heart rhythm [1, 2], occurs due to abnormal electrical activity within the atria of the heart, resulting in both dyssynchronous atrial contraction and irregularity of ventricular excitation [3]. It is primarily characterized as a tachyarrhythmia with the heart rate being above normal [1]. Non-valvular atrial fibrillation (NVAF) refers to AF occurring in the absence of mitral stenosis and valvular prostheses. Permanent NVAF, a subtype, is defined as AF lasting for more than 1 year that cannot be terminated or recurs after termination, requiring management strategies focused on rate control and stroke prevention [4].

The global prevalence of NVAF has increased markedly, along with the simultaneous decline in the prevalence of rheumatic heart disease [5]. It accounts for 95% of all AF cases [6]. However, valvular AF is more common in Egypt, with rheumatic valvular heart disease being established as a significant underlying cause for the onset of AF [7].

According to the Global Burden of Disease project, the global prevalence of AF has increased substantially from 46.3 million people in 2016 to 59.70 million in 2019 [7, 8]. AF has become a global healthcare problem as its prevalence is expected to rise in the next 30–50 years [9]. In Middle Eastern counties, a high prevalence of AF, ranging between 475 and 550 cases per 100,000 inhabitants) was recorded in 2010. However, few epidemiological studies and clinical trials about AF have been conducted in the Middle East and North Africa (MENA) region [10].

Egypt is known to exhibit a high prevalence of cardiovascular diseases (CVD), which has been a leading cause of premature death. AF ranks as the second most common risk factor contributing to heart failure (HF) decompensation in Egypt [11]. Yet, real-world studies on NVAF in Egypt are sparse, yielding gaps in the understanding of AF/NVAF, and in turn hampering optimal management of patients [10].

AF is associated with an increased risk of cardiovascular and cerebrovascular morbidity,

including stroke, transient ischemic attack (TIA), HF, and myocardial infarction (MI) [12]. In addition, several studies have shown that it is a leading cause of mortality among patients [13, 14]. In line with the global trend, Egypt is experiencing an escalating trend in cardiovascular-related healthcare expenditure. This is partly associated with the increasing prevalence of AF and its complications, resulting in higher medical costs, and exerting a significant public health and economic burden [12].

Given that AF is a major risk factor for ischemic stroke and its therapeutic treatment may subject the patient to the risk of bleeding, the international guidelines primarily recommend the assessment of an individual's stroke and bleeding risk to ensure optimal patient care [15–18].

Egypt is a low- to middle-income country with significantly elevated prevalence of risk factors for NVAF [19]. It ranks 18th in terms of the prevalence of obesity and 9th in the prevalence of diabetes mellitus worldwide [20, 21]. In addition, hypertension is highly prevalent and is estimated to affect about 26.3% of the Egyptian population [22]. Between 2005 and 2015, Egypt recorded an increase of 11.4% in smoking-attributable mortality rate [23]. Despite the evolving need, studies assessing the clinical characteristics, treatment patterns, and the clinical and economic burden of NVAF are scarce in Egypt [19].

To our knowledge, the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) is the only currently existing AF registry that included patients from Egypt. However, Egypt-specific results were not derived [24]. To address this gap, the (atrial FibriLlatiOn real World management registry in the Middle East and Africa (FLOW-AF) collected data on demographic and clinical characteristics, treatment patterns, clinical outcomes, and healthcare resource utilization (HCRU) of newly diagnosed patients with NVAF in the MENA region, including Egypt. This manuscript presents the findings from the Egypt cohort, aiming to enhance understanding of NVAF, particularly permanent NVAF, in the Egyptian population.

METHODS

Patient Population and Study Design

The FLOW-AF registry was a multicenter, prospective, observational study that enrolled participants across Egypt, Lebanon, the Kingdom of Saudi Arabia (KSA), and the United Arab Emirates (UAE). The detailed methodology of the FLOW-AF registry has been extensively outlined in a prior publication [25].

This manuscript focuses on the Egypt cohort. Seven sites participated in Egypt. Originally intended to span 12 months, the recruitment period was extended to about 30 months (January 2019 to June 2021) due to the impact of the coronavirus disease 2019 (COVID-19) pandemic. Patient information was prospectively collected for a 12-month duration from the baseline date. The study observation period spanned between January 2019 and July 2022. A geographically representative sample of sites routinely involved in managing patients with NVAF were selected. Patients eligible for inclusion in the study had to meet the following criteria: male or female, at least 18 years old, and newly diagnosed with NVAF either within the enrollment period or up to 90 days before the baseline visit. Additionally, their treating physician must have initiated care for the prevention of stroke/SE. Exclusion criteria included improbable follow-up (e.g., due to invalid residency permits or plans to leave the country), enrollment in an interventional clinical trial, prescription of a VKA or non-VKA OAC for a condition other than AF, diagnosis of a severe psychiatric illness, AF due to a reversible cause (such as non-cardiac surgery, postcardiac surgery within 3 months after surgery, hyperthyroidism, pulmonary embolism, pneumonia, or acute MI), presence of mechanical heart valves, or valve disease. Pregnant or breastfeeding women were also excluded.

Data Collection

Electronic case report forms (eCRFs) were used to collect patient-level data from medical records through a secure online system.

Structured questionnaires were used to collect healthcare resource costs at the hospital level, detailing expenses by unit (e.g., per laboratory test, image, or operation). Data were collected at enrollment (baseline), 6-month (± 2 months), and 12-month (± 2 months) follow-up. Data collected at baseline included demographics (age, sex, body mass index [BMI], ethnicity, blood pressure, heart rate, hospital type, AF characteristics (time [days] since NVAF diagnosis, method of NVAF diagnosis, family history of NVAF, stroke, venous thromboembolism), medical history (including comorbidities, CHA_2DS_2-VASc stroke, HAS-BLED risk score, smoking habits, alcohol consumption), antithrombotic treatment (ATT) patterns, HCRU, and associated direct costs. Follow-up data included clinical outcomes (stroke, TIA, SE, bleeding events, MI, all-cause mortality), HCRU, and direct costs. Rigorous processes and procedures were consistently implemented throughout data collection to ensure the data were clean and accurate for subsequent analysis.

ATT line was determined based on the date of initiating treatment; "first line" referred to the initial ATT prescribed to newly diagnosed patients with NVAF at baseline, i.e., the primary regimen initiated. “Second line” was defined as any treatment change (a switch or addition of therapy) after first line, “third line” as any treatment change following second line, and so on.

Cost data were collected directly from participating hospitals through questionnaires developed by the Health Economics and Outcomes Research (HEOR) team at IQVIA and approved by Pfizer. During the data review, missing information was identified and resolved by following up with the participating hospitals to gather the necessary details. To ensure accuracy, drug names and costs were validated against the official Egyptian Drug Authority (EDA) database (http://eservices.edaegypt.gov.eg/EDASearch/SearchRegDrugs.aspx), which serves as the standard reference for drug prices in Egypt. Costs were collected in Egyptian pounds and after validation, they were converted to USD using the currency exchange rate at that time, to standardize the data across countries included in the broader study.

Data Analysis

The sample-size estimation was based on a presumed 50% outcome frequency, the estimated population size of atrial fibrillation patients in Egypt, a 4% margin of error, and an anticipated 10% attrition rate. Using a 95% confidence level, the minimum required sample size was calculated to be 696 patients. Descriptive statistics were used to summarize baseline demographics, clinical characteristics, medical history, treatment patterns, HCRU, and related costs. Time-to-event analyses for clinical outcomes were conducted using the Kaplan–Meier method, an approach widely adopted for survival and event-time data in observational studies.

The economic burden of NVAF management was calculated by multiplying the unit costs of healthcare resources by their observed utilization rates. Only patients with complete cost data for a given HCRU estimate contributed to the cost analysis. The number of dispensed packages of antithrombotic medications was derived from recorded package sizes, drug strengths, total daily doses, and treatment durations. Missing values for drug strengths and package sizes were imputed using the mean of observed non-missing values for each specific medication. Other data were analyzed as recorded in the electronic case report forms (eCRFs), without additional imputation for missing values. Antithrombotic therapy (ATT) data were stratified according to CHA_2DS_2-VASc and HAS-BLED scores at baseline. All statistical analyses were conducted using R version 4.1.1, a widely utilized software for data analytics [26].

Compliance with Ethical Guidelines

The study protocol (available upon request) was submitted and approved by the Alexandria University Hospital (MOH) Ethics Committee and the Institutional Review Board of each participating hospital (Table S4, Supplementary Material).

The registry was conducted in accordance with the principles of the Declaration of Helsinki, local regulatory requirements, and the

International Conference on Harmonisation-Good Pharmacoepidemiological and Clinical Practice guidelines [27]. All study participants provided written informed consent, and the confidentiality and anonymity of all enrolled patients were maintained.

RESULTS

Study Population

A total of 754 patients were screened in seven sites across Egypt. A total of 723 (95.88%) patients met the eligibility criteria and were enrolled in the study, and 31 (4.11%) patients were excluded. The mean standard deviation (SD) follow-up of patients over the course of the study was 358.9 (44.5) days. Out of the total 723 patients enrolled in the study, 690 (95.4%) successfully completed the follow-up.

Baseline Demographic Characteristics and Vital Signs

The mean (SD) age was 61.91 (13.53) years, with a slightly higher proportion of females ($n=375$, 51.87%) compared to males ($n=348$, 48.13%). The majority of patients were White ($n=720$, 99.59%). Almost half of the patients were obese ($n=350$, 48.54%) and 44.80% were overweight ($n=323$); mean (SD) BMI was 30.15 (4.37) kg/m^2. The mean (SD) systolic and diastolic blood pressure and heart rate were 132.74 (21.11) mmHg, 82.20 (12.01) mmHg, and 102.00 (27.52) beats/min, respectively. All enrolled patients attended private hospitals (Table 1).

The overall mean (SD) time since NVAF diagnosis was 15.89 (23.44) days. Electrocardiogram (ECG) was the most common method used for NVAF diagnosis ($n=602$, 83.50%), followed by the Holter monitor ($n=116$, 16.09%). None of the patients had a family history of venous thromboembolism. Only three (0.41%) and two (0.28%) patients had a first-degree family history of stroke and NVAF, respectively (Table 2).

Medical History and Risk Factors of Patients at Baseline

The most common comorbidities were hypertension ($n=422$, 58.37%), followed by hypercholesterolemia ($n=210$, 31.12%), diabetes mellitus ($n=216$, 29.88%), coronary artery disease ($n=127$, 17.57%), and congestive HF/left ventricular dysfunction ($n=102$, 14.11%). Thirty-seven (4.70%) patients had a history of stroke/TIA at baseline (Table 3).

The majority of patients had a high CHA_2DS_2-VASc stroke risk score ≥ 2 ($n=488$, 67.59%), with an overall mean (SD) score of 2.37 (1.55) at baseline. In contrast, the majority of patients ($n=576$, 79.78%) fell within the low HAS-BLED risk score category of <3, with an overall mean (SD) score of 1.46 (1.18) at baseline (Table 4).

At baseline, most of the patients ($n=526$, 72.85%) were non-smokers, and 80 (11.08%) were current smokers. Almost all patients were non-alcohol consumers ($n=717$, 99.31%) (Table 4).

Patterns of Care of Newly Diagnosed Patients with NVAF

All patients received ATT for stroke prevention at baseline. A total of 763 treatments were prescribed, NOAC being the major therapy received ($n=477$, 62.52%), of which rivaroxaban ($n=295$, 61.84%) and apixaban ($n=177$, 37.11%) were most common. Rivaroxaban was used once daily in most patients ($n=280$, 94.92%), with a mean (SD) daily dose of 18.97 (2.80) mg, median dose of 20 mg, and mean (SD) treatment duration of 145.85 (80.53) days. Apixaban was used twice daily in almost all patients ($n=169$, 95.48%), with mean (SD) dose of 8.67 (2.40) mg, median dose of 10 mg and mean (SD) treatment duration of 137.74 (81.76) days. The second most common therapy was VKA OAC ($n=170$, 22.28%), followed by antiplatelet therapy ($n=75$, 9.83%), and other antithrombotic therapies ($n=39$, 5.11%). Warfarin was the commonly used VKA OAC ($n=162$, 95.29%). Warfarin was used once daily in almost all patients ($n=161$, 99.38%),

Table 1 Demographic characteristics and vital signs of patients at baseline

Number of patients enrolled	*N*	723
Sex	*N*	723
	Male	348 (48.13%)
	Female	375 (51.87%)
	Missing	0 (0.00%)
Race	*N*	723
	White (including Arab)	720 (99.59%)
	Other White (non-Arab)	1 (0.14%)
	Asian	1 (0.14%)
	African (Black African)	1 (0.14%)
	Hispanic/Latino	0 (0.00%)
	Unknown	0 (0.00%)
	Other, specify	0 (0.00%)
	Missing	0 (0.00%)
Type of hospital	*N*	723
	Private	723 (100.00%)
	Public	0 (0.00%)
	Semi-governmental	0 (0.00%)
	Missing	0 (0.00%)
Age at baseline (years)	*N*	723
	Mean (SD)	61.91 (13.53)
	Median [Q1–Q3]	64.00 [54.00,71.00]
	Min–max	18.00–95.00
	Missing	0 (0.00%)
BMI (kg/m^2)	*N*	721
	Mean (SD)	30.15 (4.37)
	Median [Q1–Q3]	29.75 [27.34,32.44]
	Min–max	14.19–70.00
	Missing	2 (0.28%)

Table 1 continued

BMI (categorical)	*N*	721
	Underweight (BMI < 18.5)	1 (0.14%)
	Normal weight (18.5 ≤ BMI < 25.0)	47 (6.52%)
	Overweight (25.0 ≤ BMI < 30.0)	323 (44.80%)
	Obese (BMI ≥ 30.0)	350 (48.54%)
	Missing	2 (0.28%)
Systolic blood pressure (mmHg)	*N*	723
	Mean (SD)	132.74 (21.11)
	Median [Q1–Q3]	130.00 [120.00,147.50]
	Min–max	80.00–200.00
	Missing	0 (0.00%)
Diastolic blood pressure (mmHg)	*N*	723
	Mean (SD)	82.20 (12.01)
	Median [Q1–Q3]	80.00 [70.00,90.00]
	Min–max	60.00–120.00
	Missing	0 (0.00%)
Heart rate (beats/min)	*N*	723
	Mean (SD)	102.00 (27.52)
	Median [Q1–Q3]	100.00 [80.00, 120.00]
	Min–max	40.00–200.00
	Missing	0 (0.00%)

BMI body mass index, *SD* standard deviation, *Q1* first quartile, *Q3* third quartile

with mean (SD) dose of 3.52 (1.87) mg, median dose of 3 mg, and for a mean (SD) duration of 225.30 (119.32) days. Among antiplatelet therapies, aspirin was the most frequently used ($n=49$, 65.33%). Aspirin was used once daily in most patients ($n=46$, 97.87%), with a mean (SD) dose of 87.87 (15.01) mg, median dose of 81 mg, and for a mean (SD) duration of 138.14 (109.14) days (Table S1, Supplementary Material).

Across all CHA_2DS_2-VASc stroke risk categories and HAS-BLED score groups, NOAC was the most commonly prescribed medication. Among the 488 patients with CHA_2DS_2-VASc score ≥ 2, 521 ATTs were prescribed, of which 312 (59.88%) were NOAC and 128 (24.57%) were VKA OAC. Similarly, among the 146 patients with high HAS-BLED risk score (≥ 3), 166 ATTs were prescribed, of which 81 (48.80%) were NOAC and 34 (20.48%) were VKA OAC. Regarding the antiplatelet therapy, it was the second most used ATT in patients with HAS-BLED risk score ≥ 3 ($n=37$, 22.29%) (Figs. 1, 2).

A total of 37 (4.97%) patients received second-line ATT, and none received third-line ATT. NOAC was the most common first line ($n=477$, 62.52%) and second line ($n=26$, 70.27%) ATT.

Table 2 Atrial fibrillation characteristics at baseline

Number of patients enrolled	*N*	723
Time (days) since NVAF diagnosis	*N*	723
	Mean (SD)	15.89 (23.44)
	Median [Q1–Q3]	3.00 [1.00, 24.00]
	Min–max	1.00–90.00
	Missing	0 (0.00%)
Method of NVAF diagnosis	*N*	721
	Electrocardiogram	602 (83.50%)
	Implantable devices	3 (0.42%)
	Holter monitor	116 (16.09%)
	Online/smart applications	0 (0.00%)
	Other	0 (0.00%)
Family history of related diseases among first-degree relatives		
NVAF	*N*	723
	No	721 (99.72%)
	Yes	2 (0.28%)
	Missing	0 (0.00%)
Stroke	N	723
	No	720 (99.59%)
	Yes	3 (0.41%)
	Missing	0 (0.00%)
Venous thromboembolism	N	723
	No	723 (100.00%)
	Yes	0 (0.00%)
	Missing	0 (0.00%)

Some patients have several methods for NVAF diagnosis

NVAF non-valvular atrial fibrillation, *SD* standard deviation, *Q1* first quartile, *Q3* third quartile

Rivaroxaban was the most common NOAC used in both first-line ($n=295$, 61.84%) and second-line ($n=14$, 53.85%) treatment.

VKA was the second most commonly used first-line treatment ($n=170$, 22.28%), and only represented 2.7% ($n=1$) in the second-line treatment. Warfarin was the most common ($n=162$, 95.29%) VKA at first line and the only VKA used at second line. Regarding the antiplatelet therapy, it constituted 9.83% ($n=75$) of the first-line and 27.03% ($n=10$) of the second-line treatment. Across the two lines, aspirin was the most common antiplatelet therapy

Table 3 Comorbidities of patients at baseline

Number of patients enrolled	*N*	723
Stroke/TIA	*N*	723
	No	689 (95.30%)
	Yes	34 (4.70%)
	Missing	0 (0.00%)
Congestive heart failure/left ventricular dysfunction	*N*	723
	No	621 (85.89%)
	Yes	102 (14.11%)
	Missing	0 (0.00%)
Coronary artery disease	*N*	723
	No	596 (82.43%)
	Yes	127 (17.57%)
	Missing	0 (0.00%)
Myocardial infarction	*N*	723
	No	707 (97.79%)
	Yes	16 (2.21%)
	Missing	0 (0.00%)
Hypercholesterolemia	*N*	723
	No	498 (68.88%)
	Yes	225 (31.12%)
	Missing	0 (0.00%)
Hypertension	*N*	723
	No	301 (41.63%)
	Yes	422 (58.37%)
	Missing	0 (0.00%)
Chronic kidney disease	*N*	723
	No	655 (90.59%)
	Yes	68 (9.41%)
	Missing	0 (0.00%)
Diabetes mellitus	*N*	723
	No	507 (70.12%)
	Yes	216 (29.88%)
	Missing	0 (0.00%)

TIA transient ischemic attack

used (first line: $n=49$, 65.33%; second line: $n=7$, 70.00%) (Table 5).

A total of 628 (86.86%) patients received at least one concomitant treatment at baseline, of which anti-arrhythmics ($n=308$,49.0%) and beta-blockers ($n=243$, 38.7%) were most commonly used (Table S2, Supplementary Material). During the follow-up period, other anti-hypertensive drugs ($n=101$, 52.1%) and beta-blockers ($n=33$, 17.0%) were the most frequently used concomitant medications (Table S3, Supplementary Material).

Clinical Outcomes During Follow-Up

Overall, 33 (4.6%) patients experienced at least one of the assessed clinical outcomes during the follow-up period. The clinical outcomes occurred at the following rates: stroke ($n=3$, 0.41%), bleeding ($n=3$, 0.41%), TIA ($n=19$, 2.63%), MI ($n=1$, 0.13%), SE ($n=1$, 0.13%), and all-cause mortality ($n=6$, 0.83%). Due to the small number of events that occurred during the follow-up period, it was not possible to compute the median (95% CI) estimates for time to first event for the clinical outcomes (Table 6).

Table 4 Risk factors of patients at baseline

Number of patients enrolled	*N*	723
Risk factors		
CHA2DS2-VASc stroke risk score	*N*	722
	Score = 0	74 (10.25%)
	Score = 1	160 (22.16%)
	Score ≥ 2	488 (67.59%)
	Missing	1 (0.14%)
	Mean (SD)	2.37 (1.55)
	Median [Q1–Q3]	2.00 [1.00, 3.00]
	Min–max	0.00–8.00
HAS-BLED score	N	722
	Low	576 (79.78%)
	High	146 (20.22%)
	Missing	1 (0.14%)
	Mean (SD)	1.46 (1.18)
	Median [Q1–Q3]	1.00 [1.00, 2.00]
	Min–max	0.00–5.00
Smoking habits defined at baseline	*N*	722
	Current smoker	80 (11.08%)
	Former smoker	74 (10.25%)
	Non-smoker	526 (72.85%)
	Passive smoking	42 (5.82%)
	Missing	1 (0.14%)
Number of cigarettes per day	*N*	77
	Mean (SD)	22.77 (14.37)
	Median [Q1–Q3]	20.00 [10.00, 30.00]
	Min–max	5.00–60.00
	Missing	3 (3.75%)
Current alcohol consumption	*N*	722
	No	717 (99.31%)
	Yes	5 (0.69%)
	Missing	1 (0.14%)

Table 4 continued

If yes, number of alcohol units per week	*N*	4
	Mean (SD)	2.00 (0.82)
	Median [Q1–Q3]	2.00 [1.75, 2.25]
	Min–max	1.00–3.00
	Missing	2 (33.33%)

CHA_2DS_2-VASc congestive heart failure, hypertension, age > 75 years [doubled], type 2 diabetes mellitus, previous stroke, transient ischemic attack or thromboembolism [doubled], vascular disease, age of 65–75 years, and sex, *HAS-BLED* hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly, *SD* standard deviation, *Q1* first quartile, *Q3* third quartile

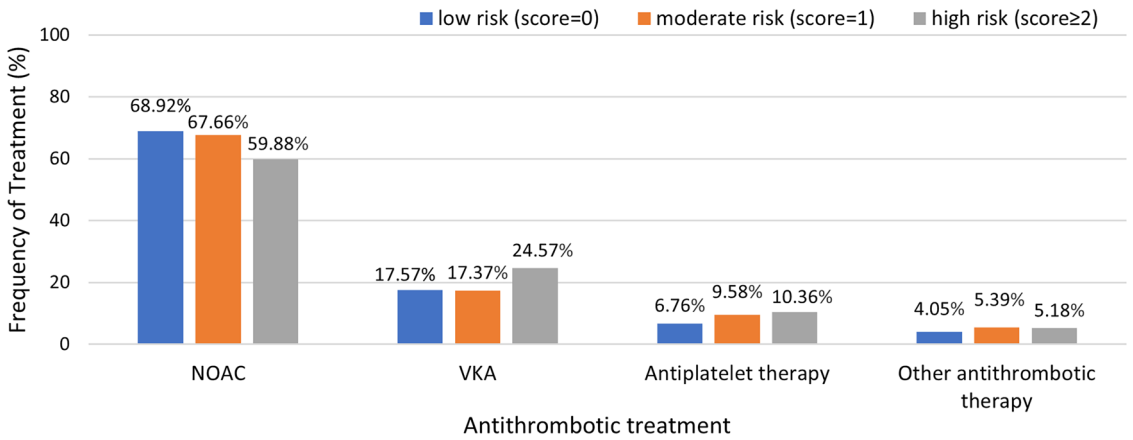

Fig. 1 Percentage of antithrombotic drugs prescribed by CHA_2DS_2-VASc score at baseline. *CHA_2DS_2-VASc* congestive heart failure, hypertension, age > 75 years [doubled], type 2 diabetes mellitus, previous stroke, transient ischemic attack or thromboembolism [doubled], vascular disease, age of 65–75 years, and sex, *NOAC* non-vitamin K antagonist oral anticoagulant, *VKA* vitamin-K antagonist

Healthcare Resource Utilization and Direct Costs Associated with the Management of Patients with NVAF

During the study, the most frequently used healthcare resources were laboratory assessments ($n = 721$, 99.72%), imaging exams ($n = 673$, 93.08%), and outpatient visits ($n = 641$, 88.65%). The mean (SD) annual resource use per patient and the associated mean (SD) total annual costs per patient were: laboratory assessments: 10.1 (6.6) assessments, USD 5.4 (6.3); imaging exams: 7.0 (2.5) exams, USD 96.5 (48.2), surgical/non-surgical procedures: 1.1 (0.4) procedure, USD 101.8 (196.3); inpatient admissions: 1.0 (0.2) admissions, USD 127.9 (41.9); outpatient visits: 3.4 (1.8) visits, USD 70.0 (36.05), and antithrombotic medications: 14.0 (4.2) medications, USD 381.2 (98.6).

The unit cost of inpatient admissions was the highest at USD 123.9, followed by surgical/non-surgical procedures at USD 91.7, and outpatient visits at USD 20.5 USD). The highest total annual costs per patient were attributed to antithrombotic medications (USD 381.2), followed by inpatient admissions (USD 127.9), and surgical/non-surgical procedures (USD 101.8) (Table 7).

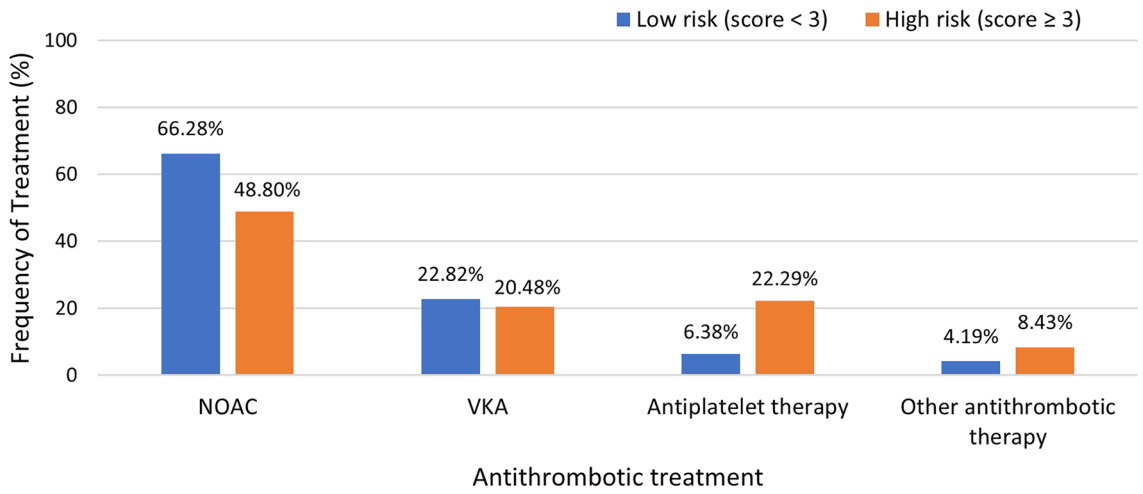

Fig. 2 Percentage of antithrombotic drugs prescribed by HAS-BLED score at baseline. *HAS-BLED* hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly, *NOAC* non-vitamin K antagonist oral anticoagulant, *VKA* vitamin-K antagonist

DISCUSSION

The FLOW-AF Registry was a multi-country, multicenter, prospective observational study that enrolled patients with NVAF across the MENA region (Egypt, Lebanon, KSA, and UAE). Real-world studies investigating NVAF in the MENA region are scarce, despite the differences in patient profile and management compared with Western countries. To our knowledge, this is one of few studies to prospectively assess characteristics, treatment patterns, clinical outcomes, and HCRU among newly diagnosed patients with NVAF in Egypt.

CVD accounts for approximately 24.58% of total deaths in Egypt, thus ranking Egypt as the 23rd worldwide in terms of CVD-related deaths [28]. A cross-sectional study conducted among 1000 patients with AF in cardiac centers in Egypt showed that HF, hypertension, and CHD were the most prevalent comorbidities [6]. Considering the increasing prevalence of AF/NVAF risk factors in Egypt, generation of local real-world data is critical to support healthcare decision makers to better understand the disease epidemiology and outcomes, and thereby optimize management.

In this study, the mean age of patients was 61.91 years. This is consistent with the findings of a multinational, prospective, registry-based study including 6 Gulf counties, in which the mean age was 57 years [29]. This is also comparable with other research conducted in Egypt (mean age: 59.43 years) and UAE (mean age: 58.6 years) [7, 30]. Results are also replicated in the GARFIELD-AF study which showed that Middle East population was younger than the non-Middle East with median age of 64.0 versus 71.0, respectively [31]. Yet, in contrast, recent Western studies mainly in Europe, Canada, and United States of America (USA) reported a mean age of patients with AF > 70 years [32–34], approximately a decade older compared to patients in the Middle East. This younger age profile in the Middle East suggests potential regional-specific factors influencing AF onset, which may require a different clinical approach.

The observed differences between our findings and Western studies may be attributed to several demographic and clinical factors. The higher proportion of male patients in this study may reflect regional healthcare-seeking behaviors or selection biases at participating sites. The lower incidence of thromboembolism and stroke in our cohort is likely related to differences in baseline thromboembolic risk profiles, as evidenced by the lower CHA_2DS_2-VASc scores compared to Western populations [35]. Additionally, the prevalence of heart failure in this

Table 5 First-line, second-line, and subsequent lines of antithrombotic treatment for stroke prevention in patients with NVAF

Variables	Line of treatment[a]		
	First-line	Second-line	Third and subsequent line
Number of patients receiving antithrombotic treatment	*N* = 723	*N* = 36	*N* = 0
Number of drugs at baseline	*N* = 763	*N* = 37	*N* = 0
Oral anticoagulant: NOAC, *N* (%)	477 (62.52%)	26 (70.27%)	–
Apixaban	177 (37.11%)	12 (46.15%)	–
Rivaroxaban	295 (61.84%)	14 (53.85%)	–
Dabigatran	1 (0.21%)	0 (0.00%)	–
Edoxaban	4 (0.84%)	–	–
Oral anticoagulant: VKA, *N* (%)	170 (22.28%)	1 (2.70%)	–
Warfarin	162 (95.29%)	1 (100.00%)	–
Unknown	8 (4.71%)	–	–
Acenocoumarol	0 (0.00%)	–	–
Antiplatelet therapy, *N* (%)	75 (9.83%)	10 (27.03%)	–
Clopidogrel	26 (34.67%)	3 (30.00%)	–
Aspirin	49 (65.33%)	7 (70.00%)	–
Ticagrelor	0 (0.00%)	–	–
Dipyridamole	0 (0.00%)	–	–
Other antithrombotic therapy, *N* (%)	39 (5.11%)	0 (0.00%)	–

NOAC non-vitamin K antagonist oral anticoagulant, *VKA* vitamin-K antagonist, *NVAF* non-valvular atrial fibrillation

[a]ATT line was determined based on the date of initiating treatment; "first-line" referred to the initial ATT prescribed to newly diagnosed patients with NVAF at baseline, i.e., the primary regimen initiated before any subsequent treatment change (e.g., a switch or addition of therapy)

study population was lower than that reported in Western studies, which may have contributed to the observed differences in clinical outcomes and comorbidity burden [36]. These findings underscore the importance of regional and demographic considerations when interpreting data from different populations.

The results showed a high burden of comorbidities among patients with NVAF in Egypt, including hypertension (58.37%), obesity (48.54%), hypercholesterolemia (31.12%), and diabetes (29.88%). These results are in line with findings from the GARFIELD-AF and the Gulf SAFE registry studies, which showed that patients from the Middle East have a high prevalence of comorbidities, such as HF, vascular disease, SE, and diabetes [29, 31]. Additionally, research conducted in KSA and UAE showed that the rate of AF was higher in patients with associated chronic diseases [2, 37]. In contrast, the prevalence of comorbidities among patients with NVAF in Western countries has been

Table 6 Clinical outcomes during the follow-up period

Time to first event	Parameter	
Number of patients enrolled		723
Any	*N* at risk	721
	N with event	33
	N censored	688
	Median [Q1–Q3] (95% CI)	Too short follow-up
	Min, max	19, 390
Stroke	*N* at risk	721
	N with event	3
	N censored	718
	Median [Q1–Q3] (95% CI)	Too short follow-up
	Min, max	19, 343
Bleeding events	*N* at risk	721
	N with event	3
	N censored	718
	Median [Q1–Q3] (95% CI)	Too short follow-up
	Min, max	62, 227
Transient ischemic attack	*N* at risk	721
	N with event	19
	N censored	702
	Median [Q1–Q3] (95% CI)	Too short follow-up
	Min, max	64, 390
Myocardial infarction	*N* at risk	721
	N with event	1
	N censored	720
	Median [Q1–Q3] (95% CI)	Too short follow-up
	Min, max	38, 38

Table 6 continued

Time to first event	Parameter	
Systemic embolism	*N* at risk	721
	N with event	1
	N censored	720
	Median [Q1–Q3] (95% CI)	Too short follow-up
	Min, max	25, 25
All-cause mortality	*N* at risk	721
	N with event	6
	N censored	715
	Median [Q1–Q3] (95% CI)	Too short follow-up
	Min, max	26, 186

CI confidence interval, *Too short follow-up* estimates cannot be calculated due to too short follow-up, *Q1* first quartile, *Q3* third quartile

reported to be lower compared with the Middle East, e.g., prevalence of diabetes in Canada (20.4%) and Europe (20.6%) is around 10% lower compared with the results of the present Egypt study (29.88%) [38–40].

At baseline, most patients had a CHA_2DS_2-VASc stroke risk score ≥ 2 (67.59%), and the overall mean score was 2.37. This is consistent with findings from other Egypt studies; for example, one study showed that the CHA_2DS_2-VASc stroke risk score ranged between 2.49 and 3.36 [41], and another revealed 83.5% of patients had a score ≥ 2 [6]. Other studies conducted in the MENA region report similar CHA_2DS_2-VASc stroke risk score results [2, 31]. In contrast, in the global GLORIA-AF study ($N = 15,119$ newly diagnosed patients with NVAF), the CHA_2DS_2-VASc score was higher (median score > 3). Considering older patients are at increased risk of stroke, the higher score in the global study compared to the present study may partly be attributed to the difference in the mean patient age between the 2 studies (72 vs 61.91 years, respectively) [42]. In addition, most of the patients enrolled in the current study did not have a history of stroke (TIA) or congestive HF at baseline (95% and 86%, respectively).

Concerning the HAS-BLED risk score, most patients had a low score (< 3), and the overall mean score was 1.46. This was in line with the Jordan atrial fibrillation (JoFib) prospective, multicenter study ($N = 1849$ patients with NVAF), which reported a mean (SD) HAS-BLED score of 1.7 (1.1) [42].

The treatment patterns in this study are consistent with the established global guidelines and recommendations for managing AF [15–18]. The OACs accounted for > 80% of ATT received by patients, with NOACs contributing 68%, while VKA represented 22.28%. In addition, the antiplatelet therapy constituted 10% of the antithrombotic regimen. These results were similar among patients with CHA_2DS_2-VASc score ≥ 2 and HAS-BLED risk score ≥ 3, in which NOAC was the most used therapy (59.88% and 48.80%, respectively), followed by VKA (24.57% and 20.48%, respectively). The most frequently used NOACs were rivaroxaban (61.84%) and apixaban (37.11%), indicating they were the preferred NOACs for both initial and subsequent therapy in patients with NVAF. Treatment preferences observed in this study are aligned with findings of other ME, studies including Jordan, UAE, and KSA [2, 44], but contrast with data from other

Table 7 Healthcare resource utilization and costs associated with the management of patients with NVAF

Number of patients enrolled	723	
Laboratory assessments in total		
Number of patients that had laboratory assessment(s) per year	*N*	721
Number of laboratory assessments per patient per year	Mean (SD)	10.1 (6.6)
Unit cost of a laboratory assessment [USD]	*N*	2.8[a]
Total cost of laboratory assessments per patient per year [USD]	Mean (SD)	5.4 (6.3)
Imaging Exams, in total		
Number of patients that had exam(s) per year	*N*	673
Number of exams per patient per year	Mean (SD)	7.0 (2.5)
Unit cost of an exam [USD]	*N*	16.4[a]
Total cost of exams per patient per year [USD]	Mean (SD)	96.5 (48.2)
Surgical/non-surgical procedures, in total		
Number of patients that had procedure(s) per year	*N*	198
Number of procedures per patient per year	Mean (SD)	1.1 (0.4)
Unit cost of a procedure [USD]	*N*	91.7[a]
Total cost of procedures per patient per year [USD]	Mean (SD)	101.8 (196.3)
Inpatient admissions, in total		
Number of patients that had inpatient admission(s) per year	*N*	321
Number of inpatient admissions per patient per year	Mean (SD)	1.0 (0.2)
Unit cost of an inpatient admission [USD]	*N*	123.9[a]
Total cost of inpatient admissions per patient per year [USD]	Mean (SD)	127.9 (41.9)
Outpatient visits, in total		
Number of patients that had outpatient visit(s) per year	*N*	641
Number of outpatient visits per patient per year	Mean (SD)	3.4 (1.8)
Unit cost of an outpatient visit [USD]	*N*	20.5[a]
Total cost of outpatient visits per patient per year [USD]	Mean (SD)	70.0 (36.5)
Other events, in total		
Number of patients that had other event(s) per year	*N*	2
Number of other events per patient per year	Mean (SD)	1.0 (–)
Unit cost of other events [USD]	*N*	–
Total cost of other events per patient per year [USD]	Mean (SD)	Too few events

Table 7 continued

Antithrombotic medications, in total		
Number of patients that had medication(s) per year	*N*	721
Number of medications per patient per year	Mean (SD)	14.0 (4.2)
Unit cost of a medication [USD]	*N*	13.6[a]
Total cost of medications per patient per year [USD]	Mean (SD)	381.2 (98.6)

SD standard deviation, *USD* United States Dollars, *NVAF* non-valvular atrial fibrillation

[a]No unique unit cost. Mean across events are displayed in the table

global regions such as North America, Europe, Asia, and Latin America, where VKAs are more commonly used (≥32%) [45, 46].

In contrast to the results of this study, the Delta of Egypt Atrial Fibrillation Registry showed high use of VKA (72.6%), with NOAC being used in the minority of cases [7]. This discrepancy may partly be attributed to the type of healthcare setting in each study. While all patients enrolled in the FLOW study were treated in the private health sector and were monitored by PhD-holding cardiologists (which potentially may be associated with better quality of care and elevated use of NOACs), it may be possible that Delta study comprised a more diverse patient pool including those treated in the public sector which has greater access to VKA due to their low procurement costs. Although warfarin has been the gold standard for the prevention of stroke in patients with NVAF for several decades, the FLOW study suggests a modern inclination towards NOACs use, at least within the private healthcare setting. This may be due to the reduced need for frequent monitoring and improved safety profile of NOACs [18, 47, 48].

Moreover, the mean daily dose of rivaroxaban was 18.97 mg with a median of 20 mg and the mean daily dose of apixaban was 8.67 mg with a median dose of 10 mg. These doses are consistent with the specifications outlined in each product label [49].

The 1-year rate of clinical outcomes was low in this study population, with only 4.6% of patients experiencing at least one clinical outcome during the follow-up period. The most frequent clinical outcome was TIA (2.93%), followed by all-cause mortality (0.83%), stroke (0.41%) and bleeding events (0.41%); MI and systemic embolism each occurred at a rate of 0.14%. These rates are lower compared with data from both Middle Eastern and global studies [43, 50, 51]. For example, the Gulf survey of AF (*N* = 1721 patients with NVAF) reported 1-year rates of 4.2% and 15.3% for stroke/TIA and all-cause mortality, respectively [49]. The JoFib study showed that the 1-year CV mortality was 7.8%, stroke/TIA was 4.5%, and major bleeding events were 2.6% [43]. The low rate of clinical outcomes in our study may partly be related to the characteristics of the patient population (e.g., young age, low mean baseline CHA_2DS_2-VASc score) and management, including predominant use of NOAC [52–54]. Moreover, all participating sites were private hospitals, and participating investigators were all PhD-holding cardiologists; hence, the quality of care received by patients in this study (e.g., including high use of NOACs) may be better compared with the general NVAF patient population in Egypt [55].

Antithrombotic medications accounted for the highest total yearly cost of managing patients with NVAF (per patient per year) (USD 381.9), followed by inpatient admissions (USD 127.9), and surgical/non-surgical procedures (USD 101.8). Laboratory assessments were the most frequently used resource (99.72%) yet accounted for the least total yearly cost (USD 5.4).

Several factors may have contributed to the unusually high annual cost attributed to antithrombotic medications compared to inpatient admissions. Data collection for drug strengths, package sizes, and costs relied on a

combination of primary sources and imputation methods. Missing data were addressed by returning to participating hospitals and validating drug names and prices using the official Egyptian Drug Authority (EDA) database. Despite these measures, imputations for certain variables (e.g., package sizes and strengths) may have introduced some uncertainty into the estimates. Furthermore, the COVID-19 pandemic may have reduced hospital admissions and clinic visits, potentially underestimating inpatient costs during the study period. Despite these limitations, the analysis provides critical insights into the economic burden of NVAF management in Egypt and highlights areas for future investigation, such as incorporating sensitivity analyses and extending the dataset to include longer follow-up periods.

A greater total annual cost of ATT than inpatient admissions is an unusual finding of this study, which may be explained by several factors. First, there were limited data on drug strengths and package sizes in the FLOW registry, which necessitated imputations, potentially impacting the medication costs. Second, the COVID-19 pandemic may have influenced the frequency of hospitalizations and clinic visits during the time of this study, thereby resulting in an underestimation of costs related to inpatient admissions. Third, it is possible that errors in recording resource costs in the costing questionnaire may have occurred at the site level (e.g., for insured patients, only costs incurred at the individual patient level may have been recorded). The HCRU and cost data in this study should be interpreted taking into account these caveats. Despite these limitations, this study is one of the first to shed light on HCRU/associated costs among patients with NVAF in Egypt and paves the way for further research to expand on these results.

Limitations

This study has several limitations inherent to its observational design, including potential bias and confounding. The exclusive enrollment of patients from private healthcare facilities limits the generalizability of the findings to the broader Egyptian population, particularly those treated in the public sector, where access to advanced resources, such as NOACs, and specialized care may differ significantly. The inclusion of patients managed by PhD-holding cardiologists in private hospitals may have influenced the observed outcomes, reflecting optimal care scenarios rather than the full spectrum of care available in Egypt. The COVID-19 pandemic may have further impacted the study results by disrupting patient recruitment and follow-up due to movement restrictions and healthcare resource reallocation. However, healthcare access in Egypt remained largely uninterrupted, with primary PCI drugs and essential medications being adequately supplied, which minimized disruptions in NVAF care. Nonetheless, the pandemic's indirect effects on healthcare utilization, such as reduced hospital visits due to precautionary measures, may have influenced the observed outcomes.

Another limitation of this study is the lack of detailed data on heart failure (HF) phenotypes. The absence of this information prevents a more nuanced analysis of the relationship between NVAF and different HF subtypes, such as HF with preserved ejection fraction (HFpEF) or reduced ejection fraction (HFrEF). This limitation may have influenced the interpretation of our findings and restrict insights into potential phenotype-specific management strategies. Future studies should incorporate HF phenotyping to provide a more comprehensive understanding of the interplay between NVAF and HF.

Additionally, the study did not assess the appropriateness of dosing for DOACs or collect INR data to calculate the time in therapeutic range (TTR) for patients treated with VKAs. These metrics are critical for evaluating anticoagulation quality and clinical outcomes but were beyond the scope of this study. Future research should include these measures to provide a more comprehensive evaluation of anticoagulation management in patients with NVAF.

The relatively short follow-up period of 12 months was insufficient to fully assess long-term clinical outcomes. Future research should include a more representative patient sample from both private and public healthcare settings, alongside extended follow-up durations,

to provide a comprehensive understanding of NVAF management across diverse healthcare contexts in Egypt.

CONCLUSIONS

The FLOW-AF study provides valuable real-world data on the characteristics, treatment patterns, and outcomes of newly diagnosed patients with NVAF in Egypt. Compared to Western populations, these patients were younger, exhibited lower stroke and bleeding risk scores, and experienced fewer clinical events over one year. However, the findings are limited by the exclusive focus on private healthcare settings, which may not fully capture the broader Egyptian NVAF population. Future studies should aim to include both private and public sector patients and extend follow-up durations to enhance the generalizability and depth of these insights into NVAF management in Egypt.

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Data Availability. The data that support the findings of this study are not publicly available due to privacy or ethical restrictions.

Declarations

Conflict of Interest. Magdy Abdelhamid received speaker honoraria from Pfizer, Novartis, and AstraZeneca, is an advisory board member with Bayer, and received research grants or other funding from Pfizer. Mohamed Sobhy, Adel Mohamed El Etriby, Hany Ragy, Ashraf Reda, Maichel Sobhy, and Mostafa Nawar have no conflicts to disclose. Natasha Khalife is an employee of IQVIA, which conducted the study on behalf of the sponsor. Mohamed Fathy Soliman Gamaleldin and Ahmed Mohamed Helmy Youssef are employees of Pfizer Inc., the study sponsor.

Ethical Approval. The study protocol (available upon request) was submitted and approved by the Alexandria University Hospital (MOH) Ethics Committee and the Institutional Review Board of each participating hospital (Table S4, Supplementary Material). The registry was conducted in accordance with the principles of the Declaration of Helsinki, local regulatory requirements, and the International Conference on Harmonisation Good Pharmacoepidemiological and Clinical Practice guidelines [28]. All study participants provided written informed consent, and the confidentiality and anonymity of all enrolled patients were maintained.

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