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REVIEW



Atrial fibrillation in the Middle East: unmapped, underdiagnosed, undertreated

Warkaa Al-Shamkhani^a, Harold Ayetey^a and Gregory Y. H. Lip^{a,b}

^aInstitute of Cardiovascular Sciences, University of Birmingham, Birmingham, UK; ^bAalborg Thrombosis Research Unit, Department of Clinical Medicine, Faculty of Health, Aalborg University, Aalborg, Denmark

ABSTRACT

Introduction: Atrial fibrillation (AF) is the commonest persistent cardiac arrhythmia with an estimated incidence rate of between 1.5–2% and an important cause of strokes. Few epidemiological studies and clinical trials on the management of AF have been conducted outside Europe and North America. These gaps in our understanding of AF likely lead to sub-optimal management of patients with AF in the rest of the world.

Areas covered: We discuss the epidemiology, treatment and clinical outcomes for AF in the Middle East after systematic review of published work for AF from the Middle East. We also discuss important clinical trials on AF conducted in the West in the same period to help contextualize our findings.

Expert commentary: The few available Middle East studies suggest important epidemiological differences between Middle Eastern and Western AF populations. In particular, the Middle Eastern AF population is younger and have more co-morbidities than patients in the West. We find that significant numbers of moderate to high risk patients with AF are either undertreated or untreated placing them at increased risk of complications such as stroke. More studies in the Middle Eastern population are required to aid the development of region-specific clinical guidelines to improve patient care.

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KEYWORDS

Atrial fibrillation; Middle East; epidemiology

1. Introduction

Atrial fibrillation (AF) is the commonest sustained cardiac arrhythmia, with a lifetime risk of 1 in 4 in the adult general population and an increasing prevalence as populations age [1,2]. AF is associated with significant mortality and morbidity, most notably stroke which is 5× more likely to occur in patients with AF [3,4]. Anticoagulation with oral anticoagulants (OACs) using Vitamin K antagonists (VKAs) result in a 64% reduction in strokes and a 26% reduction in all-cause mortality in patients with AF, compared to control or placebo [5]. More recently, the non-VKA oral anticoagulants (NOACs) offer relatively improved efficacy, safety, and convenience compared to the VKAs [6].

While the study of the epidemiology, treatment, and clinical outcomes in AF has been extensive in the last decade in Europe and North America [2,7,8], there remains a paucity of data for the rest of the world beyond these regions. These gaps in our understanding of AF likely lead to sub-optimal management of patients with AF in the rest of the world. A handful of recent studies have contributed to our understanding of the disease in AF in Asia and Latin America [9,10]. For example, AF prevalence has increased in Asia and, the risk of bleeding on standard anticoagulation therapy is higher there than in Western populations [9] leading to many clinicians using a lower target International Normalised Ratios (INRs) for Asian AF patients on VKAs [11].

Much less is known about the epidemiology of AF in the Middle East however. Thus, clinical management of AF patients and in particular stroke prevention strategies, are

not well supported by evidence. The aim of this article was to review available studies from the Middle East related to the epidemiology, treatment, and clinical outcomes of AF in the Middle East to better inform the development of clinical practice guidelines for the region. Given the heterogeneity and sparsity of reports, no meta-analysis was performed.

2. Methods

2.1. Eligibility criteria

Original research articles, registries, and interventional trials that reported data on the incidence of AF in Middle Eastern Countries, clinical management and outcomes. We included subgroup analysis from global trials. Case Reports, Reviews, Editorials, Commentaries, letters, small observation studies ($n < 400$) and case reports conducted outside the Middle East were excluded.

2.2. Search strategy

We performed a descriptive analysis of published data by searching the PubMed/MEDLINE and associated databases for a combination of the following keywords: 'atrial fibrillation,' and 'middle east,' and in addition substituted 'Middle East' with each Middle Eastern country in succession to enable a more detailed search of AF in each country. Only English-language articles published between 2007 and 2017 were included. PRISMA guidelines were fully adhered to (Figure 1).

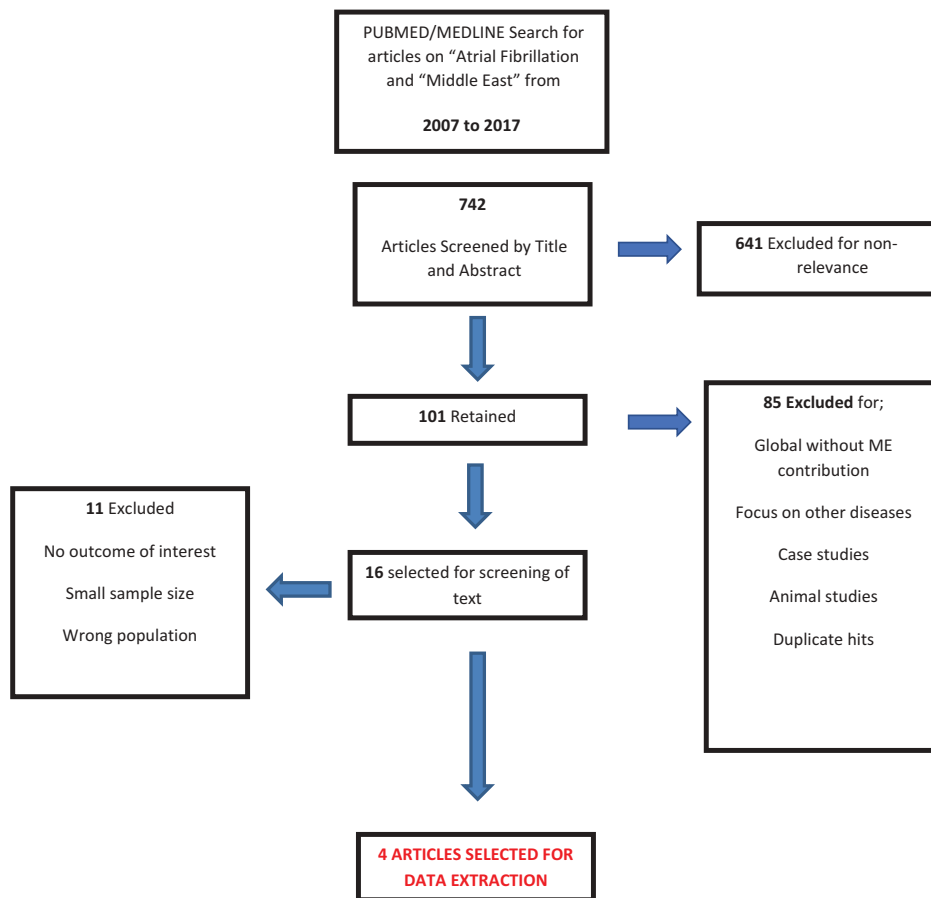


Figure 1. Search strategy (21/11/2017).

2.3. Ethical review

Given the study type (review article), ethical approval was not necessary.

3. Results

Our search yielded 742 articles (Figure 1). 641 were excluded after screening titles and abstracts of articles for relevance. A further 95 articles were also excluded for reporting no outcome of interest, focusing on specific patient populations, having too small a sample size ($n < 400$) or simply reporting cases.

A total of 4 registries/trials (and sub-studies) were considered appropriate and used this review.

The Gulf Survey of Atrial Fibrillation Events (Gulf SAFE) [12,13], was a multinational, prospective observational registry that enrolled consecutive patients with AF presenting to hospitals in Kuwait, Bahrain, Qatar, UAE, Oman, and Yemen – all Middle Eastern Gulf countries. This study enrolled 2043 patients from 23 hospitals with non-valvular AF and followed them up for 1 year. 44% were women (mean age 59 ± 16 years). Commonest comorbidities included hypertension (52%), hyperlipidemia (33%), diabetes mellitus (30%), and coronary heart disease (28%). Patients with AF in the region were a decade younger on average and had a higher cardiovascular risk compared to similar registries in the west [13,14] (Table 1).

There was an overall one-year rate of stroke/TIA and all-cause mortality of 4.2% and 13%, respectively. As expected, warfarin initiation in hospital was associated with a reduced 1 year rate of stroke/TIA (odds ratio [OR], 0.38; 95% confidence interval [CI], 0.17–0.85; $P = .015$) and all-cause mortality (OR, 0.51; 95% CI, 0.32–0.83; $P = .006$). Anticoagulation treatment was generally suboptimal in these patients and reflected in the relatively high 1 year all-cause mortality and stroke/TIA event rates.

The GLORIA AF registry was a prospective global registry of patients with newly diagnosed non-valvular atrial fibrillation at risk of stroke which enrolled patients from 44 countries. In total, 15,641 patients were enrolled as follows; Europe (47.1%), North America (22.5%), Asia (20.3%), Latin America (6.0%), and the Middle East/North Africa (4.0%). The majority of enrolled patients had a high stroke risk (CHA₂DS₂VASC Score ≥ 2 ; 86.1%). At baseline, GLORIA AF phase I [15] which preceded the advent of NOACs for the management of AF, only 32% of eligible patients ($n = 1063$) were on VKA anticoagulation therapy. 41.7% were on acetylsalicylic acid with over 20.2% no antithrombotic therapy at all. In the Middle East subgroup, 45% of eligible participants ($n = 59$) were on NKA. In phase II of the GLORIA AF study [16] (i.e. at 24 month follow up), about 80% of patients were on anticoagulants under half (47.6%) of who were on NOACs and a third (32%) on VKAs. Approximately 12.1% of patients received antiplatelets alone with a further 7.8% on no-antithrombotic treatment at all.

Table 1. Baseline characteristics of studies examined.

Characteristics	GULF SAFE [12,13]	GLORIA-AF Phase 2 (Global) [16]	GLORIA-AF (ME)-Phase 1 [15]	HEART[20]	GARFIELD [17].
Number of participants	2043	15641	59	2593(449 with AF)	28,624(M-F)%
Age (years)	57±16	71.0	65 (57, 74)	62+/-15	67.2–72.4
Hypertension	1072(52)	11,255 (74.6)	47 (79.7)		
Coronary Artery Disease	576(28)	3068 (20.3)	16 (27.4)	42.3%	1496 (5.2)
Heart Failure	516(27)	6715 (44.5)	15 (25.4)		988 (3.5) ^b
Significant Valvular HD	494(24)				
Rheumatic Heart Disease	318(16)				
Chronic GIT disease		73 (6.9)	3 (5.1)		
Chronic Obstructive PD	103(5)				
Thyroid disease	103(5)				
Diabetes Mellitus	605(30)	3487 (23.1)	22 (37.5)	55.9%	3479 (21.9)–2728 (21.5)
Hyperlipidemia	680(33)	6026 (39.9)			6232 (39.9)–5276 (42.3)
Tobacco use	465(23)				7210 (50.1%) – 1850 (15.9%)
BMI (kg/m ²)	28±6	27.5	27.3 (24.2, 33.3)		27.7–27.9
Stroke	186(9)	1582 (10.5)	6 (10.2)	15%	1243 (7.8) –1013 (8.0)
TIA	78(4)				1839 (11.6) –1583 (12.5)
Prior major bleeding	60(3)	842 (5.6)			
Dialysis	31(2)				
Alcohol use	160(8)				
Admitted	1612(79)				
Type of AF					
• Don't know	69(3)				
• First attack ever	754(37)				45.8–44.5
• Paroxysmal	353(17)	(53.4)	40 (67.8)		25.1–29.1
• Permanent	674(33)	(11.1)	6 (10.2)		12.9–12.5
• Persistent	193(19)	(35.5)	13 (22.0)		16.2–14
• Lone AF	398(19)				
CHADS ₂ score					
0	582(29)	1221 (8.1)	2 (3.4)		676 (4.4) –
1	563(27.5)	5150 (34.1)	21 (35.6)		2966 (19.1) –370 (3.0)
2	484(24)	8719 (57.8) ^a	36 (61.0) ^a		11 857 (76.5)–12 082 (97.0) ^a
3	241(12)				
4	113(5.5)				
5	49(2)				
6	11(0.5)				

^aCHADS₂ score ≥2; ^bnumbers recalculated from cases of NYHC2 +.

In the European arm of the study, treatment with NOAC was also more widespread than treatment with VKA (52.3% and 37.8%, respectively) at the 24 month follow up; 6.0% of patients received antiplatelet treatment; and 3.8% received no antithrombotic treatment.

In North America, 52.1%, 26.2%, and 14.0% of patients received NOAC, VKA, and antiplatelet drugs, respectively; 7.5% received no antithrombotic treatment (Table 1).

The GARFIELD registry, set up in 2009 to assess the management and outcomes of patients with newly diagnosed non-valvular AF in the ‘real-world’ setting. 57,262 patients have now been enrolled from 35 countries across all continents [17]. The three countries included from the Middle East/Africa Region were Egypt, UAE, and South Africa. No focused sub-analysis of extracted data for these countries have been published but two recent sub-studies have incorporated patients from Egypt and UAE, although patient numbers from these countries were low. The first [18], looked at gender differences in cardiovascular event rates in patients with AF. 44% vs. 55.6% of the 28,624 patients enrolled at this stage were women, with more women 46.9% vs. 30.4% over 75 years old. All-cause mortality rates per 100 person years (95%CI) for women and men were 4.48 (4.12–4.87) and 4.04 (3.74–4.38), respectively, stroke/systemic emboli (1.62 (1.41–1.87) and 1.17 (1.01–1.36)) and major bleeding (0.93 (0.78–1.13) and 0.79 (0.66–0.95)). Women had a higher risk of stroke and systemic emboli than men (1.3-fold higher in women, HR 1.30 (1.04–1.63)) but had a smaller risk reduction in

stroke/systemic emboli events and all-cause mortality on OACs even though OAC treatment patterns were similar between men and women.

A second publication from the GARFIELD registry [19] has recently showed that large numbers of patients (58.9% of 9934) had a time in therapeutic range (TTR) of <65% which reflected the higher risk of stroke/systemic emboli, major bleeding and all-cause mortality and points out an urgent need for improvement in VKA management of AF patients.

The clinical characteristics and outcomes of patients with Atrial Fibrillation were recently captured in the multicenter **Saudi Arabian Heart Function Assessment Registry** which reported the clinical features and outcomes of patients admitted with heart failure [20]. Of the 2593 in the registry 449 (17.8%) had AF at presentation. 46% of these were male and 31.8% female. Patients with AF were older (mean age 65.2 ± 15) than those in sinus rhythm (60.5 ± 14.8) but younger than documented in the West. Significantly more patients (15%) with AF gave a history of stroke compared to the sinus rhythm group (8.5%). Patients with AF were less likely to have diabetes (66% vs. 55.9%) or coronary heart disease (55.6% vs. 42.3%). Crude mortality rates were significantly higher in patients with AF at 1-, 2-, and 3-year follow up (23.2% vs. 18.3%, 27.4% vs. 22.3%, and 27.8% vs. 23.2%, respectively), although this significance was lost after age and gender adjustment.

3.1. Hospital management of AF in the Middle East

The GULF SAFE registry was the only one of the studies included that provided data on the clinical management of AF patients in the Middle East. Admissions to 23 hospitals across the Middle East were examined. Treatment settings, for example, level of care (secondary, tertiary, etc.), medications prescribed, type of services offered, and the medical teams responsible for patient care were evaluated [13] (Table 2).

Amiodarone was the most commonly available and utilized drug for the treatment of new-onset AF. Although CCU services were offered, EP services were generally unavailable with only one hospital offering catheter ablation services. In general, cardiologists were responsible for the management of the majority of cases. An unacceptably high percentage of patients with an intermediate-to-high risk of stroke ($\text{CHA}_2\text{DS}_2\text{VASc} \geq 2$) were not on an OAC.

Several European studies examine the clinical management of AF including adherence to clinical guidelines [21–24]. The PREFER Registry [25] for example, which enrolled AF patients from 461 centers in seven European countries including the UK between January 2012 and January 2013 found that OACs were prescribed to over 80% of eligible patients. Adequate rate control achieved in 72–81% of participants. For rhythm control, a variety of drugs were used including Amiodarone, Flecainide, Sotalol, and Quinidine. Amiodarone was the most common drug used among eligible patients ranging between 11% (UK) and 40% in (France). Unlike the Middle East, several European centers offer ablation for symptomatic AF patients.

Table 2. Available data on clinical management of AF in the Middle East.

	GULF SAFE [12,13]	GLORIA-AF Phase 2 (Global) [16]	GLORIA-AF (ME)-Phase 1 [15]
Hospital type	N(%) 23 (100)		59 (100)
• Secondary	14(61)	(26.3)	2 (3.4)
• Tertiary	9(39)		
• University	5(22)	(60)	36 (61.0)
• Other			(21)
Available antiarrhythmic			
• Amiodarone	23(100)		
• Propafenone	12(52)		
• Flecainide	9(39)		
VKA		(64)	(45)
NOAC			
Dedicated anticoagulation clinic	7(30)	(2.5)	0 (0.0)
CCU on site	23(100)		
EP Lab on site	5(22)		
EP lab within 1 h driving	4(17)		
AF ablation performed	1(4)		0 (0.0)
Admitting Doctor			
• Cardiologist	10(43)		
• Internist only	0(0)		
• Both	13(57)		
Responsibility for Continuing Care		Majority	
• Cardiologist	17(74)		
• Internist only	0(0)		
• Both	6(26)		

All tables and figures used in this review were originally produced.

The ESC-EHRA Atrial Fibrillation Ablation Long-Term Registry is a prospective multinational study that looked at contemporary real-world ablation management of AF and outcomes in 7243 patients from 27 European countries who were followed up for 1 year post ablation [26]. The study found that AF ablation was mainly offered to otherwise healthy young patients with an overall satisfactory success rate, although adherence to anticoagulation guidelines post ablation was unsatisfactory.

4. Discussion

Few high-quality epidemiological studies and clinical trials have been performed for AF in the Middle East. Therefore, best practice for the clinical management of patients with AF are based on guidelines developed on the back of evidence from studies conducted in the West. The four Registries/Studies presented in this paper have provided an overview of the epidemiology and clinical outcomes for AF in the Middle East.

Data from the studies discussed here suggest that the average age of AF onset in the Middle East is approximately a decade younger [12] than in key European studies such as the National Registry of AF [27] and the Euro Heart Survey for AF [28]. Both the GLORIA AF and GULF SAFE Registries reveal a disproportionately high number of AF patients who remain untreated or under-treated with respect to anticoagulation despite a moderate-to-high risk of stroke. Unfortunately, despite almost a decade of robust evidence demonstrating the reduction of mortality due to stroke and all-causes in AF less than 50% of patients were on OACs (46.4% VKAs and 1.4% NOACs) with 35.9% on antiplatelet therapy alone and 16.2% untreated even in the UK [29]. Catheter ablation for AF is commonly performed in symptomatic AF patients in the west based on a growing body of evidence illustrating benefit compared to antiarrhythmic drug therapy [30]. However, the availability of cardiac electrophysiologists and devices-capable centers in the Middle East is limited most likely due to adequate numbers of trained personnel. It is also unclear why amiodarone is commonly used although this may reflect efforts at rhythm control despite the absence of evidence as to whether this is an efficient management option.

The advent of NOACs has improved the levels of thromboprophylaxis in AF but this could be associated with an increased risk of bleeding as was discovered in Asian studies [9]. Few studies have addressed this question in the Middle East despite high levels of NOAC use (55.6%) versus 52% of patients on NOACs in Europe and North America in the GLORIA AF study.

Differences exist between Middle East and Gulf region countries with respect to epidemiology and clinical impact of cardiovascular disease. A recent study demonstrated that the prevalence of hypertension, obesity, diabetes and coronary heart disease – all of which are associated with AF – in the region may be related to national income after categorizing countries into lower middle income (Egypt), upper middle income (Algeria, Kuwait), and high income (Saudi Arabia and UAE) [31].

The authors show that the prevalence of hypertension, which is present in roughly 50% of patients with AF, was 33% in lower middle-income Middle Eastern countries

compared to 44% in high-income Middle Eastern countries in the region although the number of controlled versus uncontrolled hypertensives was almost twice as high (58% vs. 30%) in high versus low middle-income Middle Eastern country dwellers. Notably, there were approximately 500 cardiovascular deaths (Cerebrovascular, Ischaemic and Hypertensive Heart Disease) per 100,000 in Egypt compared to 380/100,000 in Saudi Arabia and 150/100,000 in the UK, USA, and Germany (WHO, mortality, and health status). This was broadly consistent in a recent study of 17 countries globally [32].

Thus, while the prevalence of cardiovascular risk factors and diseases normally associated AF with may be high in the region, their effect on mortality is mitigated by the level of access to good quality healthcare. Studies directly examining the prevalence and mortality of AF amongst Gulf countries will be more informative.

The available evidence however shows that the region has a relatively younger population than the West with a higher prevalence of obesity, valvular heart disease, hypertension, and smoking, and notably lower levels of diabetes mellitus, coronary heart disease, and heart failure [33]. While plausible that the parameters of the popularly used stroke and bleeding risk assessment tools CHA₂DS₂VASc and HASBLED (e.g. age, hypertension, and diabetes) might carry a lower predictive accuracy than the populations in which they were developed, one recent study suggests that patients fare well in this region when these risk assessment tools are used [14].

5. Conclusion

There are little data on the epidemiology, treatment, and clinical outcomes of AF in the Middle East. AF in the region is essentially uncharted, underdiagnosed, and untreated. More adequately powered studies are needed as a matter of urgency to help fill knowledge gaps and reduce mortality and disability due to AF in the region.

6. Expert commentary

Stroke is a feared and common complication of AF. The clinical scenario in which a patient with known AF but sub-optimally managed with respect to their thromboembolic risk and comorbidities such as hypertension, heart failure, is rushed to an emergency department with a dense stroke remains a common possibility in several regions of the world including countries with strong primary care services and clinical guidelines that are visible to practicing physicians.

The prevalence of thrombo-embolic complications such as strokes in the Middle East could be even higher as AF occurs earlier, is associated with more comorbidities and is, as in other parts of the world, undertreated. Significantly, comorbidities such as diabetes and hypertension noted to be highly prevalent in the Middle East increase stroke risk [34–36]. Since the prevalence of AF increases with age, the disease burden of AF can be expected to increase in the medium-to-long term in consonance with the improving life expectancy in the Middle East. This increase will likely translate into significant health-care costs in the region in the long term.

The finding that the uptake of NOACs in the Middle East compared favorably with data from Europe and North America where patients and physicians have benefited from the knowledge and experience gleaned from extensive epidemiological studies, clinical trials and guidelines and patient education initiatives over several years bodes well for the future. The use of OACs for stroke prevention in AF however remains sub-optimal in the region. Reasons for this may include the absence of local guidelines, targeted clinician education and policy implementation tools.

Stroke and bleeding risk assessments also require continued evaluation and improvement. Strategies to ensure improved risk stratification of AF and bleeding risk, and to minimize interruption of anticoagulant therapy by patients and physicians are essential and require implementation. Clinical investigators will need to remain cognizant of the fact that population intrinsic factors may affect the validity of assessment tools as has been discovered elsewhere [9]. Concerns remain about the safety of NOAC use in the elderly and in patients with advanced renal disease [37,38]. The next few years should see continued improvement in our understanding of the safety profiles of NOACs in vulnerable patient groups with AF such as these to further improve their safe access to thrombo-prophylaxis. This will become more relevant for Middle Eastern patients as regional life expectancy continues to improve [39].

While the seemingly lower prevalence of AF outside Europe and North America may reflect the low number of well-powered epidemiological studies, lower detection rates may also be a hidden problem as some studies have revealed the very limited access to essential diagnostic devices such as the 24 h ECG (holter) [40]. Given the early onset of AF revealed in Middle Eastern studies, a priority area for countries in that region should perhaps include strategies for early and efficient detection of AF. Thankfully, low cost, high tech tools [41] for accessing cardiac rhythm are becoming available.

Improved understanding of the epidemiology of AF and clinical outcomes in the Middle East will likely lead to better patient care and improvements in morbidity and mortality in the region. Strategies to encourage systemic collection of accurate clinical research data should therefore be prioritized for urgent implementation by policy makers. However, like all clinical studies, real-world data will be needed to validate findings from trials which are never fully representative.

7. Five-year view

Despite evidence to the contrary, bleeding continues to be an ever-present worry for doctors prescribing NOACs [25,42]. Unlike warfarin, the majority of NOACs do not have widely available reversal agents which can be of immense benefit in patients who bleed. Idarucizumab has recently been licensed in the UK as an antidote to dabigatran etexilate following an interim analysis of the ongoing REVERSE AD trial [43]. One will expect more antidotes to be developed for other NOACs to improve their safety profiles further.

Biomarkers for AF and other cardiovascular diseases [44] continue to be sought and studied in labs across Europe and North America as they may lead to earlier diagnosis and

improved risk-stratification of AF and complications. The potential emergence of NTpro-BNP and others as biomarkers capable of predicting AF [45,46] may help improve the assessment of AF and stroke risk beyond current clinical scoring systems if the high cost of assays can be overcome in the future. The recent suggestion that GDF-15 may be a risk indicator for major bleeding and all-cause mortality in AF patients on OACs [47] could also help improve bleeding risk assessment tools such as the HASBLED scoring system if it proves cost effective.

Key issues

- There is currently little epidemiological data on AF Exists in the Middle East
- Available studies suggest an earlier onset of AF and the existence of greater numbers of co-morbidities compared to patients in Europe and North America
- Similar to Europe and America, a significant number of patients are undertreated in the Middle East, especially with respect to thrombo-prophylaxis for stroke
- Regional AF burden is likely to increase in future with concomitant increases in healthcare costs if action is not taken now to manage both the causes and consequences of AF
- More studies in the local Middle Eastern population are required to aid the development of well-validated and relevant region-specific clinical guidelines for improved patient care

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Declaration of interest

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