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Secondary stroke prevention and guideline adherent antithrombotic treatment in patients with atrial fibrillation: Insights from the Gulf Survey of atrial fibrillation events (Gulf SAFE)☆

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ABSTRACT

Background: Anticoagulation therapy in patients with atrial fibrillation (AF) is well established as effective thromboprophylaxis. However, AF patients with prior stroke are often treated with suboptimal antithrombotic treatment (ATT). In the present study, we investigated clinical characteristics and outcomes in AF patients with versus without prior stoke, in relation to guideline adherence in ATT.
Methods: We used data from the Gulf SAFE registry, which included patients with AF who presented to hospitals in Gulf countries of the Middle East. Adherence to guideline recommended ATT was assessed against the European Society of Cardiology guidelines.
Results: Of 1860 patients, 15.4% had a history of stroke (secondary stroke prevention). For secondary stroke prevention, 62.0% of patients were prescribed oral anticoagulants, while 27.9% were still prescribed antiplatelet therapy alone and 10.1% received no ATT. Overall, 49.0% were treated with guideline adherent ATT, 25.5% were undertreated, and 25.4% were overtreated. On multivariable logistic regression analysis, undertreatment (OR; 2.763, 95% CI; 1.426–5.352, p = 0.003) was significantly associated with an increased risk of 1-year stroke. On the other hand, overtreatment was significantly associated with an increased risk of 1-year bleeding (OR; 3.294, 95% CI; 1.517–7.152, p = 0.003).
Conclusions: Only half of the AF patients received optimal ATT for stroke prevention if we apply guideline recommendations. Guideline adherent ATT significantly reduced the risk of stroke and bleeding compared with non-guideline adherent ATT.

1. Introduction

Atrial fibrillation (AF) is independently associated with increased risk of mortality and morbidity, as a result of ischaemic stroke, systemic thromboembolism and heart failure [1,2]. A history of stroke or transient ischemic stroke (TIA) is one of the most powerful predictors for recurrent stroke in AF patients, but patients who experience an ischemic stroke before are often prescribed antiplatelets alone or remain untreated despite being at a high risk for stroke recurrence.

Strokes related to AF are largely preventable because oral anticoagulants (OACs) are well established as effective thromboprophylaxis [3]. In meta-analysis, Vitamin K antagonists (VKAs; e.g. warfarin) reduced stroke or systemic embolism by 64% and all-cause mortality by 26% compared with placebo or control, while aspirin did not significantly reduce the risk of stroke and had no impact on all-cause mortality in patients with AF [4]. Therefore, current guidelines for AF management recommend that OACs should be offered to all AF patients except for those with a truly low risk of stroke (i.e. those with the CHA_2DS_2-VASc score of 0 in male or 1 in female, where event rates are <1% per year) [3].

☆ The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Nonetheless, contemporary observational AF registries have consistently demonstrated that OAC treatment is underused or suboptimal in AF patients who are at risk of stroke [5]. Furthermore, most of these registries have been carried out in Europe and North America, where patients are older and more Caucasians with higher prevalence of AF than those from Asia [6]. Given the differences in demographics and health care settings, the stroke risk profiles in AF may vary depending on ethnic origin [7]. Guidelines have also evolved over the years, and it would be of value to examine a 'what if' scenario, whereby contemporary evidence-based approaches to stroke prevention happened to be retrospectively applied.

In the present post hoc study from the largest Middle East registry on AF patients, we sought to investigate clinical characteristics and outcomes in AF patients with versus without prior stoke or TIA, in relation to contemporary guideline adherence in antithrombotic treatment (ATT) in the Gulf region of the Middle East.

2. Methods

2.1. Study population

The design of the Gulf Survey of Atrial Fibrillation Events (Gulf SAFE) has been previously described [8]. In brief, the registry was a multinational, prospective, observational registry of consecutive adult (≥18 years) patients with AF presenting to emergency rooms (ER) of 23 hospitals in 6 Gulf countries of the Middle East; Bahrain, Kuwait, Qatar, Oman, United Arab Emirates, and Yemen. All patients had AF documented on a 12-lead electrocardiogram (ECG) or rhythm strip, lasting >30 s while they were in the ER. Regardless of the primary reason for their ER visit, patients were enrolled after giving written informed consent and were followed prospectively for one year. Enrollment started on October 15, 2009 and ended on June 30, 2010. Follow-up by clinic visit or telephone interview was planned at 1-, 6-, and 12-month from time of enrollment. The study was approved by the ethics committees of each institution or country.

Data were prospectively collected on a standardized case report form and entered online. Patients with incomplete data at baseline or lost during follow-up were excluded in the present analysis. Likewise, patients who died during ER or hospitalization were also excluded.

2.2. Thromboembolic risk and guideline adherence in ATT

Thromboembolic risk was retrospectively assessed using the CHA_2DS_2-VASc score [9]; 'low risk' was defined as the CHA_2DS_2-VASc score 0 in male and 1 in female, 'moderate risk' as a CHA_2DS_2-VASc score 1 in male and 2 in female, and 'high risk' as the CHA_2DS_2-VASc score ≥2 in male and ≥3 in female, based on current guidelines.

Guideline adherence in ATT was assessed against the 2010 ESC guideline for AF management [10]. We categorized ATT use into 3 categories: (i.e. guideline adherent, undertreatment [OAC underuse], and overtreatment [OAC overuse]) as follows: (i) **Guideline adherent ATT** was defined as OAC in moderate- and high-risk patients, or no OAC in low-risk patients or in patients with reported contraindications to OAC, or combination therapy (OAC plus antiplatelet) in patients with acute coronary syndrome (ACS); (ii) **Undertreatment** was defined as no OAC (but antiplatelet or no therapy) in moderate- or high-risk patients or no OAC in patients without reported contraindications to OAC, or no combination therapy (OAC plus antiplatelet) in patients with acute coronary syndrome; and (iii) **Overtreatment** was defined as OAC in low- risk patients, or OAC in patients with reported contraindications to anticoagulation therapy, or combination therapy (OAC plus antiplatelet) in patients with no evidence of ACS.

2.3. Assessment of anticoagulation control

Subgroup analyses were performed in patients receiving warfarin at discharge from ER or hospital, who had at least three international normalized ratios (INRs) measured at discharge, 1-, 6-, and 12-month follow-up. We calculated time in therapeutic range (TTR) using the method of Rosendaal, which incorporates both frequency of INR measurement and actual values to interpolate daily INR values and define the percentage of time in therapeutic range for each patient [11].

2.4. Statistical analysis

Continuous variables were presented as means and standard deviations (SD), and categorical variables as frequencies and percentages. Censoring was done for the first event recorded. We compared categorical variables using chi-square test and continuous variables using independent samples *t*-test for normally distributed data or Mann-Whitney *U* test for non-normal distribution. Baseline characteristics, stroke risk profiles, and ATT, as well as outcome events, were tabulated between patients with and without prior stroke.

To determine independent risk factors for 1-year stroke and major bleeding, we performed multivariate logistic regression using components of the CHA_2DS_2-VASc score (age assessed as a continuous variable) and ATT (undertreatment, overtreatment, and guideline adherent [as reference]) as co-varieties. These analyses were performed using IBM SPSS Statistics, Version 24.0 software (IBM Corp). Statistical significance was set as a two-sided p-value of <0.05.

3. Results

3.1. Clinical characteristics

Baseline characteristics of patients are shown in Table 1. Of 1860 patients with AF, 287 patients (15.4%) had a history of stroke. Patients with prior stroke were older with fewer females and had more often comorbidities including hypertension, diabetes mellitus, dyslipidemia, vascular disease, and dementia, as compared with those without prior stroke. AF in patients with prior stroke was more frequently asymptomatic, but there was no significant difference in first diagnosed AF between patients with and without prior stroke. The proportion of patients with and without prior stroke in relation to the stroke risk scores are shown in Fig. 1A ($CHADS_2$ score) and 1B (CHA_2DS_2-VASc score).

Overall, 58.8% of patients were prescribed OACs (34.4% OAC alone and 19.5% in combination with antiplatelet), while 37.4% received antiplatelet therapy alone and 8.0% remained untreated. In particular, 62.0% of patients with prior stroke were prescribed OACs, while 27.9% were still prescribed antiplatelet therapy alone and 10.1% received no ATT. The proportion of patients treated with guideline adherent ATT was 49.0%, while undertreatment was evident in 25.5%, and overtreatment in 25.4%. There were no significant differences in the proportion of guideline adherence in ATT between patients with and without prior stroke. Furthermore, the detail of each ATT category was shown in Supplementary Table 1.

3.2. Clinical outcomes and guideline adherence in ATT

During 1-year follow-up, the observed rate of stroke was 3.0% ($n = 56$). Compared to patients without prior stroke, stroke or TIA events occurred more often in those with prior stroke (18 [6.3%] vs. 38 [2.4%], $p < 0.001$). The rate of bleeding events was 8.1% ($n = 150$); of these, major bleeding occurred in 1.9% ($n = 36$) and non-major bleeding in 6.8% ($n = 126$). No significant difference was found in the incidence of bleeding events between AF patients with and without prior stroke (10.5% vs. 7.6%, $p = 0.106$). Details of 1-year outcomes in relation to patients with and without prior stroke are shown in Table 2.

Multivariable logistic regression analysis (Table 3) demonstrated that in the entire population, a history of stroke or TIA (odds ratio [OR]; 2.810, 95% confidence interval [CI]; 1.825–5.004, $p = 0.001$) and undertreatment (OR; 2.763, 95% CI; 1.426–5.352, $p = 0.003$) were significantly associated with an increased risk of 1-year stroke rate. Even

Table 1
Baseline characteristics of patients with and without prior stroke.

	Overall n = 1860	History of prior stroke		
		Yes (n = 287)	No (n = 1573)	p value
Demographics				
Age, mean ± SD	56.4 ± 16.4	64.3 ± 15.3	55.0 ± 16.2	<0.001
Age 65–74 y	382 (20.5)	81 (28.2)	301 (19.1)	<0.001
Age > 75 y	258 (13.9)	81 (28.2)	177 (11.3)	<0.001
Female gender (no. [%])	892 (48.0)	155 (46.9)	737 (54.0)	0.026
Smoking (no. [%])	421 (22.8)	62 (21.7)	359 (23.0)	0.613
No symptom (no. [%])	474 (25.5)	125 (43.6)	349 (22.2)	<0.001
First AF detection (no. [%])	809 (43.5)	119 (41.5)	690 (43.9)	0.450
Medical history (no. [%])				
Hypertension	985 (53.0)	196 (68.3)	789 (50.2)	<0.001
Diabetes mellitus	557 (29.9)	103 (35.9)	454 (28.9)	0.017
Dyslipidemia	637 (34.4)	129 (45.3)	508 (32.5)	<0.001
Heart failure	632 (34.0)	97 (33.8)	535 (34.0)	0.944
Vascular disease	628 (33.8)	127 (44.3)	501 (31.8)	<0.001
Dementia	66 (3.6)	35 (12.3)	31 (2.9)	<0.001
Thromboembolic risk, mean ± SD				
$CHADS_2$ score	1.6 ± 1.4	3.7 ± 1.1	1.2 ± 1.1	<0.001
CHA_2DS_2-VASc score	2.8 ± 2.0	5.2 ± 1.8	2.3 ± 1.7	<0.001
Antithrombotic therapy (no. [%])				
None	149 (8.0)	29 (10.1)	120 (7.6)	0.155
Oral anticoagulant	654 (34.3)	107 (37.3)	547 (34.8)	0.413
Antiplatelet	695 (37.4)	80 (27.9)	615 (39.1)	<0.001
Oral anticoagulant + antiplatelet	362 (19.5)	71 (24.7)	291 (18.5)	0.014
Contraindication to oral anticoagulant	155 (8.3)	33 (11.5)	122 (7.8)	0.035
Guideline adherence for antithrombotic therapy (no. [%])				
Guideline adherent	912 (49.0)	146 (50.9)	766 (48.7)	0.498
Undertreatment	475 (25.6)	77 (26.8)	398 (25.3)	0.585
Overtreatment	473 (25.4)	64 (22.3)	409 (26.0)	0.185
Rhythm control therapy (no. [%])				
Anti-arrhythmic drug	229 (12.3)	28 (9.8)	201 (12.8)	0.152
Catheter/surgical ablation	10 (0.5)	2 (0.7)	8 (0.5)	0.688

in the secondary and primary prevention subgroups, undertreatment was also an independent risk factor for 1-year stroke (OR; 3.275, 95% CI; 1.015–10.563, p = 0.047, OR; 2.690, 95% CI; 1.203–6.014, p = 0.016, respectively). In contrast, overtreatment was not significantly associated with the risk of stroke (OR; 1.599, 95% CI; 0.786–3.253, p = 0.195, for the entire population, OR; 1.730, 95% CI; 0.460–6.504, p = 0.417, for secondary prevention subgroup, and OR; 1.551, 95% CI; 0.663–3.628, p = 0.311, for primary prevention subgroup). We performed additional multivariable logistic regression analysis on 1-year stroke using the detailed ATT categories (Supplementary Table 2), which showed that combination therapy in patients without evidence of ACS in the overtreatment group was not significantly associated with the risk of stroke (OR; 1.011, 95% CI; 0.410–2.495, p = 0.981), but low risk patients who were overtreatment with ATT was significantly associated with an increased risk of stroke (OR; 3.521, 95% CI; 1.286–9.643, p = 0.014).

For 1-year major bleeding rate, overtreatment was the only factor significantly associated with an increased risk of major bleeding in the entire population (OR; 3.294, 95% CI; 1.517–7.152, p = 0.003). Undertreatment was not associated with lower risk of major bleeding (OR; 1.424, 95% CI; 0.524–3.867, p = 0.488, for the entire population, OR; 3.707, 95% CI; 0.284–48.459, p = 0.318, for secondary prevention subgroup, and OR; 1.264, 95% CI; 0.408–3.919, p = 0.685, for primary prevention subgroup). In the additional analysis on 1-year major bleeding, no anticoagulation in moderate- or high-risk patients in the undertreatment ATT group was not associated with lower risk of major bleeding, although there were no or small numbers of patients in some categories (Supplementary Table 3). Overtreatment ATT was not associated with an increased risk of major bleeding in the secondary prevention subgroup (OR; 2.461, 95% CI; 0.135–44.974, p = 0.544), but was significant in the primary prevention subgroup (OR; 3.579, 95% CI; 1.584–8.087, p = 0.002) (Table 3). In the additional analysis, combination therapy in patients with no evidence of ACS was not associated with the risk of major bleeding in the entire population and the subgroup populations, but anticoagulation in low risk patients was significantly associated with an increased risk of major bleeding in the entire population and in the primary stroke prevention subgroup (OR; 8.396, 95% CI; 2.894–24.358, p < 0.001, OR; 7.806, 95% CI; 2.580–23.623, p < 0.001, respectively) (Supplementary Table 3).

3.3. Quality of anticoagulation control

Overall, 497 (26.7%) patients receiving warfarin were identified, of which 90 (18.1%) constituted a secondary prevention subgroup. Mean TTR in the entire population was 57.5 ± 36.0%. There was no significant difference in TTR between secondary and primary prevention subgroups (61.9 ± 34.4% vs. 56.5 ± 36.3%, p = 0.145). Similarly, no significant difference was found between patients with and without combination therapy (OAC plus antiplatelet) (60.9 ± 34.3% vs. 56.1 ± 36.6%, p = 0.176), but mean TTR in low-risk patients was significantly lower than moderate- or high-risk patients (41.3 ± 40.1% vs. 61.4 ± 33.9%, p < 0.001).

4. Discussion

The present study found that guideline adherent ATT significantly reduced the risk of stroke and bleeding compared with non-guideline adherent ATT in this Middle East cohort. Furthermore, approximately half of the AF patients received optimal treatment for stroke prevention in line with guideline recommendations, even among secondary stroke prevention patients. Of note, 38% of patients with secondary stroke prevention were still prescribed antiplatelet therapy alone or remained untreated. In addition, anticoagulation control was suboptimal even when guideline adherent ATT was followed.

The present study provides important new insights into risk profile and appropriate assessment of AF patients in the Middle East. Risk factors for ischemic stroke in AF patients are well recognized as components of the CHA_2DS_2-VASc score, which is now well-established for stroke risk stratification scheme [9]. Among stroke risk factors, advanced age and prior stroke or TIA are most important predictors [12],

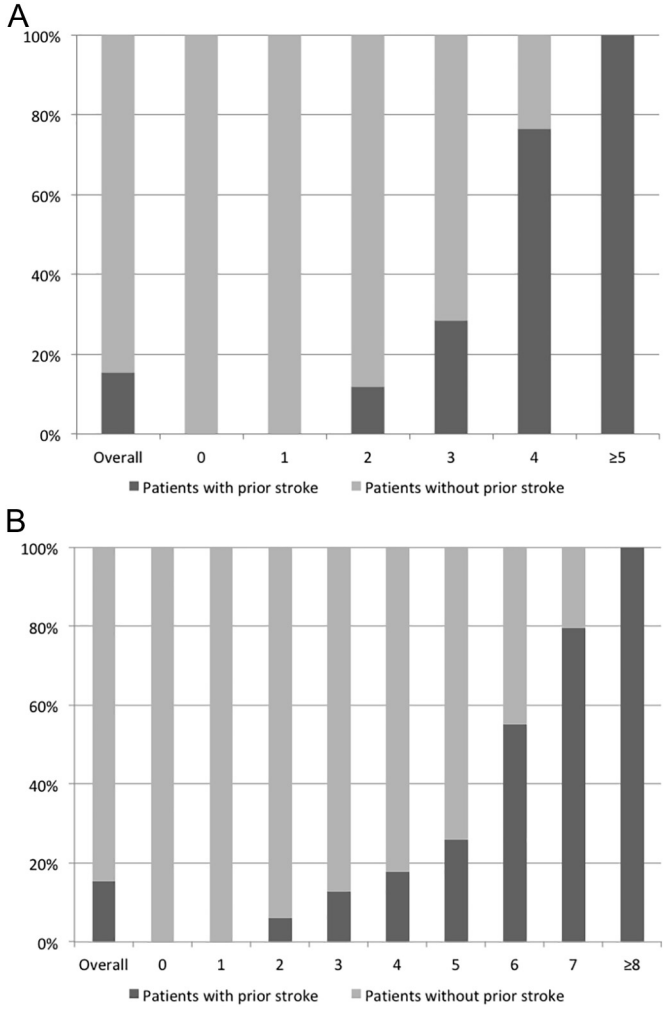

Fig. 1. The proportion of patients with and without prior stroke in relation to stroke risk scores (A: the $CHADS_2$ score and B: the CHA_2DS_2-VASc score).

emphasizing the need for OAC in these patients. In particular, the highest risk of recurrent stroke is in the early phase after a first stroke or TIA [13]. Therefore, rapid diagnosis and treatment initiation are crucial, especially in patients with secondary stroke prevention.

However, screening of all AF is still challenging because approximately one third of AF patients do not report any symptoms commonly attributable to AF (e.g. palpitation, shortness of breath, and chest pain) [14]. Indeed, an undiagnosed AF was present in 16% of patients who admitted with cryptogenic stroke [15]. The present study demonstrated that 25% of patients had no symptoms regarding AF, and 41% of patients in secondary stroke prevention cohort were diagnosed with AF at the enrollment of this study. Importantly, AF is also associated with cognitive impairment even in the absence of manifest stroke [16]. The mechanism underlying the association between AF and cognitive impairment may be explained by the presence of shared risk factors such as hypertension, diabetes mellitus, and heart failure [17]. Moreover, another possible mechanism is a hypercoagulable state and stasis of blood in the left atrium that may lead to formation of microthrombi and ultimately to subclinical strokes [18,19]. In the present study, approximately 4% of patients had dementia or cognitive impairment, which was more frequently observed in patients with prior stroke. Cognitive impairment may affect adherence and persistence to long-term ATT, which are associated with the risks of stroke and death [20]. Thus, screening for cognitive impairment and education about management of medications to AF patients as well as their carer(s) are also an important part of AF management, resulting in better anticoagulation control and better outcomes [21], especially for secondary stroke prevention.

4.1. Current use of antithrombotic treatment

Despite good advance in management of AF patients, AF remains one of the major causes of stroke [22]. There is still substantial number of patients not receiving appropriate ATT in accordance with guideline recommendations. Contemporary registry data showed that one third of patients at high risk of stroke were not prescribed OAC where indicated, but instead were treated with antiplatelet therapy alone or remained untreated [23]. Furthermore, previous studies have reported approximately 40–50% of AF patients were treated with ATT not following guideline recommendations, which was independently associated with an increased risk of stroke [24–27]. Although guideline adherence in ATT depends on the definition of applied guidelines, the present study applied 2010 ESC guidelines because Gulf SAFE registry was conducted between 2009 and 2011 [10], yet 51% of patients in overall cohort and 49% in secondary stroke prevention cohort received non-guideline adherent ATTs based on contemporary approaches.

4.2. Antithrombotic treatment and clinical outcomes

Despite clear evidence for the efficacy of OAC in AF patients, the underutilization of ATT is evident, especially for secondary stroke prevention. Recurrent strokes have been reported to account for 25–30% of all strokes, which are more disabling, fatal, and costly compared to first-ever strokes [28]. In the present study, stroke rates in patients with prior stroke were 2.5-fold higher than those without prior stroke, and a previous stroke or TIA was an independent risk factor for 1-year stroke rate. Concern for bleeding risk and clinical factors such as advanced age, dementia, and previous bleedings all contribute to the low prescription rate in clinical practice. Indeed, the present study demonstrated that 45% of patients received antiplatelet alone or no treatment, and even in patients receiving warfarin anticoagulation control was suboptimal. Overall, 25% of ATTs were categorized as undertreatment, which was associated with a 2.5-fold greater risk of stroke. Regardless of primary or secondary stroke prevention, guideline-adherent ATT significantly reduced the risk of stroke compared with non-guideline adherent ATT.

Similarly, 25% of patients received overtreatment ATT, which was not associated with the risk of stroke, but was significantly associated with a higher chance for 1-year major bleeding rate. Previous studies have demonstrated that there was no significant association between

Table 2
Clinical outcomes during 1-year follow-up in patients with and without prior stroke.

Clinical outcomes	Overall n = 1860 (no. [%])	Patients with prior stroke n = 287		Patients without prior stroke n = 1573		OR (95% CI)	p value
		No. of events	%/year	No. of events	%/year		
Stroke	56 (3.0)	18	6.3	38	2.4	2.703 (1.520–4.806)	<0.001
Bleeding	150 (8.1)	30	10.5	120	7.6	1.413 (0.927–2.154)	0.106
Major bleeding	36 (1.9)	4	1.4	32	2.0	0.681 (0.239–1.939)	0.469
Non-major bleeding	126 (6.8)	26	9.1	100	6.4	1.467 (0.935–2.304)	0.094

CI; confidence intervals, OR; odds ratio.

Table 3
Multivariable logistic regression analysis for 1-year stroke and major bleeding[a].

Outcomes and variables	Overall		Patients with prior stroke		Patients without prior stroke	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Stroke						
Age	1.005 (0.975–1.008)	0.610	1.003 (0.966–1.042)	0.879	1.002 (0.979–1.027)	0.842
Female gender	1.126 (0.723–1.763)	0.669	0.571 (0.212–1.534)	0.266	1.507 (0.773–2.936)	0.228
Hypertension	0.827 (0.672–2.082)	0.564	0.903 (0.256–3.187)	0.873	0.810 (0.378–1.736)	0.588
Diabetes mellitus	0.949 (0.486–1.413)	0.871	0.933 (0.290–2.998)	0.908	0.984 (0.459–2.109)	0.967
Heart failure	1.415 (1.172–3.084)	0.243	0.811 (0.269–2.442)	0.710	1.747 (0.866–3.527)	0.119
Stroke or TIA	2.810 (1.825–5.004)	0.001	N/A		N/A	
Vascular disease	0.613 (0.686–1.987)	0.144	0.511 (0.164–1.586)	0.245	0.684 (0.303–1.544)	0.360
ATT						
Guideline adherent	(Reference)		(Reference)		(Reference)	
Undertreatment	2.763 (1.426–5.352)	0.003	3.275 (1.015–10.563)	0.047	2.690 (1.203–6.014)	0.016
Overtreatment	1.599 (0.786–3.253)	0.195	1.730 (0.460–6.504)	0.417	1.551 (0.663–3.628)	0.311
Major bleeding						
Age	0.979 (0.952–1.006)	0.121	0.989 (0.882–1.109)	0.856	0.976 (0.948–1.005)	0.109
Female gender	1.167 (0.594–2.293)	0.654	0.263 (0.024–2.838)	0.271	1.337 (0.650–2.752)	0.430
Hypertension	0.836 (0.346–2.019)	0.690	0.555 (0.040–7.622)	0.660	0.781 (0.297–2.052)	0.616
Diabetes mellitus	1.829 (0.822–4.123)	0.146	0.696 (0.085–5.710)	0.736	2.139 (0.884–5.175)	0.092
Heart failure	1.165 (0.545–2.490)	0.694	0.409 (0.038–4.402)	0.461	1.445 (0.644–3.242)	0.373
Stroke or TIA	0.856 (0.293–2.503)	0.776	N/A		N/A	
Vascular disease	0.931 (0.386–2.247)	0.874	2.876 (0.228–36.325)	0.414	0.604 (0.217–1.682)	0.334
ATT						
Guideline adherent	(Reference)		(Reference)		(Reference)	
Undertreatment	1.424 (0.524–3.867)	0.488	3.707 (0.284–48.459)	0.318	1.264 (0.408–3.919)	0.685
Overtreatment	3.294 (1.517–7.152)	0.003	2.461 (0.135–44.974)	0.544	3.579 (1.584–8.087)	0.002

ATT; antithrombotic treatment, CI; confidence intervals, TIA; transient ischeamic attack, OR; odds ratio.
[a] Adjusted covariates included components of the CHA_2DS_2-VASc score (age assessed as a continuous variable) and antithrombotic treatment (guideline adherent [as a reference], undertreatment, and overtreatment).

overtreatment in ATT and a risk of major bleeding [24,26]. In contrast to the present study, other studies did not take the presence of contraindications into account in adherence to ATT. A previous cohort reported that 13% of patients with AF had contraindications to OAC such as prior bleed, patient refusal/preference, and high bleeding risk [29].

Interestingly, the additional analysis using the detailed ATT categories demonstrated that anticoagulation in low-risk patients who had overtreatment with ATT was significantly associated with an increased risk of stroke compared with guideline adherent ATT. On the other hand, there was no association between combination therapy (OAC plus antiplatelet) in patients with no evidence of ACS and the risk of stroke. Various residual confounding factors may explain this, but quality of anticoagulation control (e.g. TTR) may contribute to these results, given that poor anticoagulation control as reflected by low TTR is known to be associated with the risk of stroke [30]. In a previous study, TTR in patients with $CHADS_2$ score of ≤1 was lower than those with $CHADS_2$ score of ≥2 [31], suggesting that poor anticoagulation control leads to a more strokes, even in patients with low incidence of stroke. Furthermore, the combined use of warfarin and antiplatelets requires careful consideration when balancing thromboembolic and bleeding risks [32] Previous studies have shown that the use of antiplatelet in patients receiving warfarin was not an independent factor associated with poor anticoagulation control [33,34]. Like previous studies, the present study demonstrates that poor anticoagulation control was not observed in patients receiving combination therapy, but seen in those with low risk of stroke.

4.3. Limitations

The present study has some limitations. The Gulf SAFE registry was conducted from 2009 to 2011, and stroke risk stratification was essentially based on the $CHADS_2$ score. However, we used the CHA_2DS_2-VASc score in this retrospective post hoc modelling exercise, for the assessment of adherence to guideline recommended ATT. OAC prescription was at the discretion of each physician and was based on the guidelines at that time. Second, the analysis on the specific bleeding outcomes such as intra-cranial hemorrhage was not performed because there were small numbers of each event, especially intra-cranial hemorrhage which occurred in only 4 patients during follow-up. Therefore, the present study defined major bleeding as a composite event including fatal bleeding, and/or symptomatic bleeding in a critical area or organ such as intra-cranial, intra-spinal, intra-ocular, retroperitoneal, intra-articular or pericardial or intra muscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of >5 g/dL, or leading to transfusion of two or more units of whole blood or red cells, minor bleeding as overt clinical bleeding associated with a fall in hemoglobin of 3 to 5 g/dL. Third, compared with previous studies, there were a relatively substantial number of patients with vascular disease and combination therapy (OAC plus antiplatelet) used in the present study. Use of combination therapy has been associated with an increased risk of major bleeding and but with no reduction in the risk of stroke [32].

5. Conclusions

Guideline adherent ATT significantly reduced the risk of stroke and bleeding compared with non-guideline adherent ATT in this Middle East cohort. Only half of the AF patients received optimal anticoagulation therapy for stroke prevention if we apply recommendations from contemporary guidelines. Despite a high risk of stroke, 38% of patients with secondary stroke prevention were still prescribed antiplatelet therapy alone or remained untreated.

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None.

Conflicts of interest

Drs. Miyazawa, Li and Rashed report no competing interests. Dr. Lip: Consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo. Speaker

for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.07.120.

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