One-year risks of stroke and mortality in patients with atrial fibrillation from different clinical settings

The Gulf SAFE registry and Darlington AF registry

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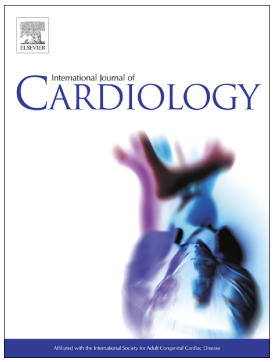

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One-year risks of stroke and death in patients with atrial fibrillation from different clinical settings: The Gulf SAFE Registry and Darlington AF Registry

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Declarations of interest

None directly related to this paper. GYHL: Consultant for Bayer/Janssen, BMS/Pfizer, 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.

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Keywords: Atrial fibrillation, Stroke prevention, Anticoagulation, Stroke and Mortality, Clinical setting

ABSTRACT

Background: AF patients from different clinical settings may have varying outcomes. We aimed to provide patient-level comparisons using two cohorts of patients with AF from different settings.

Methods: The clinical characteristics, prescription of OAC, one-year risks of stroke and mortality were compared between patients with AF included into the Darlington AF registry (general practice-based cohort from the United Kingdom, n=2258) and the Gulf SAFE (Survey of atrial fibrillation events) registry (emergency room-based cohort from the Gulf countries, n=1740).

Results: Patients from the Gulf SAFE registry were younger, had high prevalence of diabetes, vascular disease, heart failure. Patients from the Darlington registry had higher prevalence of hypertension, previous thromboembolism event, and higher mean stroke risk. OAC use was <60% in high stroke risk patients in both registries. On multivariate analyses, patients from Gulf SAFE were independently associated with higher risks of stroke (odds ratio, 2.18 [1.47-3.23]) and mortality (odds ratio, 1.67 [1.31-2.14]), especially in those with high CHA_2DS_2-VASc score (≥2 in males, ≥3 in females) (Darlington vs. Gulf SAFE: 3.51% vs. 5.63 for stroke; 11.4% vs. 16.8% for mortality)

Conclusions: Differences regarding AF patients profile, OAC use and outcomes exist in varying clinical settings as reflected by registries from different origins. Tailored AF management strategy are needed to fit in different clinical settings.

Introduction

Atrial fibrillation (AF) is the most prevalent arrhythmia worldwide, conferring an increased risk of ischemic stroke, systemic embolism (SE), heart failure (HF) and mortality[1, 2]. During the past decades, the prevalence of AF has increased significantly because of increasingly prevalent contributing factors, including an ageing population, hypertension, diabetes mellitus (DM), coronary artery disease (CAD) and HF[3]. Nevertheless, more limited data on AF epidemiology are available from the Middle East (ME), when compared to Western countries and Asia[4-6].

Management of AF requires a holistic and integrated procedure, to Avoid stroke, achieve Better symptom management and reduce Cardiovascular and comorbidity (the ABC pathway)[7]. AF-related ischemic stroke is one of the most devastating outcomes for AF, which can be reduced by oral anticoagulation (OAC) [8, 9].

Nevertheless, the prescription rates of OAC and the quality of anticoagulation control varies between different geographical areas[10], which may have implications for outcomes among AF patients[11-13]. There is also the perception that outcomes differ by region, ethnicity and **healthcare provider**, even amongst patients with AF. Hence, evaluating AF epidemiology and outcomes between **different populations** may help us understand the global scenario of this common arrhythmia. For example, differences in OAC prescription rates and related outcomes among AF patients from the United Kingdom (UK) and the Middle East (ME) have never been previously reported.

In this study, we aimed to provide patient level comparisons of clinical characteristics, OAC use, and one-year risks of stroke and mortality amongst two diverse cohorts of patients with AF.

Materials and Methods

Individual data from two registries were used in this study, including the Darlington AF Registry from UK and the Gulf SAFE (Gulf Survey of Atrial Fibrillation Events) Registry from ME. Details of both registries have been published[14, 15].

In brief, the study population of the Darlington Registry was derived from 11 general practices serving the town of Darlington, County Durham, UK. All patients with known vital status in March 2013 were eligible for inclusion. Majority of the AF patients in the Darlington Registry were Caucasian (over 96%)[16]. Data collection of this study was performed with GRASP-AF (Guidance on Risk Assessment and Stroke Prevention in Atrial Fibrillation) audit tool, which can interrogate primary care database with a pre-defined set of search criteria. Information regarding demographic profile, AF diagnosis, comorbidities, treatment, and outcomes were collected. All events during 12 months of follow-up were manually reviewed and confirmed by imaging and/or stroke physician opinion. Details about antithrombotic therapy (ATT), OAC were identified through database audit. **Patients were classified as using anticoagulants or antiplatelet agents if a prescription was issued within the last 6 months of the data collection.**

The Gulf SAFE study was a prospective, multinational, observational registry of patients visiting the emergency room with AF with a 12-month of follow-up. Detailed methodology was previously described[15]. Patients were recruited between October 2009 and June 2010

from emergency room of 23 hospitals in six Gulf countries from ME, including Bahrain, Kuwait, Qatar, Oman, Yemen, and United Arab Emirates. Data was collected by standardized case report form and entered online. Aspects regarding the data included patient demographics, medical history, and outcomes. ATT and OAC prescription were also identified **at discharge which was also the start of follow-up**. **For patients on Vitamin K antagonists who had at least three INR checks, the time in therapeutic range (TiTR) was calculated using the well accepted Rosendaal method[17].**

After the exclusion of patients who died within 30 days after recruitment (n=137) and severe mitral stenosis (n=167), a total of 3998 patients with AF entered the final analysis, with 2258 from the Darlington and 1740 from the Gulf SAFE Registry (**Supplementary Figure S1**).

Definitions

Individual risks of stroke were assessed using the CHA_2DS_2-VASc score. **The CHA_2DS_2-VASc score was calculated based on patients' risk profile at recruitment. For patients from the Gulf SAFE registry, during which time the CHA_2DS_2-VASc score was in its initial period, this score was retrospectively calculated based on information from detailed patient records.** Low-risk was defined as the CHA_2DS_2-VASc score of 0 in males and 1 in females, medium-risk as 1 in males and 2 in females, and high-risk as ≥2 in males or ≥3 in females. The $CHADS_2$ (congestive HF, hypertension, age ≥75, DM, stroke/SE/TIA [doubled]) score of each patient was also calculated. ATT was defined as prescription of OAC (warfarin or non-vitamin K antagonist anticoagulant [NOAC]) or antiplatelets drugs (aspirin or clopidogrel). Major outcomes recorded included stroke events and all-cause mortality during one-year follow-up. Both ischemic stroke and transient ischemic attack (TIA) were identified as stroke events.

Statistical analysis

Descriptive analyses were used in this study. Following testing for normality, continuous variables in normal distribution were expressed as mean ± standard deviation (SD), or median ± interquartile range (IQR) for non-parametric distributions. Categorical variables were expressed as observed number of patients and percentages. Comparison between continuous variables were analysed using Student's T test or Mann-Whitney U test, as appropriate. Difference between categorical variables were analysed using Pearson chi-square test.

Multivariable logistic regression analysis was used for testing independent risk factors for one-year outcome. The performance of the CHA_2DS_2-VASc score for predicting risk of stroke and mortality was analysed by area under curve (AUC). **Bootstrap procedure with 1000 replicates was also used for validating the performance of the CHA_2DS_2-VASc score in the combined population**, **considering the differences among the two cohorts**. All tests were two-tailed. A p value <0.05 was considered as statistically significant. Analyses were performed using SPSS Statistics, version 23.0 (IBM, SPSS Inc) and STATA Software, version 14.0 (Stata Corp, College Station, TX).

Results

Baseline characteristics of the two populations are summarised in Table 1. Patients from Darlington were older and had higher prevalence of hypertension, previous stroke and TIA, with higher $CHADS_2$ and CHA_2DS_2-VASc scores. Patients from Gulf SAFE countries had higher prevalence of DM, vascular disease and HF. The prescription rate of antiplatelet agents was higher in the patients from Gulf SAFE, as well as the rate of dual antithrombotic therapy, i.e., OAC plus antiplatelet drug. A higher percentage of AF patients from Darlington were categorised as high-risk (**Supplementary Figure S2**).

OAC prescription in Darlington *and* Gulf countries

ATT use increased with higher stroke risk strata in both populations, from 49.4% to 88.4% in Darlington and 85.1% to 93.7% in Gulf SAFE countries (Figure 1). OAC use also increased with higher stroke risk strata, from 23.5% to 46.8% in Darlington and 32.0% to 58.4% in Gulf countries. In both populations, OAC use in non-low risk categories of the both populations were less than 60%. In the high-risk categories, patients from Gulf SAFE countries had more use of dual antithrombotic therapy (28.8% vs. 5.2%). **In the Gulf SAFE registry, for patients on anticoagulation (n=747), a total of 353 patients (47.3%) had at least three INR checks, and these had a mean TiTR of 63.5% (SD=37.0).**

One-year risks of stroke and mortality

Patients from Gulf SAFE registry had higher rates of stroke for each risk category (Table 2). Stroke rates increased with higher risk strata in patients from Gulf SAFE countries. Mortality rates also increased with higher risk strata in both populations (Table 2). Among high-risk patients, one-year mortality rates were 11.4% and 16.8% in patients from Darlington and

Gulf SAFE countries, respectively. A relatively higher mortality risk was observed in each risk category in AF patients from Gulf SAFE **registry** compared with Darlington **registry** (Table 2). **Among patients with high stroke risk, patients on OAC from the Gulf SAFE registry had high risk of stroke and mortality. Such difference was not shown in the non-OAC patients (see Supplementary Table S1).**

Multivariable analysis for stroke and mortality events

On multivariable analysis, female sex, and previous stroke were independently associated with stroke events (see Table 3). Elderly age, female sex, HF and vascular disease were independent risk factors for mortality (see Table 3). Patients from Gulf SAFE countries had a doubled risk of stroke and a 67% higher risk of mortality compared with those from Darlington. OAC significantly reduced the risk of all-cause mortality by 45% in the whole study population.

In the multivariable analysis, OAC did not show a significant reduction of stroke events. We then performed a baseline comparison between patients with and without OAC. Patients with OAC had a significantly higher CHA_2DS_2-VASc score (3, IQR [2-5] vs. 3, IQR [1-4]; p=0.000) and higher percentage of patients with CHA_2DS_2-VASc score ≥2 (see Supplementary Table S2).

As demonstrated in the multivariable analysis, OAC was independently associated with mortality reduction; however, such reduction was only shown among patients from the Darlington registry (OAC vs. No-OAC: 6.2% vs. 12.4%, Darlington; 11.8% vs. 10.9% Gulf SAFE).

Predicting risks of stroke and mortality

The CHA_2DS_2-VASc score was a good predictor for the one-year risk of stroke in non-anticoagulated patients, with an AUC of 0.71 (95% confidence intervals [CI], 0.65-0.76) in the combined population (n=2036) (**Supplementary Figure S3**), also in UK and ME cohorts separately (AUC for Darlington [n=1179] of 0.74 [95% CI, 0.67-0.81]; AUC for Gulf [n=857] of 0.70 [95% CI, 0.63-0.77]). The CHA_2DS_2-VASc score also had good predictive ability for one-year mortality, with an AUC of 0.70 (95%CI, 0.68-0.72) in the combined population (**Supplementary Figure S3**), also in UK and ME cohorts separately (AUC for Darlington of 0.70 [95% CI, 0.67-0.73]; AUC for Gulf of 0.72 [95% CI, 0.68-0.76]).

The performances of the CHA_2DS_2-VASc score were confirmed by bootstrap procedure in the combined population, which gave an AUC of 0.64 (95%CI, 0.58-0.69) for stroke and of 0.62 (95%CI, 0.60-0.65) for mortality.

Discussion

In the present study, we have performed the first patient level comparisons of clinical characteristics, OAC use, and one-year risks of stroke and mortality amongst two cohorts of patients with AF. We show differences in stroke risk distribution, OAC use and one-year risks of stroke and mortality between patients with AF enrolled in the Darlington AF registry (UK) and the Gulf SAFE registry (ME).

Our principal findings are as follows: (i) While large percentages of patients with AF would be candidates for OAC in both populations, overall OAC use was suboptimal; (ii) High one-year rates of stroke and mortality were observed in both populations, especially in the high-risk patient category, but patients from Gulf SAFE registry had higher risk of stroke and mortality compared with those from Darlington registry; (iii) Female sex and previous stroke were independent factors associated with stroke, while elderly age, female sex, HF and vascular disease were independent risk factors for mortality; and (iv) The CHA_2DS_2-VASc score showed good discrimination in predicting one-year risk of stroke in non-anticoagulated patients and mortality in the whole study population, as well as in the Darlington and Gulf SAFE cohorts separately

As expected (and shown in the present study), the majority of patients with AF are candidates for OAC, given that the latter reduces stroke and mortality[9]. In a prior study from Saudi Arabia, this percentage was as high as 92%[18]. Wide regional differences in OAC used among patients with AF have been reported. The EORP-AF registry (EURObservational Research Programme of AF) showed a high OAC use among European countries (84.9%)[19]. Also, the GLORIA-AF registry found highest OAC use in Europe (90.1%), followed by Africa/ME

(87.4%)[10]. In the present study, there was still an unmet need given that OAC use was suboptimal, as is reflected by high one-year stroke and mortality risks.

Our study shows that even in anticoagulated patients, the one-year rate of stroke was still high, with 3.0% in Darlington and 5.3% in Gulf countries. This may suggest a suboptimal OAC management in these at-risk patients from both populations, given that OAC use was mainly vitamin K antagonists (VKA, e.g. warfarin). The effectiveness of the latter is highly dependent on the quality of anticoagulation control[20]. **In the Gulf SAFE registry, only 47.3% (n=353) patients had at least three INR checks across the 12 months of follow-up, and the TiTR was suboptimal (mean 63.5%). For the other patients without INR checks and corresponding dosage adjustment, the TiTR might be even lower.** The **suboptimal anticoagulation quality** may translate to higher stroke and mortality rates in Gulf SAFE countries compared to Darlington, or to other differences not accounted for on multivariate analysis which did show an independent effect of study cohort (i.e., 2.18-fold higher risk in Gulf SAFE, vs. Darlington) on stroke. **Unfortunately, we were unable to provide the TiTR information in the Darlington registry, which might have provided more details of anticoagulation quality in this population. We would speculate that these patients may have higher TiTR, considering a good anticoagulation quality control has consistently been shown in AF patients from the UK[21, 22].**

In the multivariable analysis, OAC was associated with mortality reduction, which was only shown in the Darlington registry, but not in Gulf SAFE registry. A widely used active medical surveillance in the UK for anticoagulated patients might be the major reason, enabling routine good anticoagulation quality control and management of other

comorbidities. Indeed, in another study from UK, among patients with high stroke risk, OAC was associated with 11% to 73% reduced mortality[23].

For a reduced mortality among patients with AF, good OAC use may be not enough and management of other comorbidities is equally important. In the EORP-AF registry, one-year mortality was high (5.7%), with cardiovascular death being responsible for the majority (70%)[24]. In a prospective, multicentre registry in China, the one-year all-cause mortality in patients with AF was 14.6%[25]. In the present study, mortality was high in both populations, especially among those with high CHA_2DS_2-VASc score. On multivariate analysis there was an independent effect of study cohort (i.e., 1.67-fold higher risk in Gulf SAFE, vs. Darlington) on mortality. Reasons for this may include a different health care level and relatively high prevalence of comorbidities (DM, HF and vascular disease) in Gulf SAFE at baseline.

Indeed, multiple risk factors were associated with the risks of stroke and mortality in patients with AF[26]. Also, we confirm the good performance of the CHA_2DS_2-VASc score in predicting stroke and mortality as was demonstrated previously[27-31]. Stroke only accounts for 10% of the mortality seen in AF; whilst other cardiovascular diseases account for nearly 70%[32, 33]. Hence, management of other coexisting cardiovascular diseases and risk factors is also necessary. To adequately identify at-risk patients may help implement more aggressive management strategies in a holistic and integrated manner to ensure a better outcome[7].

Limitations

The present study is the first patient level comparisons of two cohorts of patients with AF, from the UK and ME. Nevertheless, there are some limitations. We did not consider patients'

preference which could affect the OAC decision[34]. We did not have data on time in therapeutic range among patients on vitamin K anticoagulants **in the Darlington cohort**, and data on our two cohorts were collected before the wide use of non-VKA OACs (NOACs). Also, we could not report the risks of major bleeding and intracranial haemorrhage, which were not recorded. Darlington is one region in UK, while Gulf SAFE is from multiple countries and each may have differences in implementation and guideline adherence. **The two registries were conducted among different healthcare providers, which could be another reason for the differences. This study was not able to differentiate which was the predominant factor, which needs further investigation.** In addition, the two cohorts were collected in slightly different time periods. **The Gulf SAFE study was conducted between 2010 to 2012, which was 2 to 3 years earlier than the Darlington registry. Over time, there might be some improvement, but considering that the Gulf SAFE study covers 23 centres from 6 Gulf countries, the improvement over 2-3 years may not be profound and thus, should not change the major conclusions of the present study.**

Conclusion

Stroke prevention was generally suboptimal in two patient cohorts from UK and ME, which was associated with high one-year risks of stroke and mortality, particularly so amongst patients from ME. The higher risks for stroke and mortality in AF patients from ME countries (compared to a UK cohort) merits further studies to enable implementation of cardiovascular prevention strategies.

Declarations of interest

None directly related to this paper. GYHL: Consultant for Bayer/Janssen, BMS/Pfizer, 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.

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References

1. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the renfrew/paisley study. *The American journal of medicine*. 2002;113:359-364
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: The framingham study. *Stroke; a journal of cerebral circulation*. 1991;22:983-988
3. Guo Y, Tian Y, Wang H, Si Q, Wang Y, Lip GYH. Prevalence, incidence, and lifetime risk of atrial fibrillation in china: New insights into the global burden of atrial fibrillation. *Chest*. 2015;147:109-119
4. Bai Y, Wang YL, Shantsila A, Lip GYH. The global burden of atrial fibrillation and stroke: A systematic review of the clinical epidemiology of atrial fibrillation in asia. *Chest*. 2017;152:810-820
5. Al-Shamkhani W, Ayetey H, Lip GYH. Atrial fibrillation in the middle east: Unmapped, underdiagnosed, undertreated. *Expert review of cardiovascular therapy*. 2018;16:341-348
6. Hersi AS, Alsheikh-Ali AA, Zubaid M, Al Suwaidi J. Prospective observational studies of the management and outcomes in patients with atrial fibrillation: A systematic review. *J Saudi Heart Assoc*. 2012;24:243-252
7. Lip GYH. The abc pathway: An integrated approach to improve af management. *Nat Rev Cardiol*. 2017;14:627-628
8. Li YG, Pastori D, Lip GYH. Fitting the right non-vitamin k antagonist oral anticoagulant to the right patient with non-valvular atrial fibrillation: An evidence-based choice. *Ann Med*. 2018;50:1-15

9. Lip G, Freedman B, De Caterina R, Potpara TS. Stroke prevention in atrial fibrillation: Past, present and future. Comparing the guidelines and practical decision-making. *Thromb Haemost*. 2017;117:1230-1239

10. Mazurek M, Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener HC, et al. Regional differences in antithrombotic treatment for atrial fibrillation: Insights from the gloria-af phase ii registry. *Thromb Haemost*. 2017;117:2376-2388

11. Zoppellaro G, Granziera S, Bertozzo G, Denas G, Marigo L, Petruzzellis F, et al. Consequences of warfarin suspension after major bleeding in very elderly patients with non valvular atrial fibrillation. *Thromb Haemost*. 2017;117:1828-1830

12. Rivera-Caravaca JM, Roldan V, Esteve-Pastor MA, Valdes M, Vicente V, Lip GYH, et al. Cessation of oral anticoagulation is an important risk factor for stroke and mortality in atrial fibrillation patients. *Thromb Haemost*. 2017;117:1448-1454

13. Wilson MR, Parakramawansha R, Quinn TJ, Tait RC. Quality and predictors of anticoagulant control with vitamin k antagonist for stroke prevention in atrial fibrillation. *Thromb Haemost*. 2016;116:578-580

14. Shantsila E, Wolff A, Lip GY, Lane DA. Optimising stroke prevention in patients with atrial fibrillation: Application of the grasp-af audit tool in a uk general practice cohort. *Br J Gen Pract*. 2015;65:e16-23

15. Zubaid M, Rashed WA, Alsheikh-Ali AA, Almahmeed W, Shehab A, Sulaiman K, et al. Gulf survey of atrial fibrillation events (gulf safe): Design and baseline characteristics of patients with atrial fibrillation in the arab middle east. *Circ Cardiovasc Qual Outcomes*. 2011;4:477-482

16. Senoo K, An Y, Ogawa H, Lane DA, Wolff A, Shantsila E, et al. Stroke and death in elderly patients with atrial fibrillation in japan compared with the united kingdom. *Heart*. 2016;102:1878-1882

17. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost*. 1993;69:236-239

18. Al-Turaiki AM, Al-Ammari MA, Al-Harbi SA, Khalidi NS, Alkatheri AM, Aldebasi TM, et al. Assessment and comparison of chads2, cha2ds2-vasc, and has-bled scores in patients with atrial fibrillation in saudi arabia. *Annals of thoracic medicine*. 2016;11:146-150

19. Lip GY, Laroche C, Boriani G, Dan GA, Santini M, Kalarus Z, et al. Regional differences in presentation and treatment of patients with atrial fibrillation in europe: A report from the eurobservational research programme atrial fibrillation (eorp-af) pilot general registry. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. 2015;17:194-206

20. Liu S, Li X, Shi Q, Hamilton M, Friend K, Zhao Y, et al. Outcomes associated with warfarin time in therapeutic range among us veterans with nonvalvular atrial fibrillation. *Curr Med Res Opin*. 2018;34:415-421

21. Cotte FE, Benhaddi H, Duprat-Lomon I, Doble A, Marchant N, Letierce A, et al. Vitamin k antagonist treatment in patients with atrial fibrillation and time in therapeutic range in four european countries. *Clin Ther*. 2014;36:1160-1168

22. Ingram SJ, Kirkdale CL, Williams S, Hartley E, Wintle S, Sefton V, et al. Moving anticoagulation initiation and monitoring services into the community: Evaluation of the brighton and hove community pharmacy service. *BMC Health Serv Res*. 2018;18:91

23. Gallagher AM, Setakis E, Plumb JM, Clemens A, van Staa TP. Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. *Thromb Haemost*. 2011;106:968-977

24. Lip GY, Laroche C, Ioachim PM, Rasmussen LH, Vitali-Serdoz L, Petrescu L, et al. Prognosis and treatment of atrial fibrillation patients by european cardiologists: One year follow-up of the eurobservational research programme-atrial fibrillation general registry pilot phase (eorp-af pilot registry). *Eur Heart J*. 2014;35:3365-3376

25. Yang YM, Shao XH, Zhu J, Zhang H, Liu Y, Gao X, et al. One-year outcomes of emergency department patients with atrial fibrillation: A prospective, multicenter registry in china. *Angiology*. 2015;66:745-752

26. Pastori D, Pignatelli P, Angelico F, Farcomeni A, Del Ben M, Vicario T, et al. Incidence of myocardial infarction and vascular death in elderly patients with atrial fibrillation taking anticoagulants: Relation to atherosclerotic risk factors. *Chest*. 2015;147:1644-1650

27. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The euro heart survey on atrial fibrillation. *Chest*. 2010;137:263-272

28. Lahewala S, Arora S, Patel P, Kumar V, Patel N, Tripathi B, et al. Atrial fibrillation: Utility of chads2 and cha2ds2-vasc scores as predictors of readmission, mortality and resource utilization. *International journal of cardiology*. 2017;245:162-167

29. Chen YL, Cheng CL, Huang JL, Yang NI, Chang HC, Chang KC, et al. Mortality prediction using chads2/cha2ds2-vasc/r2chads2 scores in systolic heart failure patients with or without atrial fibrillation. *Medicine*. 2017;96:e8338

30. Su CH, Tsao TF, Chen AC, Chang KW, Yang YS, Ueng KC, et al. Cha2 ds2 -vasc scores for outcome prediction in acute ischaemic stroke. *European journal of clinical investigation*. 2018;48:e12884

31. Diemberger I, Fantecchi E, Reggiani MLB, Martignani C, Angeletti A, Massaro G, et al. Atrial fibrillation and prediction of mortality by conventional clinical score systems according to the setting of care. *International journal of cardiology*. 2018

32. Pokorney SD, Piccini JP, Stevens SR, Patel MR, Pieper KS, Halperin JL, et al. Cause of death and predictors of all-cause mortality in anticoagulated patients with nonvalvular atrial fibrillation: Data from rocket af. *Journal of the American Heart Association*. 2016;5:e002197

33. Fauchier L, Villejoubert O, Clementy N, Bernard A, Pierre B, Angoulvant D, et al. Causes of death and influencing factors in patients with atrial fibrillation. *The American journal of medicine*. 2016;129:1278-1287

34. Loewen PS, Ji AT, Kapanen A, McClean A. Patient values and preferences for antithrombotic therapy in atrial fibrillation. A narrative systematic review. *Thromb Haemost*. 2017;117:1007-1022

FIGURE LEGENDS

Figure 1. Oral anticoagulant use in patients with atrial fibrillation in Darlington and Gulf SAFE countries (%)

APT=antiplatelet therapy; ATT=antithrombotic therapy; OAC=oral anticoagulation

Table 1. Baseline characteristics and antithrombotic therapy in patients with AF from Darlington and Middle East

Characteristics	All (n=3,998)	Darlington Registry (n=2,258)	Gulf SAFE Registry (n=1,740)	P value
Demographics				
Age, mean ± SD (y)	67.8 ± 16.6	75.6 ± 12.2	57.7 ± 16.0	< 0.001
Female, No. (%)	1846 (46.2)	1040 (46.1)	806 (46.3)	0.868
Medical history, No. (%)				
Hypertension	2389 (59.8)	1404 (62.2)	985 (56.6)	< 0.001
Diabetes mellitus	1041 (26.0)	489 (21.7)	552 (31.7)	< 0.001
Vascular disease	945 (23.6)	388 (17.2)	557 (32.0)	< 0.001
Previous stroke or TIA	631 (15.8)	428 (19.0)	203 (11.7)	< 0.001
Heart failure	905 (22.6)	455 (20.2)	450 (25.9)	< 0.001
Thrombotic risk				
$CHADS_2$ score, median (IQR)	2 (1-3)	2 (1-3)	1 (0-2)	< 0.001
CHA_2DS_2-VASc score, median (IQR)	3 (2-4)	4 (2-5)	2 (1-4)	< 0.001
Antithrombotic therapy, No. (%)				
OAC	1962 (49.1)	1079 (47.8)	883 (50.7)	0.063
APT	1962 (49.1)	921 (40.8)	1041 (59.8)	< 0.001
OAC plus APT	449 (11.2)	110 (4.9)	339 (19.5)	< 0.001
No ATT	423 (10.6)	368 (16.3)	155 (8.9)	< 0.001

APT=antiplatelet therapy; ATT=antithrombotic therapy; $CHADS_2$ score=congestive heart failure, hypertension, age>75; diabetes mellitus, previous stroke or TIA [doubled]; CHA_2DS_2-VASc score=congestive heart failure, hypertension, age≥75 [doubled], diabetes mellitus, previous stroke or TIA [doubled], vascular disease, age 65-74, sex category [female]; IQR=inter quartile range; OAC=oral anticoagulant; SD=standard deviation; TIA=transient ischemic attack.

Table 2. One-year risks of stroke and mortality in Darlington and Gulf SAFE countries

Characteristics	Stroke				Mortality			
	Risk* (95% CI)		Relative risk (95% CI)	P value	Risk* (95% CI)		Relative risk (95% CI)	P value
	Darlington	Gulf SAFE			Darlington	Gulf SAFE		
Low risk	0.59 (0.00-1.75)	2.84 (1.25-4.44)	4.95 (0.64-38.3)	0.115	0.59 (0.00-1.75)	2.61 (1.08-4.13)	4.52 (0.58-35.3)	0.091
Medium risk	0.00 (N/A)	5.25 (2.81-7.69)	**N/A**	**0.001**	0.42 (0.00-1.25)	5.86 (3.29-8.44)	**14.7 (1.95-110.6)**	**< 0.001**
High risk	3.51 (2.67-4.35)	5.63 (4.20-7.07)	**1.64 (1.14-2.37)**	**< 0.001**	11.40 (9.95-12.9)	16.80 (14.5-19.1)	**1.57 (1.26-1.96)**	**0.007**

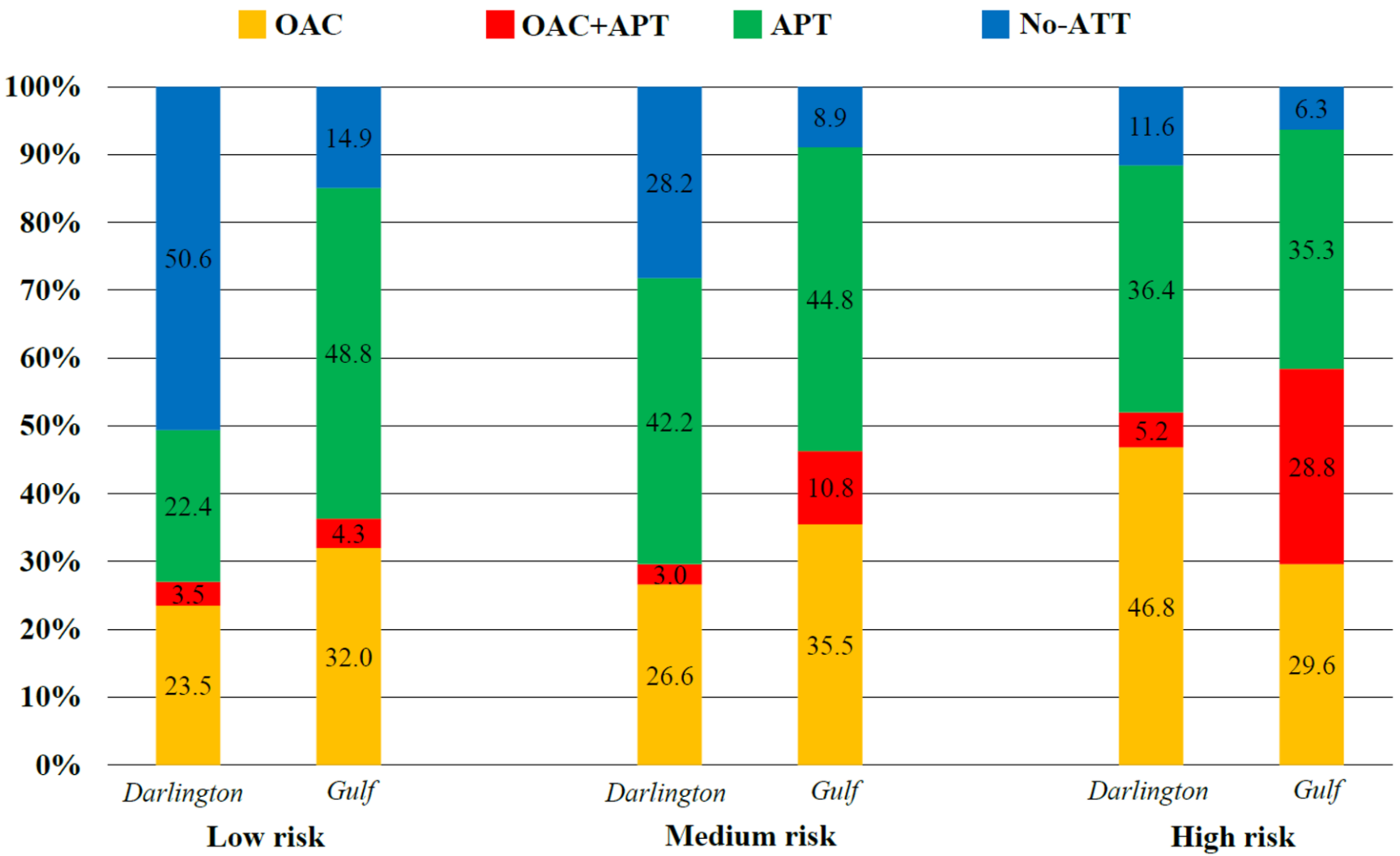
*per 100 patient-years; CI=confidence interval; N/A=not applicable, because of no events in this patient group.

Table 3. Multivariable analysis of risk factors for stroke and death

Characteristics	Stroke			Death		
	OR	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Elderly (≥ 75)	1.40	0.94-2.08	0.097	**3.80**	**2.77-5.22**	**< 0.001**
Female	**1.51**	**1.08-2.12**	**0.017**	**1.31**	**1.06-1.64**	**0.015**
Study cohort*	**2.18**	**1.47-3.23**	**< 0.001**	**1.67**	**1.31-2.14**	**< 0.001**
Heart failure	1.27	0.87-1.86	0.213	**2.78**	**2.21-3.50**	**< 0.001**
Hypertension	0.91	0.63-1.32	0.622	0.90	0.71-1.15	0.413
Diabetes mellitus	1.14	0.78-1.65	0.505	1.150	0.90-1.46	0.258
Previous stroke	**3.52**	**2.46-5.03**	**< 0.001**	1.21	0.92-1.58	0.175
Vascular disease	1.07	0.72-1.59	0.729	**1.92**	**1.51-2.45**	**< 0.001**
OAC use	1.01	0.72-1.40	0.974	**0.55**	**0.44-0.69**	**< 0.001**

* Darlington as reference; CI= confidence interval; OAC=oral anticoagulant; OR=odds ratio.

Figure 1



Highlights:

(i) Patients profiles regarding demographic factors, baseline comorbidities, and evaluated stroke risks were different between the two registries derived from different clinical settings;
(ii) While large percentages of patients with AF would be candidates for OAC in both populations, overall OAC use was suboptimal;
(iii) High one-year rates of stroke and mortality were observed in both populations, especially among patients from Gulf SAFE;
(iv) Female sex and previous stroke were independent factors associated with stroke; while elderly age, female sex, HF and vascular disease were independent risk factors for mortality.