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CLINICAL RESEARCH

Contemporary management of atrial fibrillation and the predicted vs. absolute risk of ischaemic stroke despite treatment: a report from ESC-EHRA EORP-AF Long-Term General Registry

Wern Yew Ding [1], Carina Blomström-Lundqvist [2], Laurent Fauchier [3], Francisco Marin [4], Tatjana S. Potpara [5,6], Giuseppe Boriani [7†], and Gregory Y. H. Lip [1,8*†]; on behalf of the ESC-EHRA EORP-AF Long-Term General Registry Investigators

[1]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK; [2]Department of Cardiology, School of Medical Sciences, Faculty of Medicine and Health, Örebro University, Örebro, Sweden; [3]Service de Cardiologie, Centre Hospitalier Universitaire Trousseau, Tours, France; [4]Department of Cardiology, Hospital Universitario Virgen de la Arrixaca, IMIB-Arrixaca, University of Murcia, CIBERCV, Murcia, Spain; [5]School of Medicine, University of Belgrade, Belgrade, Serbia; [6]Intensive Arrhythmia Care, Cardiology Clinic, Clinical Center of Serbia, Belgrade, Serbia; [7]Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy; and [8]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

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Background Risk stratification in patients with atrial fibrillation (AF) is important to facilitate guideline-directed therapies. The Calculator of Absolute Stroke Risk (CARS) scheme enables an individualized estimation of 1-year absolute risk of stroke in AF. We aimed to investigate the predicted and absolute risks of ischaemic stroke, and evaluate whether CARS (and CHA_2DS_2-VASc score) may be useful for identifying high risk patients with AF despite contemporary treatment.

Methods We utilized the EORP-AF General Long-Term Registry which prospectively enrolled patients with AF from 250 centres across 27 participating European countries. Patients with sufficient data to determine CARS and CHA_2DS_2-VASc score, and reported outcomes of ischaemic stroke were included in this analysis. The primary outcome of ischaemic stroke was recorded over a 2-year follow-up period.

Results A total of 9444 patients were included (mean age 69.1 [±11.4] years; 3776 [40.0%] females). There was a high uptake (87.9%) of anticoagulation therapy, predominantly with vitamin K antagonist (50.0%). Over a mean follow-up period of 24 months, there were a total of 101 (1.1%) ischaemic stroke events. In the entire cohort, the median CARS and absolute annual risks of ischaemic stroke were 2.60 (IQR 1.60–4.00) and 0.53% (95%CI 0.43–0.64%), respectively. There was no statistical difference between the predictive performance of CARS and CHA_2DS_2-VASc score (0.621 [95%CI 0.563–0.678] vs. 0.626 [95%CI 0.573–0.680], $P = 0.725$).

Conclusion Contemporary management of AF was associated with a low risk of ischaemic stroke. CARS and CHA_2DS_2-VASc score may be useful to identify high risk patients despite treatment who may benefit from more aggressive treatment and follow-up.

Keywords Atrial fibrillation • Predictive stroke risk • Absolute stroke risk • Ischaemic stroke • CARS • CHA_2DS_2-VASc score • EORP-AF

* Corresponding author. Tel: +0151 794 9020. *E-mail address*: gregory.lip@liverpool.ac.uk
† Joint senior authors.

What's new?

- Contemporary management, including anticoagulation, among patients with atrial fibrillation was associated with a reduction of 86% of the absolute risk of ischaemic stroke as predicted by CARS.
- Both CARS and CHA_2DS_2-VASc score had modest predictive capability for absolute ischaemic stroke events among anticoagulated patients with atrial fibrillation.
- The predictive capability of CARS and CHA_2DS_2-VASc score was comparable for ischaemic stroke events.
- The predictive capability of CARS was similar in subgroups by CHA_2DS_2-VASc risk category and anticoagulation therapy.

Introduction

Atrial fibrillation (AF) is associated with a significant risk of thromboembolism and a doubling of the mortality rate, with increased hospitalizations and healthcare costs.[1,2] Management of patients with AF includes a detailed stroke risk assessment, typically performed using the CHA_2DS_2-VASc score.[3] The information derived from this assessment may be used to guide the prescription of anticoagulation therapy,[4,5] which was traditionally the only established treatment associated with a prognostic benefit in AF. However, there is emerging evidence to suggest that appropriate characterization and evaluation[6,7] followed by a more holistic or integrated care management approach[8] as well as early rhythm control[9,10] may also offer a survival advantage. Hence, it is important to determine the residual risk of stroke in patients receiving contemporary treatment for AF to identify those who may benefit from additional forms of intervention. Yet, there is currently no validated model for this purpose.

Recently, Lee *et al.* proposed the Calculator of Absolute Stroke Risk (CARS) which enables an individualized estimation of 1-year absolute risk of stroke in AF.[11] CARS was derived from a large real-world retrospective Danish cohort of non-anticoagulated patients from 1997 to 2015 with first-diagnosed AF. It utilizes the same risk factors as the CHA_2DS_2-VASc score but analyses age as a continuous variable and considers the individual contribution of risk factors. The role of CARS in a prospective cohort of patients receiving treatment for AF remains to be determined.

Herein, we aimed to investigate the predicted and absolute risks of ischaemic stroke, and evaluate whether CARS (and CHA_2DS_2-VASc score) may be useful for identifying high risk patients in a prospective cohort of patients with AF receiving contemporary management. We investigated this using the European Society of Cardiology-European Heart Rhythm Association (ESC-EHRA) EURObservational Research Programme EORP-AF General Long-Term Registry.

Methods

The EORP-AF General Long-Term Registry is a prospective, observational, large-scale multicentre registry from 250 centres across 27 participating European countries. A detailed description of the study design has previously been provided.[12] In brief, patients with AF who presented to cardiology services were enrolled between October 2013 and September 2016. All patients were over 18 years old and had electrocardiographic confirmation of AF within 12 months of enrolment. Institutional review board approval of the study protocol was obtained for every institution, and the study was performed in accordance to the European Union Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki. For the purposes of this analysis, we included only patients with sufficient data to calculate their individual CARS and CHA_2DS_2-VASc score, and without missing information on the outcome of ischaemic stroke.

Table 1 Baseline characteristics

Baseline characteristics	*n* = 9444
Age (years), mean (±SD)	69.1 (±11.4)
Female sex, *n* (%)	3776 (40.0%)
BMI (kg/m^2), mean (±SD)	28.3 (±5.1)
eGFR (mL/min/1.73 m^2), mean (±SD)	69.4 (±21.2)
LA diameter (mm), mean (±SD)	45.4 (±8.2)
LV ejection fraction (%),mean (±SD)	53.7 (±13.0)
Left ventricular hypertrophy, *n* (%)	2181 (27.5%)
AF classification, *n* (%)	
First-detected	1452 (15.6%)
Paroxysmal	2468 (26.6%)
Persistent	1850 (19.9%)
Long-standing persistent	420 (4.5%)
Permanent	3099 (33.4%)
EHRA classification, *n* (%)	
I	4283 (45.4%)
II	3373 (35.7%)
III	1592 (16.9%)
IV	196 (2.1%)
Comorbidities, *n* (%)	
Cardiomyopathy	1367 (14.5%)
Congenital heart disease	103 (1.1%)
COPD	815 (8.7%)
Coronary artery disease	2551 (28.3%)
Diabetes mellitus	2142 (22.7%)
Heart failure	3569 (37.8%)
Hypertension	5843 (61.9%)
Liver disease	236 (2.5%)
Peripheral vascular disease	748 (7.9%)
Previous haemorrhagic event	501 (5.3%)
Previous thromboembolic event	1093 (11.6%)
Previous ischaemic stroke	572 (6.1%)
Sleep apnoea	440 (4.8%)
Hyperthyroidism	168 (1.8%)
Hypothyroidism	511 (5.5%)
Valvular heart disease	4629 (49.7%)
Prior catheter AF ablation, *n* (%)	457 (6.0%)
CHA_2DS_2-VASc score, mean (±SD)	3.1 (±1.8)
HAS-BLED score, mean (±SD)	1.6 (±1.1)

AF, atrial fibrillation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; EHRA, European Heart Rhythm Association; LA, left atrium; LV, left ventricle; SD, standard deviation.

Data on demographics, comorbidities and medications were collected at baseline. These were used to determine the predicted stroke risk by CARS[11] and CHA_2DS_2-VASc score. Estimated glomerular filtration rate (eGFR) was assessed using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation. Patients with a CHA_2DS_2-VASc score of 0, 1–3 and more than 3 were designated as low risk, high risk and very high risk, respectively. The predicted residual 1-year stroke risk

Table 2 Baseline medication use

Baseline medication use	*n* = 9444
Anti-thrombotic, *n* (%)	8876 (94.0%)
Any antiplatelet	1769 (18.7%)
Acetylsalicylic acid	1588 (16.8%)
Clopidogrel	547 (5.8%)
Oral anticoagulants, *n* (%)	8296 (87.9%)
Vitamin K antagonist	4721 (50.0%)
Any NOAC	3429 (36.3%)
Apixaban	956 (10.1%)
Dabigatran	756 (8.0%)
Edoxaban	94 (1.0%)
Rivaroxaban	1623 (17.2%)
Heparin	146 (1.5%)
Anti-arrhythmics, *n* (%)	2610 (27.7%)
Amiodarone	1638 (17.4%)
Flecainide	341 (3.6%)
Propafenone	325 (3.5%)
Sotalol	275 (2.9%)
Other medications, *n* (%)	
ACE inhibitors	3944 (41.9%)
Aldosterone blockers	1673 (17.8%)
Angiotensin receptor blocker	1843 (19.6%)
Beta-blockers	6529 (69.4%)
Dihydropyridine CCB	1617 (17.2%)
Digoxin	1321 (14.0%)
Diuretics	4761 (50.6%)
Insulin	510 (5.4%)
Oral antidiabetics	1425 (15.1%)
Statins	3999 (42.5%)

ACE, angiotensin converting enzyme; CCB, calcium-channel blocker; eGFR, estimated glomerular filtration rate; NOAC, non-vitamin K antagonist oral anticoagulant.

('mCARS') was estimated as previously described.[13] For this analysis, the primary study outcome was ischaemic stroke. This was recorded over a 2-year follow-up period.

Statistical analyses

Continuous variables were described with mean and standard deviation (SD), and tested for differences with *t*-test if normally distributed. Non-parametric variables are shown as median (IQR, interquartile range). Categorical variables were described with count and percentage, and tested for differences with chi-squared test. Absolute stroke risk at 1-year was expressed as incidence risk with 95% confidence intervals (CI). The predictive capability of CARS for absolute stroke risk at 1-year was investigated using receiver-operating characteristic (ROC) curves and area under the curve (AUC) was used to represent its ability to predict ischaemic stroke events. The performance of CARS was tested against the CHA_2DS_2-VASc score using DeLong's test.[14] Further subgroup analyses were performed according to stroke risk profile by CHA_2DS_2-VASc score and oral anticoagulation agent (vitamin K antagonist [VKA] or non-vitamin K antagonist oral anticoagulant [NOAC]). A two-sided *p* value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 24 (IBM Corp, Armonk, NY) and R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Table 3 Predicted vs. absolute stroke risk

CARS, %	
Mean (±SD)	3.81 (±4.06)
Median (IQR)	2.60 (1.60–4.00)
Range	0.10–24.10
mCARS, %	
Mean (±SD)	1.37 (±1.46)
Median (IQR)	0.94 (0.58–0.94)
Range	0.04–8.68
Absolute stroke risk	
Number of events, *n*	101
Annual risk (95% CI), %	0.53 (0.43–0.64)

CARS, Calculator of Absolute Stroke Risk; CI, confidence interval; IQR, interquartile range; SD, standard deviation.

Results

A total of 9444 patients were included in the present analysis, corresponding to 85.1% of the original cohort of 11 096 patients. The mean age of patients was 69.1 (±11.4) years with 3776 (40.0%) females (*Table 1*). Majority of patients had permanent AF (33.4%), and the mean left atrial diameter and eGFR were 45.4 (±8.2) mm and 69.4 (±21.2) mL/min/1.73 m^2, respectively. Few patients (19.0%) had severe symptoms based on European Heart Rhythm Association symptom scale (III–IV). The most common comorbidities were hypertension (61.9%), valvular heart disease (49.7%), heart failure (37.8%), coronary artery disease (28.3%), diabetes mellitus (22.7%), and cardiomyopathy (14.5%). Mean CHA_2DS_2-VASc score was 3.1 (±1.8).

There was a high uptake (87.9%) of anticoagulation therapy, predominantly with VKA (50.0%). The use of anticoagulation therapy according to CHA_2DS_2-VASc score is shown in Supplementary material online, *Table S1*. Rivaroxaban was the most frequently (17.2%) prescribed NOAC, followed by apixaban (10.1%), dabigatran (8.0%), and edoxaban (1.0%). Other medications used at baseline can be found in *Table 2*.

Predicted vs. absolute stroke risk

Over a mean follow-up period of 24 months, there were a total of 101 (1.1%) ischaemic stroke events. In the entire cohort, the absolute annual risk of ischaemic stroke was 0.53% (95%CI 0.43–0.64%) (*Table 3*). The median CARS and mCARS were 2.60 (IQR 1.60–4.00) and 0.94 (IQR 0.58–0.94), respectively. Based on the absolute risk of ischaemic stroke, there was an 86% reduction from predicted stroke risk in this cohort. The relative risk reduction appeared to be more pronounced in patients with greater CHA_2DS_2-VASc score (*Table 4*).

Predictive performance of CARS and CHA_2DS_2-VASc score

Receiver-operating characteristics curves for absolute stroke events by CARS and CHA_2DS_2-VASc score are shown in *Figure 1*. The AUCs for CARS and CHA_2DS_2-VASc score were 0.621 (95%CI 0.563–0.678) vs. 0.626 (95%CI 0.573–0.680), respectively. There was no statistical

Table 4 Predicted vs. absolute stroke risk stratified by CHA_2DS_2-VASc score

CHA_2DS_2-VASc score	CARS (%)		mCARS (%)		Absolute stroke risk	
	Mean (±SD)	Range	Mean (±SD)	Range	Number of events, n	Annual risk (95% CI), %
CHA_2DS_2-VASc score 0 ($n = 627$)	0.68 (±0.80)	0.10–10.60	0.25 (±0.29)	0.04–3.82	3	0.24 (0–0.51)
CHA_2DS_2-VASc score 1 ($n = 1225$)	1.15 (±0.85)	0.10–12.00	0.42 (±0.30)	0.04–4.32	6	0.24 (0.05–0.44)
CHA_2DS_2-VASc score 2 ($n = 1736$)	2.00 (±1.37)	0.10–17.10	0.72 (±0.49)	0.04–6.16	14	0.40 (0.19–0.61)
CHA_2DS_2-VASc score 3 ($n = 1959$)	3.04 (±2.10)	0.10–15.90	1.09 (±0.76)	0.04–5.72	17	0.43 (0.23–0.64)
CHA_2DS_2-VASc score 4 ($n = 1871$)	4.35 (±3.03)	0.40–20.10	1.57 (±1.09)	0.14–7.24	22	0.59 (0.34–0.83)
CHA_2DS_2-VASc score 5 ($n = 1171$)	5.90 (±4.16)	1.00–20.60	2.12 (±1.50)	0.36–7.42	22	0.94 (0.55–1.33)
CHA_2DS_2-VASc score 6 ($n = 550$)	9.45 (±5.66)	2.40–22.70	3.40 (±2.04)	0.86–8.17	11	1.00 (0.41–1.59)
CHA_2DS_2-VASc score 7 ($n = 219$)	13.69 (±5.26)	3.80–24.10	4.93 (±1.89)	1.37–8.68	5	1.14 (0.14–2.14)
CHA_2DS_2-VASc score 8 ($n = 74$)	16.90 (±1.99)	13.60–22.20	6.08 (±0.72)	4.90–7.99	1	0.68 (0–2.02)
CHA_2DS_2-VASc score 9 ($n = 12$)	17.63 (±1.62)	15.90–21.00	6.35 (±0.58)	5.72–7.56	0	NA

CARS, Calculator of Absolute Stroke Risk; CI, confidence interval; IQR, interquartile range; NA, not available; SD, standard deviation.

difference between the predictive performance of CARS and CHA_2DS_2-VASc score, $P = 0.725$.

Subgroup analysis by CHA_2DS_2-VASc score and risk category

The predicted and absolute stroke risks stratified by CHA_2DS_2-VASc score are displayed in *Table 4*. The mean CARS ranged from 0.68% to 17.63% while the absolute annual stroke risk ranged from 0.24% to 1.14%. In general, both CARS and absolute annual stroke risk were greater with increasing CHA_2DS_2-VASc score (*Figure 2*). Patients in the low risk category (score 0) had an absolute annual stroke risk of 0.24% compared with 0.38% in the high risk category (score 1–3) and 0.78% in the very high risk category (score >3) (see Supplementary material online, *Table S2*).

Receiver-operating characteristic curves for absolute stroke events by CARS according to CHA_2DS_2-VASc risk category are shown in Supplementary material online, *Figure S1*. The AUCs for CARS in low risk, high risk and very high risk patients were 0.595 (95%CI 0.361–0.829, 0.512 (95%CI 0.432–0.592) and 0.623 (95%CI 0.553–0.693), respectively. There were no statistical difference between the AUCs for each risk category (high risk vs. low risk, $P = 0.444$; very high risk vs. low risk, $P = 0.822$).

Subgroup analysis by anticoagulation therapy

The baseline characteristics of subgroups treated with either VKA or NOAC are shown in Supplementary material online, *Table S3*. Patients in the VKA subgroup were older with higher prevalence of permanent AF, worse echocardiographic parameters, and a greater burden of comorbidities. As a result, the mean CHA_2DS_2-VASc and HAS-BLED scores were increased among patients treated with VKA compared to NOAC (CHA_2DS_2-VASc: 3.4 vs. 3.1, $P = 0.022$; HAS-BLED 1.8 vs. 1.4, $P < 0.001$). The mean CARS in the VKA subgroup was 4.02 (±4.08) and NOAC subgroup was 3.78 (±4.11) (see Supplementary material online, *Table S4*). The absolute annual stroke risk in the VKA and NOAC subgroups were 0.49 (95%CI 0.35–0.63) % and 0.24 (95%CI 0.16–0.32) %, respectively.

Receiver-operating characteristic curves for absolute stroke events in patients receiving VKA vs. NOAC therapy are shown in Supplementary material online, *Figure S2*. The AUCs for CARS in the VKA subgroup was 63.3% (95%CI 54.9–71.7%) and NOAC subgroup was 67.1% (95%CI 57.5–76.7%). There was no statistical difference between the predictive performance of CARS in either of these subgroups with $P = 0.557$.

Discussion

The main findings from this study of predominantly anticoagulated patients with AF in a prospective multicentre registry across 27 participating European countries were as follows: (1) absolute risk of ischaemic stroke was 86% lower than the predicted risk by CARS among this cohort; (2) both CARS and CHA_2DS_2-VASc score had modest predictive capability for absolute ischaemic stroke events among anticoagulated patients; (3) predictive capability of CARS and CHA_2DS_2-VASc score was comparable for ischaemic stroke events; and (4) predictive capability of CARS was similar in subgroups by CHA_2DS_2-VASc risk category and anticoagulation therapy.

In this contemporary cohort of treated patients with AF, the risk of ischaemic stroke in this cohort was lower compared with the predicted risk by CARS. Furthermore, the relative risk reduction of predicted vs. absolute ischaemic stroke risk appeared to be greater in patients with increased CHA_2DS_2-VASc score. The reduction in risk of ischaemic stroke was likely driven by the high uptake of oral anticoagulation therapy which is known to be beneficial for this purpose in AF. Nonetheless, the observed risk reduction was greater than 64%, as previously reported in a meta-analysis comparing OAC use against controls,[15] suggesting the interplay of other factors. Although our study was not designed to compare the effects of contemporary vs. historical treatment in AF patients, it may be postulated that better understanding of the underlying pathophysiological mechanisms of AF,[16] alongside the implementation of newer oral anticoagulation agents[17] may have led to improved outcomes in this condition.

In this study, we evaluated the use of CARS and CHA_2DS_2-VASc score to predict ischaemic stroke risk in real-world patients. Although the CHA_2DS_2-VASc score had a marginally better predictive score, this was not statistically significant. The advantage of CARS over the CHA_2DS_2-VASc score in this situation is that it may be modified (mCARS) to provide an individual risk estimate of absolute risk that is easy to interpret and may be useful to facilitate patient-centred discussions. Furthermore, CARS is a more dynamic tool that allows for the adjustment of age in a continuous manner.

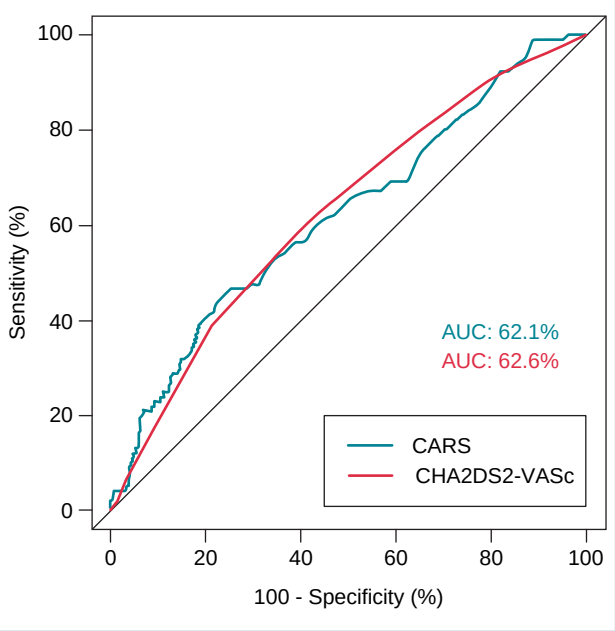

Figure 1 Receiver-operating characteristic curves for absolute stroke events by CARS vs. CHA_2DS_2-VASc score.

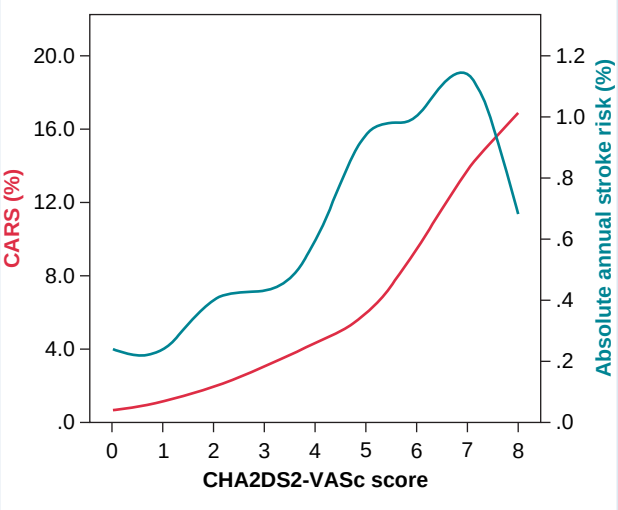

Figure 2 Plot of CARS vs. absolute annual stroke risk stratified by CHA_2DS_2-VASc score.

Using CARS and CHA_2DS_2-VASc score, patients with a high residual risk of ischaemic stroke despite treatment[18,19] may be identified for more intensive follow-up and holistic management strategies. Indeed, adherence to the guideline-recommended Atrial fibrillation Better Care (ABC) pathway is associated with a 45% reduction in ischaemic stroke, compared to non-adherence.[8] To reinforce the possible role of CARS, we also demonstrated that the (individualized) predictive capability of this tool was maintained regardless of CHA_2DS_2-VASc risk category and choice of anticoagulation therapy. Additionally, the calculated baseline absolute risk with CARS could be used to estimate the impact of specific treatments in various study cohorts. It may also be incorporated with reported outcomes to determine the NNTnet (number needed to treat for net effect), which combines the benefit-and-harm of an intervention or therapy.[20]

Limitations

The major limitation of this study relates to its observational nature with potential for misclassification bias. Furthermore, as the EORP-AF General Long-Term Registry was based exclusively on cardiology practices, our findings may not be generalizable to other cohorts. The annual absolute stroke risk was determined by assuming a linear event rate over the 2 year follow-up period. There were few ischaemic stroke events in patients with a high CHA_2DS_2-VASc score which may have influenced the results of our subgroup analysis. Moreover, we used somewhat arbitrary risk categories to classify patients according to their CHA_2DS_2-VASc score.

Conclusions

Contemporary management of patients with AF across cardiology practices in Europe was associated with an 86% relative risk reduction in ischaemic stroke. CARS and CHA_2DS_2-VASc score may be useful to identify high risk patients despite treatment who may benefit from more aggressive treatment and intensive follow-up. CARS may facilitate future research using real-world cohorts and registries to determine the impact of specific treatments or intervention on the baseline absolute risk of ischaemic stroke in AF.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Appendix 1

EURObservational Research Programme Atrial Fibrillation (EORP-AF) Long-Term General Registry Committees and Investigators (ESC Member Countries)

Executive committee: G.Boriani (Chair), G.Y.H. Lip, L. Tavazzi, A. P. Maggioni, G-A. Dan, T. Potpara, M. Nabauer, F. Marin, Z. Kalarus, L. Fauchier.

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