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CLINICAL RESEARCH
Atrial fibrillation

Clinical utility and prognostic implications of the novel 4S-AF scheme to characterize and evaluate patients with atrial fibrillation: a report from ESC-EHRA EORP-AF Long-Term General Registry

Wern Yew Ding [1], Marco Proietti [1,2,3], Giuseppe Boriani [4], Laurent Fauchier[5], Carina Blomström-Lundqvist[6], Francisco Marin[7], Tatjana S. Potpara [8,9,†], and Gregory Y.H. Lip[1,10,*,†]; 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 Clinical Sciences and Community Health, University of Milan, Milan, Italy; [3]Geriatric Unit, IRCCS Istituti Clinici Scientifici Maugeri, Milan, Italy; [4]Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy; [5]Service de Cardiologie, Centre Hospitalier Universitaire Trousseau, Tours, France; [6]Department of Medical Science and Cardiology, Uppsala University, Uppsala, Sweden; [7]Department of Cardiology, Hospital Universitario Virgen de la Arrixaca, IMIB-Arrixaca, University of Murcia, CIBERCV, Murcia, Spain; [8]School of Medicine, University of Belgrade, Belgrade, Serbia; [9]Intensive Arrhythmia Care, Cardiology Clinic, Clinical Center of Serbia, Belgrade, Serbia; and [10]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

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Aims The 4S-AF classification scheme comprises of four domains: stroke risk (*St*), symptoms (*Sy*), severity of atrial fibrillation (AF) burden (*Sb*), and substrate (*Su*). We sought to examine the implementation of the 4S-AF scheme in the EORP-AF General Long-Term Registry and compare outcomes in AF patients according to the 4S-AF-led decision-making process.

Methods and results Atrial fibrillation patients from 250 centres across 27 European countries were included. A 4S-AF score was calculated as the sum of each domain with a maximum score of 9. Of 6321 patients, 8.4% had low (*St*), 47.5% EHRA I (*Sy*), 40.5% newly diagnosed or paroxysmal AF (*Sb*), and 5.1% no cardiovascular risk factors or left atrial enlargement (*Su*). Median follow-up was 24 months. Using multivariable Cox regression analysis, independent predictors of all-cause mortality were (*St*) [adjusted hazard ratio (aHR) 8.21, 95% confidence interval (CI): 2.60–25.9], (*Sb*) (aHR 1.21, 95% CI: 1.08–1.35), and (*Su*) (aHR 1.27, 95% CI: 1.14–1.41). For CV mortality and any thromboembolic event, only (*Su*) (aHR 1.73, 95% CI: 1.45–2.06) and (*Sy*) (aHR 1.29, 95% CI: 1.00–1.66) were statistically significant, respectively. None of the domains were independently linked to ischaemic stroke or major bleeding. Higher 4S-AF score was related to a significant increase in all-cause mortality, CV mortality, any thromboembolic event, and ischaemic stroke but not major bleeding. Treatment of all 4S-AF domains was associated with an independent decrease in all-cause mortality (aHR 0.71, 95% CI: 0.55–0.92). For each 4S-AF domain left untreated, the risk of all-cause mortality increased substantially (aHR 1.35, 95% CI: 1.16–1.56).

Conclusion Implementation of the novel 4S-AF scheme is feasible, and treatment decisions based on this scheme improve mortality rates in AF.

*Corresponding author. Tel: 0151 794 9020. *E-mail address*: gregory.lip@liverpool.ac.uk

†The last two authors are joint senior authors.

‡Members are listed in Supplementary material online, *Appendix*.

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Keywords Atrial fibrillation • 4S-AF • Characterization • Classification • EORP-AF registry • Validation • Prognostic implications • Mortality • Thromboembolism • Stroke • Bleeding

What's new?

- The 4S-AF scheme provides a means for clinical characterization of patients with Atrial fibrillation (AF).
- Each of the domains within the 4S-AF scheme were independently associated with adverse long-term outcomes.
- The 4S-AF score may provide prognostic data in terms of all-cause mortality, CV mortality, any thromboembolic event, and ischaemic stroke.
- Implementation of treatment based on the 4S-AF scheme was associated with a significant reduction in all-cause mortality, independent of other risk factors.

Introduction

Atrial fibrillation (AF) is a multisystemic condition that is diagnosed by electrocardiographic confirmation of irregular atrial activity. With greater understanding of the underlying mechanisms in AF,[1] we have recognized different types of disease patterns. The heterogeneous nature of this arrhythmia therefore presents unique challenges for clinicians and researchers alike. Current classification systems recommended by major international guidelines are based on a single domain of AF: temporal pattern, symptom severity, or underlying comorbidity.[2–4] Lack of integration between these various elements limits our approach to patients with AF and acts as a barrier against the delivery of better holistic care.

The temporal-based classification of AF is the most commonly used system[5,6] to categorize patients according to relatively arbitrary groups of first diagnosed, paroxysmal, persistent, long-standing persistent, or permanent AF. It provides a simple tool to facilitate communication between clinicians and has implications for certain treatment decisions (e.g. AF ablation). However, the temporal-based classification lacks clinical accuracy with frequent misclassification as proven by continuous cardiac monitoring.[7,8] Furthermore, it neglects to inform us about other important elements of the disease, such as stroke risk, patient symptoms, cardiovascular risk factors, and left atrial substrate. Hence, the need for an improved classification system in AF has been acknowledged for over a decade.[9]

Recently, a novel structured pathophysiology-based characterization scheme for AF that includes 4 AF- and patient-related domains has been proposed.[10] This paradigm shift from the traditional classification system towards a simple but comprehensive *characterization* of AF has a great potential to improve patient care. However, the clinical utility and prognostic value of the 4S-AF scheme remain untested. Notably, the 4S-AF scheme is not intended to replace existing risk stratification tools. In this study, we sought to examine the implementation of the 4S-AF scheme in the EORP-AF General Long-Term Registry, and compare the outcomes in AF patients treated based on the 4S-AF scheme vs. the rest of the cohort.

Methods

Study design and population

The EORP-AF General Long-Term Registry is a prospective, observational, large-scale multicentre registry from 250 centres across 27 participating European countries. Detailed description of the study design has previously been provided,[11] as well as main results from the 1-year follow-up observation.[12] In brief, patients with AF who presented to cardiology services between October 2013 and September 2016 were enrolled. All patients were over 18 years old and had electrocardiographic confirmation of AF within 12 months prior to enrolment. Institutional review board approval of the study protocol was obtained for every institution, and the study was performed in accordance with the European Union Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki.

Data collection and study outcomes

Data on demographics and comorbidities were collected at baseline. The 4S-AF classification scheme is comprised of four domains: stroke risk (*St*), symptoms (*Sy*), severity of AF burden (*Sb*), and substrate (*Su*).[10] The definition and interpretation of each are presented in *Table 1*. The CHA_2DS_2-VASc score and European Heart Rhythm Association (EHRA) symptom classification were determined as previously described.[13,14] Clinical severity of AF burden was based on the European Society of Cardiology guidelines for temporal classification of AF.[2,15] Cardiovascular (CV) risk factors were hypertension, hypercholesterolaemia, diabetes mellitus, coronary artery disease, heart failure, and peripheral artery disease. Left atrial (LA) enlargement was defined as LA diameter over 40 mm (>50 mm for severe enlargement). A 4S-AF score was calculated using the sum of each individual domain with a maximum score of 9 ($St = 1$, $Sy = 2$, $Sb = 2$, and $Su = 4$). For the purposes of this analysis, we included only patients with sufficient data to determine each of their individual 4S-AF domains. The outcomes of interest were all-cause mortality, CV mortality, any thromboembolic event, ischaemic stroke, and major bleeding. These events were recorded over a 2-year follow-up period.

Treatment based on 4S-AF scheme

As the 4S-AF scheme was designed to assist with clinical decision making, we assessed the effects of treatment in the following subgroups based on 4S-AF domains:

($St = 1$): Any patient with non-low risk for thromboembolic event and, therefore, had an indication for anticoagulation therapy. Treatment was based on the use of anticoagulation therapy at baseline.

($Sy = 2$): Any patient with severe or disabling symptoms at baseline. Treatment was based on the implementation of a rhythm control strategy during follow-up.

($Su \geq 1$): Any patient with at least one CV risk factor at baseline. Treatment was evaluated as follows: (i) treated hypertension if baseline

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Table 1 Definition of 4S-AF classification scheme

4S-AF domains	Sub-domains	Score	Interpretation	Definition
Stroke risk (*St*)		0	Low risk	CHA_2DS_2-VASc score 0 in males or ≤1 in females
		1	Non-low risk; OAC indicated	CHA_2DS_2-VASc score ≥1 in males or ≥2 in females
Symptoms (*Sy*)		0	No or mild symptoms	EHRA I
		1	Moderate symptoms	EHRA II
		2	Severe or disabling symptoms	EHRA III–IV
Severity of AF burden (*Sb*)		0	New or short and infrequent episodes	Newly diagnosed or pAF
		1	Intermediate and/or frequent episodes	PersAF
		2	Long or very frequent episodes	Long-standing persAF or permAF
Substrate (*Su*)	CV risk factor	0	No CV risk factors	No HTN, hypercholesterolaemia, DM, CAD, HF, and PAD
		1	Single CV risk factor	Either HTN, hypercholesterolaemia, DM, CAD, HF, or PAD
		2	Multiple CV risk factors	≥2 of HTN, hypercholesterolaemia, DM, CAD, HF, and/or PAD
	LA enlargement	0	No LA enlargement	LA diameter <40 mm
		1	Mild-mod LA enlargement	LA diameter 40–50 mm
		2	Severe LA enlargement	LA diameter >50 mm

AF, atrial fibrillation; CAD, coronary artery disease; CV, cardiovascular; DM, diabetes mellitus; EHRA, European Heart Rhythm Association; HF, heart failure; HTN, hypertension; LA, left atrial; OAC, oral anticoagulation; PAD, peripheral artery disease; pAF, paroxysmal AF; permAF, permanent AF; persAF, persistent AF.

blood pressure was below 140/90; (ii) treated hypercholesterolaemia if statin was used; (iii) treated diabetes mellitus if oral anti-diabetic medication and/or insulin was used; (iv) treated coronary artery disease if beta blocker and statin were used; (v) treated heart failure if angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and beta blocker were used; and (vi) treated peripheral artery disease if statin was used.

Statistical analysis

Continuous variables were described as median and interquartile range (IQR) and tested for differences with Mann–Whitney *U* test. Categorical variables were described as count and percentage and tested for differences with the χ^2 test. The incidence rate [per 100 patient-years (PYs)] of all-cause mortality was calculated based on the 4S-AF score and compared against a reference subgroup (score of 2) using incidence rate ratio (IRR). Plots of Kaplan–Meier curves were performed, and survival distributions were compared using the log-rank test. The predictive capability of the 4S-AF score for each study outcome was investigated using receiver-operating characteristic (ROC) curves and area under the curve (AUC) analysis. Multivariable Cox regression analysis was performed for the outcomes of interest by including each domain of the 4S-AF scheme as covariates, and to test the prediction of outcomes based on the 4S-AF score and effects of treatment(s) based on the 4S-AF scheme after adjustment for age, gender, estimated glomerular filtration rate, chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus, heart failure, hypercholesterolaemia, hypertension, peripheral artery disease, prior thromboembolism, and sleep apnoea. A two-sided *P*-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 24 (IBM Corp, Armonk, NY, USA) and R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 6321 patients were included in the present analysis, corresponding to 57.0% of the original cohort of 11 096 patients. The remainder of patients had insufficient data to determine their 4S-AF status. The median age of included patients was 70 (IQR 62–77) years with 2615 (41.4%) females (*Table 2*). Median follow-up duration was 24 months. Atrial fibrillation classification was as follows: first-detected AF (13.7%), paroxysmal AF (26.8%), persistent AF (18.0%), long-standing persistent AF (4.5%), and permanent AF (37.0%). Majority of patients had mild-moderate symptoms based on EHRA classification—EHRA I (47.5%), EHRA II (34.4%), EHRA III (16.4%), and EHRA IV (1.7%). Median CHA_2DS_2-VASc score and LA diameter

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Table 2 Baseline characteristics

Baseline characteristics	n = 6321
Age (years), median (IQR)	70 (62–77)
Female sex, *n* (%)	2615 (41.4%)
BMI (kg/m^2), median (IQR)	27.5 (24.8–31.1)
eGFR (mL/min/1.73 m^2), median (IQR)	69.6 (54.9–85.2)
LA diameter (mm), median (IQR)	45 (40–50)
LV ejection fraction (%), median (IQR)	56 (46–62)
Left ventricular hypertrophy, *n* (%)	1877 (29.9%)
AF classification, *n* (%)	
First-detected	863 (13.7%)
Paroxysmal	1695 (26.8%)
Persistent	1138 (18.0%)
Long-standing persistent	284 (4.5%)
Permanent	2341 (37.0%)
EHRA classification, *n* (%)	
I	3001 (47.5%)
II	2176 (34.4%)
III	1038 (16.4%)
IV	105 (1.7%)
Comorbidities, *n* (%)	
Cardiomyopathy	974 (15.4%)
Congenital heart disease	77 (1.2%)
COPD	550 (8.7%)
Coronary artery disease	1890 (29.9%)
Diabetes mellitus	1503 (23.8%)
Heart failure	2565 (40.6%)
Hypercholesterolaemia	2729 (43.2%)
Hypertension	4178 (66.1%)
Liver disease	166 (2.6%)
Peripheral vascular disease	514 (8.1%)
Previous haemorrhagic event	333 (5.3%)
Previous thromboembolic event	715 (11.4%)
Previous ischaemic stroke	412 (6.6%)
Sleep apnoea	291 (4.7%)
Hyperthyroidism	115 (1.9%)
Hypothyroidism	324 (5.2%)
Valvular heart disease	3435 (54.5%)
Prior catheter AF ablation, *n* (%)	289 (5.5%)
CHA_2DS_2-VASc score, median (IQR)	3 (2–4)
HAS-BLED score, median (IQR)	1 (1–2)

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

were 3 (IQR 2–4) and 45 (IQR 40–50) mm, respectively. The most common CV risk factors were hypertension (66.1%), hypercholesterolaemia (43.2%), heart failure (40.6%), coronary artery disease (29.9%), diabetes mellitus (23.8%), and peripheral artery disease (8.1%). In comparison to patients who were excluded ($n = 4775$), those in this study were younger ($P < 0.001$) with greater left ventricular ejection fraction ($P < 0.001$), lower CHA_2DS_2-VASc score ($P < 0.001$), more advanced forms of AF ($P < 0.001$), lower EHRA score ($P < 0.001$), and greater incidence of diabetes mellitus ($P = 0.025$), heart failure ($P = 0.007$), hypercholesterolaemia ($P < 0.001$), hypertension ($P < 0.001$), and valvular heart disease ($P < 0.001$). All other baseline characteristics were comparable between the groups.

Distribution of cohort according to 4S-AF scheme

Distribution of patients according to the various domains of the 4S-AF scheme is shown in *Table 3*. Few patients were defined as having low stroke risk (8.4%) or low substrate (5.1%). A detailed breakdown of the entire cohort based on the 4S-AF scheme is shown in the Supplementary material online, *Table S1*. The median 4S-AF score was 5 (IQR 4–6).

Impact of 4S-AF domains on adverse outcomes

Using multivariable Cox regression analysis, independent predictors of all-cause mortality using the 4S-AF domains were (*St*) [hazard ratio (HR) 8.21, 95% confidence interval (CI): 2.60–25.9], (*Sb*) (HR 1.21, 95% CI: 1.08–1.35), and (*Su*) (HR 1.27, 95% CI: 1.14–1.41) (*Table 4*). (*Sy*) (HR 1.08, 95% CI: 0.95–1.22) was not associated with all-cause mortality. In terms of CV mortality, only (*Su*) (HR 1.73, 95% CI: 1.45–2.06) was found to be statistically important. For any thromboembolic event, only (*Sy*) was associated with a significantly increased risk (HR 1.29, 95% CI: 1.00–1.66). None of the 4S-AF domains were independently linked to ischaemic stroke or major bleeding.

Outcomes based on 4S-AF score

There was a total of 498 (7.9%) all-cause deaths during follow-up. The incidence rate of all-cause mortality per 4S-AF score ranged from 0 to 7.43 per 100 PYs (Supplementary material online, *Table S2*). Using Kaplan–Meier survival curves, we found that increasing 4S-AF score was related to a significant increase in all-cause mortality (log-rank $P < 0.001$), CV mortality (log-rank $P < 0.001$), any thromboembolic event (log-rank $P = 0.012$), and ischaemic stroke (log-rank $P = 0.043$) (*Figure 1*). There was no association between the 4S-AF score and major bleeding (log-rank $P = 0.389$). Multivariable Cox regression analysis showed that the 4S-AF score was an independent predictor of CV mortality (HR 1.14, 95% CI: 1.02–1.27) but not all-cause mortality (HR 1.06, 95% CI: 0.99–1.14), thromboembolic event (HR 1.08, 95% CI: 0.94–1.25), ischaemic stroke (HR 1.13, 95% CI: 0.93–1.37), or major bleeding (HR 0.94, 95% CI: 0.76–1.16).

Notwithstanding that the 4S-AF paradigm shift was not proposed for the purpose of risk assessment, we explored the predictive ability of a 4S-AF score for 'hard' outcomes. The 4S-AF score had a modest predictive capability for all-cause mortality (AUC 61.5%, 95% CI: 59.0–64.0), CV mortality (AUC 65.0%, 95% CI: 61.2–68.9), major bleeding (AUC 52.9%, 95% CI: 45.4–60.4), thromboembolic event (AUC 54.4%, 95% CI: 48.7–60.2), and ischaemic stroke (AUC 58.4%, 95% CI: 51.3–65.5).

Effects of treatment(s) based on 4S-AF scheme

Treatment based on each of the 4S-AF domains is shown in *Table S3*. On multivariable Cox regression analysis, we demonstrated that the

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Table 3 Distribution according to 4S-AF scheme

4S-AF domains	Score	Interpretation	*n* (%)
Stroke risk (*St*)	0	Low risk	528 (8.4%)
	1	Non-low risk	5793 (91.6%)
Symptoms (*Sy*)	0	EHRA I	3002 (47.5%)
	1	EHRA II	2176 (34.4%)
	2	EHRA III–IV	1143 (18.1%)
Severity of AF burden (*Sb*)	0	Newly diagnosed or pAF	2558 (40.5%)
	1	PersAF	1138 (18.0%)
	2	Long-standing persAF or permAF	2625 (41.5%)
Substrate (*Su*)	0	No CV risk factors or LA enlargement	322 (5.1%)
	1	Single CV risk factor or mild-mod LA enlargement	818 (12.9%)
	2	Single CV risk factor and mild-mod LA enlargement, or multiple CV risk factors or severe LA enlargement	1805 (28.6%)
	3	Multiple CV risk factors and mild-mod LA enlargement, or single CV risk factor and severe LA enlargement	2363 (37.4%)
	4	Multiple CV risk factors and severe LA enlargement	1013 (16.0%)

AF, atrial fibrillation; CV, cardiovascular; EHRA, European Heart Rhythm Association; LA, left atrial; pAF, paroxysmal AF; permAF, permanent AF; persAF, persistent AF.

Table 4 The effects of risk factors in 4S-AF on all-cause mortality, CV mortality, any thromboembolic event, ischaemic stroke, and major bleeding

Risk factors	All-cause mortality	CV mortality	Any thromboembolic event aHR[a] (95% CI)	Ischaemic stroke	Major bleeding
Stroke risk (*St*)	8.21 (2.60–25.9)	3.23 (0.78–13.4)	1.62 (0.61–4.26)	1.30 (0.37–4.57)	2.29 (0.51–10.27)
Symptoms (*Sy*)	1.08 (0.95–1.22)	1.12 (0.93–1.36)	1.29 (1.00–1.66)	1.17 (0.84–1.64)	0.80 (0.53–1.21)
Severity of AF burden (*Sb*)	1.21 (1.08–1.35)	1.13 (0.95–1.34)	1.05 (0.83–1.32)	1.21 (0.89–1.64)	1.33 (0.94–1.86)
Substrate (*Su*)	1.27 (1.14–1.41)	1.73 (1.45–2.06)	1.12 (0.90–1.38)	1.20 (0.91–1.59)	0.92 (0.68–1.25)

AF, atrial fibrillation; aHR, adjusted hazard ratio; CI, confidence interval; CV, cardiovascular.
[a]Adjusted for each domain within the 4S-AF scheme.

use of anticoagulation therapy in (*St* = 1) and the implementation of a rhythm control strategy during follow-up in (*Sy* = 2) were each associated with significantly lower all-cause mortality (adjusted HR 0.73, 95% CI: 0.54–0.98) and (adjusted HR 0.22, 95% CI: 0.09–0.54), respectively (*Table 5*). Risk factor management in (*Su* ≥1, based on CV risk factors) was not associated with a reduction in all-cause mortality (adjusted HR 0.67, 95% CI: 0.44–1.03). Overall, treatment of all 4S-AF domains was associated with an independent decrease in all-cause mortality (adjusted HR 0.71, 95% CI: 0.55–0.92). For each 4S-AF domain left untreated, the risk of all-cause mortality increased substantially (adjusted HR 1.35, 95% CI: 1.16–1.56).

Discussion

In this study, we described the first implementation of the novel 4S-AF scheme in a large-scale cohort of patients with AF across 27

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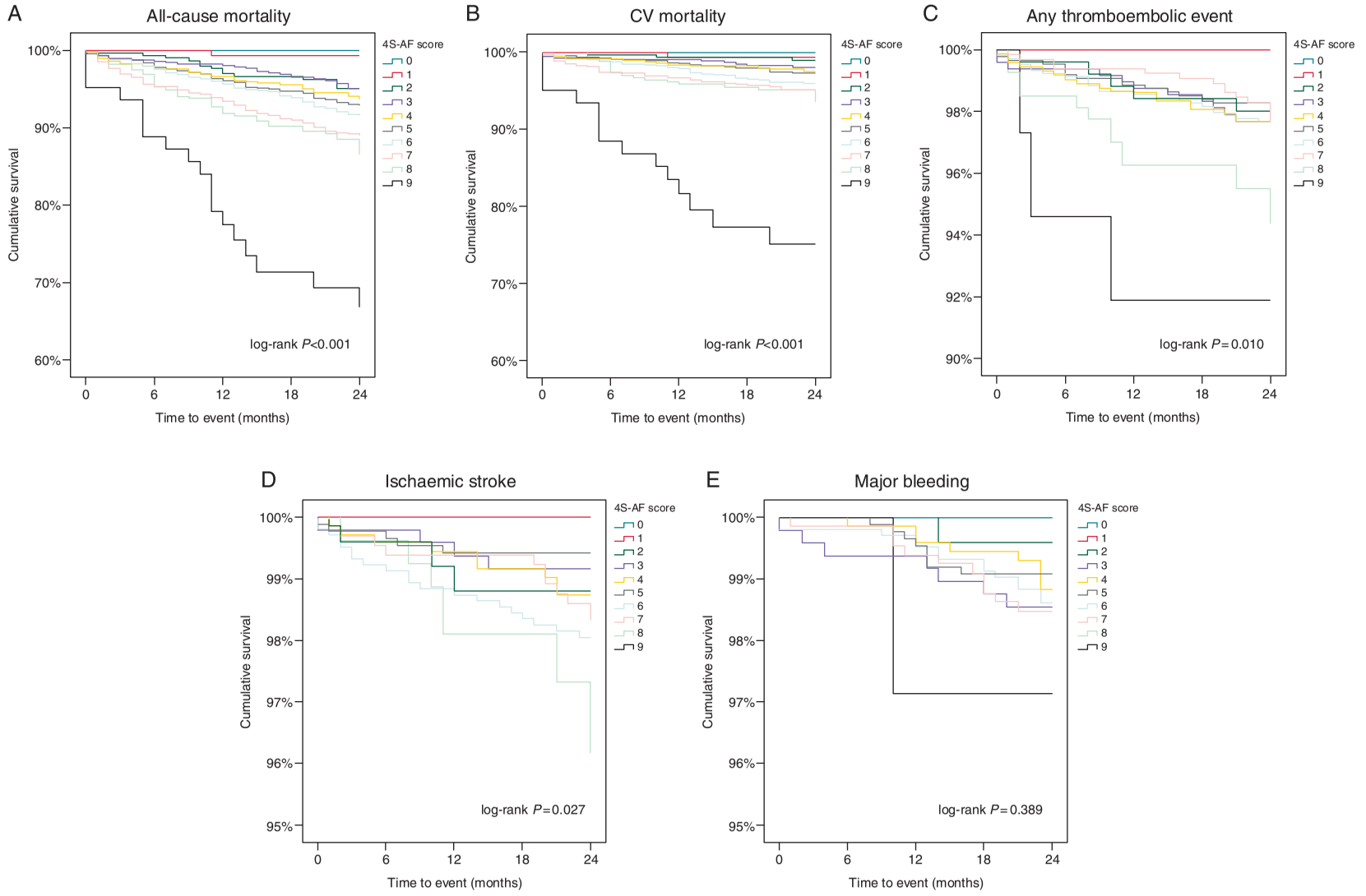

Figure 1 Kaplan–Meier survival curves for all-cause mortality (*A*), CV mortality (*B*), any thromboembolic event (*C*), ischaemic stroke (*D*), and major bleeding (*E*). CV, cardiovascular.

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Table 5 Effects of treatment according to 4S-AF scheme

Treatment	All-cause mortality aHR[a] (95% CI)	*P* value
(*St* = 1) Anticoagulation therapy	0.73 (0.54–0.98)	0.038
(*Sy* = 2) Rhythm control during follow-up	0.22 (0.09–0.54)	0.001
(*Su* ≥ 1)[b] Risk factor management	0.83 (0.66–1.05)	0.121
All 4S-AF domains treated[c]	0.71 (0.55–0.92)	0.009
For each 4S-AF domain left untreated	1.35 (1.16–1.56)	<0.001

aHR, adjusted hazard ratio; CI, confidence interval.
[a]Adjusted for age, gender, estimated glomerular filtration rate, chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus, heart failure, hypercholesterolaemia, hypertension, peripheral artery disease, prior thromboembolism and sleep apnoea.
[b]Based on cardiovascular risk factors only.
[c]Excludes (*Sb*).

European countries from the EORP-AF Long-Term registry. Our principal findings were as follows: (i) the 4S-AF scheme may be used to provide clinical characterization of patients with AF using routinely collected data; (ii) each of the domains within the 4S-AF scheme were independently associated with adverse long-term outcomes; (iii) the 4S-AF score may provide some prognostic data in terms of all-cause mortality, CV mortality, any thromboembolic event, and ischaemic stroke; and (iv) implementation of treatment based on the 4S-AF scheme was associated with a significant reduction in all-cause mortality, independent of other risk factors.

The 4S-AF scheme comprised of four domains: *St*, *Sy*, *Sb*, and *Su*.[10] Clinical characterization of patients using the 4S-AF scheme was possible with routinely collected data on comorbidities, patient symptoms, severity of AF burden, and LA substrate. Importantly, the various domains in the 4S-AF scheme were each independently associated with adverse long-term outcomes of all-cause mortality, CV mortality, and/or any thromboembolic event. Furthermore, the assimilation of the four domains to produce a 4S-AF score was demonstrated to provide prognostic information on all-cause mortality, CV mortality, any thromboembolic event, and ischaemic stroke. However, it is important to emphasize that this tool was designed to *characterize* AF rather than provide risk stratification. Indeed, 4S-AF was introduced to facilitate a structured comprehensive evaluation of AF patients and support treatment decision making, and not as a prognostic score *per se* for adverse outcomes. Presently, we do not recommend using the 4S-AF scheme for prediction of clinical outcomes over designed risk scores, such as the CHA_2DS_2-VASc score.

The 4S-AF scheme is distinctive from other classification systems in AF[13,16–18] as it removes the focus from mere stroke and bleeding risk factors to provide a comprehensive overview of individual patients by incorporating several domains within this multisystemic disease. Although the 4S-AF scheme is new, the various domains included represent well-established clinically relevant aspects of evaluating the patients with AF. The 4S-AF scheme has been adopted in the latest European Society of Cardiology 2020 guidelines on the management of AF.[2] Nonetheless, it has limited validation until now. We demonstrated that the classification of patients using the 4S-AF scheme was feasible in a retrospective cohort of patients with AF. Additionally, the implementation of appropriate treatment based on the 4S-AF scheme was associated with a significant reduction in all-cause mortality, independent of other important risk factors. A limitation of this scheme is that it remains subject to the individual shortcomings in the assessment of specific domains (e.g. the temporal classification of AF, as described above). However, it will likely evolve over time to include more sophisticated assessments, whereas the essential purpose of the 4S-AF to encourage a multidimensional approach towards AF characterization will remain.

Each domain within the 4S-AF scheme was found to have important prognostic implications among our cohort of patients with AF. Moreover, the 4S-AF score, determined by the sum of the individual domains, had a modest predictive capability for adverse outcomes during long-term follow-up, suggesting that the characterization of patients using this scheme may allow for the identification of high-risk patients. These high-risk patients may be suitable for more intensive follow-up and aggressive intervention. However, if intended for this purpose, further development of the 4S-AF score is needed, specifically with regards to the weighting of different domains. Treatment decisions based on the 4S-AF scheme were found to improve long-term outcomes in patients with AF. The finding that early rhythm control in patients with AF improves mortality corroborates other recent studies on the topic.[19,20] Moving forward, a streamlined method of characterizing patients is crucial in facilitating future research to evaluate the potential prognostic benefits of specific treatment strategies, such as AF ablation and LA appendage occlusion.

Limitations

The main limitation of this study is related to potential misclassification bias due to its observational nature and/or restricted use of continuous cardiac monitoring. Also, the exclusion of a significant proportion of patients from this analysis may have introduced a source of bias. Furthermore, we could not exclude the possibility of residual confounders and there is some overlap between the various domains of the 4S-AF scheme. As the EORP-AF General Long-Term Registry was based exclusively on cardiology practices, our results may not be generalizable to the wider AF population. In terms of the 4S-AF scheme, we were unable to assess whether episodes of AF were spontaneously terminating and the presence of LA fibrosis. Moreover, we had limited data on the severity of AF burden (*Sb*) at follow-up which precluded an analysis of treatment effects in this domain and future studies are needed to investigate this issue.

Conclusions

We demonstrate the feasibility of implementing the novel 4S-AF scheme in a large contemporary European cohort of patients with AF and show that treatment decisions based on this scheme improve mortality rates in AF. Overall, the 4S-AF scheme provides a unique method to *characterize* AF that overcomes many of the barriers encountered with traditional classification systems by integrating a multidimensional approach.

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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.

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