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CLINICAL RESEARCH
Atrial fibrillation epidemiology and diagnosis

Clinical utility of the 4S-AF scheme in predicting progression of atrial fibrillation: data from the RACE V study

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Aims

The recent 4S-AF (scheme proposed by the 2020 ESC AF guidelines to address stroke risk, symptom severity, severity of AF burden and substrate of AF to provide a structured phenotyping of AF patients in clinical practice to guide therapy and assess prognosis) scheme has been proposed as a structured scheme to characterize patients with atrial fibrillation (AF). We aimed to assess whether the 4S-AF scheme predicts AF progression in patients with self-terminating AF.

Methods and results

We analysed 341 patients with self-terminating AF included in the well-phenotyped Reappraisal of Atrial Fibrillation: Interaction between HyperCoagulability, Electrical remodelling, and Vascular Destabilization in the Progression of AF (RACE V) study. Patients had continuous monitoring with implantable loop recorders or pacemakers. AF progression was defined as progression to persistent or permanent AF or progression of self-terminating AF with >3% burden increase. Progression of AF was observed in 42 patients (12.3%, 5.9% per year). Patients were given a score based on the components of the 4S-AF scheme. Mean age was 65 [interquartile range (IQR) 58–71] years, 149 (44%) were women, 103 (49%) had heart failure, 276 (81%) had hypertension, and 38 (11%) had coronary artery disease. Median CHA_2DS_2-VASc (the CHA_2DS_2–VASc score assesses thromboembolic risk. C, congestive heart failure/left ventricular dysfunction; H, hypertension; A_2, age ≥ 75 years; D, diabetes mellitus; S_2, stroke/transient ischaemic attack/systemic embolism; V, vascular disease; A, age 65–74 years; Sc, sex category (female sex)) score was 2 (IQR 2–3), and median follow-up was 2.1 (1.5–2.6) years. The average score of the 4S-AF scheme was 4.6 ± 1.4. The score points from the 4S-AF scheme did not predict the risk of AF progression [odds ratio (OR) 1.1 95% CI 0.88–1.41, C-statistic 0.53]. However, excluding the symptoms domain, resulting in the 3S-AF (4S-AF scheme without the domain symptom severity, only including stroke risk, severity of AF burden and substrate of AF) scheme, predicted the risk of progression (OR 1.59 95% CI 1.15–2.27, C-statistic 0.62) even after adjusting for sex and age.

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Conclusions In self-terminating AF patients, the 4S-AF scheme does not predict AF progression. The 3S-AF scheme, excluding the symptom domain, may be a more appropriate score to predict AF progression.

Trial registration numbers Clinicaltrials.gov NCT02726698 for RACE V

Keywords Atrial fibrillation • Progression • Score • 4S-AF • Continuous monitoring

What's new?

- In patients with self-terminating atrial fibrillation (AF) included in the Reappraisal of Atrial Fibrillation: Interaction between HyperCoagulability, Electrical remodelling, and Vascular Destabilization in the Progression of AF study, the 4S-AF (Scheme proposed by the 2020 ESC AF guidelines to address Stroke risk, Symptom severity, Severity of AF burden and Substrate of AF to provide a structured phenotyping of AF patients in clinical practice to guide therapy and assess prognosis) scheme does not predict AF progression.
- Although symptoms are an important component of the 4S-AF scheme for choosing the treatment strategy in AF patients, they may be less relevant to determine AF progression in patients with self-terminating AF.
- In patients with self-terminating AF, a scheme without the symptoms domain, the 3S-AF (4S-AF scheme without the domain symptom severity, only including stroke risk, severity of AF burden and substrate of AF) scheme, may be more appropriate to assess AF progression.

Background

Atrial fibrillation (AF) is a progressive disease that generally starts with sporadic, short, and self-terminating episodes and progresses to more frequent, long-standing, and non-self-terminating episodes.[1] AF progression is the phenotypical representation of continuous atrial remodelling causing atrial cardiomyopathy.[2,3] AF progression rates vary in different populations ranging from 2% to 20% per year depending on the population included, follow-up duration, and type of monitoring of AF progression.[2,4,5] AF progression is associated with worse prognosis, including more heart failure hospitalizations,[2,6] stroke,[7] increased mortality,[7] and detriment in quality of life.[8]

The HATCH (the HATCH score assesses the risk of AF progression. H, Hypertension; A, Age (above 75 years); T, Transient ischemic attack or stroke; C, Chronic obstructive pulmonary disease; H, Heart failure) score was proposed more than a decade ago to determine the risk of AF progression in patients with self-terminating AF.[6] Contrasting results of the HATCH score suggest room for improvement.[4,9] The introduction of continuous rhythm monitoring devices, deep phenotyping, and new techniques studying early markers of atrial remodelling may contribute to an improved AF progression risk score.[5,10]

The 2020 European Society of Cardiology (ESC) AF guidelines have proposed an integrated frame, the 4S-AF scheme, which addresses stroke risk, symptom severity, severity of AF burden, and substrate of AF to provide a structured phenotyping of AF patients in clinical practice to guide therapy and assess prognosis.[11–13] Its clinical utility, however, in predicting AF progression remains to be validated. We therefore aimed to pursue the following two objectives: (i) to assess the clinical profile of patients with self-terminating AF using the 4S-AF scheme and (ii) to evaluate whether the 4S-AF scheme score predicts AF progression in deeply phenotyped patients with self-terminating AF.

Methods

Study population

The Reappraisal of Atrial Fibrillation: Interaction between HyperCoagulability, Electrical remodelling, and Vascular Destabilization in the Progression of AF (RACE V) is an investigator-initiated, prospective, multicentre study performed in the Netherlands, and it is part of the translational RACE V consortium aiming to determine mechanisms and predictors of AF progression. The design and methods have previously been described.[10] In brief, the RACE V included patients aged >18 years with a history of less than 10 years of self-terminating AF and a maximum CHA_2DS_2-VASc (the CHA_2DS_2-VASc score assesses thromboembolic risk. C, congestive heart failure/left ventricular dysfunction; H, hypertension; A_2, age ≥ 75 years; D, diabetes mellitus; S_2, stroke/transient ischaemic attack/systemic embolism; V, vascular disease; A, age 65-74 years; Sc, sex category (female sex)) score of 5. Patients were eligible if they had at least two documented episodes of self-terminating AF or one documented episode in combination with ≥ two symptomatic episodes suspected of being AF and were willing to undergo implantation of a Medtronic (MN, USA) Reveal LINQ® implantable loop recorder. Patients who already had Medtronic pacemakers were also eligible if atrial high rate episodes > 190 beats per minute lasting > 6 min, qualified as AF episodes, were detected. Patients with other types of pacemakers were not included due to incompatibility of algorithms for AF episode detections. Patients with a history of persistent AF, with AF solely due to transient triggers, currently pregnant, treated with amiodarone, on the waiting list for pulmonary vein isolation (PVI), or with a life expectancy <2.5 years were not eligible to participate. Of the 417 patients included in RACE V, 341 (82%) had ≥ 1 year follow-up of continuous rhythm monitoring as of 1 May 2020 and had available echocardiography data. This subset of patients is considered in the current analysis. The study was performed in concordance with the Declaration of Helsinki. The Institutional Review Board approved the protocol, and the study was registered at Clinicaltrials.gov (identifier NCT02726698). All centres approved the protocol and all patients gave written informed consent.

Clinical assessment

Clinical history, physical examination, symptoms, medication use, and a 12-lead electrocardiogram (ECG) were assessed at baseline. In addition, echocardiography was performed and analysed offline in an anonymized format in a central core lab.[5] In addition to the standard echocardiography measurements, speckle tracking was used to analyse strain deformation of the left atrium (LA) and the left ventricle in a vendor-independent software (TOMTEC-ARENA, Imaging Systems, Germany) (see Supplementary material online, Table S1 and Figure S1).

Follow-up

All patients were treated according to the ESC AF guidelines.[11] Follow-up visits were performed at 1 and 2.5 years. Patients could consent for 2.5 years continuous rhythm monitoring, until the end of battery of Reveal LINQ, or for 4 years in case patients had a pacemaker.

To collect continuous data on arrhythmias, all patients received a home monitoring device (Medtronic Carelink®). Both Reveal LINQ and pacemaker were set to AT/AF detection settings. Episodes of AF ≥2 min were automatically detected and later independently validated by five physicians. Arrhythmias with ≥ 182 beats per minute and at least for ≥24 beats were automatically classified as tachycardia. Arrhythmias with ≤ 30 beats

Table 1 Domains, description and definition of the 4S-AF scheme[12]

Domain	Score	Description	Definition	
Stroke (*St*)				4S-AF
(max 1 point)	0	Low risk	CHA_2DS_2-VASc score = 0 (males) or ≤1 (females)	3S-AF
	1	Not low risk, OAC indicated	CHA_2DS_2-VASc score ≥1 (males) or ≥2 (females)	
Symptoms (*Sy*)				4S-AF
(max 2 points)	0	No or mild symptoms	EHRA I—IIa	
	1	Moderate symptoms	EHRA IIb	
	2	Severe or disabling symptoms	EHRA III—IV	
Severity of AF burden (*Sb*)				4S-AF
(max 2 points)	0	Short episodes and infrequent episodes	Self-terminating AF or first onset	3S-AF
	1	Intermediate duration and/or frequent episodes	Persistent	
	2	Long or frequent episodes	Long-standing persistent AF or permanent AF	
Substrate (*Su*) (max 5 points)				
Comorbidity/CV risk factors[a] (max 2 points)				4S-AF
	0	No	No comorbidity/CV risk factor	3S-AF
	1	Single	At least one comorbidity/risk factor	
	2	Multiple	More than one comorbidity/risk factor	
LA enlargement/dysfunction (max 2 points)				
LA enlargement	0	No	LAVI <29 mL/m^2	
	1	Mild-moderate	LAVI ≥29 mL/m^2 and LAVI <40 mL/m2	
	2	Severe	LAVI ≥40 mL/m^2	
LA dysfunction	+1	Impairment in LA strain phase	One extra point if any of the following: reservoir Strain < 38% or conduit strain < 21% or contractile strain <16%)	
Age >75 (max 1 point)				
	0	No	≤ 75 years	
	1	Yes	> 75 years	

CV, cardiovascular; EHRA, European Heart Rhythm Association; LA, left atrium; LAVI, left trial volume index; OAC, oral anticoagulation. The CHA2DS2-VASc score assesses thromboembolic risk. C, congestive heart failure/left ventricular dysfunction; H, hypertension; A2, age ≥ 75 years; D, diabetes mellitus; S2, stroke/transient ischaemic attack/systemic embolism; V, vascular disease; A, age 65–74 years; Sc, sex category (female sex).
[a]Comorbidities and risk factors were considered as any of the following: hypertension, heart failure, diabetes mellitus; coronary artery disease, body mass index > 25 kg/m^2, moderate or severe mitral valve regurgitation and kidney dysfunction (estimated glomerular filtration rate < 60 mL/min/1.73 m^2).

per minute for at least 12 beats were automatically classified as bradycardia. Asystole ≥ 4.5 s were automatically classified as pauses.[5]

Covariate and outcome definitions

Patients were classified as having heart failure in the presence of a left ventricular ejection fraction (LVEF) ≤ 45% at baseline or LVEF > 45% with symptoms associated with heart failure (New York Heart Association functional class II or III) or previous hospitalization for heart failure. Hypertension was defined by a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or use of antihypertensive medication. Chronic kidney dysfunction was defined as estimated glomerular filtration rate < 60 mL/min/1.73 m^2. Obesity was defined as body mass index (BMI) > 30 kg/m^2. Left atrial volume index (LAVI) was categorized as normal (< 29 mL/m^2) or increased (mild, 29–33 mL/m^2; moderate, 34–39 mL/m^2; severe, ≥ 40 mL/m^2). LA strain impairment was defined as having at least one low value of any of the strain phases expressed in strain percentage deformation (reservoir strain < 38% or conduit strain < 21% or contractile strain < 16%) (see Supplementary material online, *Table S1*).[14] AF progression was defined as either one of the following verified in the implantable loop recorder or pacemaker in comparison to the first 6 months, (1) development of persistent or permanent AF during follow-up, or (2) an increase of > 3% AF burden over 6 months or total follow-up.[5]

4S-AF scheme assessment

Patients were assessed based on the components of the 4S-AF scheme awarding maximum points per domain as stated in the 2020 ESC AF guidelines (stroke = 1; symptoms = 2; severity of burden = 2; substrate = 5) to a total maximum of 10 points (*Table 1*).[11,12] Stroke risk was assessed using the CHA_2DS_2-VASc score, awarding 1 point to the risk of stroke with a CHA_2DS_2-VASc score of 1 or higher for men and a score of 2 or higher for women. Symptoms were assessed using the European Heart Rhythm Association symptom classification, awarding 0 points to patients in category I or IIa, 1 point to patients in category IIb, and 2 points to patients in category III or IV. The severity of AF burden was assessed based on the duration and frequency of the AF episodes. Given that the population in this study had self-terminating AF, all patients were given 0 points in this category. Substrate was assessed based on three subdomains: (i) Comorbidity/cardiovascular risk subdomain, by awarding 0 points to patients without comorbidities, 1 point to patients with any comorbidity (hypertension, heart failure, diabetes mellitus, BMI > 25 kg/m^2, moderate to severe mitral valve regurgitation, or kidney dysfunction) and 2 points to patients with more than one comorbidity; (ii) LA enlargement/dysfunction subdomain; points were awarded to patients based on the presence of atrial enlargement assessed by LAVI values (0 points if LAVI < 29 mL/m^2, 1 point if LAVI ≥ 29 mL/m^2, and LAVI <40 mL/m^2; 2 points if LAVI ≥ 40 mL/m^2) and 1 extra point if patients presented LA dysfunction in any of the LA phases

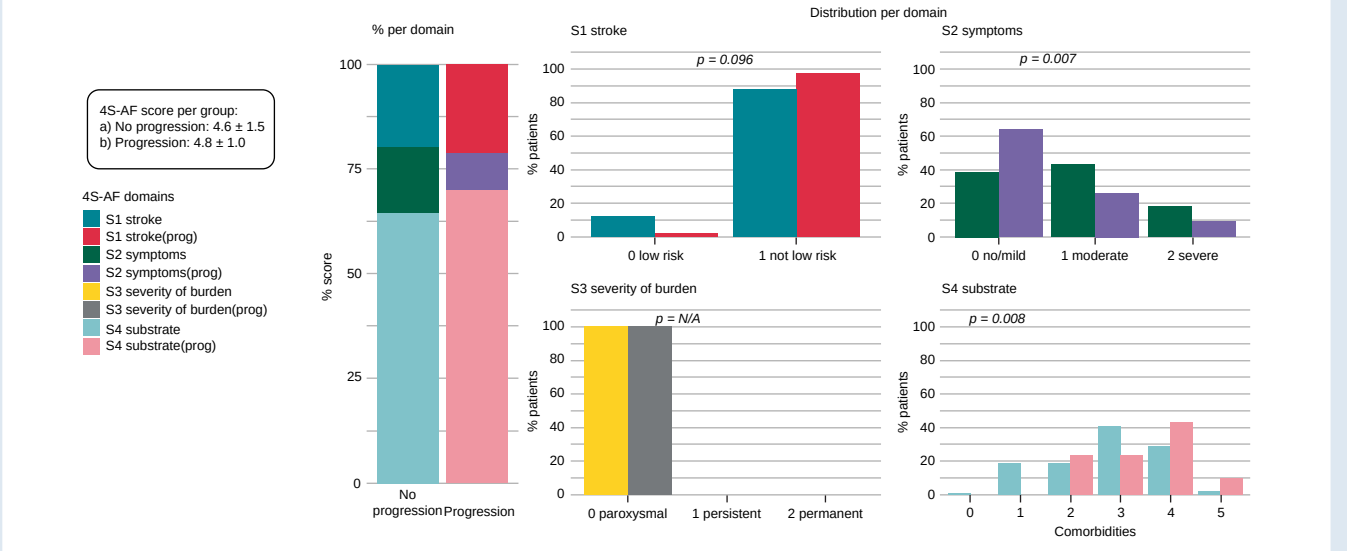

Figure 1 Characterization of patients with self-terminating AF using the 4S-AF scheme grouped by progression status. The bar '% per domain' shows the percentage of score explained by each domain of the 4S-AF scheme. Each of the panels per S domain shows the percentage of patients characterized using each of the S domains in the 4S-AF scheme grouped by progression status. Darker colours in the bars represent the group of patients with atrial fibrillation progression. *P* values represent the difference in patient distribution per progression status in each of the 4S-AF scheme domains. 4S-AF scheme, maximum score per domain (stroke = 1; symptoms = 2; severity of AF burden = 2; substrate = 5) to a total maximum of 10 points; AF, atrial fibrillation.

assessed by two-dimensional speckle tracking strain (reservoir strain < 38% or conduit strain < 21% or contractile strain <16%) (*Table 1* and see Supplementary material online, *Table S1*) adding to a maximum of 2 points; and (iii) age subdomain; awarding a point to patients who were 75 years or older. A modified 4S-AF scheme was derived by eliminating the symptom domain, resulting in a 3S-AF scheme.

Statistical analysis

Continuous variables with normal distribution are expressed as mean ± standard deviation (SD), otherwise as median with interquartile range (IQR). Categorical variables are presented as observed number with percentage. Continuous variables are compared using independent Student's *t*-test or the Mann–Whitney U test, as appropriate. Logistic regression was performed to assess association with AF progression. Models were adjusted for sex and age. Interactions were examined in the models. C-statistic was performed to assess the prediction of the score, for both the 4S-AF and the modified 3S-AF scheme. The Likelihood ratio test was used to assess the goodness of fit of a model. The analysis was performed using software R v 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical characteristics

We included 341 (82%) from the 417 patients in RACE V. There were no differences in baseline characteristics between the present analysed group and the ones not included in the analysis (see Supplementary material online, *Table S2*). Median age was 65 (58–71) years, 149 (44%) were women, 103 (49%) had heart failure, 276 (81%) had hypertension, and 38 (11%) had coronary artery disease (*Table 2*). The majority had a CHA_2DS_2-VASc score ≥ 2 (*n* = 258, 76%) (*Table 2*). Median number of comorbidities was 2 (2-3) and 16 (5%) patients had no identified comorbidities.

4S-AF and 3S-AF schemes

The average score of the 4S-AF scheme was 4.6 ± 1.4. The majority had less than half of the maximum possible score [4S-AF score <5, *n* = 243 (71%)]. Of the total score, 20% was explained by the stroke domain, 17% by the symptoms domain, and 67% by the substrate domain (*Figure 1*, *Table 3*). Most of the patients did not have a low stroke risk [*n* = 303, 89% (no progression group *n* = 262, 88%; progression group *n* = 41, 98%, *P* = 0.096)]. More than half had multiple comorbidities and/or cardiovascular risk factors [*n* = 232, 68% (no progression group *n* = 198, 66%; progression group *n* = 34, 81%, *P* = 0.141)]. Most had LA enlargement or dysfunction [*n* = 292, 86% (no progression group *n* = 258, 86%; progression group *n* = 34, 81%)] with more severe dysfunction in patients with progression (*P* = 0.006) (*Table 3*).

The average score of the 3S-AF scheme, the 4S-AF scheme without the symptom domain, was 3.9 ± 1.2. The majority had less than half of the maximum possible score [3S-AF score < 4, *n* = 226 (66%)]. From the total score, 25% was explained by the stroke domain and 75% by the substrate domain (*Table 4*).

Progression

Median follow-up of continuous rhythm monitoring was 2.1 (1.5–2.6) years. AF progression was seen in 42 patients (12.3%, 5.9% per year). Two thirds of the patients progressed from self-terminating AF to persistent or permanent AF (*n* = 28, 67%). Few patients had severe AF symptoms (*n* = 58, 17%), and patients who developed progression had less AF symptoms (*P* = 0.007) (*Figure 1*).

There were no differences in the 4S-AF scheme scores between patients without and with progression (*P* = 0.401) (*Table 3*). However, when using the 3S-AF scheme, patients without progression were more often in the lower half of maximum possible score (3S-AF score < 4, *n* = 206 [69%] vs. *n* = 20 [49%], *P* = 0.011) and had a lower

Table 2 Baseline characteristics of the population

	n = 341
Clinical characteristics	
Age, years	65 (58–71)
Female sex, *n* (%)	149 (44)
Total history AF, years	2.7 (0.7–5.0)
Heart failure, *n* (%)	103 (49)
HFrEF, *n* (%)	6 (2)
HFpEF, *n* (%)	97 (46)
Hypertension, *n* (%)	276 (81)
Diabetes mellitus, *n* (%)	30 (9)
Coronary artery disease, *n* (%)	38 (11)
Atherosclerosis[a], *n* (%)	162 (48)
Ischaemic stroke, *n* (%)	16 (5)
Pacemaker, *n* (%)	17 (5)
Number of comorbidities[b]	2 (2–3)
Patients without identified comorbidity, *n* (%)	16 (5)
CHA_2DS_2-VASc score	2 (2–3)
CHA_2DS_2-VASc score, *n* (%)	
< 2	83 (24)
≥ 2	258 (76)
EHRA class, *n* (%)	
I	33 (10)
IIa	110 (32)
IIb	140 (41)
III	56 (16)
IV	2 (1)
Height, cm	176 (168–184)
Weight, kg	85 (74–97)
BMI, kg/m^2	27 (24–30)
Obesity BMI > 30, *n* (%)	93 (27)
Waist circumference, cm	100 (93–108)
Systolic blood pressure, mmHg	133 (125–145)
Diastolic blood pressure, mmHg	80 (74–85)
Laboratory results	
eGFR, mL/min/1.73m^2	81 (70–90)
Electrocardiogram	
PR-interval, ms	165 (150–186)
QRS-interval, ms	96 (88–102)
Medications, *n* (%)	
β-blocker	172 (51)
Verapamil/diltiazem	61 (18)
Digoxin	6 (2)
Antiarrhythmic drugs	94 (28)
ACE-inhibitor	64 (19)
Angiotensin receptor blocker	68 (20)
Statin	120 (35)
Diuretic	52 (15)
Anticoagulant	235 (69)
Vitamin K antagonist	49 (14)
NOAC	186 (55)
Echocardiographic variables	
Left atrial volume, mL	58 (48–75)
Left atrial volume index (mL/m^2)	29 (23–36)
Left atrial reservoir function, %	36.0 (29.2–42.8)
Left atrial contractile function, %	16.3 (12.7–21.6)
Left atrial conduction function, %	19.3 (13.9–24.4)
Left ventricular ejection fraction, %	50 ± 8
Left ventricular mass, g	150 (130–181)
Left ventricular mass index, g/m^2	76 (67–88)
Left ventricle global longitudinal strain, %	−14.0 ± 2.4

ACE, Angiotensin-converting enzyme; AF, atrial fibrillation; BMI, body mass index; eGFR, estimated glomerular filtration rate; EHRA, European Heart Rhythm Association symptoms classification; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NOAC, novel oral anticoagulation. The CHA2DS2-VASc score assesses thromboembolic risk. C, congestive heart failure/left ventricular dysfunction; H, hypertension; A2, age ≥ 75 years; D, diabetes mellitus; S2, stroke/transient ischaemic attack/systemic embolism; V, vascular disease; A, age 65–74 years; Sc, sex category (female sex).
[a]Atherosclerosis is presence of history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, ischaemic cerebral infarction, peripheral vascular disease, Agatston score > 400 or plaque.
[b]The number of comorbidities was calculated by awarding a point to each of the following comorbidities, hypertension, heart failure, age > 65 years, diabetes mellitus; coronary artery disease, BMI > 25 kg/m^2, moderate or severe mitral valve regurgitation and kidney dysfunction (eGFR < 60 mL/min/1.73 m^2).

total score (3.8 ± 1.2 vs. 4.4 ± 1.0, $P = 0.006$) as compared to those with progression (*Table 4*).

The 4S-AF scheme score was not associated with AF progression [odds ratio (OR) 1.11 95% CI 0.88–1.41, $P = 0.40$]. The 3S-AF scheme score, without the symptom domain, was associated with AF progression (OR 1.59 95% CI 1.15–2.27, $P = 0.007$); this association persisted after adjusting for sex and age (see Supplementary material online, *Table S3*). The 3S-AF scheme showed a significant predictive value of AF progression (C-statistic 0.62, 95% CI 0.53–0.71) (*Figure 2* and see Supplementary material online, *Table S3*). There were no significant interactions for sex and age for any of 4S-AF or 3S-AF schemes (see Supplementary material online, *Table S3*). From the individual domains of the 4S-AF scheme, an increase in the substrate domain score was associated with progression (OR 1.62 95% CI 1.14–2.36, $P = 0.010$). This association persisted after adjusting for sex and age. The association with progression within the substrate domain was mainly driven by comorbidities and/or cardiovascular risk factors (OR 1.48 95% CI 1.09–2.02, $P = 0.010$) (see Supplementary material online, *Table S3*). When comparing the models associated with progression, the 3S-AF scheme performed better than the substrate domain alone (likelihood ratio test $P < 0.001$).

Discussion

In a population of well-phenotyped self-terminating AF patients included in the RACE V study, we characterized patients using the 4S-AF scheme. The main findings are as follows: (i) the 4S-AF scheme was not associated with progression in patients; (ii) the 3S-AF scheme,

Table 3 Characterization using the 4S-AF scheme in the total patient population and per progression status

	Total population $n = 341$	No progression $n = 299$	Progression $n = 42$	*P* value
4S-AF scheme score	4.6 ± 1.4	4.6 ± 1.5	4.8 ± 1.0	0.401
4S-AF scheme score <5 points, *n* (%)[a]	243 (71)	121 (71)	31 (74)	0.835
Domain scores				
S1 stroke	1 (1–1)	1 (1–1)	1 (1–1)	0.054
S2 symptoms	1 (0–1)	1 (0–1)	0 (0–1)	**0.003**
S3 severity of AF burden	0 (0–0)	0 (0–0)	0 (0–0)	N/A
S4 substrate	3 (2–4)	3 (2–4)	4 (3–4)	**0.014**
Percentage of score explained by each domain[b]				
S1 stroke	20 (17–25)	20 (17–25)	20 (17–25)	0.181
S2 symptoms	17 (0–25)	17 (0–25)	0 (0–17)	**0.002**
S3 severity of AF burden	0	0	0	N/A
S4 substrate	67 (57–75)	67 (57–75)	75 (67–80)	**0.002**
Characterization per each domain				
S1 stroke				0.096
Low risk	38 (11)	37 (12)	1 (2)	
Not low risk, anticoagulation indicated	303 (89)	262 (88)	41 (98)	
S2 symptoms *n (%)*				**0.007**
No or mild symptoms	143 (42)	116 (39)	27 (64)	
Moderate symptoms	140 (41)	129 (43)	11 (26)	
Severe or disabling symptoms	58 (17)	54 (18)	4 (10)	
S3 severity of burden *n (%)*				N/A
Paroxysmal AF or first onset	341 (100)	299 (100)	42 (100)	
Persistent	0 (0)	0 (0)	0 (0)	
Long-standing persistent AF or permanent AF	0 (0)	0 (0)	0 (0)	
S4 substrate *n (%)*				**0.008**
0 points	3 (1)	3 (1)	0 (0)	
1 points	26 (7)	26 (8)	0 (0.0)	
2 points	65 (19)	55 (18)	10 (24)	
3 points	132 (39)	122 (41)	10 (24)	
4 points	104 (31)	86 (29)	18 (43)	
5 points	11 (3)	7 (2)	4 (9)	
Comorbidities/CV risk factors[a], *n* (%)				0.141
No	23 (6)	22 (7)	1 (2)	
Single	86 (25)	79 (27)	7 (17)	
Multiple	232 (68)	198 (66)	34 (81)	
LA enlargement/dysfunction, *n* (%)				**0.006**
No	49 (14)	41 (13.7)	8 (19.0)	
Mild-moderate	143 (42)	135 (45.2)	8 (19.0)	
Severe	149 (44)	123 (41.1)	26 (61.9)	
Age >75, *n* (%)				0.148
No	309 (91)	274 (92)	35 (83)	
Yes	32 (9)	25 (8)	7 (17)	

4S-AF scheme, maximum score per domain (stroke = 1; symptoms = 2; severity of AF burden = 2; substrate = 5) to a total maximum of 10 points. Data are presented as number of patients *n* (%), mean (standard deviation), or median (interquartile range).
AF, atrial fibrillation; CV, cardiovascular; LA, left atrium; N/A, not available.
[a]5 points is the half of scale based on the maximum score of the 3S-AF scheme.
[b]Calculated by dividing the points of the domain by total score the scheme.

Table 4 Characterization using the 3S-AF scheme in the total patient population and per progression status

	Total population $n = 341$	No progression $n = 299$	progression $n = 42$	*P*-value
3S-AF scheme score	3.9 ± 1.2	3.8 ± 1.2	4.4 ± 1.0	**0.006**
3S-AF scheme score <4 points, *n* (%)[a]	226 (66)	206 (69)	20 (49)	**0.011**
Percentage of score explained by each domain[b]				
S1 stroke	25 (20–25)	25 (20–25)	20 (20–25)	0.587
S3 severity of AF burden	0	0	0	N/A
S4 substrate	75 (75–80)	75 (75–80)	80 (75–80)	0.587

3S-AF scheme, maximum score per domain (stroke = 1; severity of AF burden = 2; substrate = 5) to a total maximum of 8 points. Data are presented as number of patients *n* (%), mean (standard deviation), or median (interquartile range).
AF, atrial fibrillation; N/A, not available.
[a]4 points is the half of scale based on the maximum score of the 3S-AF scheme.
[b]Calculated by dividing the points of the domain by total score the scheme.

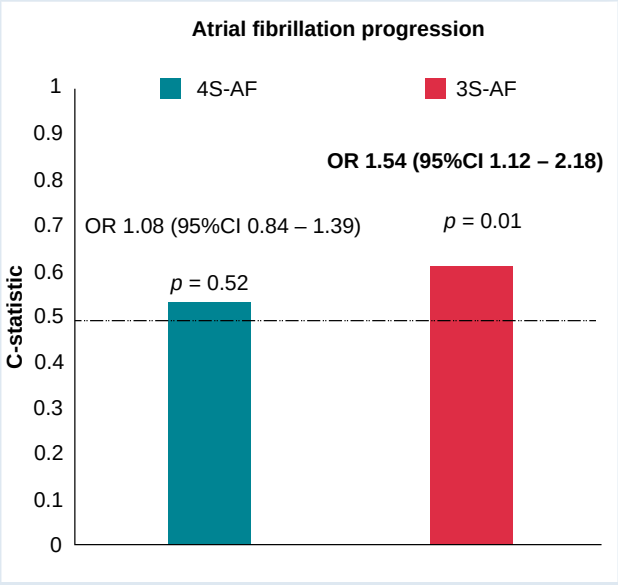

Figure 2 Prediction of progression in patients with self-terminating AF using the 4S-AF and the 3S-AF scheme scores. Dotted line represents minimum value for C-statistic to be considered predictive. *P*-values represent significance of the association between each scheme and the outcome based on logistic regression after adjusting for sex and age. 4S-AF scheme, maximum score per domain (stroke = 1; symptoms = 2; severity of AF burden = 2; substrate = 5) to a total maximum of 10 points; 3S-AF scheme, same domains as in 4S-AF scheme without the symptoms domain adding up to a total maximum of eight points; AF, atrial fibrillation.

a modified scheme that excludes the symptoms domain from the 4S-AF scheme, predicted AF progression in patients with self-terminating AF albeit with low predictive value; and (iii) the substrate domain explained most of the 4S-AF scheme score, driven mainly by comorbidities.

Characterization of AF patients

Characterization of AF patients according to the 4S-AF scheme is based on the stroke risk, symptoms, severity of AF, and substrate. The latter is composed of a number of risk factors, comorbidities, atrial remodelling, and older age.[12] In this analysis, the median 4S-AF score was lower than reported in previous studies characterizing patients with AF.[13,15–17] One of the reasons may be that we only included younger patients with less comorbidities and with paroxysmal self-terminating AF.

According to the 4S-AF scheme definition, the stroke risk was not low. However, the total CHA_2DS_2-VASc score was lower in the current analysis in comparison to previous studies. For example, Guo *et al.*[16] evaluated patients with AF in the Optimal Thromboprophylaxis in Elderly Chinese Patients with Atrial Fibrillation registry finding patients with slightly higher CHA_2DS_2-VASc score (median 3, IQR 2–5). Similarly, Rivera-Caravaca *et al.*[15] and Ding *et al.*[13] characterized AF patients using the 4S-AF scheme in the EurObservational Research Programme (EORP)-AF Long-Term General Registry, reporting both slightly higher CHA_2DS_2-VASc score (median 3, IQR 2–4 for both). Malavasi *et al.*[17] reported a CHA_2DS_2-VASc score with median 2 (IQR 2–5) from the Fibrillazione Atriale in Modena (FAMo) cohort. Higher scores of CHA_2DS_2-VASc may indicate a population with a higher risk of morbidity and mortality.

The severity of symptoms, the second S, was low in the current population. This might be explained by the fact that we excluded symptomatic patients who may want to undergo PVI because of symptoms. A similar proportion of patients had severe symptoms in the EORP-AF Long-Term General Registry (18%) and explained a similar percentage of the total 4S-AF scheme score (15%).[13] On the other hand, the percentage of patients with severe symptoms was higher in FAMo cohort (26%). It was not possible to determine the percentage of the 4S-AF scheme score explained by the symptoms domain.[17]

Since we only included patients with self-terminating AF, the third S, all patients had the same 4S-AF scheme score under this domain. Both the EORP-AF Long-Term General Registry and the FAMo cohort included less than half of the patients with self-terminating AF.[13,15,17] The scores in these two studies were therefore increased by the points awarded to patients with more advanced stages of AF. In the EORP-AF Long-Term General Registry, 18% of the 4S-AF scheme score was explained by the severity of AF burden.

The substrate, the fourth S, depends on the number of comorbidities, atrial remodelling, and age. We included relatively young patients with a limited number of comorbidities. However, comorbidities were identified in almost all of our patients. The substrate domain explained more than half of the 4S-AF scheme score in the current study population, driven mainly by comorbidities and risk factors for cardiovascular disease. This is different from the burden of comorbidities reported

from the FAMo cohort (67% with zero to two comorbidities); however, the comorbidities included into the definition may have differed.[17] The cardiovascular risk factors (hypertension, hypercholesterolaemia, diabetes mellitus, coronary artery disease, heart failure, and peripheral artery disease) reported in the EORP-AF Long-Term General Registry occurred less frequently (12% of patients without cardiovascular risk factors) in comparison to the current study population, with similar definitions.[13] In the latter study, the substrate domain explained less than half of the 4S-AF scheme score whereas in the current analysis it explained most of the score, predominantly in patients with AF progression. The higher reported number of cardiovascular risk factors in the current analysis may be due to more comprehensive deep phenotyping of our patients.[18]

AF progression

AF progression ranges from 2% to 20% per year[2,4,19] and its progression depends on the AF population investigated, duration of follow-up and type of monitoring of AF progression. We observed lower progression rates as compared to data from 42 meta-analysed studies assessing progression in patients with self-terminating AF.[19] In comparison to previous studies, patients in our study were followed for a relatively short follow-up time and were a relatively healthy population.[19]

In contrast to previous studies, we used continuous monitoring for the detection of AF progression.[5] Most of the data on progression come from registry studies using electrocardiographic or Holter monitoring, or alternatively only symptoms to assess AF progression. In previous studies, follow-up was often longer and AF patients were at higher risk. We included only paroxysmal AF patients. This all may explain differences in AF progression rates between our data and previous studies.[19] In addition, better current handling of comorbidities, for example high percentage of patients with hypertension but with a low average blood pressure in our population, may have reduced the progression rate.[4,11]

We showed that a modified scheme without the symptoms domain, the 3S-AF scheme, was associated with AF progression in the current study. However, the predictive value was low in spite of having patients phenotyped in depth. This association, however, prevailed after adjusting for sex and age. In line with our finding that symptoms seem less relevant for the prediction of AF progression, Ding *et al.*[13] also did not find an association between the symptoms domain and all-cause mortality nor for cardiovascular mortality. Needless to say, symptoms are difficult to interpret and depend on the type of patients included as well as the way they are interpreted by the health care professional. To implement symptoms into a score assessing outcome may therefore be difficult. In our study patients who developed progression had less AF symptoms. The latter may be explained by the institution of a more aggressive rhythm control approach in patients with more severe symptoms. Alternatively, the absence of symptoms could have led to less consultation and therefore less treatment, allowing atrial remodelling to progress.[2,20] A scheme omitting the symptom severity could probably be a better alternative to predict AF progression. The HATCH score was proposed more than a decade ago to determine the risk of AF progression[6]; however, validating results are contrasting.[9] Schnabel *et al.*[2] showed in PREvention oF thromboembolic events-European Registry study that the use of the individual components rather than the HATCH score to predict AF progression performed significantly better (C-statistic 0.64 vs. 0.52, $P = 0.0001$) but still with a low predictive value. The CHA_2DS_2-VASc score has also shown to predict progression.[4] Since the CHA_2DS_2-VASc score includes comorbidities and cardiovascular risk factor components it is expected to be related to AF progression.[4,9]

The 4S-AF is a practical scheme to help characterize patients with AF. However, this scheme remains to be validated. It is a dynamic score that warrants periodic reassessment in all its domains.[12] Incidence of comorbidities included in both the stroke and substrate domain may change punctuation within the domain, may cause progression of atrial remodelling and increasing risk of AF progression.[4] In our current study, unfortunately, the 4S-AF scheme was only assessed at baseline. For assessing the risk on AF progression, a modified 3S-AF scheme may be more informative since symptoms seem not to be relevant for AF progression, in contrast to the severity of the substrate. Further validation of modified 3S-AF scheme to predict AF progression will be needed to prove its utility.

Limitations

The current study involves only patients with self-terminating AF and the results cannot be generalized to the whole AF spectrum. Second, it is an observational study and treatment was at the discretion of the treating physician, having potential impact on AF progression. It was not possible to adjust for treatment strategy. Third, given the relatively healthy population with the majority having a low score in the scheme and the short follow-up time, less progression occurred. Fourth, we validated the score as proposed without making additions, such as P wave intervals; neither did we evaluate dynamic changes in the score, such as comorbidities incidence, which could have modified the score. Among the strengths of the current analysis, AF patients included were in-depth phenotyped and had continuous monitoring providing the opportunity to assess more accurately AF episodes and burden. Moreover, speckle tracking was used, in place of volume measures, to assess atrial function within the substrate domain. This may have led to the identification of early atrial remodelling as it is less affected by loading conditions in comparison to volumetric methods.

Conclusion

In self-terminating AF patients, the 4S-AF scheme does not predict AF progression. The 3S-AF scheme, however, excluding the symptom domain, may be a more appropriate score to predict AF progression.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study

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