*Viewpoint*

**Characterizing (rather than classifying) atrial fibrillation to support clinical decision-making: The 4S-AF scheme (Stroke risk; Symptoms; Severity of burden; Substrate)**

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**Abstract**

Atrial fibrillation (AF) is a complex condition requiring holistic management with multiple treatment decisions about optimal thromboprophylaxis, symptom control and identification and management of concomitant cardiovascular risk factors and comorbidity. Sometimes the information needed for treatment decisions is incomplete, as available classifications of AF mostly address a single domain of AF(or patient)-related characteristics.

The most widely used classification of AF based on AF episode duration and temporal patterns (that is, the classification to first-diagnosed, paroxysmal, persistent and long-term persistent AF) has contributed to a better understanding of AF prevention and treatment but its limitations and the need for a multi-dimensional AF classification have been recognized.

We propose a paradigm shift from classification towards a structured *characterization* of AF addressing specific domains that have treatment and prognostic implications to become a standard in clinical practice, thus streamlining the assessment of AF patients at any healthcare level, facilitating communication among physicians, treatment decision-making and optimal management of AF patients.

Specifically, we propose the 4S-AF structured pathophysiology-based *characterization* (rather than classification) scheme that includes four AF- and patient-related domains - Stroke risk, Symptoms, Severity of AF burden, and Substrate severity and provide a hypothetical model for the use of 4S-AF characterization scheme to aid treatment decision making concerning the management of patients with AF in clinical practice.

**Key words:** atrial fibrillation, classification scheme, temporal-based classification, characterization, stroke risk, symptom severity, burden, substrate.

**Introduction**

Ever since the term *auricular fibrillation* was coined in 1909[1], the understanding of atrial fibrillation (AF) leading to important developments for its management has been constantly evolving, with great improvements having been achieved in the last few decades[2, 3]. The more we learn about AF and its interaction with underlying comorbidity, realizing that it is not just the arrhythmia but also underlying comorbidities that determine outcome[4], the greater is our ability to characterize the medical profile of each patient to provide information relevant for optimal management decisions.

Currently, international AF guidelines and consensus documents list multiple classifications of AF (Table 1)[5-11], each classification addressing a single domain of AF(or patient)-related characteristics. Although these classifications have been gradually evolving towards better precision and clinical utility[12, 13], they separately address specific features relevant for the arrhythmia, the patient or the clinical setting in which AF occurs. Lack of integration becomes burdensome and sometimes the information needed for treatment decisions is incomplete.

The most widely used classification of AF based on AF episode duration and temporal patterns (that is, the classification to first-diagnosed, paroxysmal, persistent and long-term persistent AF) has contributed to a better understanding of AF prevention and treatment but its limitations and the need for a multi-dimensional AF classification have been recognized[14, 15].

Importantly, the pattern-based classification of AF provided a standardization of AF-related nomenclature and was easily adopted owing to its simplicity. However, despite generally correlating with the extent of atrial substrate, remodelling and AF-related outcomes, the pattern-based classification of AF lacks precision in differentiating among specific features relevant for optimal treatment decisions with regards to stroke prevention and rhythm control such as catheter ablation[16]. Indeed, formal recommendations for the management of AF are not based on the pattern of AF, except for the decision to restore sinus rhythm, but the terms paroxysmal and persistent AF include a large conglomerate of patients with wide variations in AF patterns, substrates and other characteristics and, consequently, different needs in management. The differentiation between paroxysmal and persistent AF is often very cumbersome, both patterns may be observed in the same patient during follow-up, and the heterogenicity of recurrences and progression of AF poses a challenge to a rhythm-based classification. In addition, it describes only the arrhythmia, whereas other relevant features such as, for example, cardiovascular risk factors and underlying comorbidities are not included[17].

Given the multiplicity of factors relevant for optimal management of AF in clinical practice, advances in monitoring of AF and risk assessment tools, evolving treatment options and complexity of AF itself, it is not very likely that a simple but comprehensive classification of AF will be soon proposed.

From this viewpoint, we propose a paradigm shift from classification towards a structured *characterization* of AF addressing specific domains that have treatment and prognostic implications to become a standard in clinical practice, thus streamlining the assessment of AF patients at any healthcare level, facilitating communication among physicians, treatment decision-making and optimal management of AF patients.

Specifically, we propose the 4S-AF structured pathophysiology-based *characterization* (rather than classification) scheme that includes four AF- and patient-related domains (Stroke risk; Symptoms; Severity of AF burden; Substrate severity), Figure 1.

**The need for a structured AF characterization**

Being a multifaceted, complex and very heterogeneous disease, AF requires structured patient management and multiple treatment decisions addressing different treatment domains such as stroke prevention, symptom improvement and management of concomitant conditions[18]. Importantly, these decisions should be regularly re-evaluated, owing to dynamic changes in the patients’ individual risk profile[19, 20].

Sometimes the complexity of patient- and/or AF-related features requires multidisciplinary engagement to facilitate treatment decisions-relating to thrombo-embolic protection, cardioversion, antiarrhythmic drug therapy, left atrial catheter ablation or rate control[5]. In daily clinical work, AF-related communication among practitioners including expert consultants needs to be rapid but comprehensive, efficiently providing all the relevant information to facilitate treatment decisions[12].

Modern medicine is characterized by rapidly evolving means of communication of health-related information among physicians (and patients), including computer- or mobile application-based decision support tools for clinicians and/or patients. Recently, several such tools have been developed specifically for AF, and preliminary data suggest a potential for improving AF management and patient outcomes using these tools[21, 22]. Importantly, their output strongly depends on comprehensiveness (and accuracy) of AF-related and other health information entered for a given patient.

Finally, the use of electronic medical and health records is increasing worldwide. These systems provide an opportunity for rapid creation of large datasets that can be used for research purposes. The use of a uniformly structured characterization of AF patients across various datasets would improve the compatibility of data from various sources.

In all these circumstances, including routine clinical practice, the use of a structured characterization of AF patients, with well-defined descriptors would facilitate not only the communication among involved practitioners, but also treatment decisions and overall management of AF patients[18].

Indeed, using such a structured AF patient characterization scheme would help physicians achieve a good balance of simplicity, practicality and information-based treatment decision-making.

**The 4S-AF scheme for characterization of patients with clinically diagnosed AF**

The two key AF-specific treatment decisions are: *i*) the need for thrombo-prophylaxis to prevent stroke or systemic embolic events, including the choice of optimal thromboprophylactic strategy (most commonly the use of oral anticoagulant therapy [OAC]), and *ii*) appropriate choice of rate and/or rhythm control to improve symptoms and prevent complications of AF such as heart failure [18]. In addition, the rhythm control treatment strategy often involves choosing between long-term antiarrhythmic drug medication or atrial ablation[5].

Whereas patient’s age (and other demographic features), cardiovascular risk factors and comorbid diseases should be routinely noted in the patient’s medical, a more detailed characterisation of AF-specific features combined into a structured system for comprehensive description of AF would facilitate the choice of optimal treatment, not only affecting the success of interventional procedures but also the patient outcome.

We therefore propose a structured characterization of AF patients in clinical practice using the 4S-AF scheme that addresses Stroke risk; Symptom severity; Severity of AF burden and Substrate for AF (Figure 1). This approach is based on the principles generally similar to the most widely used tumour clinical staging system (i.e., the TNM tumour classification) but unlike tumours, AF would be *characterized* rather than staged.

The **4S-AF scheme** would provide essential information needed for decision-making on the use of OAC, rate or rhythm control and AF ablation or antiarrhythmic medication. At this point, we do not propose this system as a definitive treatment-decision tool, since data on its association with treatment outcomes are currently lacking, but rather as a structured aid in the decision process. Nevertheless, we certainly do not exclude that with acquisition of data in the future and evaluation of the proposed characterization scheme, this might become the case.

*The 4S-AF scheme domains (see Figure 1)*

The **Stroke risk (St)** domain characterisation is currently based on the routinely used and guideline-recommended clinical risk factor-based CHA2DS2-VASc score for stroke risk assessment, and the indication for OAC use is established as per guideline recommendations from the ESC and other international bodies[5, 23, 24].

Multiple blood biomarkers (e.g., B-type natriuretic peptide, cardiac troponin, biomarkers of renal function, etc.) and indices of atrial structural and functional remodelling obtained by various imaging tools have been shown to correlate with individual AF-related thrombo-embolic risk, and several biomarker-based stroke risk scores[25] have been validated, showing modest but statistically significant improvement in stroke risk prediction when biomarkers are added to clinical risk factors[26].

Recent evidence suggest that the burden of AF may be associated with thromboembolic risk. Whereas the landmark trials of non-vitamin K antagonist oral anticoagulants (NOACs) versus warfarin for stroke prevention in AF consistently showed that the residual thromboembolic risk among anticoagulated patients was significantly lower in those with paroxysmal as compared to persistent AF (even after adjustment for baseline characteristics)[27-29], data from earlier trials that included non-anticoagulated controls [30] and contemporary AF registries or population-based studies[31, 32] are conflicting.

While the clinically assessed burden of AF using only intermittent electrocardiographic (ECG) monitoring might not significantly impact stroke risk (that is, a clinically evident AF could mean that the stroke risk has already crossed certain threshold for elevated stroke risk), increasing body of evidence derived from cohorts of patients implanted with pacemakers or defibrillators capable of continuous heart rhythm monitoring or high-risk cohort of patients with insertable cardiac monitors or wearable monitoring devices suggest that even the burden of subclinical AF could impact the risk of stroke[33]. However, it remains to be clarified whether stroke risk is a continuum or there is a specific threshold of AF burden at which the risk significantly increases.

Owing to the rapidly advancing technologies for computer-based decision support tools and machine learning application in medicine, the description of stroke risk in AF patients may evolve beyond clinical risk factor-based approach, but the decision to use OAC will always be a binary yes/no entity.

The **Symptom severity (Sy)** domain addresses the patient-centred, symptom-directed focus of AF management. This component focuses on severity of symptoms, currently using the European Heart Rhythm Association (EHRA) symptom score, and is important for treatment decisions [5, 18]. Of note, the EHRA symptom severity score has been shown to be prognostically relevant for adverse cardiovascular events[34].

However, the EHRA symptom score is physician-assessed, reflecting how physicians weigh the symptoms of their AF patients rather than the patients’ own perception that may substantially differ[35]. In addition, the EHRA score cannot precisely differentiate between AF-related and concomitant comorbidity-related symptoms. Indeed, in symptomatic patients with underlying comorbidities, optimal management of concomitant diseases is necessary before proceeding with symptom-guided treatment decision for left atrial ablation, and the descriptor(s) of the symptom severity domain may change in the future to include the assessment of quality of life, patient-perceived burden of treatment and other features.

The **Severity of AF burden (Sb)** domain characterizes the proportion of time spent in AF and density of AF episodes in time (if the arrhythmia is not permanent), including also the mode of termination (spontaneously terminating or not) as a potential indicator of the propensity towards chronic arrhythmia and/or substrate complexity.

As mentioned, the clinical adjudication of AF burden using the classification to paroxysmal, persistent or permanent AF may be imprecise in distinguishing between paroxysmal and persistent AF (and, occasionally, even permanent AF). The 4S-AF scheme proposes an empirical, clinical assessment-based semi-quantification of AF burden that reflects the elements relevant for treatment decision with regards to rhythm control, antiarrhythmic drug therapy and catheter ablation (see Figures 1 and 2).

In routine practice, clinicians may roughly assess the duration of symptomatic AF episodes via detailed history taking and intermittent ECG monitoring. Thus, AF episodes lasting for hours to days can be arbitrarily labeled as short, those lasting weeks to months would be intermediate and long AF episodes would be those lasting 12 or more months. The density of AF episodes can be expressed as the annual number of episodes, for example up to 1-3 per year (infrequent), >3 per year (frequent) or occurring daily to monthly (very frequent). Given that this is only an arbitrary, not validated stratification, the widely adopted and guideline-recommended temporal pattern-based classification of AF can be used instead.

The assessment of AF burden is evolving in parallel with rapidly advancing wearable and insertable technologies for prolonged monitoring of AF that are becoming increasingly affordable and convenient for long-term use. Hence, the description and grading of AF burden will likely change in the near future as our knowledge on the association of AF burden with outcomes increases.

The **Substrate for AF (Su)** domain pertains to the complexity of AF pathophysiology, including age, cardiovascular risk factors (e.g., obesity) and underlying comorbidities, as well as the presence and extent of the left atrium enlargement, atrial function impairment and fibrosis of atrial myocardium, all of which have been shown to play a role in the development and progression of AF[17, 36].

Diagnostic assessment for the presence of cardiovascular risk factors and underlying comorbidities is not only a routine part of comprehensive clinical evaluation of any patient suspected of having a heart condition but is also highly relevant for treatment decisions with regards to thromboprophylaxis and likelihood of successful rhythm control. Of note, the cardiovascular risk factor burden closely correlates with the lifetime risk of AF development[37], whereas optimal management of modifiable cardiovascular risk factors and comorbidities has been associated with reduction in AF burden[38]. Indeed, the structured characterisation using the 4S-AF scheme would prompt practicing physicians to identify and manage these risk factors, whereas the acknowledgement of multimorbidity that is included in the 4S-AF would influence the arrhythmia-related treatment decisions.

Atrial structural and functional remodelling predisposing to or resulting from AF is an important indicator of substrate complexity and correlates well with outcome of AF-directed treatment interventions[39]. Of note, left atrial size and function generally correlate well with cardiovascular outcomes including all-cause mortality[40, 41]. Transthoracic echocardiography is widely available in routine clinical practice and provides basic information on the atrial size and function, whereas more sophisticated assessment including advanced transthoracic echocardiography, transoesophageal echocardiography, cardiac computed tomography or nuclear magnetic imaging provide additional indices of atrial dysfunction and structural alterations including fibrosis[39] that have both treatment and prognostic implications and may inform expert decision-making (e.g., choosing the appropriate ablation strategy)[42].

With increasing evidence about clinical application of the recently proposed concept of atrial cardiomyopathy[11], the assessment, classification and staging of the atrial disease may become the cornerstone of the Su domain in the 4S-AF scheme.

*The use of 4S-AF scheme for characterising AF patients – hypothetical examples in clinical practice*

The 4S-AF characterization of AF patients using the descriptors obtained by routine diagnostic assessment (see Figures 1 and 2) would provide the basis for treatment decision-making supporting optimal management of AF by primary care physicians, internal medicine specialists or general cardiologists, also facilitating optimal referral for expert consultation where needed (see Figure 2), whereas further refinement of AF characterization using advanced diagnostic imaging tools would facilitate expert decision-making.

Importantly, the 4S-AF characterization of AF patients must be accompanied by information on the patient age and comorbidities and personal preferences.

**Example 1**. The 4S-AF characterisation is **St=0, Sy=2, Sb=3, Su=0**, and medical report describes a female patient aged 59 years, with no cardiovascular or other co-morbidity besides AF.

It is immediately obvious that this patient does not need long-term OAC (low stroke risk) but is eligible for rhythm control including consideration for AF ablation as a first-line treatment owing to severe symptoms, high AF burden and low substrate complexity[5].

Warning: this patient would still need OAC before and after AF ablation, as recommended, and her 4S-AF status should be re-assessed regularly in order not to miss dynamic changes in her risk profile over time[5].

**Example 2.** The 4S-AF characterisation is **St=1, Sy=0, Sb=3, Su=4**. As per medical report, it is a male patient, 79 years old, with prior stroke, myocardial infarction, diabetes mellitus and hypertension, whereas transthoracic echocardiogram showed preserved left ventricular function and a left atrial anteroposterior diameter of 48mm with mild mitral regurgitation.

We can easily read that this patient has a high risk of stroke, mild symptoms, high AF burden (i.e., long-standing persistent or permanent AF – see Figure 2) and significant substrate for AF. Hence, the patient needs lifelong OAC and rate control[5]. Again, the 4S status of this patient should be reviewed regularly. In addition, the patient should be monitored for adherence to treatment, occurrence of AF-related complications (e.g., stroke, bleeding, heart failure) and comorbidities.

**Example 3.** A 63-year female patient is referred for expert consultation for further AF management after electrical cardioversion failure in local hospital. Her 4S-AF characterisation is **St=1, Sy=2, Sb=3, Su=5.** She is obese, has hypertension, bilateral aortic-femoral graft and chronic obstructive pulmonary disease, and severely increased left atrium volume (42 ml/m2) on transthoracic echocardiographic examination. The 12-lead ECG shows AF with ventricular rate of 125 bmp.

The patient is highly symptomatic but a Suof 5 suggest advanced substrate for AF. Indeed, her symptoms could be attributed to poor ventricular rate control and possible exacerbation of pulmonary obstruction. Hence, she would be first assigned to optimization of rate control, treatment of pulmonary obstruction and weight reduction, all of which could have been done in the local healthcare centre. Should she remain highly symptomatic after optimization of her medical condition and weigh control, an advanced substrate evaluation using additional imaging could be undertaken, but it is less likely that she would be scheduled for left atrial ablation.

**Limitations of the 4S-AFcharacterization scheme**

Identifying most informative descriptor(s) for each of the domains relevant for the characterization of AF is challenging, and many diagnostic tools, risk stratification scores[43] and imaging techniques are being validated. Currently, the 4S-AF scheme mostly includes the AF-related descriptors that are easily obtainable in clinical practice, still acknowledging the possibility of more sophisticated assessment of all four domains.

The 4S-AF system does not provide information about bleeding risk, repeated cardioversions or AF ablations, prior and current antiarrhythmic drug therapy, etc. Nevertheless, the risk of bleeding is routinely assessed in patients considered for or taking OAC and should be noted in the medical records along with other features mentioned above. In addition, the 4S-AF currently does not reflect patient-assessed symptoms or treatment burden, patient preferences, adherence to treatment, etc.

The 4S-AF structured characterization of AF pertains exclusively to clinically diagnosed AF and does not include so-called ‘subclinical AF’ or atrial high rate episodes (AHRE) detected by intracardiac devices. However, when more evidence informing the management of AHRE with regards to stroke prevention become available, the 4S-AF scheme could be updated accordingly.

**Advantages of the 4S-AF characterization scheme**

As previously discussed, adherence to the 4S-AF scheme for characterization of AF patients would provide rapid, concise and clear communication among all physicians engaged in the management of a given AF patient, at all healthcare system levels, thus minimizing the risk of misunderstanding. Streamlining the assessment of AF-related features and AF patients via the use of the structured 4S-AF scheme would also facilitate treatment decision-making and could potentially reduce the costs of repeated expert consultations and/or unnecessary conducting various expensive diagnostic tests. In the future, the 4S-AF scheme could facilitate combining different datasets for research purposes.

Importantly, the 4S-AF scheme has a great potential for future refinements as needed with advances in technology used for the assessment of AF-related features such as the burden of AF and substrate for the arrhythmia. We therefore believe that implementation of the 4S-AF scheme for AF patient characterization in routine clinical practice would substantially facilitate overall AF management and AF research.

Given the descriptors of AF included in the 4S-AF scheme, the characterization of AF patients using 4S-AF could also provide prognostic information, but the clinical utility and prognostic value of the 4S-AF scheme for the characterization of AF needs extensive validation in different AF cohorts and clinical settings.

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**Table 1. Classifications of AF in current international AF guidelines.**

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| --- | --- | --- | --- | --- |
|  | Major international AF Guidelines | | | |
| AF classification | **2016 ESC[5]** | **2019 AHA/ACC/HRS[6, 23]** | **2018 (2014) CCS[7]** | **2018 NHFA/CSANZ[8]** |
| **Temporal pattern** |  |  |  |  |
|  | * First diagnosed * Paroxysmal * Persistent * Long-standing persistent * Permanent | * First diagnosed * Paroxysmal * Persistent * Long-standing persistent * Permanent | * First diagnosed * Paroxysmal * Persistent * Permanent | * First diagnosed * Paroxysmal * Persistent * Long-standing persistent * Permanent |
| **Symptom severity** | *EHRA Symptom severity score:*   * I No symptoms * IIa Mild * IIb Moderate * III Severe * IV Disabling | * Asymptomatic (silent) * Symptomatic | *SAF score:*   * 0 (asymptomatic) * 1 (minimal impact on QoL) * 2 (minor impact on QoL) * 3 (moderate impact on QoL) * 4 (severe impact on QoL) | * Asymptomatic (silent) * Symptomatic |
| **Underlying comorbidity** |  |  |  |  |
| * Valvular AF | Replaced with “AF in patients with MS or prosthetic heart valves” | Yes | Yes | Yes |
| **Clinical type reflecting different causes of AF** | * Secondary to struct. heart disease * Focal * Polygenic / Monogenic * Post-operative * In athletes | No specific list | No specific list | No specific list |
| **Surface ECG appearance**  Coarse / Fine | No | No | No | No |
| **Mode of onset**  Vagal / Adrenergic | No | No | No | No |

AF: Atrial Fibrillation; ESC: European Society of Cardiology; AHA: American Heart Association; ACC: American College of Cardiology; HRS: Heart Rhythm Society; CCS: Canadian Cardiovascular Society; NHFA/CSANZ: National Heart Foundation of Australia / Cardiac Society of Australia and New Zealand; EHRA: European Heart Rhythm Association; SAF: Symptom severity in AF; QoL: Quality of Life; MS: Mitral Stenosis.

**Figure 1. The 4S-AF scheme for characterization of patients with atrial fibrillation.**

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AF = atrial fibrillation; EHRA = European Heart Rhythm Association; QoL = quality of life; TTE = transthoracic echocardiogram; TOE = transoesophageal echocardiogram; CT = computed tomography; MRI = magnetic resonance imaging.

**Figure 2. A hypothetical treatment decision supporting tool using the 4S-AF scheme for characterization of patients with atrial fibrillation in clinical practice.**





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OAC: Oral anticoagulant therapy; AF: Atrial fibrillation; CV: Cardiovascular; LA: Left atrium.