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Challenges in the classification of atrial fibrillation

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Abstract

The incidence and prevalence of atrial fibrillation (AF) are increasing worldwide. AF is of public health importance as it accounts for substantial morbidity, mortality, and health-care costs. AF may be transient initially, but many patients have progressive disease marked by increasing frequency and duration of episodes. Various classification schemes for AF have been proposed, although current guidelines are based on temporal rhythm-based patterns. We discuss existing schemes for the classification of AF, focusing on the advantages and limitations of the pattern-based scheme, in the context of new knowledge about AF pathophysiology, AF patterns, and clinical outcomes. Furthermore, we address gaps in knowledge that present opportunities to re-examine the current pattern-based classification of AF. A future classification scheme should ideally combine elements such as the risk of stroke, an assessment of symptoms, and the impairment of the atrial substrate.

Introduction

The incidence and prevalence of atrial fibrillation (AF) are increasing worldwide.^{1–7} This arrhythmia is of public health importance, as it accounts for substantial morbidity, mortality, and health-care costs.^{8–10} AF is marked by the loss of coordinated atrial electrical and mechanical function, and may be transient or permanent.¹¹ The disease may progress in severity from a transient to a permanent state in some patients. Variability in the duration and frequency of AF episodes, and observations of disease progression within a given individual, have prompted the proposal of a classification scheme for AF that relies on rhythm-based patterns.¹² This scheme for AF classification is currently endorsed by the American Heart Association (AHA), American College of Cardiology (ACC) and European Society of Cardiology (ESC).

Knowledge of AF patterns gathered through the use of continuous rhythm monitoring technologies, and advances in our understanding of the pathogenesis and natural history of AF present an opportunity to re-examine rhythm-based classification schemes for AF. We sought to address the following questions about the current rhythm-based classification scheme: Is it accurate and reproducible? Do patterns reflect distinct etiologic disease

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subtypes? Are patterns associated with AF-related morbidity or mortality? Are AF pattern-based classes associated with patient symptoms or well-being? In this Review, we will discuss pattern-based classification of AF in the context of new knowledge about AF pathophysiology, AF rhythm-based patterns, and clinical outcomes. Furthermore, we will discuss gaps in our current knowledge that provide an opportunity to revise the pattern-based classification of AF.

The ideal classification scheme

Disease-based classification schemes are used to inform clinical management decisions or describe the longitudinal evolution of the disease. Whether for clinical or research purposes, an optimal categorization must accurately reflect and distinguish one class of disease from another, assuming distinct classes exist. A reliable classification system must be applicable and reproducible across diverse patient populations with the disease. The relevance of a clinical classification scheme is demonstrated by its ability to discriminate between patients on the basis of the stage and severity of the underlying disease, prognosis, clinically meaningful symptoms, or indications for therapeutic intervention. A research classification scheme should distinguish the pathophysiological mechanisms or etiological subtypes of a disease. Clinical and research classification schemes need not overlap, although it is convenient if they do.

Existing classification scheme for AF

A variety of different classification schemes for AF, with a basis on etiology, electrophysiological characteristics, temporal pattern, symptoms, and quality of life have been proposed.¹²⁻²¹ The scheme currently recommended by the American and European cardiology societies emphasizes temporal rhythm-based patterns of AF (Figure 1).¹² AF is classified as ‘first-detected’ in patients who have no history of this arrhythmia. AF that recurs after the first-detected episode is considered ‘paroxysmal’ if it self-terminates within 1 week, ‘persistent’ if it continues beyond this period and is not self-terminating, or ‘permanent’ if efforts to terminate the rhythm fail or are not attempted.¹² At the individual level, patients are generally considered to have the class of AF that corresponds to the rhythm that has occurred most often for the patient up to the time of assessment.

The current AF classification scheme acknowledges that an individual may experience periods of both paroxysmal and persistent AF, as some episodes may self-terminate whereas others may not. An important concept within the scheme is the notion that longstanding paroxysmal or persistent AF may progress and become permanent.¹² However, the current guidelines do not explicitly define AF patterns as stages, likely in part due to inconsistent patterns of progression and recurrence. With the advent of catheter ablation interventions for AF, patients with persistent AF for longer than 1 year that are considered for ablation have been referred to as having ‘longstanding, persistent disease’ by the Heart Rhythm Society, European Heart Rhythm Association, and European Cardiac Arrhythmia Society in collaboration with other major international cardiovascular societies.²² Thus, patients with ‘longstanding, persistent disease’ are distinguished from those with permanent AF in whom attempts to restore sinus rhythm are unsuccessful or not attempted.

In addition to rhythm-based patterns, guidelines acknowledge that AF may be referred to as ‘lone’ if it occurs in young individuals in the absence of cardiopulmonary or other acute illness that may precipitate the arrhythmia.^{12,23} Although the appropriateness of distinguishing lone AF as a distinct subset is debatable, we utilize this nomenclature to provide a succinct summary of published reports. Individuals with lone AF may have all of the rhythm-based patterns defined within the current classification.

Secondary forms of AF, which are attributable to an underlying disorder (such as cardiac surgery or pericarditis), are excluded from the rhythm-based scheme proposed in the existing guidelines. Such forms of AF may resolve with proper treatment of the underlying disorder and recurrence is thought to be unlikely, unless it occurs independently of the treated disorder.¹²

Advantages of the pattern-based scheme

The ACC, AHA, and ESC originally endorsed the existing pattern-based classification scheme for AF in 2001.²⁴ Standardization of nomenclature and definitions for classes of AF are major advantages of this scheme that led to its endorsement. Before this declaration, the labels used to describe AF were inconsistent and included additional terms such as 'intermittent', and 'chronic'. Labels such as paroxysmal, persistent, and permanent were used with different definitions. The endorsed system was adopted by the ACC and AHA committees on data standards for AF in 2004,²⁵ has become widely used in the clinical literature since its introduction, and has gradually led to the disuse of terms such as 'chronic' AF. An important strength of the scheme is its simplicity.

An additional strength of the current classification scheme is the fact that pattern-based classes correlate with the degree of atrial substrate impairment or remodeling. This observation has led to the recommendation of different approaches for catheter ablation for AF based, in part, on AF pattern.²² Generally, more extensive ablation beyond just isolation of the pulmonary veins is advocated for those with longstanding persistent AF. Pattern-based classes of AF also correlate with patient well-being, a primary determinant of medical therapy, as will be discussed further below.²⁶

The distinction of secondary AF is another advantage, as it connotes to clinicians that the diagnosis of AF in the setting of a reversible disorder does not carry the same risks of recurrence of AF or AF-related morbidity that are attributable to non-secondary forms the arrhythmia.

Challenges to the existing scheme

Challenges to the existing pattern-based classification scheme include several shortcomings as well as gaps in knowledge about the nature of AF.

Accuracy and reproducibility

As existing AF pattern-based classes are empiric, the accuracy and reliability of these labels are uncertain. The often transient and variable nature of AF poses limits to clinician-guided, pattern-based categorization and is a challenge to AF classification. Evidence suggests that AF episodes are frequently asymptomatic, that symptoms do not reliably identify AF episodes, and that prolonged monitoring reveals otherwise undetected episodes of AF.^{27–31} Therefore, classification of the predominant AF pattern in patients on the basis of clinical encounters and office-based electrocardiograms, as is typically done in both practice and research, may result in misclassification by substantially underestimating the actual burden of AF.

Accuracy is also threatened by the ambiguity that exists in differentiating between paroxysmal and persistent AF. Patients that are cardioverted within 1 week of initiation of an AF episode may be misclassified as having persistent AF when they otherwise would have converted spontaneously to sinus rhythm within that week, whereas those with persistent AF lasting longer than 1 week may have self-terminating episodes. Similarly, the distinction between permanent and persistent AF may depend on a provider's preference to

restore sinus rhythm or not, or on the aggressiveness with which they pursue restoration of sinus rhythm. Thus, classification of AF may be heterogeneous across providers or in different settings.

An additional prerequisite for the clinical utility of a classification scheme is that it be reproducible both across providers and populations. We are unaware of any investigations that specifically address the intraobserver or interobserver variability and reliability of AF classification as outlined in existing guidelines, or the applicability of patterns in different populations.

Longitudinal history of AF

In several studies, attempts have been made to characterize the natural history of AF (Table 1).^{23,32–45} Direct comparison of studies is challenging owing to differences in study design, follow-up, and definitions of AF categories. Nonetheless, existing data suggest that recurrent episodes of AF are detected in most patients.^{23,32,33,35,36,43,46}

AF not only recurs, but progresses from paroxysmal and persistent to permanent AF in a considerable proportion of individuals. For example, the cumulative incidence of permanent AF after an initial diagnosis of either paroxysmal or persistent AF has been reported to be as high as 34% at 4 years of follow-up.^{34,36,41,42} Among individuals with paroxysmal disease, the cumulative incidence of persistent disease was 20%, at 4 years after initial diagnosis,⁴¹ although as paroxysmal and persistent AF can coexist, ‘progression’ might not be an appropriate term for comparing the frequencies of these patterns over time. In a study of individuals with paroxysmal AF and bradyarrhythmias necessitating pacemaker implantation, the daily burden of AF did not increase, which demonstrates that AF patterns may be static in some individuals.⁴⁷

Risk factors for progression include advanced age,^{34,36,38,39,44,48} valvular heart disease,^{36,39,42,44} cardiomyopathy, heart failure,^{36,38,39,48} increased left atrial size or volume,^{39,40,44,49} and prior occurrence of stroke or systemic thromboembolism^{45,48} (Box 1). AF stability and recurrence seem to be mediated by both electrical^{50,51} and structural⁵² remodeling. Such remodeling may manifest as calcium overload with a reduction in L-type calcium currents,⁵³ intracellular glycogen accumulation accompanied by sarcomere loss,⁵⁴ and a variety of characteristic proarrhythmic electrophysiological changes such as shortening of the atrial electrical refractory period.^{50,53} Hence the commonly cited adage, “atrial fibrillation begets atrial fibrillation.”⁵⁰

Although AF progresses in a substantial number of individuals, it is unclear whether progression can be prevented, or even if a clinical imperative to prevent progression exists. Areas of uncertainty include the exact incidence of progression, whether progression itself is associated with morbidity independent of other comorbid conditions, and whether an optimal time exists to target the prevention of AF progression. If AF progression is independently associated with morbidity, efforts to interrupt progression might be clinically relevant. Comparative studies in patients at high risk for progression that assess the efficacy of therapies for preventing AF progression, or that of intermediate outcomes such as atrial remodeling, might be worthwhile. Observations from secondary prevention trials have demonstrated a reduction in recurrent AF burden with antiarrhythmic drugs,⁵⁵ statin therapy,⁵⁶ and pulmonary vein isolation,^{38,57} which all may be of relevance for preventing AF progression. Some data suggest that inhibition of the renin–angiotensin–aldosterone axis is associated with a reduction in recurrent AF,⁵⁸ although a randomized controlled trial comparing valsartan to placebo found no difference in the time to recurrent AF.⁵⁹ We are unaware of any studies that tested the primary hypothesis that an intervention prevents AF

progression. Future studies targeting risk factors for AF progression (Box 1) may be warranted.

The heterogeneous nature of recurrence and progression of AF poses a challenge to rhythm-based classification of this arrhythmia. The degree to which a pattern on one occasion is associated with the pattern on future occasions is variable and, therefore to classify individuals followed over a period of time as only having paroxysmal, persistent, or permanent AF, as is commonly done in the research setting, becomes problematic.

Relevance to prognosis

An additional challenge to the existing pattern-based classification scheme is the lack of evident relevance to clinical prognosis. Few studies have attempted to clarify whether current pattern-based classes of AF are associated with differences in AF-related morbidity or mortality. A notable limitation of comparing reported associations between patterns and prognosis, however, is the fact that many studies were published prior to standardization of pattern definitions.

Among AF-related morbidities that have been assessed according to pattern-based classes of AF, stroke is the best studied. Stroke occurs approximately three to five times more often in individuals with AF than in those without.^{60,61} Risk stratification schemes applied to patients with AF have evolved that help identify individuals at increased risk of stroke, but none rely on the distinction between rhythm-based classes of AF.⁶² Indeed, stroke risk does not seem to differ according to pattern in most,^{35,63–70} though not all,^{45,71} reports. In 1994, a pooled analysis including 3,706 individuals from five randomized controlled trials comparing either warfarin or aspirin to placebo for the prevention of stroke in individuals with AF demonstrated that stroke risk was independent of AF pattern.⁶⁹ Although some data suggest that the temporal burden of AF may help discriminate individuals at risk of stroke,^{72,73} existing pattern-based AF classification schemes have not proven useful for the prediction of stroke.

Heart failure is another major AF-related morbidity.⁷⁴ However, little research has been done to assess the relation between AF classification schemes and heart-failure outcomes. Data from the Euro Heart Survey, a prospective cohort study of 4,192 individuals with prevalent AF at the time of enrollment and followed for 1 year, demonstrated similar rates of new-onset heart failure in individuals with paroxysmal, persistent, and permanent AF, although the rate of hospitalization for existing heart failure was highest for those with permanent AF.³⁹

Several studies have examined the association between AF pattern and mortality.^{39,41,42,75} In general, unadjusted analyses indicate a greater risk of mortality among those with permanent AF than among those with other patterns of AF, although differences were either attenuated or absent after adjustment for multiple potentially confounding factors. Some,^{41,75} but not all,⁴² studies have reported lower mortality rates among those with persistent AF than among those with paroxysmal or permanent AF after adjustment for potential confounding factors. Whether the increased risk of mortality observed in individuals with paroxysmal AF relative to those with persistent AF is explained by residual confounding by variables that were not accounted for in the analyses, misclassification of AF pattern, or other forms of bias remains unclear.

Lone AF—AF-related morbidity has also been assessed specifically in individuals with lone AF.^{23,33,76} Among 97 patients with lone AF identified at the Mayo Clinic, the probability of survival following diagnosis of AF was 94% after 15 years, and did not differ from that of the general population.²³ Survival was similar among those with initial,

paroxysmal, and what was referred to as chronic AF. Rates of stroke were low (incidence rate 0.35 per 100 person-years), and did not differ between AF patterns. In a separate analysis of 157 individuals from Italy, neither survival nor rates of thromboembolism differed between those with paroxysmal and chronic lone AF.³³

Relevance to quality of life

The clinical relevance of the existing pattern-based classification scheme is further challenged by gaps in knowledge about the relations between AF patterns and quality of life, a major driver of medical therapies in AF. The impairment in quality of life among some patients with AF has been increasingly recognized.^{77–80} The importance of patient well-being, as it relates to AF, is underscored by the attention that this outcome has received in clinical trials of therapeutic interventions, which generally report improved quality of life achieved with a broad array of interventions.⁷⁸ Although improvements in quality of life may differ with specific therapies,^{20,21} management decisions are heavily influenced by patient symptoms.¹²

Numerous instruments have been implemented in the research setting to assess quality of life or symptoms, although only some have been designed specifically for the assessment of patients with AF.^{20,21,81,82} The reproducibility of such instruments within individuals, and their validity in diverse races and/or ethnicities and across clinical samples or cohorts, has not been consistently examined. In addition, little is known about quality of life as it relates to the long-term course of AF, or whether patient well-being differs according to rhythm-based patterns or frequency of AF episodes.⁷⁸ Moreover, it is unclear to what extent current instruments distinguish between a reduction in symptoms and improvement in quality of life. Distinguishing between symptom burden and quality of life may have important implications for measuring effectiveness of therapies, particularly since many patients may have nonspecific symptoms or have asymptomatic episodes of AF.

In one recent example in which AF-related symptoms were related to rhythm-based patterns and quality of life, Dorian *et al.* developed the Canadian Cardiovascular Society Severity of Atrial Fibrillation (CCS–SAF) scale, modeled after the CCS angina and NYHA heart failure classifications.⁸² The CCS–SAF is a 0–4 scale that characterizes patient symptoms, the association of symptoms with AF, and the functional consequences of these symptoms. In a validation study, the CCS–SAF class differed significantly according to the pattern of AF and quality of life.²⁶ Only 26% of patients with paroxysmal AF were categorized as having class 0 (asymptomatic) AF, as compared with 74% of patients with persistent or permanent AF when pooled together. After multivariable adjustment, both AF pattern and CCS–SAF class were significantly associated with patient quality of life. In each CCS–SAF class, patients with persistent or permanent AF scored lower on measures of quality of life than those with paroxysmal AF.

Evaluation of the clinical utility of parsimonious schemes that assess quality of life is warranted. Assessment of novel schemes should focus on determining whether instruments help to identify indications for therapy and predict therapeutic response, morbidity, or prognosis. Despite the widespread use of symptom scores and quality-of-life measures in clinical trials of AF, nonuniformity across trials is common, making standardized cross-trial comparisons of the accuracy and predictive value of these measures difficult. Furthermore, a pressing need exists for a simple and practical disease-specific symptom and quality-of-life scale that can be used in routine clinical practice. While provider-based assessments, such as the CCS–SAF, may ultimately fill this need it is possible that a scale based on objective patient-derived data that captures and quantifies a combination of AF-related symptoms, quality of life, functional status, and AF burden may explain a substantial proportion of variance in patient well-being. As demonstrated by Dorian *et al.*,²⁶ rhythm-based patterns

and patient symptoms are additively associated with quality of life. Instruments of this type are expected to emerge and evolve over the near term. A consensus among professional groups and specialty organizations will be required to achieve adoption and widespread use of a standardized and validated symptom scale in clinical practice.

Relevance to clinical management

An additional challenge to the existing classification scheme is that clinical management recommendations for the treatment of AF generally do not depend on rhythm-based patterns of disease. Indeed, only the decision to restore sinus rhythm clearly depends on the pattern of AF.^{12,22} However, expert opinion indicates that individuals with persistent AF may require more extensive tissue ablation than individuals with paroxysmal AF when undergoing catheter ablation for AF, presumably as a result of more advanced atrial remodeling.²² As such, rhythm-based patterns may be a surrogate for the degree of atrial substrate impairment or remodeling in patients with AF. The designation 'longstanding persistent AF' seems to be biologically and clinically arbitrary, and may not distinguish a precise threshold after which ablation success rates decline significantly and the disease is thus classified as permanent.

Nonetheless, evidence that rhythm-based patterns are associated with different rates of success after pulmonary vein isolation for AF was demonstrated in a report of 1,104 prospectively enrolled patients with paroxysmal, persistent, or longstanding persistent disease referred for ablation.⁸³ In addition to targeting AF triggers, the investigators performed additional left atrial ablation in those with nonparoxysmal AF. The rates of freedom from recurrent atrial tachyarrhythmia after a single ablation procedure over follow-up periods up to 7 years were nearly identical among patients with either paroxysmal or persistent disease (78% versus 76%), though they were substantially lower for those with longstanding persistent disease (61%). Cautious interpretation is warranted, as success rates may depend on the mode of surveillance following ablation, particularly when surveillance is conditional on the presence of symptoms.⁸⁴ The value of AF patterns for predicting long-term success with other forms of rhythm control therapy, such as electrical cardioversion, is not explicitly known. However, cardioversion success seems to be more durable in patients when performed in the initial weeks to months following AF onset than when performed later.⁸⁵

Thus, rhythm-based patterns alone rarely inform clinical management decisions. Rhythm-based patterns are most applicable to clinical management when used in conjunction with other metrics. For example, AF patterns may help guide general catheter ablation approaches in a given individual, once a symptom or quality of life assessment indicates that ablation is appropriate.

Relevance to etiology and mechanism of AF

As discussed, substantial heterogeneity in AF patterns exists across and within individuals. Some heterogeneity may be accounted for by external factors, such as physician preference to restore sinus rhythm, development of comorbid conditions, or environmental factors that promote recurrence and progression. A current gap in knowledge exists as to whether factors intrinsic to a particular individual promote specific AF patterns. In other words, are AF patterns heritable? Do certain genetic variants or patient-specific processes increase the propensity to develop permanent AF, whereas others manifest exclusively as paroxysmal AF? To what degree do potential intrinsic factors act jointly with environmental factors to affect AF patterns?

The recognition that pathophysiological processes culminating in AF may differ between individuals,^{54,86} paired with knowledge that specific genetic mutations are associated with distinct electrophysiological AF mechanisms that lead to AF,^{87,88} raise the possibility that individuals may have an intrinsic propensity to develop a particular AF pattern. Although investigators have sought to determine whether features measured by medical history,⁸⁹ physical examination,⁹⁰ or molecular,⁹¹ circulating biochemical,^{92–96} and/or electrophysiological metrics^{90,97–99} distinguish between pattern-based classes or mechanism of AF, results have been mixed. Most studies are single-center and cross-sectional, and have not been replicated. Therefore, observed associations between the studied variables and AF patterns may merely serve as markers of the progression of AF, and may not signify distinct AF subtypes. Furthermore, most study samples are comprised of patients of European ancestry, which limits the ability to generalize findings to individuals of other races or ethnicities. Little knowledge exists to relate patterns and either AF etiology or mechanism although, as noted above, patterns may distinguish degrees of substrate impairment or remodeling. Understanding the mechanisms of AF may facilitate attempts to determine whether a propensity to develop specific rhythm-based patterns of AF exists, and if so, may provide further justification for rhythm-based classification of AF.

Future directions

Areas of research

An ideal clinical classification system is one that stratifies prognosis and informs patient management. Currently available data do not consistently demonstrate associations between existing pattern-based classes of AF and either clinical outcomes or indicated therapies. Gaps in knowledge exist, creating opportunities for future research with the aim of enhancing both our understanding of AF and the management of patients (Table 2).

The identification of biological mechanisms through which genetic variation at common susceptibility loci mediates AF^{100–102} will improve our understanding of AF, and has the potential to explain some of the variability in the patterns and natural history of AF. Given that the majority of the epidemiological and pathophysiological AF data are derived from the study of individuals of European ancestry,¹⁰³ the longitudinal course, characteristics of recurrence, and progression of AF in individuals of other racial and ethnic groups warrant further investigation. Other promising areas for future research include determining whether biological subtypes of disease predispose to specific AF patterns, and testing whether patterns associate with clinically relevant outcomes or indicate the appropriateness of different therapies.

The increasing availability of continuous ambulatory electrocardiographic monitoring may facilitate efforts to more precisely define pattern-based classes of AF. Electrophysiological measurements, coupled with genetic, imaging, and biomarker data, may identify features that correlate with the tendency for AF to self-terminate, recur, or progress, and replace arbitrary distinctions between AF classes based on time or duration of rhythm.

Unbiased approaches aimed at organizing or clustering AF into different categories on the basis of features such as clinical symptoms, genetic variation, biomarker patterns, imaging characteristics, electrophysiological parameters, and clinical outcomes may help better explain the biological basis of AF and identify distinct AF subtypes. Such insights might facilitate the discovery of therapeutic interventions that reduce morbidity attributable to AF.

Unifying disparate elements

As clinical management is often dependent on consideration of disparate elements, it may not be possible for any single scale to comprehensively capture all clinically relevant aspects

of AF. However, stroke risk, patient symptoms or well-being, and the degree of atrial substrate remodeling all exist on continuums and factor prominently in the management of patients with AF (Figure 2). With the exception of stroke, the severity of symptoms or atrial substrate impairment that merit specific clinical interventions are not clear.

Adoption of an approach that considers each of three relevant ‘S’s’—stroke risk, symptoms, and substrate impairment—might allow for standardization and hence convenient comparison of patients in both the clinical and research arenas. Assessment of severity for each of the elements in the scheme could involve either established or new metrics, although acceptance of common standards by an expert consensus panel would be required in order to compare patients. Stroke risk stratification, for example, could be adopted by using any of several existing schemes.¹² Perhaps an even more parsimonious scale than the CCS–SAF could be used to effectively stratify individuals with AF into meaningful prognostic and treatment classes on the basis of symptoms. Symptom assessment might follow the model of the NYHA classification scheme for heart failure. The NYHA scheme is simple, reproducible, and informs treatments and outcomes. Substrate impairment could be defined using the current pattern-based designation for AF, given its widespread acceptance.

A scheme that combines elements of stroke risk, symptoms, and substrate impairment has some limitations; for example, the scheme would not capture AF etiology, mechanisms, or other clinically relevant features. Confidently ascribing an etiology to AF in any individual may not be possible, however, considering the multitude of factors that increase one’s propensity to develop AF. Consideration of specific AF mechanisms may become increasingly important in the event that efficacy of therapies, such as pharmacologic agents, depend on specific mechanisms of AF onset or maintenance. Each of the individual domains of the composite scale for clinical classification of AF might be improved upon. Indeed, poor discrimination and calibration of established stroke risk stratification schemes has been reported,¹⁰⁴ existing symptom scales might be too onerous to be clinically adopted, and pattern-based designation as a surrogate for substrate impairment is subject to ambiguity, arbitrary temporal thresholds, and misclassification.

Any future classification instrument must be evaluated for reproducibility and broad applicability. The prognostic value and clinical utility of new classification instruments should be established by their ability to discriminate between individuals, adequately calibrate observed risk, and improve classification of individuals into accurate categories of risk compared with that of preexisting classification schemes. Moreover, the validity of any instrument should be demonstrated in both sexes, different age strata, and across races and/or ethnicities.

Conclusions

Pattern-based classification schemes for AF have standardized definitions of AF patterns, are parsimonious, and are widely accepted. Yet the validity, reliability, and clinical utility of these patterns are largely untested. Moreover, a large proportion of the variability in the natural history of AF is unexplained, and whether distinct patterns of AF can be predicted or prevented remains unclear. Whether biological subtypes of AF predispose to existing pattern-based classes is also unknown. These gaps in knowledge, in conjunction with advances in our understanding of AF, present unique opportunities to re-examine the classification of AF.

Box 1 Risk factors for the progression of AF

- Advancing age^{34,36,38,39,44,48}

- Valvular heart disease^{36,39,42,44,45}
- Cardiomyopathy or heart failure^{36,38,39,48}
- Increased left atrial size or volume^{39,40,44,49}
- Prior occurrence of stroke or systemic thromboembolism^{45,48}
- Prior occurrence of myocardial infarction⁴⁴
- Obesity⁴⁰
- Chronic obstructive pulmonary disease⁴⁸
- Hypertension⁴⁸
- Diabetes mellitus³⁸
- Moderate or high alcohol consumption⁴²
- P-wave dispersion and duration^{49,105}
- Impaired chemoreflex sensitivity⁴⁹
- Increased daily AF burden⁴⁷
- Decreased heart rate during AF³⁶

Abbreviation: AF, atrial fibrillation.

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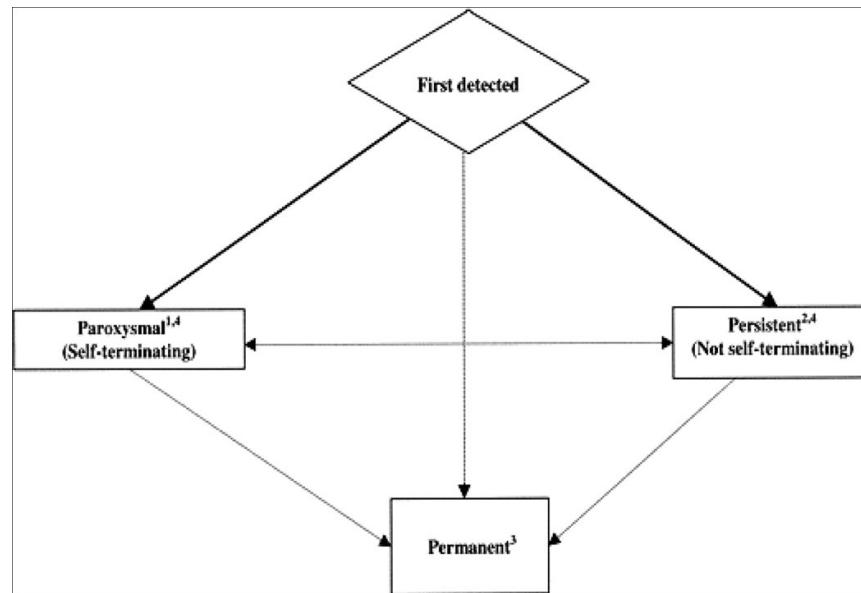


Figure 1. Rhythm-based patterns of atrial fibrillation (AF), as defined in the 2006 AHA, ACC and European Society of Cardiology guidelines for the management of patients with AF. Paroxysmal AF is characterized by episodes that generally last 7 days or less, with most lasting less than 24 h. Persistent AF is characterized by episodes that usually last longer than 7 days. When cardioversion failed or is not attempted, AF is classified as permanent. Both paroxysmal and persistent AF may be recurrent. Permission obtained from the American Heart Association.¹²

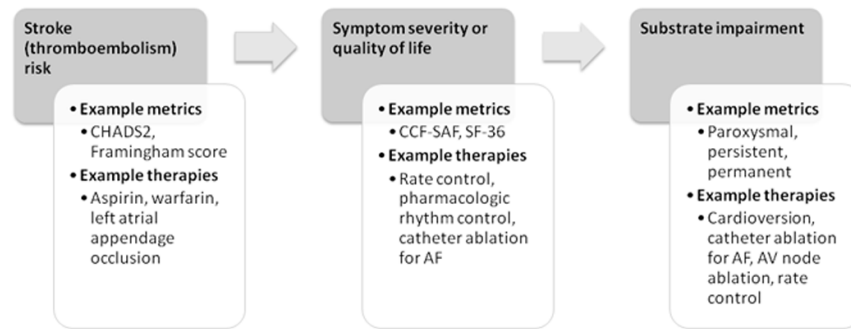


Figure 2.

Proposed elements for inclusion in a unifying clinical classification scheme for AF. Elements with established or potential roles in guiding management of patients with AF are displayed. Examples of metrics that measure these elements are shown, along with potential management decisions that might depend on the degree of severity on each scale. Elements and decisions might be inter-related. Arrows indicate a proposed sequential flow of assessments. Abbreviations: AF, atrial fibrillation; AV, atrial-ventricular; CCF-SAF, Canadian Cardiovascular Society Severity of Atrial Fibrillation; CHADS2, where “C” denotes congestive heart failure, “H” denotes hypertension, “A” denotes age > 75 years, “D” denotes diabetes mellitus, and “S” denotes stroke or transient ischemic attack; SF-36, 36-item short-form survey for health and quality of life.

Table 1

Progression of first-detected AF according to various pattern-based classification schemes

Study	Classification*	n(n followed from first-detected episode)	Follow-up, years [†]	Recurrence after first-detected episode	Transition to permanent AF [§]
Takahashi <i>et al.</i> , 1981 ³²	Paroxysmal or permanent	94 (94) ^{, ¶}	9 (study period)	27%	20%
Petersen <i>et al.</i> , 1986 ⁴⁵	Paroxysmal or chronic	426 (426)	3.5 (median)	NR	33%
Kopecny <i>et al.</i> , 1987 ²³	Isolated, recurrent or chronic	97 (97) [#]	14.8 (mean)	21%	NR
Kato <i>et al.</i> , 2004 ⁴⁴	Paroxysmal or chronic	171 (171) ^{, **}	14.1 (mean)	NA	77%, incidence rate of 5.5% per year
Jahangir <i>et al.</i> , 2007 ³⁷	Paroxysmal, persistent or permanent	76 (76) ^{#, ††}	25.2 (mean)	NR	29% cumulative incidence of permanent AF at 30 years
Davidson <i>et al.</i> , 1989 ⁴³	Paroxysmal or chronic	32 (NR) [#]	4.9 (mean)	44%	0%
Scardi <i>et al.</i> , 1999 ³³	Isolated, recurrent or chronic	145 (145) [#]	10.4 (mean)	17%	23%
Levy <i>et al.</i> , 1999 ³⁵	Paroxysmal, recent onset or chronic	756 (163) ^{§§}	8.6 (mean)	60.7%	8%
Al-Khatib <i>et al.</i> , 2000 ³⁴	Intermittent or permanent	231 (NR)	19 (study period)	NR	18% cumulative incidence of permanent at 4 years
Kerr <i>et al.</i> , 2005 ³⁶	Paroxysmal or chronic	757 (757)	8 (median)	16%	25% cumulative incidence of chronic AF at 5 years
Pappone <i>et al.</i> , 2008 ³⁸	Paroxysmal, persistent or permanent	106 (106) ^{, ¶¶}	5 (study period)	47%	15%
Nieuwlaat <i>et al.</i> , 2008 ³⁹	First detected, paroxysmal, persistent or permanent	4192 (708)	1 (study period)	46%	20%
Keating <i>et al.</i> , 2005 ⁴¹	Paroxysmal, persistent or permanent	270 (270)	2.9 (mean)	0% ^{##}	34% cumulative incidence of permanent AF at 4 years
Ruigomez <i>et al.</i> , 2005 ⁴²	Paroxysmal or chronic	525 (525)	2.7 (mean)	30%	22% cumulative incidence of chronic AF at 4.5 years
Tsang <i>et al.</i> , 2008 ⁴⁰	Paroxysmal, persistent or permanent	3,248 (3,248)	5.1 (median)	NR	17%

Study	Classification*	n(n followed from first-detected episode)	Follow-up, years [‡]	Recurrence after first-detected episode	Transition to permanent AF [§]
de Vos <i>et al.</i> , 2010 ⁴⁸	First-detected, paroxysmal, persistent or permanent	1219 (165) ^{***}	1 (study period)	NR	14%

* AF types had different definitions across classifications schemes despite similar labels.

[‡]The mean, median, or duration of the study period is reported.

[§]Or most chronic form per respective classification scheme. Calculation refers only to those with first-detected AF in whom progression to a more chronic form was possible.

// All paroxysmal at baseline.

¶ Data do not account for censoring.

Lone AF only.

** All had recurrent AF.

^{††} Follow-up subset from Kopecky *et al.*²³

^{§§} Refers to paroxysmal group only.

/// All intermittent at baseline.

^{¶¶} 51% individuals had lone AF and 10% of the overall sample underwent catheter ablation for AF and experienced no recurrent disease.

^{###} Only individuals with recurrent AF were included.

^{***} Subset from Nieuwlaat *et al.*³⁹ with sinus rhythm after first-detected AF.

Abbreviations: AF, atrial fibrillation; N/A, not applicable; NR, not reported.

Table 2

Future directions to improve AF classification

Potential questions	Examples of study measures that can be performed to address the questions
Are existing pattern-based AF classes valid and reliable?	<ul style="list-style-type: none"> • Continuous telemetry monitoring • Clinical and biological determinants of self-terminating AF • Intraobserver and interobserver reliability comparisons
Are existing pattern-based AF classes or AF progression associated with differences in health outcomes that are independent of comorbid conditions?	<ul style="list-style-type: none"> • Heart failure • Dementia • Quality of life • Mortality • Health-care expenditures
Do biological subtypes of disease manifest as different pattern-based classes of AF?	<ul style="list-style-type: none"> • Patterns of genetic variation • Phenotypic features
Can individuals at risk of new-onset, recurrent, or progressive AF be identified?	<ul style="list-style-type: none"> • Genetic variants • Biomarkers • Electrocardiographic monitoring • Imaging characteristics
Can new-onset, recurrent, or progressive AF be prevented?	<ul style="list-style-type: none"> • Antiarrhythmics, dietary supplements • Ablation
How does AF class change over time in each individual?	<ul style="list-style-type: none"> • Longitudinal correlation of AF classification
Is there utility in preventing the progression of AF?	<ul style="list-style-type: none"> • Health outcomes • Cost-effectiveness assessment
What accounts for variability in AF patterns and progression?	<ul style="list-style-type: none"> • Patterns of genetic variation • Sex-specific patterns • Racial-specific and ethnic-specific patterns • Environmental exposures • Comorbid conditions
Does classification of patient well-being inform prognosis and clinical management?	<ul style="list-style-type: none"> • Quality of life • Symptoms • Novel well-being instruments
Can novel classification schemes explain variability in clinical outcomes better than existing pattern-based classification?	<ul style="list-style-type: none"> • Predictors of AF outcomes • Classification, discrimination, reclassification

Abbreviation: AF, atrial fibrillation