Journal of Interventional Cardiac Electrophysiology
https://doi.org/10.1007/s10840-020-00859-y

REVIEWS

Clinical classification and the subclinical atrial fibrillation challenge: a position paper of the European Cardiac Arrhythmia Society

Samuel Lévy[1] · Luca Santini[2] · Riccardo Cappato[3] · Gerhard Steinbeck[4] · Alessandro Capucci[5] · Sanjeev Saksena[6]

Received: 14 August 2020 / Accepted: 26 August 2020

Abstract

Symptomatic atrial fibrillation (AF) or clinical AF is associated with impaired quality of life, higher risk of stroke, heart failure, and increased mortality. Current clinical classification of AF is based on the duration of AF episodes and the recurrence over time. Appropriate management strategy should follow guidelines of Scientific Societies. The last decades have been marked by the advances in mechanism comprehension, better management of symptomatic AF, particularly regarding stroke prevention with the use of direct oral anticoagulants and a wider use of AF catheter or surgical ablations. The advent of new tools for detection of asymptomatic AF including continuous monitoring with implanted electronic devices and the use of implantable cardiac monitors and recently wearable devices or garments have identified what is called "subclinical AF" encompassing atrial high-rate episodes (AHREs). New concepts such as "AF burden" have resulted in new management challenges. Oral anticoagulation has proven to reduce substantially stroke risk in patients with symptomatic clinical AF but carries the risk of bleeding. Management of detected asymptomatic atrial arrhythmias and their relation to clinical AF and stroke risk is currently under evaluation. Based on a review of recent literature, the validity of current clinical classification has been reassessed and appropriate updates are proposed. Current evidence supporting the inclusion of subclinical AF within current clinical classification is discussed as well as the need for controlled trials which may provide responses to current therapeutic challenges particularly regarding the subsets of asymptomatic AF patients that might benefit from oral anticoagulation.

Keywords Atrial fibrillation · Clinical classification · Subclinical AF · AF screening · Device-derived AF · Oral anticoagulants · Stroke risk · Cryptogenic stroke

1 Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in daily practice and represents an increasing epidemic related to aging population in the Western World and in developing countries [1, 2]. Symptomatic AF may be associated with alteration of quality of life, limited exercise tolerance, increased risk of stroke, heart failure, dementia, and mortality. The global prevalence of AF in 2010 was estimated to be 33.5 million persons [2]. In Europe, the prevalence of AF is as high as approximately 3% of the adult (> 21 years) population [3]. The risk of stroke in the AF population is fivefold that of the general population [4].

The cost of care of patients with AF is driven in large part by the frequent hospitalizations of AF patients representing around 44–78% management costs [5–7]. The reported mean annual cost of AF per patient per year in Europe ranges between a mean total spending of 3209 Euro per patient per year in France [5], 3225 Euro in Italy [6], and from 2464 to 6000 Euro in Germany [7].

Among the major advances of the last decades in AF management, stroke prevention using direct oral anticoagulants (DOACs) [8] and non-pharmacological therapy with a wider use of catheter and surgical AF ablation, deserve special

✉ Samuel Lévy
samuel@samuel-levy.com

1 Marseille School of Medicine, Aix-Marseille University, Marseille, France

2 Cardiology Division, G. B. Grassi Hospital, Via G. Passeroni 28, Ostia Lido, RM, Italy

3 Arrhythmia and Elecrtrophysiology Center, IRCCS-MultiMedica Group, Via Milanese 300, 20099 Milan, Sesto San Giovanni, Italy

4 Ludwig Maximilians University, Munich, Germany

5 Department of Cardiology, Università Politecnica delle Marche, Ancona, Italy

6 Rutgers-Robert Wood Johnson Medical School, Piscataway, NJ, USA

Published online: 13 October 2020

mention [9]. Recently, a number of new tools have been developed for detection of asymptomatic AF, both in patients with and without symptomatic clinical AF. This has created new therapeutic challenges but offered also new opportunities for further research. Reviewing the literature, it appears that the enormous amount of publications on AF each year differs by the nomenclature used and dissimilar patient populations. This is partly due to the heterogeneous clinical presentations of AF encountered in daily practice. Current clinical classification into paroxysmal, persistent, and permanent AF characterizes an episode of symptomatic AF diagnosed in ambulatory services, emergency wards, or in hospitals at a given time, but does not address asymptomatic AF and its various aspects. This position paper aims—based on the review of current literature on subclinical AF—to define its prevalence and potential thromboembolism risk and to determine if it is time to be integrated in the clinical AF classification.

2 Definitions and nomenclature

2.1 Definitions

Atrial fibrillation is easily recognized on 12-lead electrocardiogram (ECG). It is characterized by "the absence of consistent P wave before each QRS complex." Instead, there are rapid oscillations or "f" waves which vary in size, shape, and timing, and there is usually an irregular ventricular rate according to Bellet definition [10]. The ventricular response depends on atrioventricular (AV) nodal properties, the level of vagal and sympathetic tone, and drugs that affect AV nodal conduction, such as beta-blockers, non-dihydropyridine calcium channel blockers, and digitalis glycosides and disease of the AV node and the His-Purkinje system. The RR intervals are typically not equidistant in AF. However, regular RR intervals may occur either with fast rates or in AF associated with advanced AV block and in patients with permanent ventricular pacing. The diagnosis of AF may be overlooked should the only criterium used is the irregular ventricular rate. Atrial fibrillation may be triggered by other arrhythmias most often atrial flutter or atrial tachycardias commonly combined to AF. We will restrict the term "clinical AF" to symptomatic, 12-lead ECG-documented AF.

2.2 Clinical AF in perspective

There is still no consensus on the minimum duration that defines an episode of AF particularly in regard to the stroke risk. For example, in the 2012 HRS/EHRA/ECAS Consensus Statement [9], AF was defined as "continuously present on an ECG for 30 seconds or more, or occupying a complete 12 lead ECG monitoring" [9] whereas in the 2016 European Society of Cardiology Guidelines, AF is defined "irrespective of the duration of the arrhythmia" [11]. In any case, the duration of AF is not the only parameter that guides the clinician in his evaluation of stroke risk.

Historically, the numerous terms used to describe AF clinical patterns raised some confusion and there was a need for an International Consensus on Nomenclature and Classification of Atrial Fibrillation [12] which proposed the well-known clinical classification of AF (Table 1). In brief, the first ECG-documented episode can be paroxysmal (self-terminating in < 7 days) or persistent (non-self-terminating within 7 days). It can remain isolated or followed by AF recurrences. Recurrent AF episodes may be paroxysmal self-terminating within minutes, hours, or days or persistent. Some episodes of symptomatic AF may require rapid cardioversion, either electrical or pharmacological using antiarrhythmic agent given intravenously or orally, provided that the patient is hemodynamically stable and that the safety of oral

Table 1 Clinical classification of atrial fibrillation (from J of Cardiovascular Electrophysiology with permission [12])

Terminology	Clinical features	Arrhythmia pattern	Therapeutic implications
Initial event (first ECG-documented episode)	Symptomatic Asymptomatic (first documented) Onset unknown (first documented)	May or may not recur	Initial event (first documented episode)
Paroxysmal	Spontaneous termination < 7 days Most often < 48 h	Recurrent	Prevention of recurrence class I or III antiarrhythmic drugs Consider AF ablation Rate control and anticoagulation if needed
Persistent	Not self terminating Lasting > 7 days or early cardioversion	Recurrent	Rate control and anticoagulation if needed Rhythm control strategy Consider AF ablation
Permanent	Not terminated Terminated but relapsed After failure of cardioversion or/and AF ablation	Established	Rate control and anticoagulation if indicated

antiarrhythmic agent has been previously tested in hospital for the safe use of the so-called "Pill in the pocket" approach [13]. Pharmacological cardioversion is commonly indicated as part of a rhythm control strategy or as a tool to control patient symptoms and avoid hospitalization in patients with a clinically stable condition. If AF requires cardioversion before 24 or 48 h, the AF episode may still be called persistent. This time frame represents the duration beyond which formal anticoagulation must be undertaken prior to cardioversion.

The duration of 7 days was initially selected based on the observation that after such period of time, the likelihood for AF to terminate either spontaneously or using pharmacological cardioversion is low. Permanent AF is an established form which either failed one or more cardioversion attempts or catheter ablation attempts to maintain sinus rhythm or the clinician and/or the patient decides to accept the arrhythmia as a reasonable approach. Following the first report on Recommendations for AF management [14], the ACC/AHA/ESC and NASPE (today, Heart Rhythm Society (HRS)) guidelines [15] used this clinical AF classification followed by subsequent guidelines [15–18] and consensus documents with minor changes [7, 15–20].

At the time the clinical AF classification was proposed, the management of asymptomatic AF was supposed to be the same as that of symptomatic particularly regarding the thromboembolic risk and its prevention using oral anticoagulation. The risk of stroke and systemic embolism in clinical AF patients is currently evaluated using $CHADS_2$ score [18] or CHA_2DS_2Vasc score [21]. Ruff et al. [22] in a sub-analysis of the ENGAGE AF-TIMI 48 trial involving 4880 patients compared the CHA_2DS_2Vasc score with a biomarker score comprising cardiac troponin, N-terminal pro-B-type peptide, and D-dimers at baseline. The multimarker biomarker score significantly enhanced risk assessment for stroke, systemic embolic events, or death.

2.3 Long-standing persistent AF

In the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation [19], long-standing persistent AF was added and defined "as continuous AF of greater than 12 months duration". This is a persistent form of AF particularly encountered when a rhythm control strategy using AF ablation is contemplated.

3 Valvular versus "non-valvular AF"

In a number of controlled trials, particularly those comparing DOACs with warfarin, the term non-valvular AF is frequently used [8]. Valvular AF refers mainly to patients with significant (moderate to severe) mitral stenosis or with mechanical valve prosthesis according to the definition of the Canadian Cardiac Society [23] in 2017. Such definition concerns indeed, two groups of patients thought to require warfarin and therefore not included in DOAC trials [8]. Other types of valvular heart disease, such as significant mitral incompetence and aortic valve disease (stenosis or regurgitation) do not enable to consider AF as a valvular AF. Indeed, as pointed out by Fauchier et al. [24], non-valvular AF does not exclude other types of valvular heart disease to benefit from the use of non-vitamin K antagonists. Such assumption was confirmed by a meta-analysis of AF trials showing that, despite the fact that in patients with valvular heart disease the rate of stroke or systemic embolism (SSE) was higher than in patients without valvular heart disease, the efficacy and safety of high-dose DOACs was similar in AF patients with and without valvular heart disease [25]. A study which included patients with a mechanical valve prosthesis in which dabigatran was compared with warfarin was prematurely interrupted because of increased rates of thromboembolic and bleeding complications in the dabigatran-treated patients [26]. The phase 3 major randomized trials on DOACs versus dose-adjusted warfarin all showed that DOACs were non-inferior to warfarin and reduced the incidence of intracerebral hemorrhage in non-valvular AF [8]. In any case, we agree with Breithardt [27] that "we should get away from the term" non-valvular AF" and be more specific in characterizing valvular disease.

4 Symptoms associated with atrial fibrillation

The presence of symptoms is the main reason that brings AF patients to our attention and may affect quality of life. The most common symptoms in AF patients based in France were palpitations (54%), dyspnea on exertion (49%), chest pain (10%), syncope or dizzy spells (10%), and fatigue. Patients with paroxysmal AF were more symptomatic (79%) than those with persistent or permanent AF (44%) [28]. It is important to emphasize the fact that symptoms do not necessarily correspond to the presence of AF. Palpitations represent the most suggestive symptom of the presence of arrhythmia. Several classification scales for evaluating the symptoms in AF patients have been proposed. The European Heart rhythm Association (EHRA) has proposed a classification of symptoms based on whether the patients were troubled by their arrhythmia (class 2b) or not (class 2a) [29]. Koci et al. [30] proposed also a classification of symptoms and burden in patients with AF. These classifications are based both on patient-generated symptom severity compared with the health-provider assessment.

In a prospective study [31] correlating the recurrences of atrial tachyarrhythmias with symptoms in patients with AF and a standard indication for permanent pacing, one episode or more of atrial tachyarrhythmia occurred in 34 patients.

Patients logged symptomatic events into the device memory via an external manual activator. Eleven patients had only asymptomatic episodes and 23 patients both symptomatic or asymptomatic episodes. In this study, symptoms felt to be related to AF, often were not associated with atrial arrhythmias and 95% of tachyarrhythmia episodes were asymptomatic and corresponded to episodes shorter in duration than symptomatic episodes.

5 Asymptomatic AF

5.1 Detection of asymptomatic atrial fibrillation in patients without implantable devices

Detection of AF has always been a challenge as undetected or asymptomatic AF, also called "silent AF," was estimated to be more common than symptomatic AF. When AF was incidentally recorded, it was treated as clinical AF. Both symptomatic and asymptomatic AF episodes can obviously coexist in the same patient [31]. In that case, diagnosis and management of AF should follow current guidelines [11, 32, 33]. When AF is only asymptomatic, the stroke risk may not be similar to that of the symptomatic form. For many years, our traditional tools for arrhythmia detection included 24 h (or 48 h) ambulatory recordings (Holter), external ambulatory monitors used for 2 weeks, and more recently insertable cardiac monitors (ICM). Recently, the advent of new tools for arrhythmia detection such as non-invasive ambulatory ECG monitoring for a target period of up to 30 days, several kinds of mobile apps and smartphone-based ECG or wearable sensors were found to improve AF detection significantly.

A substudy from Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study showed that asymptomatic AF patients have less serious heart diseases but more cerebrovascular disease, but the prognosis did not significantly differ in the asymptomatic patient group from the symptomatic group [34]. Go et al. [35] in a cohort of 1965 adults with paroxysmal AF and a mean age of 69 ± 11 years not taking anticoagulants who had 14-day ambulatory ECG monitoring, found that a greater burden of AF was associated with a higher risk of ischemic stroke independent of the known stroke risk factors. This was a retrospective study of patients over a 4-year period in whom the burden or percent of analyzable wear time in AF or atrial flutter was evaluated.

5.2 Screen-detected AF

Research is ongoing in order to detect AF in large populations with non-invasive tools despite the fact that the benefits of diagnosing and treating undetected AF have not been ascertained. A large group called AF-SCREEN International collaboration, advocates large screening "for unknown or undertreated AF and stroke risk" [36]. They appropriately split subclinical AF into "device-detected AF" and "screen-detected AF." Screen-detected AF is a "single time point screening for AF in a general ambulant population" defined at high risk of having AF. The evidence to support screen-detected AF or mass AF screening programs is based in part on a retrospective study published in abstract form including 4618 residents of Olmsted County, MN with first ECG documented AF [37]. Of these, 3466 had symptoms. Patients with asymptomatic (silent) AF were 3 times more likely to have sustained a stroke preceding their AF diagnosis and had subsequently the same risk of stroke and death than those with symptomatic AF. A study from the same group [38] conducted in 476 patients with new-onset AF showed that patients with no symptoms (without palpitations) or atypical symptoms (other than palpitations) were at higher risk of cardiovascular events. Asymptomatic AF was also associated with an increased risk of cardiovascular mortality and all-cause mortality when adjusted for CHA_2DS_2-Vasc score and age. This contrasts with a report from the Rate Control versus Electrical cardioversion of persistent atrial fibrillation (RACE) study [39] which showed that asymptomatic AF patients had less cardiovascular diseases, less heart failure hospitalizations, and less antiarrhythmic therapy use than symptomatic AF patients. Boriani et al. [40] in a total of 3119 AF patients found that 520 (16.7%) patients were totally asymptomatic, older, and had associated co-morbidities such as chronic kidney disease and heart failure. Furthermore, in the asymptomatic group, the mortality was twofold higher than in the symptomatic group and the embolic risk was higher as the prescription of oral anticoagulation was lower in the asymptomatic group. In the Belgrade Atrial Fibrillation Study [41], a history of diabetes and a baseline CHA_2DS_2-Vasc score of 0 were independent predictors for asymptomatic presentation and a greater risk of stroke despite oral anticoagulation.

The REHEARSE-AF Study [42] is a prospective randomized controlled trial using remote ECG acquisition using the AliveCor Kardia monitor with a handheld device and remote transmission in order to detect AF in 1001 ambulatory patients ≥65 years of age with a CHA_2DS_2-Vasc score ≥ 2 free from AF randomized to the technique or iECG arm ($n = 500$) or to routine care ($n = 501$). The iECG participants acquired twice weekly single lead ECG over 12 months (plus additional iECGs if symptomatic). Nineteen patients in the iECG group were diagnosed with AF over the 12-month study period versus 5 in the routine care (hazard ratio, 3.9; 95% confidence interval = 1.4–10.4; $P = 0.007$) at a cost per AF diagnosis of US$10,780. Although iECG increased the diagnosis of atrial fibrillation (AF) almost fourfold in patients at high risk of stroke, the study was not appropriately powered to evaluate hard clinical endpoints such as statistical differences in stroke risk between the 2 groups.

As part of studies on AF mass screening, the recent Apple Heart Study [43] used a wearable smartwatch with optical sensors able to detect irregular pulse intervals. If this was the case, the participant received a notification leading to a teleconsultation and to the use of ECG patches analyzed after a pre-defined recording period by 2 clinicians from the Stanford Center for clinical research. Over 400,000 participants were recruited owning an iPhone and a smartwatch. Of these, 2161 participants (0.52%) received a notification of irregular pulse and of 450 participants who returned ECG patches, 34% were diagnosed to have AF. The positive predictive value for observing AF in participants with an irregular pulse was 0.84% or less than 1% [43].

An international report showed the yield of screen-detected AF and estimated the risk by age groups. It included 19 studies from 14 countries with a total of 141,220 participants screened with 1539 detected new AF cases [44]. The detection rate was 1.44% in ≥ 65 years old and 0.41% for < 65 yeas old. Mean CHA_2DS_2Vasc score increased with age from 1.1 (< 60 years) to 3.9 (≥ 85 years). The majority of patients had a class-1 oral anticoagulation indication for stroke risk [44].

5.2.1 Limitations of screen-detected AF

The limitations of screen-detected AF have been analyzed by Jonas et al. [45]. Although, 1-time 12-lead ECG and twice-weekly screening with a single-lead ECG detect more cases than no screening, ECG screening did not detect more cases than opportunistic screening with pulse palpation. Furthermore, there was no statistical difference between systematic and opportunistic screening for detecting new cases of AF particularly in women [45]. If anything, screening should be limited to persons older than 65 with a CHA_2DS_2Vasc score ≥ 2 not to expose screening persons to the risk of unnecessary anticoagulation. Systematic screening has also potential harms including misinterpretation of ECGs and treatment in patients without AF. A study showed that primary care physicians cannot accurately detect AF on ECG as in 8% of cases sinus rhythm was misinterpreted as AF [46]. Even computerized interpretation, misinterpreted AF in 35% of cases and physicians did not correct the misinterpretation [47]. Oral anticoagulation reduces the risk of stroke but increases the risk of bleeding in patients without a history of stroke or transient ischemic attack (TIA). The annual risk of stroke in a population ≥ 65 years is estimated to be 4% and the increased risk of major bleeding is 5 events per year [45]. There was no trial that studied the net benefit of oral anticoagulation in this population of asymptomatic AF.

5.3 Implantable cardiac monitors for detection of asymptomatic AF

As shown in Fig. 1, subclinical AF is not a homogenous group and refers to various situations.

Hindricks et al. [48] evaluated a new leadless ICM equipped with a new detection algorithm capable of detecting AF episodes with an accuracy of 98.5% and of quantifying the AF burden. Their study included 247 patients suspected of having paroxysmal AF, and the ICM was found to have a high sensitivity and specificity. Of the total group of patients, 37% had at least one episode of AF. In a prospective multicenter study [49] (The REVEAL AF study), 385 patients with a $CHADS_2$ score ≥ 3 or 2 with an additional risk factor and no history of AF, received an ICM and were followed for a mean period of 22.5 months. Atrial fibrillation lasting ≥ 6 min at 18 months was detected in nearly 30% of patients [49].

The ASSERT II trial looked at the prevalence of subclinical AF in elderly (≥ 65 years) patients attending cardiovascular or neurologic outpatient clinics [50] with a CHA_2DS_2Vasc score of ≥ 2 and an implanted subcutaneous ECG monitor. Subclinical AF ≥ 5 min was detected in 90 of 256 (34.4%) patients followed for a mean of 16.3 ± 3.8 months. Surprisingly, the occurrence of subclinical AF did not differ significantly in patients with a history of stroke, systemic embolism, or TIA from those without such history [50].

5.4 Implantable cardiac monitors for AF detection in cryptogenic stroke

Symptomatic stroke may be the first manifestation of undetected AF. Cryptogenic stroke is defined as a symptomatic ischemic stroke related to cerebral infarct for which no cause was identified after an adequate evaluation [51]. After all investigations turned negative, these types of strokes are also called embolic stroke of undetermined source (ESUS). Cryptogenic stroke accounts for 20 to 30% of all ischemic strokes [51, 52]. Gladstone et al. [53] randomized patients (age ≥ 55 years) with a cryptogenic ischemic stroke or TIA to conventional 24-h ambulatory ECG monitoring (control group) or to 30-day ECG monitoring with an event trigger recorder. They found that AF (30 s or more) was detected in 3.2% in the control group as compared with 16.1% in the 30-day ECG monitoring group. In the Cryptogenic Stroke and Underlying Atrial Fibrillation (CRYSTAL AF) trial, Brachmann et al. [54] using continuous long-term monitoring via ICM for up to 36 months and a median time of 8.4 months were able to detect asymptomatic AF ($n = 221$) in up to 30% of patients with cryptogenic stroke as compared with only 3% of patients randomized to the control group ($n = 220$). Of interest, the majority of patients with AF were prescribed oral anticoagulation. Recently, undiagnosed AF was detected in 21.5% of 1247 patients with ischemic stroke of unknown

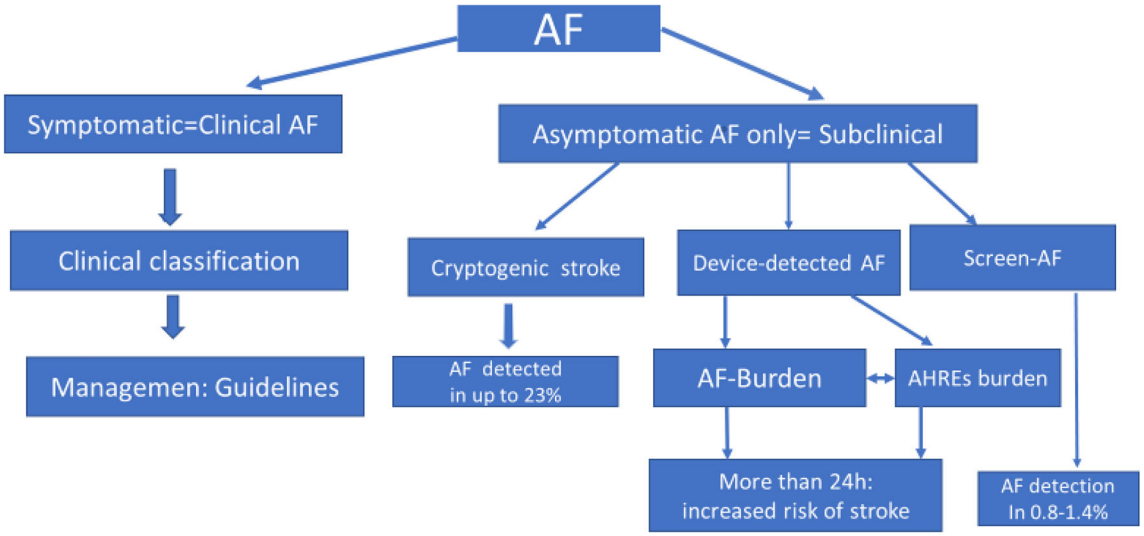

Fig. 1 Symptomatic atrial fibrillation (AF) is often associated with asymptomatic episodes. Asymptomatic AF only is device detected or found following cryptogenic stroke or screened AF in patients at risk (see text)

origin using ICM and monitored for up to 2 years [55]. Similar results were reported simultaneously by Israel et al. [56] using implantable loop recorders in 123 patients with ESUS. In their study, AF was detected in 29 patients (23.6%) during a mean follow-up of 12 ± 5 months. Most patients with ESUS are treated with antiplatelet therapy. Current working hypothesis is that oral anticoagulation might be more efficient than antiplatelet therapy in the secondary prevention of stroke in ESUS. Trials are ongoing comparing oral anticoagulation with aspirin for secondary prevention of embolic stroke. In the NAVIGATE ESUS International trial [57], patients with recent ESUS were randomized to aspirin 100 mg/day or rivaroxaban 15 mg/day and followed up for a median of 11 months. The recurrent risk of ischemic stroke was 4.6% (2.6%/year), and the effect of aspirin and rivaroxaban were similar. Further trials are needed to determine the patients that might benefit from oral anticoagulation.

5.5 Device-derived atrial arrhythmias

5.5.1 AHREs and subclinical AF: two facets of the same coin or two distinct entities?

Most cardiac-implanted electronic devices (CIEDs), including pacemakers or implantable defibrillators, have atrial recording capabilities allowing detection of atrial arrhythmias. Device-detected atrial arrhythmias include AF and other atrial arrhythmias known as atrial high-rate episodes (AHREs) with rates ranging from 175 to 220 bpm once validated by stored electrograms, as seen in Fig. 1. AHREs are considered part of subclinical AF, but they actually may represent other atrial arrhythmia than AF in 20% of cases [58]. They are found in about half of patients with implanted pacemakers and by definition in patients without clinically detected AF [59]. The use of ICM to detect AHREs was found to have a lower sensitivity and specificity than with CIEDs [58]. The duration of AHREs varies from 3 premature atrial complexes to 14 min in duration [57]. About 30% of patients with CIEDs have AHRES detected with a duration ≥ 6 min. Their presence was found to be associated with an increased risk of stroke [60–63].

The ASSERT trial [64] was a multicenter, single-blinded, randomized trial designed to determine if AHREs, often lasting seconds or minutes, detected with pacemaker telemetry in elderly (≥ 65 years) hypertensive patients, predict an increased risk of stroke. This trial showed that device-detected atrial tachyarrhythmias were found in approximately 10% of the 2580 patients enrolled and AHREs of ≥ 6 min were associated with a fivefold increased risk of clinical AF and 2.5-fold risk of ischemic stroke or systemic embolism (SSE) over a period of 3 months of monitoring [64]. The risk of stroke was lower than in patients with clinical AF. In 256 elderly (≥ 65 years) patients without AF attending cardiovascular or neurology outpatient clinic and a mean age of 74 ± years in whom ICMs were implanted, the detection rate of SCAF ≥ 5 min was 34.4%/year [50]. It is interesting that 48% had a prior SSE or TIA and the mean CHA2DS2-VASc score was 4.1 ± 1.4. The detection rate of subclinical AF was not significantly higher in those patients with prior history of SSE or TIA. The mortality was 2.3%/year, and 4 patients (1.1%/year) had ischemic stroke and 1 patient had TIA and 1 had a systemic embolism. None of the 6 patients had subclinical AF [50].

Furthermore, the time of occurrence of stroke is not related to the time when AHREs are present [62]. This only happens in about 15% of cases of stroke together with high AHRE burden [58]. Looking at the possible predictors of AHREs, only history of heart failure was found to predict device-derived subclinical AF [65]. So far, there are to our knowledge

no recommendations or guidelines that indicate to treat patients with device-detected AHREs with oral anticoagulation. For example, the 2014 AHA/ACC/HRS Guidelines simply recommend that AHREs "should prompt further evaluation to document clinically relevant AF to guide treatment decisions (class I)." [32]

5.5.2 The "AF burden" issue

The term AF burden designates the proportion of time spent in AF (or with AHREs) over a 24-h period. This implies that patients can be continuously monitored, which is the case in patients with CEIDs or with ICM in order to assess the presence and duration of AF or AHRE episodes over a given period of time [63].

A substudy analysis of Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) [67] showed that subclinical AF duration exceeding 24 h, was associated with a significantly increased risk of SSE whereas there was no difference in stroke risk between patients with 6 min and 24 h duration and patients without any subclinical AF. Of interest, the Italian AT500 Registry investigators [68], who followed for a median of 22-month patients with bradycardia and "clinical" AF implanted with antitachycardia pacemakers, showed an embolic risk of 1.9%. Embolic events were independently associated with ischemic heart disease and hypertension and the embolic risk of device-detected episodes longer than 24 h was 3.1 times increased [67].

In the TRENDS trial [60], the thromboembolic risk ranged from 1.1 to 2.4% over a follow-up of 1.4 years and was found to be a quantitative function of the "atrial tachycardia/AF burden." These authors found that atrial tachycardia/AF burden ≥ 5.5 h on any of 30 prior days, was correlated to a twofold higher thromboembolic risk. However, very few patients had subclinical AF in the month preceding SSE [59].

Boriani et al. [61] analyzed 10,016 patients belonging to 3 studies (TRENDS, PANORAMA, and the Italian ClinicalService® Registry Project) with implanted devices and a 3-month follow-up. They found that 43% of patients had at least 5 min of AF burden detected and 95 patients experienced an ischemic stroke or a TIA with increasing burden associated with age and $CHADS_2$ score. Device-detected AF burden was significantly associated with an increased risk of stroke. Botto et al. [69] proposed to combine presence and duration of atrial arrhythmias (no AF, AF > 5 min, AF > 24 h) with the $CHADS_2$ score in evaluating the stroke risk and the risk-benefit ratio of oral anticoagulation.

5.5.3 Limitations of device-derived AF

Even though CIEDs with an atrial lead record intracardiac electrograms, which are assumed to be a surrogate for ECG documented AF, this is not always the case. For example, caution has been raised by Abe [70] on the diagnostic information derived from dual-chamber devices as they depend on a number of factors including device settings, presence of ventriculo-atrial conduction, pacemaker-mediated tachycardia, and far-field sensing of R waves. This can generate false positives and artifactual noise [71]. Kaufman et al. [72] reviewing the AHREs > 6 min of the ASSERT trial, to see if they represented true atrial arrhythmia/AF, found that 17.3% were false positive, but these fall to 1.8% when the threshold duration is 24 h. In any case, the diagnosis of "device-detected AF" requires obviously that the patient has a CIED with an atrial lead which is the case for many elderly patients but not the majority of AF patients. In order to evaluate the risk of device-derived AF, Kaplan et al. [73] used both "AF duration" and the CHA_2DS_2-VASc score as suggested by Botto et al. [69]. They found that the "stroke risk crossed an actionable threshold definable as > 1%/year in patients with a CHA_2DS_2-VASc score of 2 with > 23.5 h of AF, those with a CHA_2DS_2-VASc score of 3 to 4 with more than 6 min of AF and patients with a CHA_2DS_2-VASc score ≥ 5 even with no AF. Atrial fibrillation burden as evaluated by a CIED and presence of AHREs, is useful for evaluating the risk of stroke based on the amount of subclinical AF but needs to be combined to other clinical parameters as the CHA_2DS_2-VASc score [73].

6 Is subclinical AF a challenge for AF clinical classification?

One of the criticisms made to current clinical classification is that it describes a given AF episode but does not characterize the course of AF over time. This criticism is well taken as it is difficult to know whether AF episode will recur and when? Furthermore, the progression from paroxysmal to persistent AF is difficult to predict in a given patient. This is even more true since management of patients using a rhythm control strategy with antiarrhythmic agents or/and catheter or surgical ablation, alters the natural history of AF which is therefore no longer "natural" [74]. Thus, there is a possible reverse remodeling with regression from the "permanent" to either the persistent or paroxysmal forms [75].

Current clinical temporal classification has also been recently challenged [76–78]. We agree with Lubitz et al. [76] that it should be "ideal" to "discriminate between patients on the basis of the stage and severity of the underlying disease." It was not clear if they refer to the associated conditions, such as hypertension, or to the physiopathology of AF in a given patient. Anyway, we do have the tools that allow us to define the stage of the "causal" disease and the level of fibrosis is not enough. We are not even sure that the clinical classification "correlates with the degree of atrial substrate disease and remodeling" as current knowledge of the mechanisms and

physiopathology of AF has not been unraveled. Furthermore, current treatments of AF may interfere with the natural history of the arrhythmia or/and its causal mechanisms [74]. Data gathered from the atrial defibrillator (Atrioverter®) [75] in patients with symptomatic, recurrent, drug-refractory AF, showed that there was an increase in the mean interval between long-lasting AF episodes, which were treated (treatment triggered by the patient) with repeated defibrillation, as time since implantation of the device increased, whereas the number and duration of short-lasting, nontreated episodes did not change during the 20-month study period suggesting reversion of electrical remodeling [75]. Charitos et al. [78] using the atrial tachyarrhythmia burden derived from CIEDs found that "current clinical classification does not reflect its temporal persistence." Although their observations are interesting, we believe that it is inappropriate to test a clinical classification which is aimed to be used by clinician managing clinical symptomatic AF, using the measurements of AF burden which refer to asymptomatic AF in view of the limitations of device-derived subclinical AF [70]. The latter presupposes also that the time spent in AF correlates with the clinical pattern or the stroke risk which is not certain. Although there is evidence supporting the concept that thromboembolic risk is a quantitative function of atrial arrhythmias, there is no evidence supporting that all patients with device-derived atrial arrhythmias, for example, should be on oral anticoagulants [71]. In fact, CIEDs with atrial lead records intracardiac electrograms assumed to be a surrogate of ECG documented AF which is subject to caution [45–47] and probability is higher if the burden is above 24 h [60].

7 Clinical significance of subclinical AF

The clinical significance of subclinical AF is still unsettled. It may be that subclinical AF is causal of disease in some patients or may be only a vascular risk marker in others as suggested by Bernstein et al. [79]. In the CRYSTAL trial, where ICMs were shown to detect AF much better than traditional monitoring in patients with cryptogenic stroke, no pattern of acute brain infarct topography was associated with detection of AF [80]. Stroke type and severity in patients with subclinical AF in a substudy of ASSERT did not allow to ascertain the role of subclinical AF as the cause of embolic stroke, but the rate of embolic stroke in ASSERT trial was actually low (1.7%/year) [64]. Therefore, the information derived from these results is not helpful in deciding which patients with subclinical AF should be prescribed oral anticoagulation. A pilot study showed that continuous monitoring of cardiac rhythm with an ICM and use of rapid onset DOC for targeted anticoagulation around an episode is feasible [81]. Furthermore, the IMPACT study [82] which randomized a large cohort of patients with CIEDs to start and stop anticoagulation based on remote monitoring versus usual office-based follow-up with anticoagulation based on standard clinical criteria, was interrupted prematurely after 2-year median follow-up, because there was no difference in the primary endpoints of SSE and major bleeding. Turakhia et al. [83] looked at the temporal relationship of AF in patients with AF and CIEDs remotely monitored and AF burden (≥ 5.5 h/day) in patients ($n = 187$) who suffered an acute ischemic stroke and found that 83% had little or no AF. The same team [84] analyzed anticoagulation prescription in veterans and outcomes after new device-detected AF (majority ICDs) and found a large practice variation in 90-day oral anticoagulation initiation which underlines the uncertainty regarding the appropriate treatment strategy. However, their observational study supports initiation of oral anticoagulation in patients with device-detected AF of > 24 h. Therefore, randomized studies are needed to help determine which patients with subclinical AF may benefit from anticoagulation [36]. The NOAH-AFNET 6 trial (Non-vitamin K antagonist Oral anticoagulants in patients with Atrial High rate episodes) [85] is a prospective double-blind multicenter trial which randomizes patients age ≥ 65 years with CHA_2DS_2Vasc score ≥ 1 and AHREs (≥ 180 beats/min and ≥ 6 min duration) detected by implanted devices to edoxaban (60 mg), aspirin, or no antithrombin therapy. This study will provide information on the effect of oral anticoagulation in patients with these atrial arrhythmias. Mahajan et al. [86] in a meta-analysis of subclinical device-detected AF found a prevalence of 35% in patients with pacing indication over 1–2.5 years. Subclinical AF was strongly associated with clinical AF. The Apixaban for the Reduction of Thrombo-Embolism in patients with device-detected Sub-clinical Atrial fibrillation (ARTESiA) trial [87] is a prospective, multicenter, double-blind, randomized controlled trial in patients with subclinical AF and CIEDs and additional risk factor for stroke. The NOAH and ARTESiA trials [85, 87] will report the results after a further 1 to 2 years.

The STROKESTOP study [88] looked at untreated AF in a population based in Sweden with 7173 consenting individuals 75 to 76 years old who used a handheld single lead ECG recorder for intermittent 30 s recordings over a 2-week period. New AF was found in 3.0% of the screened population as compared with 0.5% on the 12-lead ECG. Intermittent ECG screening allowed to increase the prevalence of AF in the screened population by 33%. The aim of the study was to find out if oral anticoagulant therapy can reduce the risk of ischemic stroke in 3.7% of the screened population [87]. In an editorial, Healey and Sandhu [89] rightly pointed out that we have the tools for detecting AF but it remains to be shown that this allows us to "prevent stroke in a cost effective fashion." The results of such study have not still been reported.

8 Clinical AF classification revisited

Current classification into first ECG-documented episode, paroxysmal AF, persistent and permanent AF has been reviewed based on current evidence (Table 2).

Table 2 Updated classification of atrial fibrillation

Terminology	Clinical features	Arrhythmia pattern	Therapeutic implications
First ECG documented episode	Symptomatic Asymptomatic Onset unknown	May or may not recur	Evaluate the presence of associated cardiac conditions or comorbidities Discuss anticoagulation and evaluate CHADS2Vasc score
Paroxysmal	Spontaneous termination < 7 days Most often < 48 h Intermittent AF	Recurrent Alternating AF and SR	Prevention of recurrences using class I or III antiarrhythmic drugs or Consider AF ablation as first option Rate control and anticoagulation if needed
Persistent	Not self-terminating Lasting > 7 days or prior cardioversion	Recurrent	Rate control and anticoagulation if needed or rhythm control strategy Consider AF ablation
Permanent	Not terminated Terminated but relapsed After failure of cardioversion or/and AF ablation	Established	Rate control and anticoagulation if indicated

Note that a form of AF alternating with sinus rhythm on the same was added (see text)

8.1 First ECG-documented episode

The first AF episode can be symptomatic or asymptomatic. In asymptomatic patients, AF is diagnosed fortuitously by a 12-lead ECG or through diagnostic recording devices indicated for another reason. If symptomatic, the patient seeks medical attention and the treating physician may decide to slow the rate or/and to terminate the arrhythmia either urgently or electively [90], and patient is managed according to current guidelines. In both events, the work-up will rule out a possible reversible cause and determine the presence of associated conditions and comorbidities for the proper management. In a significant percentage of patients, AF may not recur for several years after the first episode [91, 92]. There is no consensus regarding long-term oral anticoagulation for the first episode and should be individualized based on the CHA_2DS_2Vasc score to evaluate stroke risk.

8.2 New-onset atrial fibrillation and recent onset atrial fibrillation

New-onset AF and recent onset AF are frequently approached in the same way while they represent separate clinical subsets of AF. In new-onset if there is no prior diagnosis of AF and is also called first diagnosed AF. Recent-onset AF is usually defined as any episode of AF with a known duration. In current literature, the duration limits of new onset AF episode or recent-onset episode ranged from < 24 to < 48 h and even < 7 days. The prevalence of new-onset episode or recent-onset AF among all AF subsets varies from 11% when restricted to the first detected episode (new-onset AF) [93] to 26% [28] for recent-onset AF. Generally, both "recent-onset AF" or new-onset AF terms usually apply to symptomatic episodes, often managed in the Emergency Department (ED). The majority of recent-onset AF episodes terminate spontaneously. In one study, 68% of recent-onset AF episodes (symptoms < 72 h) converted to sinus rhythm spontaneously. The duration of AF < 24 h was the best predictor of spontaneous conversion [94]. The ACWAS-trial randomized consenting adults with recent-onset symptomatic AF without urgent need for cardioversion to either cardioversion (pharmacological or electrical) or to a "wait and see" approach using rate control medications in the ED. They found at 4 weeks the delayed cardioversion approach to be non-inferior to early cardioversion approach in restoring sinus rhythm [90].

8.3 Paroxysmal recurrent AF

The majority of patients with a first symptomatic episode of paroxysmal AF will experience AF recurrences. Recurrent AF episodes may be paroxysmal (< 7 days) or may be persistent (> 7 days). Some patients may have all their episodes terminate spontaneously and the course is that of "typical paroxysmal AF." Other paroxysmal AF patients may experience occasional episodes lasting more than 7 days or requiring rapid cardioversion before this time period, if AF is not well tolerated. They can still be called paroxysmal AF. Atrial fibrillation progression to persistent AF is possibly a "natural" evolution [95]. Today, management of AF affects the natural history and although the two strategies of rate and rhythm control have shown similar results in terms of long-term mortality, cardiologists often prefer rhythm control whenever possible, particularly using catheter ablation after failure or poor tolerance under antiarrhythmic drug therapy or as a first-choice treatment in selected patients.

A particular form of paroxysmal AF shows alternation of AF with sinus rhythm over a short period of time, even on the

same ECG tracing and is called intermittent AF. Some reports use also this term to refer to paroxysmal AF which can be confusing. Alternating AF will be a more specific denomination for this particular but uncommon form of paroxysmal AF. The period of time in which it should occur has not been defined, and we propose to limit it to a 24 h or less ECG recording. The risk of stroke related to alternating AF is not known. About 8 to 12% of paroxysmal AF progress to persistent AF.

8.4 Persistent AF

Persistent AF, the episodes of AF lasts 7 days or more and restoration of sinus rhythm requires interventions such as electrical cardioversion or catheter or surgical ablation. The success rates of ablation techniques are lower with persistent AF than in paroxysmal AF.

As stated previously in *long-standing persistent AF*, the arrhythmia has been continuously present for more than 1 year.

8.5 Permanent AF

Atrial fibrillation is said to be permanent when after failure of several attempts to restore or/and maintain sinus rhythm the patient and physician decide to "accept" the arrhythmia.

9 Should "subclinical AF" be integrated into the clinical AF classification?

We propose for the time not to include subclinical AF as part of clinical AF classification in order to not support the systematic use of oral anticoagulation for all patients with subclinical AF. The mechanism by which subclinical AF may induce stroke is not clear. Other factors in patients for thromboembolism may operate. Furthermore, there is no temporal relationship between the presence of subclinical AF and SSE in most instances. Subclinical AF is a heterogeneous group of asymptomatic forms of AF (some of which do not deserve to be called AF) including the search of AF after cryptogenic stroke or TIA events, device-derived AF, mass-screening of AF so-called screen-AF, are still under evaluation (Fig. 1). To our knowledge, no guidelines have taken the plunge to recommend oral anticoagulation for all patients with subclinical AF. As suggested by Gold [96], oral anticoagulation should be limited to those patients at high risk of stroke (CHA_2DS_2Vasc score ≥ 3) and patients should be informed of our uncertainties and about the risk-benefit ratio to be established for each patient. Such approach is also supported by the recent study of Kaplan et al. [73]. The results of the ongoing NOAH-AFNET 6 [85] and ARTESiA [87] trials will also be helpful in taking the appropriate decision regarding the indication of oral anticoagulation.

10 Conclusions

Current clinical classification of AF was reviewed in the light of recent information on asymptomatic AF detection. The clinical temporal classification helps to characterize an episode of AF and its pattern at a given time of the patient clinical history. The clinician should take into account the clinical context, particularly the presence of associated underlying heart disease, comorbidities, and predisposing factors to SSE, as well as the risk of hemorrhage if oral anticoagulation is considered. The prediction of AF evolution over time is difficult since the role of the clinician is to interfere with the natural history, by treating the hemodynamic disturbances associated with AF and preventing stroke or peripheral emboli using oral anticoagulation when needed. Subclinical AF has emerged as a new aspect of atrial arrhythmia/AF which covers a number of patient subsets. The treating physician should evaluate for each patient the benefit/risk ratio of stroke prevention using oral anticoagulants based on the duration of subclinical AF and the CHA_2DS_2Vasc score, but mostly, indication for anticoagulation should be withheld in subclinical AF due to its different clinical context compared with clinical AF, and due to the absence of any randomized clinical trial so far. Some ongoing clinical studies will probably help define which patient population groups with subclinical AF may benefit from oral anticoagulants in the future.

References

1. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. Nat Rev Cardiol. 2014;11:639–54.
2. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. Circulation. 2014;129:837–47.
3. Friberg L, Bergfeldt L. Atrial fibrillation prevalence revisited. Int Med. 2013;274:461–8.
4. Wolf PA, Dawber TR, Thomas HE Jr, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. Neurology. 1978;28(10):973–7.
5. Le Heuzey JY, Paziaud O, Piot O, Said MA, Copie X, Lavergne T. Cost of care distribution in atrial fibrillation patients: the COCAF study. Am Heart J. 2004;147:121–6.
6. Ringborg A, Nieuwlat R, Lindgren P, Jonsson B, Fidan D, Maggioni AP, et al. Costs of atrial fibrillation in five European countries: results from the euro heart survey on atrial fibrillation. Europace. 2008;10:403–11.
7. Reinhold T, Lindig C, Willich SN, Brüggenjürgen B. The costs of atrial fibrillation in patients with cardiovascular comorbidities–a longitudinal analysis of German health insurance data. Europace. 2011;13:1275–80.

8. López-López JA, Sterne JAC, Thom HHZ, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. BMJ. 2017;359:j5058.
9. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, et al. 2012 HRS/EHRA/ECAS expert consensus document on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints and research trial design. J Interv Card Electrophysiol. 2012;23:171–267.
10. Bellet S. Atrial fibrillation (clinical manifestations). In: Clinical disorders of the heartbeat. Philadelphia: Lea and Fibiger; 1971. p. 223–33.
11. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. ESC scientific document group. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37:2893–962.
12. Lévy S, Camm AJ, Saksena S, et al. International consensus on nomenclature and classification of atrial fibrillation. A collaborative project of the Working Group on Arrhythmias and the Working Group on Cardiac Pacing of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Europace. 2003;5:119–22 and J Cardiovasc Electrophysiol. 2003;14(4):443–5.
13. Capucci A, Boriani G, Botto GL, Lenzi T, Rubino I, Falcone C, et al. Conversion of recent-onset atrial fibrillation by a single oral loading dose of propafenone or flecainide. Am J Cardiol. 1994;74:503–5.
14. Levy S, Breithardt G, Campbell WF, et al. Atrial fibrillation: current knowledge and recommendations for management. Eur Heart J. 1998;19:1294–320.
15. Fuster V, Ryden LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Developed in Collaboration with the North American Society of Pacing and Electrophysiology. J Am Coll Cardiol. 2001;38(4):1266.
16. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation. 2006;114(7):e257–354.
17. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. ESC Committee for practice guidelines. Guidelines for the management of atrial fibrillation: the task force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace. 2010;12:1360–420.
18. Wann LS, Curtis AB, January CT, et al. 2011 ACCF/AHA/HRS focus update on the management of patients with atrial fibrillation (updating the 2006 guideline). A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;123:104–21.
19. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Europace. 2018;20(1):e1–e160.
20. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the national registry of atrial fibrillation. JAMA. 2001;285:2864–70.
21. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel factor-based approach: the EuroHeart survey on atrial fibrillation. Chest. 2010;137:263–72.
22. Ruff CT, Giugliano RP, Braunwald E, Murphy SA, Brown K, Jarolim P, et al. Cardiovascular biomarker score and clinical outcomes in patients with atrial fibrillation: a subanalysis of the ENGAGE AF-TIMI 48 randomized clinical trial. JAMA Cardiol. 2016;1(9):999–1006.
23. Andrade JG, Macle L, Nattel S, Verma A, Cairns J, et al. Contemporary atrial fibrillation management – a comparison of the current AHA/ACC/HRS, CCS, and ESC guidelines. Can J Cardiol. 2017;33:965–76. https://doi.org/10.1016/j.cjca.2017.06.002.
24. Fauchier L, Philippart R, Clémenty A, et al. How to define valvular atrial fibrillation? Arch Cardiovasc Dis. 2015;108:530–9.
25. Renda G, Ricci F, Giugliano RP, De Caterina R. Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease. J Am Coll Cardiol. 2017;69:1363–71.
26. Eikenboom JW, Connolly SJ, Brueckmann M, et al. RE-ALIGN Investigators. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med. 2013;369:1206–14.
27. Breithardt G. NOACs for stroke prevention in atrial fibrillation. Filling the gaps. J Am Coll Cardiol. 2017;69:1383–5.
28. Lévy S, Maarek M, Coumel P, Guize L, Lekieffre J, Medvedowsky JL, et al. Characterization of different subsets of atrial fibrillation in general practice in France: the ALFA study. Circulation. 1999;99:3028–35.
29. Wynn GJ, Todd DM, Webber M, Bonnett L, McShane J, Kirchhof P, et al. The European Heart Association symptom classification of atrial fibrillation: validation and improvement through a simple modification. Europace. 2014;16:965–72.
30. Koci F, Torbes P, Mansour MC, Heist EK, Singh JP, Ellinor PT, et al. New classification scheme for atrial fibrillation symptom severity and burden. Am J Cardiol. 2014;114:260–5.
31. Strickberger A, Ip J, Saksena S, Curry K, Bahnson T, Ziegler P. Relationship between atrial arrhythmias and symptoms. Heart Rhythm. 2005;2:125–31.
32. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. Circulation. 2019;140:e125–51.
33. Andrade JG, Verma A, Mitchell BL, et al. For the CCS Atrial Fibrillation Guidelines Committee* 2018 focused update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. Can J Cardiol. 2028;34:1371–92.
34. Flaker GC, Belew K, Beckman K, Vidaillet H, Kron J, Safford R, et al. Asymptomatic atrial fibrillation: demographic features and prognostic information from the atrial fibrillation follow-up investigation of rhythm management (AFFIRM) study. Am Heart J. 2005;149:657–63.
35. Go AS, Reynolds K, Yang J, et al. Association of Burden of Atrial Fibrillation with Risk of ischemic stroke in adults with paroxysmal atrial fibrillation: The KP-RHYTHM Study. JAMA Cardiol. 2018;3:601–8.
36. Freeman B, Camm JA, Calkins H, Healy JS, Rosenqvist M, Wang J, et al. Screening for atrial fibrillation. A report of the AF-SCREEN international collaboration. Circulation. 2017;135:1851–67.
37. Tsang TS, Barnes ME, Pellikka PA, Gin K, Miyasaka Y, Seward JB, et al. Silent atrial fibrillation in Olmsted County: a community based study. Can J Cardiol. 2011;27:S122.
38. Siontis K, Gersh B, Killian JM, et al. Typical, atypical and asymptomatic presentations of new-onset atrial fibrillation in the

community: characteristics and prognostic implications. Heart Rhythm. 2016;0:1–7.
39. Rienstra M, Vermond RA, Crijns HJGM, Tijssen JGP, Van Gelder IC for the RACE Investigators. Asymptomatic persistent atrial fibrillation and outcome: results from the RACE study. Heart Rhythm. 2014;0:1–7.
40. Boriani G, Laroche C, Diemberger I, Fantecchi E, Popescu MI, Rasmussen LH, et al. Real-world' management and outcomes of patients with paroxysmal vs. non-paroxysmal atrial fibrillation in Europe: the EURObservational research Programme-Atrial Fibrillation (EORP-AF) general pilot registry. Europace. 2016;18:648–57.
41. Potpara TS, Polovina MM, Marinkovic JM, Lip GY. A comparison of clinical characteristics and long-term prognosis in asymptomatic and symptomatic patients with first-diagnosed atrial fibrillation: the Belgrade atrial fibrillation study. Int J Cardiol. 2013;168:4744–9.
42. Halcox JPJ, Wareham K, Cardew A, Gilmore M, Barry JP, Phillips C, et al. Assessment of remote heart rhythm sampling using the AliveCor heart monitor to screen for atrial fibrillation: the REHEARSE-AF study. Circulation. 2017;136(19):1784–94.
43. Perez MV, Mahaffey KW, Hedlin H, Rumsfeld JS, Garcia A, Ferris T, et al. Large-scale assessment of a smartwatch to identify atrial fibrillation. N Engl J Med. 2019;381:1909–17.
44. Lowres N, Olivier J, Chao T-F, Chen S-A, Chen Y, Diederichsen A, et al. Estimated stroke risk, yield, and number needed to screen for atrial fibrillation detected through single time screening: a multicountry patient-level meta-analysis of 141,220 screened individuals. PLoS Med. 2019;16(9):e1002903. https://doi.org/10.1371/journal.pmed.1002903.
45. Jonas DE, Kahwati LC, Yun JDY, Middleton JC, Coker-Schwimmer M, Asher GN. Screening for atrial fibrillation with electrocardiography evidence report and systematic review for the US preventive services task force. JAMA. 2018;320:485–98.
46. Mant J, Fitzmaurice DA, Hobbs FD, et al. Accuracy of diagnosing atrial fibrillation on electrocardiogram by primary care practitioners and interpretative software: analysis of data from screening for atrial fibrillation in elderly (SAFE). BMJ. 2007;335:380.
47. Bogun F, Anh D, Kalahasty G, Wissner E, Bou Serhal C, Bazzi R, et al. Misdiagnosis of atrial fibrillation and its clinical consequences. Am J Med. 2004;117:636–42.
48. Hindricks G, Pokushalov E, Urban L, Taborsky M, Kuck KH, Lebedev D, et al. On behalf of the XPECT Trial Investigators. Performance of a new leadless monitor in detecting and quantifying AF. Results of the XPECT trial. Circ Arrhythm Electrophysiol. 2010;3:141–7.
49. Reiffel JA, Verma A, Kowey PR, Halperin JL, Gersh BJ, Wachter R, et al. REVEAL AF investigators. Incidence of previously undiagnosed atrial fibrillation using insertable cardiac monitors in a high-risk population: the REVEAL AF study. JAMA Cardiol. 2017;2:1120–7.
50. Healey JS, Alings M, Leong-Sit P, de Graaf J, Birnie D, Freericks M, et al. ASSERT II investigators. Subclinical atrial fibrillation in older patients. Circulation. 2017;136(14):1276–83.
51. Saver JF. Cryptogenic stroke. N Engl J Med. 2016;374(21):2065–73.
52. Schnabel RB, Haeusler KG, Healey JS, Freedman B, Boriani G, Brachmann J, et al. Searching for atrial fibrillation poststroke. A white paper of the AF-SCREEN International collaboration. Circulation. 2019;140:1834–50.
53. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, et al. EMBRACE investigators and coordinators. Atrial fibrillation in patients with cryptogenic stroke. N Engl J Med. 2014;370:2467–77.
54. Brachmann J, Morillo CA, Tommaso S, et al. Uncovering atrial fibrillation beyond short-term monitoring in cryptogenic stroke patients. Three-year results from the cryptogenic stroke and underlying atrial fibrillation trial. Circ Arrhythm Electrophysiol. 2016;e003333:9.
55. Ziegler PD, Rogers JD, Ferreira SW, Nichols AJ, Richards M, Koehler JL, et al. Long-term detection of atrial fibrillation with insertable cardiac monitors in a real-world cryptogenic stroke population. Int J Cardiol. 2017;244:175–9.
56. Israel C, Kitsiou A, Kalyani M, Deelawar S, Ejangue LE, Rogalewski A, et al. Detection of atrial fibrillation in patients with embolic stroke of undetermined source by prolonged monitoring with implantable loop recorders. Thromb Haemost. 2017;117:1962–9.
57. Hart RG, Veltkamp RC, Sheridan P, Sharma M, Kasner SE, Bangdiwala SI, et al. NAVIGATE ESUS investigators. Predictors of recurrent ischemic stroke in patients with embolic strokes of undetermined source and effects of rivaroxaban versus aspirin according to risk status: the NAVIGATE ESUS trial. J Stroke Cerebrovasc Dis. 2019;28(8):2273–9.
58. Freedman B, Boriani G, Glotzer T, Healey JS, Kirchhof P, Potpara TS. Management of high rate episodes detected by cardiac implanted electronic devices. Nat Rev Cardiol. 2017;14:7016714.
59. Camm AJ, Simantirakis E, Goette A, Lip GY, Vardas P, Calvert M, et al. Atrial high-rate episodes and stroke prevention. Europace. 2017;19:169–79.
60. Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilker C, et al. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. Circ Arrhythm Electrophysiol. 2009;2:474–80.
61. Boriani G, Glotzer TV, Santini M, West TM, de Melis M, Sepsi M, et al. Device detected atrial fibrillation and risk for stroke; an analysis of >10,000 patients from the SOS AF project (stroke prevention on strategies based on atrial fibrillation information from implanted devices). Eur Heart J. 2014;35:508–16.
62. Brambatti M, Connolly SJ, Gold MR, Morillo CA, Capucci A, Muto C, et al. Temporal relationship between subclinical atrial fibrillation and embolic events. Circulation. 2014;129:2094–9.
63. Boriani G, Laroche C, Diemberger I, Fantecchi E, Popescu MI, Rasmussen LH, et al. Asymptomatic atrial fibrillation: clinical correlates, management, and outcomes in the EORP-AF Pilot General Registry. Am J Med. 2015;128:509.e2–18.e2.
64. Hohnloser S, Capucci A, Fain C, Gold MR, Van Gelder IC, Healey J, et al. Asymptomatic atrial fibrillation and stroke evaluation in pacemakers patients and the atrial fibrillation reduction atrial pacing trial (ASSERT). Am Heart J. 2006;152:442–7.
65. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, et al. ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med. 2012;366:120–9.
66. Gonzalez M, Keating RJ, Markowitz SM, Liu CF, Thomas G, Ip JE, et al. Newly detected high rate atrial episodes predict long-term mortality outcomes in patients with implanted pacemakers. Heart Rhythm. 2014;11:2214–21.
67. Van Gelder IC, Healey JS, Crijns HJGM, Wang J, Hohnloser S, Gold MR, et al. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. Eur Heart J. 2017;38:1339–44.
68. Capucci A, Santini M, Padeletti L, Gulizia M, Botto GL, Boriani G, et al. Italian AT500 registry investigators. Monitored atrial fibrillation duration predicts arterial embolic events in patients suffering from bradycardia and atrial fibrillation implanted with antitachycardia pacemakers. J Am Coll Cardiol. 2005;46:1913–20.
69. Botto GL, Padeletti L, Santini M, Capucci A, Gulizia M, Zolezzi F. Presence and duration of atrial fibrillation detected by continuous monitoring. Crucial implications for the risk of thromboembolic events. J Cardiovasc Electrophysiol. 2009;20:241–8.
70. Abe H. Detection of atrial tachyarrhythmias in an implantable monitoring device. J Arrhythmia. 2012;28:19–25.

71. Noseworthy PA, Kaufman ES, Chen LY, Chung MK, Elkind MSV, Joglar JA, et al. Subclinical and device-detected atrial fibrillation: pondering the knowledge gap: a scientific statement of the American Medical Association. Circulation. 2019;140:e944–63.
72. Kaufman ES, Israel CW, Nair GM, Armaganijan L, Divakaramenon S, Mairesse GH, et al. ASSERT steering committee and investigators. Positive predictive value of device-detected atrial high-rate episodes at different rates and durations: an analysis from ASSERT. Heart Rhythm. 2012;9(8):1241–6.
73. Kaplan RM, Koehler J, Ziegler PD, Sarkar S, Zweibel S, Passman RS. Stroke risk as a function of atrial fibrillation duration and CHA2DS2-VASc score. Circulation. 2019;140:1639–46.
74. Sugihara C, Veasey R, Freemantle N, Podd S, Furniss S, Sulke N. The development over time in patients with permanent pacemakers: objective assessment with pacemaker diagnostics demonstrates distinct patterns of AF. Europace. 2015;17:864–70.
75. Timmermans C, Levy S, Ayers G, et al. Spontaneous episodes of atrial fibrillation after implantation of the Metrix Atrioverter®: observations on treated and nontreated episodes. J Am Coll Cardiol. 2000;35:1428–33.
76. Lubitz SA, Benjamin EJ, Ruskin JN, Fuster V, Patrick T. Challenges in the classification of AF. Nat Rev Cardiol. 2010;7:451–60.
77. Lubitz SA, Moser C, Sullinan L, Rienstra M, Fontes JT, Villalon ML, et al. Atrial fibrillation patterns and risks of subsequent stroke, heart failure and death in the community. J Am Heart Assoc. 2013;e000126:2.
78. Charitos EI, Puererfellner H, Glotzer TV, Ziegler PD. Clinical classifications of atrial fibrillation poorly reflect its temporal persistence: insights from 1,195 patients continuously monitored with implantable devices. J Am Coll Cardiol. 2014;63:2840–8.
79. Bernstein RA, Di Lazzaro V, Rymer MM, Passman RS, Brachmann J, Morillo CA, et al. Infarct topography and detection of atrial fibrillation in cryptogenic stroke: results from the CRYSTAL AF. Cerebrovasc Dis. 2015;40:91–6.
80. Perera KS, Vanassche T, Bosch J, Giruparajah M, Swaminathan B, Mattina KR, et al. Embolic strokes of undetermined source: prevalence and patient features in the ESUS Global Registry. Int J Stroke. 2016;11:526–33.
81. Passman R, Leong-Sit P, Andrei AC, Huskin A, Tomson TT, Bernstein R, et al. Targeted anticoagulation for atrial fibrillation guided by continuous rhythm assessment with an insertable cardiac monitor: the rhythm evaluation for anticoagulation with continuous monitoring (REACT.COM) pilot study. J Cardiovasc Electrophysiol. 2016;27(3):264–70.
82. Martin DT, Bersohn MM, Waldo AL, Wathen MS, Choucair WK, Lip GYH, et al. Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac synchronization devices. Eur Heart J. 2015;36:1660–8.
83. Turakhia MP, Ziegler PD, Schmitt SK, Chang Y, Fan J, Than CT, et al. Atrial fibrillation burden and short-term risk of stroke: case-crossover analysis of continuously recorded heart rhythm from cardiac electronic implanted devices. Circ Arrhythm Electrophysiol. 2015;8:1040–7.
84. Perino AC, Fan J, Askari M, Heidenreich PA, Keung E, Raitt MH, et al. Practice variation in anticoagulation prescription and outcomes after device-detected atrial fibrillation. Insights from the veteran health administration. Circulation. 2019;139:2502–12.
85. Kirchhof P, Blank BF, Calvert M, Camm J, Chlouverakis G, Diener HC, et al. Probing oral anticoagulation in patients with high rate episodes: rationale and design of the non-vitamin K antagonist oral anticoagulants in patients with atrial high rates episodes (NOAH-AFNET6) trial. Am Heart J. 2017;190:12–8.
86. Mahajan R, Perera T, Elliot AD, Twomey DJ, Kumar S, Munwar DA, et al. Subclinical device-detected atrial fibrillation and stroke risk: a systematic review and meta-analysis. Eur Heart J. 2018;0:1–9.
87. Lopes RD, Alings M, Connolly SJ, Beresh H, Granger CB, Mazuecos JB, et al. Rationale and design of the Apixaban for the reduction of thrombo-embolism in patients with device-detected sub-clinical atrial fibrillation (ARTESiA) trial. Am Heart J. 2017;189:137–45.
88. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass screening for untreated atrial fibrillation: the STROKESTOP study. Circulation. 2015;131:2176–84. https://doi.org/10.1161/CIRCULATIONAHA.114.014343.
89. Healey JS, Sandhu RK. Are we ready for mass screening to detect atrial fibrillation? Circulation. 2015;131:2167–8.
90. Pluymaekers NAHA, Dudink EAMP, Luermans JGLM, Meeder JG, Lenderink T, Widdershoven, et al. Early or delayed cardioversion in recent-onset atrial fibrillation. N Engl J Med. 2019;380(16):1499–1508 RACE 7 ACWAS Investigators. ClinicalTrials.gov NCT02248753.
91. Rostagno C, Bacci F, Martelli M, Naldoni A, Bertini G, Gensini G. Clinical course of lone AF since first symptomatic arrhythmic episode. Am J Cardiol. 1995;76:837–9.
92. Simantirakis EM, Papakonstantinou P, Kanoupakis E, Chlouverakis GI, Tzeis S, Vardas PE. Recurrence rate of atrial fibrillation after the first clinical episode: a prospective evaluation using continuous cardiac rhythm monitoring. Clin Cardiol. 2018;41:601–7.
93. Nabauer M, Gerth A, Limburg T, Schneider S, Oeff M, Kirchhof P, et al. The Registry of German competence network on atrial fibrillation: patient characteristics and initial management. Europace. 2009;11:423–43.
94. Danias PG, Caulfield TA, Weigner MJ, Silverman DI, Manning WJ. Likelihood of spontaneous cardioversion of atrial fibrillation to sinus rhythm. J Am Coll Cardiol. 1998;31:588–92. https://doi.org/10.1016/s0735-1097(97)00534-2.
95. Saksena S, Hettrick DA, Koehler JL, Grammatico A, Padeletti L. Progression of paroxysmal atrial fibrillation to persistent atrial fibrillation in patients with bradyarrhythmias. Am Heart J. 2007;154:884–92.
96. Gold MR. Treatment of subclinical atrial fibrillation. Does one plus one always equal two? Circulation. 2018;137:217–8.