

## Review

# Atrial fibrillation burden and atrial fibrillation type: Clinical significance and impact on the risk of stroke and decision making for long-term anticoagulation☆



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## ABSTRACT

Atrial fibrillation (AF) is a common arrhythmia increasing the risk of morbidity and adverse outcomes (stroke, heart failure, death). AF is found in 1–2% of the general population, with increasing prevalence with aging. Its exact epidemiological profile is incomplete and underestimated, because 10–40% of AF patients (particularly the elderly) can be asymptomatic (“clinically silent or subclinical AF”), with occasional electrocardiographic diagnosis. The research interest on silent AF has increased by the evidence that its outcome is no less severe, in terms of risks of stroke and death, than that for symptomatic patients. Data collected from more than 18,000 patients indicate that cardiac implantable electrical devices (CIEDs) are validated tools for detecting silent AF and measuring the time spent in AF, defined as “AF burden.” A maximum daily AF burden of  $\geq 5$ –6 min, but particularly  $\geq 1$  h, is associated with a significant increase in the risk of stroke, and may be clinically relevant to improve current risk stratification based on risk scores and for “personalizing” prescription of oral anticoagulants. An in-depth study of the temporal relationship between AF and ischemic stroke showed that data from CIEDs reveal a complex scenario, by which AF is certainly a risk factor for cardioembolic stroke, with a cause–effect relationship related to atrial thrombi, but can also be a simple “marker of risk,” with a noncausal association with stroke. In such cases, stroke is possibly related to atheroemboli from the aorta, the carotid arteries, or other sources.

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## 1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia, which is associated with increased risk of morbidity and adverse outcomes such as stroke, heart failure, and death. At present, it occurs in 1–2% of the general population and its prevalence is increasing constantly, with progressive aging. Thus, it is estimated that its prevalence

will double in the next decades [1,2]. The prevalence of AF varies according to age and gender, ranging from 0.12% to 0.16% in individuals with age below 49 years; 3.7% to 4.2% between 60 and 70 years; and 10% to 17% in those aged  $\geq 80$  years [1,3]. Furthermore, the incidence of AF was also found to increase with age [1,3]. In a retrospective cohort study of Medicare beneficiaries  $\geq 65$  years of age, diagnosed with AF between 1993 and 2007, the overall annual age- and sex-adjusted incidence of AF in 2007 was 28.3 per 1000 person-years, but was higher than 50 per 1000 person-years for those aged  $\geq 85$  years [4]. The increasing epidemiological burden of AF has the potential to become a global problem, not limited to Western countries, with profound effects on access to care and organization of care that require specific attention by all stakeholders [5–8].

## 2. Clinical characteristics of AF patients

The clinical characteristics of AF patients are quite heterogeneous. There is a wide range of clinical presentations, including cases where AF is itself the disease (recurrent paroxysmal “lone” AF in an apparently healthy patient) or is associated with minor diseases (high normal thyroid function, subclinical atherosclerosis, mitral valve prolapse, etc.). In other cases, arrhythmia occurs in the presence of facilitating factors (strenuous exercise, alcohol abuse, smoking, drugs, etc.) or other conditions facilitating its occurrence (hypertension, thyrotoxicosis, diabetes, obesity, sleep apnea, etc.) [1,9,10]. AF may be the complication of another heart disease (coronary heart disease, valvular heart disease, dilated cardiomyopathy, congenital heart disease, or other conditions leading to heart failure), or may occur in patients with a major extracardiac disease (advanced chronic kidney disease, hepatic diseases, neoplasm, chronic obstructive pulmonary disease, cognitive impairment, etc.) that dominates the clinical picture and induces per se a major impact on outcomes [1,2,9–11].

In the EURObservational Research Programme—Atrial Fibrillation (EORP-AF) registry, which enrolled more than 3000 AF patients across Europe, hypertension was associated with AF in approximately 70% of patients, coronary artery disease in one-third of them, heart failure in 30–40% (more common in nonparoxysmal AF), diabetes in 20%, and chronic obstructive pulmonary disease, peripheral artery disease, and chronic kidney disease in approximately 10% of patients each [11–14]. Only in 4% of patients, more commonly in paroxysmal AF types, was AF an isolated finding, with the characteristics of “lone” AF [13].

## 3. Electrocardiographic diagnosis of AF as the basis for clinical management

Although AF can be suspected by detecting an irregular pulse, the detection of AF requires precise confirmation through an electrocardiographic recording, usually a 12-lead ECG [2]. The guidelines of the European Society of Cardiology [2] report that “*Any arrhythmia that has the ECG characteristics of AF and lasts sufficiently long for a 12-lead ECG to be recorded, or at least 30 s on a rhythm strip, should be considered as AF.*” This step is the basis for subsequent clinical management, and risk stratification for stroke is the basis for decision making [2]. Only after risk stratification for stroke and the provision, if needed, of antithromboembolic prophylaxis, a series of clinical considerations on the pattern of AF and associated symptoms should suggest the choice between a rate control and rhythm control strategy [2,9,10,15].

## 4. Asymptomatic or clinically silent AF

The true epidemiological profile of AF is incomplete and underestimated, because a substantial proportion of AF patients can be asymptomatic or without clinical manifestations (“clinically silent or subclinical AF”), with occasional diagnosis of AF in the event of routine visits or other medical checks [16–18].

The proportion of asymptomatic AF patients is not well established, ranging between 10% and 40% according to the intensity of AF search through electrocardiographic monitoring; however, there is a consensus that the occurrence of subclinical or asymptomatic AF is particularly frequent in the elderly [19,20]. In a recent publication from the EORP-AF General Pilot Registry, focused on asymptomatic AF in a cohort of more than 3,100 patients, approximately 40% of patients were asymptomatic at the time of evaluation by a cardiologist, and approximately 17% were fully asymptomatic (i.e., never experienced symptoms due to AF) [13]. In this analysis, male gender, older age, previous myocardial infarction, and limited physical activity were significantly associated with asymptomatic AF. At present, the limitations of intermittent monitoring of AF, with electrocardiogram (ECG) performed only when symptoms suggestive or compatible with AF, are well recognized, and this is the basis for proposing more focused screening and monitoring in high-risk populations. In this regard, it is noteworthy to stress that, among pacemaker (PM) patients with symptomatic bradycardia and a history of AF, symptoms were weakly linked to documented AF: the positive predictive value for detected AF was only 16%, with more than 90% of atrial tachyarrhythmias resulting clinically silent [21].

A crucial question that arises from the increased recognition of clinically silent AF is “What are the prognostic implications of asymptomatic AF?” Among patients enrolled in the AFFIRM study, 12% were asymptomatic at baseline, and in a 5-year follow-up, mortality and major events did not differ between symptomatic and asymptomatic patients after correction for baseline differences [22]. In the most recent data reported by EORP-AF, mortality at 1 year was more than twofold higher in asymptomatic patients than their symptomatic counterparts, and was associated independently with older age and comorbidities, including chronic kidney disease and heart failure [13]. It is noteworthy that in asymptomatic patients, the prescription of guideline-indicated oral anticoagulants was lower [13,14].

## 5. Type of AF and AF burden

On the basis of clinical presentations of AF and taking into account the available data on arrhythmia duration, the following different types of AF have been described, independently of symptoms [2]:

- first-diagnosed AF, which is the form diagnosed at the first clinical presentation of AF, irrespective of the duration of arrhythmia or the presence and severity of AF-related symptoms;
- paroxysmal AF, which is a self-terminating form of arrhythmia, usually with arrhythmia termination within 48 h. The classification extends the duration of AF paroxysms up to 7 days, but the probability of spontaneous conversion to sinus rhythm is low after 48 h and, moreover, anticoagulation becomes necessary;
- persistent AF, which is a form of AF lasting longer than 7 days or requiring termination by cardioversion (pharmacological or electrical cardioversion) for sinus rhythm restoration;
- long-standing persistent AF, which is a form of AF lasting for  $\geq 1$  year, but with the adoption of a rhythm control strategy;
- permanent AF, which is a form of AF for which cardioversion is not attempted, since the arrhythmia is accepted by the patient and physicians.

This classification is based on the clinical presentation, but portrays only an incomplete picture of AF in view of the high proportion of AF episodes that are asymptomatic and because it depends on AF detection by ECG recordings of variable duration, with variable intensity of monitoring. The possibility of continuous monitoring of AF through implanted devices has led to the concept of “AF burden.” Although the term “AF burden” has been used in the past in different contexts and with different meanings [16], there is now convergence on defining it as the overall time spent in AF during a specified period of time, and in adopting it

to describe the temporal dynamic pattern of AF in terms of presence and duration of AF episodes, as detected by continuous monitoring through an implanted device. Cardiac implantable electrical devices (CIEDs) can, through an atrial lead, continuously monitor the atrial rhythm and store data on atrial tachyarrhythmias and AF episodes, which can then be summarized in a detailed report (Fig. 1), with data on the presence of arrhythmia, duration of each specific episode of atrial tachyarrhythmia, time of occurrence, distribution during the follow-up period, and time spent in AF.

In fact, CIEDs with an atrial lead can detect atrial high-rate episodes (AHRE), corresponding to all atrial tachyarrhythmias above a predefined atrial rate threshold (higher than 180–220 bpm), therefore including both AF and atrial flutter or regular atrial tachycardias [23, 24]. In the process of detecting and recording AHRE episodes in the device memory, a series of technical issues are involved, including atrial sensitivity, and the programming of atrial rate and episode duration cut-offs, with some variability according to the device manufacturer. There is also some variability with regard to the ability of storing electrograms (EGMs) of AHRE for diagnostic confirmation and review. For patients with subclinical AF detected by a CIED, validation of arrhythmia through device diagnostics is indicated (EGM stored in the device's memory) to rule out oversensing and confirm the diagnosis of atrial tachyarrhythmia (Fig. 2).

Although temporal cutoffs for detection and storage of AHRE data as short as 30–60 s have been used, the diagnostic accuracy is highly reliable when episodes  $\geq 5$  min in duration are considered, because, with this cutoff, the appropriateness in AF detection is 95%, minimizing the risk of oversensing due to detection of artifacts caused by myopotentials or other sources of electrical interference [25,26].

In a study published more than 10 years ago, Israel et al. [27] found that the diagnostic capabilities of CIEDs can detect AF episodes of considerable duration (more than 48 h) much more frequently than conventional regular ECG follow-up, and that episodes of AF lasting more than 48 h may be completely asymptomatic and unpredictable. It is also clear from studies on CIEDs that patients may experience both symptomatic and asymptomatic episodes of AF, of variable duration, and that the symptoms attributed to AF have, in fact, a relatively low positive predictive value for AF [21].

In patients with CIEDs, AF burden can be measured in different ways, but, at present, it has been defined as the amount of time spent in AF each day in a specific follow-up period (“daily AF burden”). The “maximum daily AF burden” (the highest daily burden observed in a long follow-up period) has been the subject of several studies focused on the temporal distribution of AF, its progression and response to antiarrhythmic interventions, and its association with an increased risk of thromboembolic events and stroke [16].

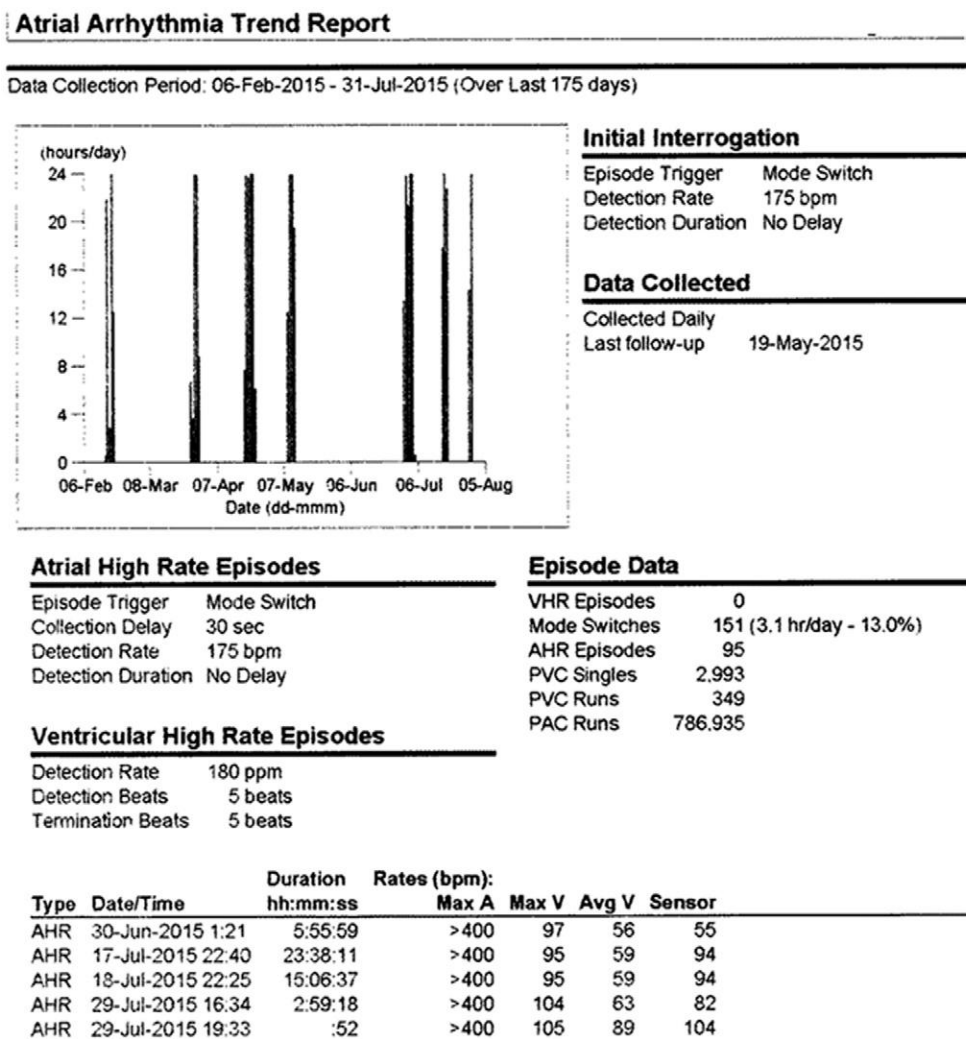
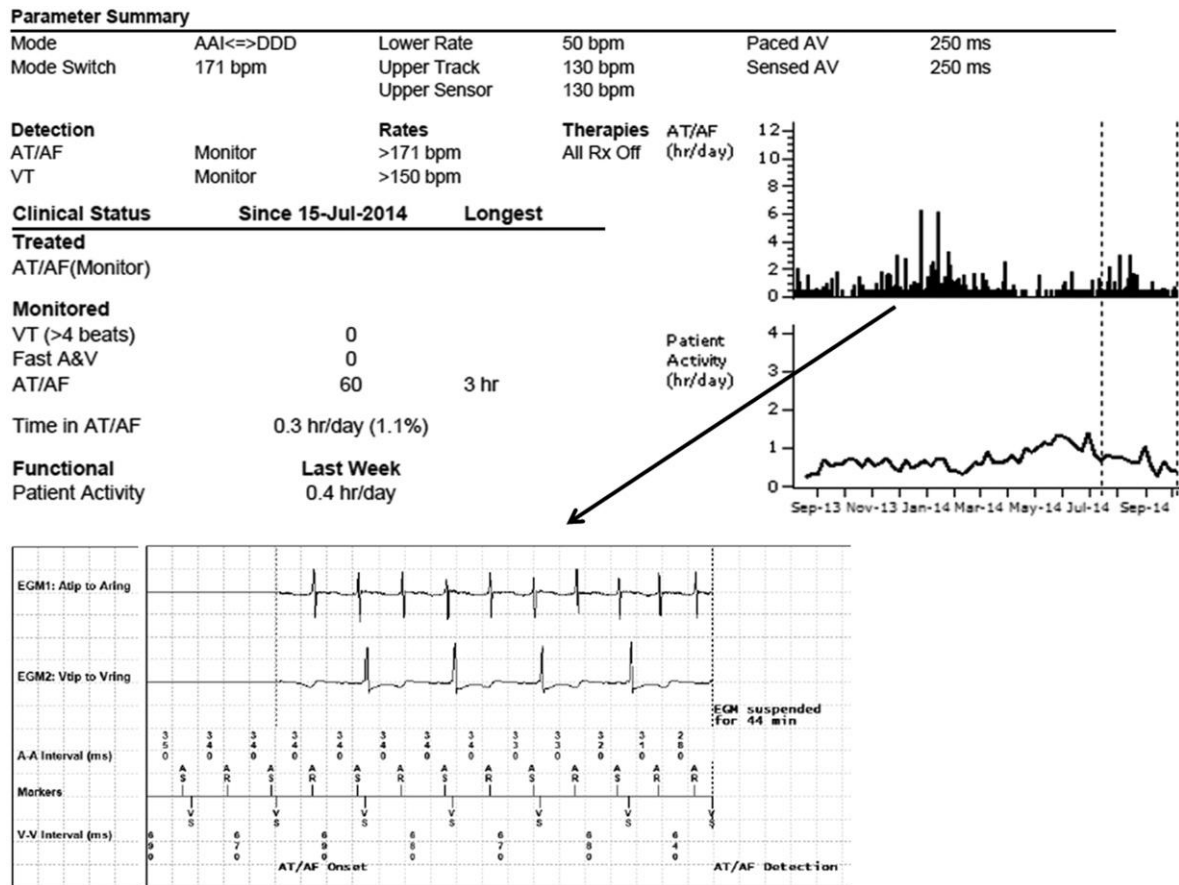


Fig. 1. An example of the report at interrogation of a pacemaker, showing (upper left) a diagram of the temporal distribution of detected atrial tachyarrhythmias (above the atrial rate cutoff of 175 bpm). At the bottom, detailed data on arrhythmia presence, atrial rate of detected tachyarrhythmias (more than 400 bpm in this case, indicating AF), date, time of occurrence, characteristics (including average ventricular rate), and duration of every specific episode of atrial tachyarrhythmia that occurred during the follow-up period.



**Fig. 2.** An example of the diagnostic features currently available in a cardiac implantable electronic device (CIED). As shown in the report, in the time elapsed since the last interrogation, the implanted pacemaker detected 60 episodes of atrial tachyarrhythmias (AT/AF), with the longest episode lasting 3 h. The daily distribution of detected episodes is shown in the graph. The electrograms (EGMs) stored in the device's memory made it possible to confirm the device diagnosis of atrial tachyarrhythmias, without a particularly fast ventricular rate. After this detection, the patient, who was asymptomatic and had a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 4, followed the cardiologist's recommendation and initiated oral anticoagulant therapy for prevention of stroke and systemic embolism.

The prevalence of atrial tachyarrhythmias, detected as AHRE, and AF burden in patients implanted with CIEDs varies, depending upon the underlying heart disease, the time of observation, and, above all, any previous history of clinically overt atrial tachyarrhythmias. In the ASSERT study, subclinical atrial tachyarrhythmias with at least 6-min duration were detected within 3 months in approximately 10% of patients implanted with a CIED [28]. During a follow-up period of 2.5 years, additional subclinical atrial tachyarrhythmias occurred in approximately 25% of patients, and about 16% of those who had subclinical atrial tachyarrhythmias developed a symptomatic AF [28]. Considering these findings, as well as previous reports from the literature, there is evidence that subclinical AF episodes are common in patients implanted with CIEDs [16–18,24,28].

## 6. Relationship between AF burden and type of AF and stroke/thromboembolism

The increased ability to detect silent AF through the extended diagnostic capabilities of CIEDs has highlighted the need to determine the amount of AF, or threshold of AF burden, that is associated with a significant risk of stroke or systemic thromboembolism to appropriately consider antithromboembolic prophylaxis (with warfarin or a non-vitamin K antagonist oral anticoagulant) in patients at risk, as evaluated through CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores.

Several studies have analyzed, in different populations, the association of different AF burden thresholds with stroke/systemic thromboembolism, with limited direct comparisons, as shown in Table 1 [28–38]. In these studies, with data collected from more than 18000 patients,

the participants were categorized according to the maximum duration of detected AHRE episodes or by the maximum detected daily AF burden (i.e., the maximum time spent in AF in 1 day of the follow-up period).

In the ASSERT study, device-detected atrial tachyarrhythmias (atrial rate >190 bpm for >6 min) were associated with an increased risk of ischemic stroke or systemic embolism (HR 2.49) during a 2.5-year follow-up [28]. However, as stressed in ref. [39], these important data from ASSERT do not identify a specific threshold of AF duration or AF burden that may justify, from a risk–benefit perspective, the starting of prophylaxis with oral anticoagulants.

The largest data set of patients implanted with a CIED was collected in the SOS AF project, a pooled analysis of individual patient data from three prospective studies, with an overall population of 10,016 patients with median age of 70 years [36]. During a median follow-up of 24 months, 43% of patients experienced at least 1 day with at least 5 min of AF burden; and in a Cox regression analysis adjusted for CHADS<sub>2</sub> score and use of anticoagulants at baseline, the AF burden was an independent predictor of stroke, with a 1-h threshold of AF burden associated with the highest HR for ischemic stroke, that is, 2.11 (95% CI 1.22–3.64,  $p = 0.008$ ) in a dichotomized analysis that compared various potential threshold cutoffs for AF burden (5 min, 1, 6, 12, and 23 h, respectively) [36].

It is noteworthy that a device-detected AF burden of >5 min has been recently found to be significantly associated with silent ischemic brain lesions at CT [38], a finding that may be of some value for interpreting the risk of cognitive impairment in AF patients, a complex issue that may also involve nonstroke-related mechanisms [40].

**Table 1**  
Studies analyzing the relationship between AF burden, as detected by an implanted CIED, and stroke/thromboembolism.

Author, year, ref.	No. of patients and characteristics	Type of CIED	Follow-up period	AF burden associated with stroke or thromboembolism	HR (95% CI) for stroke <i>p</i> value	Other findings
Glotzer et al., 2003 [29]	312 patients with sinus node dysfunction	PM	Median 27 months	≥5 min	2.79 (1.51–5.15) <i>p</i> = 0.0011	
Capucci et al., 2005 [30]	725 patients with bradyarrhythmia and history of PAF	PM	Median 22 months [16–30]	>24 h	3.1 (1.1–10.5) <i>p</i> = 0.044	
Botto et al., 2008 [31]	568 patients with bradyarrhythmia and history of PAF	PM	1 year	≥5 min or ≥24 h	OR 5.0 <i>p</i> = 0.035	Combining AF burden and CHADS <sub>2</sub> makes it possible to distinguish a subgroup at high vs. low risk of stroke (AF burden in the former: ≥24 h if CHADS <sub>2</sub> = 1, ≥5 min if CHADS <sub>2</sub> = 2, any burden, even 0 burden but AF history if CHADS <sub>2</sub> ≥ 3)
Glotzer et al., 2009 [32]	2486 patients with ≥1 stroke risk factor	PM or ICD	1.4 years (0.1–3.3)	≥5.5 h	2.20 (0.96–5.05) <i>p</i> = 0.06	
Ziegler et al., 2010 [33]	163 patients with previous thromboembolic event, no PAF	PM or ICD	1.1 ± 0.7 years	≥5 min		73% of new AF patients with previous TE experienced episodes of AF; in only <10% of follow-up days.
Boriani et al., 2011 [34]	568 patients with bradyarrhythmia and history of PAF	PM	1 year	≥5 min		Combining AF burden and CHADS <sub>2</sub> or CHA <sub>2</sub> DS <sub>2</sub> –VASc scores actually improves prediction of stroke, reaching c-statistics of 0.713 and 0.910, respectively
Healey et al., 2012 [28]	2580 patients ≥65 years, with hypertension, no history of PAF	PM or ICD	2.5 years	> 6min	2.49 (1.28–4.85) <i>p</i> = 0.007	
Shanmugam et al., 2012 [35]	560 patients with heart failure	CRT	370 days	>3.8 h	9.4 (1.8–47.0) <i>p</i> = 0.006	40% of the study population had at least 1 day with AF burden; >14 min
Boriani et al., 2014 [36]	10,016 patients without permanent AF, median age 70 years, (pooled analysis of 3 studies)	PM or ICD or CRT	24 months [14–40]	≥1 h	2.11 (1.22–3.64) <i>p</i> = 0.008	
Gonzales et al., 2014 [37]	224 patients with a dual-chamber pacemaker and no history of AF	PM	6.6 ± 2.0 years	≥5 min	9.65 (1.56–59.9) <i>p</i> = 0.015 for stroke mortality	
Benezet-Mazuecos et al., 2015 [38]	109 patients with CIEDs, in 69% with no history of AF or stroke/TIA	PM or ICD or CRT	17 ± 6 months	≥5 min	3.05 (1.06–8.81) <i>p</i> = 0.05 in overall population 9.76 (1.76–54.07) <i>p</i> = 0.05 in patients without prior history of AF or stroke/TIA	AF burden was an independent predictor for silent ischemic brain lesions at CT scan (found in 25.7% of the patients).

As reported earlier, AF patients may present with different types of arrhythmia, with permanent AF frequently reported as the most frequent form of diagnosed AF in the general population or in patients hospitalized for AF [3]. In the EORP-AF General Pilot Registry, which enrolled patients with documented AF at the time of enrolment or within 1 year and presenting to cardiologists in nine countries across Europe, 30% of patients had the so-called “first-detected AF,” 27% paroxysmal AF, 26% persistent AF, and 17% had permanent AF [41]. AF is a progressive disease, and the evolution to permanent AF may occur in up to 25% of patients at variable lengths of follow-up, depending upon the type of presentation, underlying heart disease, age, and concurrent treatments [3,16].

The relationship between the type of AF and the risk of stroke, independently of CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>–VASc scores, is currently a matter of controversy. Some randomized clinical studies [42,43] and observational registries [44,45] reported that patients with paroxysmal AF have a risk of stroke/systemic thromboembolic events similar to that in patients with nonparoxysmal AF. However, in contrast to these findings, other studies, and specifically some post hoc analyses of large randomized clinical trials of non-vitamin K antagonist oral anticoagulants reported that the risk of stroke/systemic

thromboembolic events is lower in patients whose arrhythmia at enrollment was a paroxysmal AF compared with a nonparoxysmal AF [46,47].

The analysis of the relationship between AF type and outcomes, including stroke, is complicated by the evidence that the patient profile of paroxysmal AF is different from the other types, because patients with paroxysmal AF are younger, with a lower prevalence of organic heart disease (especially valvular heart disease) and major comorbidities (heart failure, chronic kidney disease, chronic obstructive pulmonary disease, peripheral vascular disease), as well as lower estimated thromboembolic and bleeding risks [41]. All these factors, as well as the proportion of patients appropriately treated with oral anticoagulants, may act as important confounders, thus making the assessment of the causal relationship problematic.

A recent observational study conducted in Japan [48] found that paroxysmal AF was associated with a significantly higher risk of stroke than nonparoxysmal forms even after adjusting for a series of potential confounders, including oral anticoagulation. The results are also reinforced by the evidence that the risk of stroke was lower in patients maintaining a paroxysmal AF pattern than those with paroxysmal AF at the baseline who progressed to a sustained AF during the 2-year follow-up [48].

Another interesting contribution is that reported by Vanassche et al. [49], who analyzed the rates of stroke and systemic embolism in 6563 aspirin-treated AF patients from the ACTIVE-A and AVERROES databases. Multivariable analysis identified age  $\geq 75$  years, sex, history of stroke or TIA, and AF pattern as independent predictors of stroke, with a permanent AF pattern being the second strongest predictor after prior stroke or TIA. In this study, the simple assessment of the atrial rhythm at the time of baseline visit had prognostic value, since being in sinus rhythm was associated with a lower risk of stroke/systemic embolism than with being in AF [49].

In this context, it may be interesting to consider the results of a systematic study and meta-analysis of all the studies that compared paroxysmal and nonparoxysmal AFs with regard to the occurrence of stroke/thromboembolism, although the heterogeneity for study design, type of treatment, and ascertainment of outcomes in the various studies suggest caution in the interpretation. A systematic review of indexed publications from January 1966 to April 2014 of randomized controlled trials or cohort studies that analyzed the occurrence of stroke as a function of paroxysmal or permanent AF pattern identified 18 papers with 134,847 AF patients included [50]. The results of this meta-analysis indicated that the risk of stroke was lower in patients with paroxysmal AF than with permanent AF, with odds ratios (ORs) of 0.75 (95% CI 0.61–0.93) in studies with no oral anticoagulants; 0.77 (95% CI 0.68–0.88) in studies with oral anticoagulants in all patients; and 0.70 (95% CI 0.58–0.84) in studies with mixed use of oral anticoagulants. This meta-analysis suggests that patients with paroxysmal AF have a lower risk of stroke than those with permanent AF, but it remains unclear if AF pattern is an independent predictor of stroke or rather a reflection of a different patient profile with regard to risk factors and comorbidities. In order to further appreciate the complex picture of AF patients presenting with paroxysmal on nonparoxysmal AF, it is interesting to consider an analysis of the predictors of outcome taking into account not stroke, but all-cause mortality. In an analysis of the EORP-AF General Pilot Registry, patients with nonparoxysmal AF had a worse outcome for all-cause mortality at 1 year than those with paroxysmal AF, but the adverse outcome was related to the worse clinical risk profile in terms of age, underlying cardiac disease, comorbidities, and risk factors [41].

### 7. Complex relationship between AF and stroke: is AF a risk factor, a marker, or both?

The availability of CIEDs for continuous monitoring of the atrial rhythm, extended to periods of months/years, has made it possible to obtain further information on the temporal relationship between the occurrences of atrial tachyarrhythmia, measured in terms of atrial

burden, and ischemic stroke/systemic thromboembolism [16]. Moreover, continuous monitoring of the rhythm by CIEDs has also shown that the traditional clinical classifications of AF into paroxysmal or persistent AF poorly reflect the actual temporal persistence of the arrhythmia, therefore threatening any attempt to study the association between types of AF and stroke in detail [51].

Many studies performed on patients implanted with a CIED, with or without previous documented AF, found that ischemic stroke might occur without the concurrent presence of atrial tachyarrhythmias or AF at the time of stroke or in the previous days.

The first of these studies was published by Daoud et al. [52], who showed that 45% of patients with a device-detected atrial tachyarrhythmia before the ischemic event (stroke or cerebrovascular embolism) did not have any arrhythmia in the 30 days before the event. Similar findings were reported by the Anticoagulation Use Evaluation and Life Threatening Events Sentinels (ANGELS) of AF study, where, among 33 patients with stroke, transient ischemic attacks, or embolic events, 64% had an AF burden  $\geq 5$  min detected by implantable cardioverter defibrillator (ICD) diagnostics at any time before stroke, and 33% in the 30 days before the event [52]. The results of studies conducted on this intriguing topic are summarized in Table 2 [35, 52–55]. The variable association between AF and stroke/systemic embolism may be related to the presence/absence of a previous history of AF, clinical profile, and risk factors for AF-related ischemic stroke, concurrent risk factors for vascular events, concurrent treatment with anticoagulants and anti-thrombotic agents.

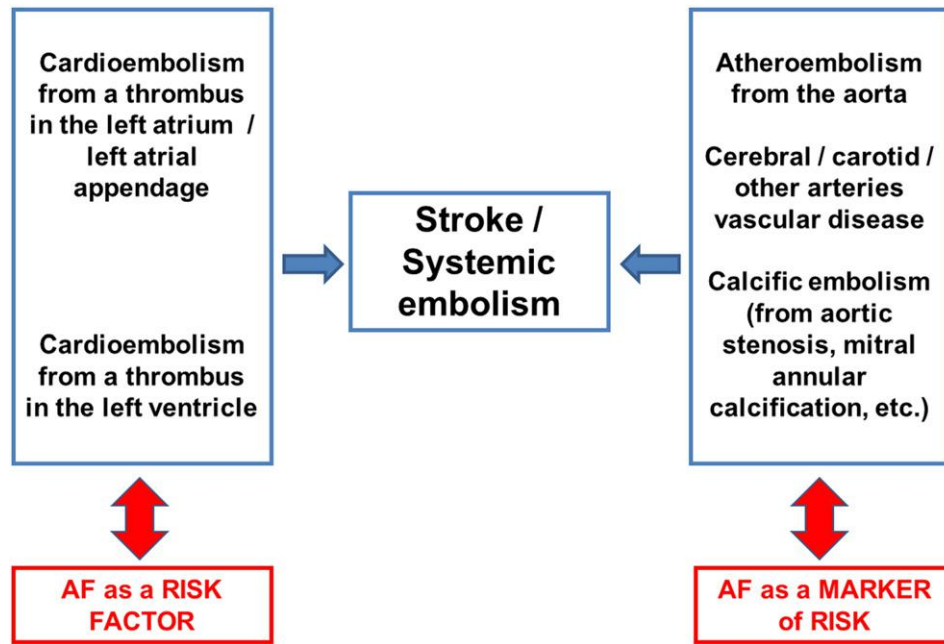
According to these data, the relationship between AF and stroke appears quite complex, and can be considered in a new perspective. The fact that AF episodes of very short duration (minutes to hours) are associated with stroke/systemic embolism, but with the thromboembolic event occurring at some temporal distance, sometimes also with AF occurring only after a stroke, with complete absence before, indicates that in some cases, AF may not have a causative role (mediated by a left atrial thrombus), but rather simply represents a marker of vascular risk. In this view, as shown in Fig. 3, AF may actually play two different roles: with regard to stroke and systemic thromboembolism. In some cases, as in the traditional view, AF is certainly a risk factor for cardioembolic stroke, with a cause–effect relationship between the arrhythmia and a thromboembolic event (stroke/systemic embolism), involving the formation of an atrial thrombus related to effects on all the components of the “Virchow triad” [56, 57]. However, the most innovative view indicates that AF may also be simply a “marker of risk,” with a relationship of simple association between the arrhythmia and stroke. In the latter cases, AF may also have no strict temporal relationship with stroke, which may be causally related to atheroemboli from the aorta or carotid

**Table 2**

Data on the time relationships between device-detected atrial tachyarrhythmias and ischemic stroke, transient ischemic attacks or systemic embolism in patients with CIEDs under continuous monitoring of the atrial rhythm.

	No. of TE events (ischemic stroke/TIA/SE)	Minimum device-detected AF/AT duration/burden	Device-detected AF/AT at any time before TE event (%)	Device-detected AF/AT in the 30 days before TE event (%)	Device-detected AF/AT at the time of TE event (%)	Device-detected AF/AT only after TE event (%)
Daoud et al., 2011 [52]	40 ischemic strokes/TIA/SE	$\geq 20$ s	50	28	15	15
Boriani et al., 2012 [53]	33 ischemic strokes/TIA/SE	$\geq 5$ min	64	33	15	NA
Shanmugam et al., 2012 [35]	11 ischemic strokes/TIA/SE	~6–10 s	64	NA	27	NA
Brambatti et al., 2014 [54]	51 ischemic strokes/SE	>6 min	35	8	2	16
Martin et al., 2015 [55]	69 ischemic strokes/SE	~6–10 s	13	6	NA	7

Legend: AF: atrial fibrillation; AT: atrial tachyarrhythmia; CIED: cardiac implantable electronic device; SE: systemic embolism; TE: thromboembolic; TIA: transient ischemic attack; NA: not available.

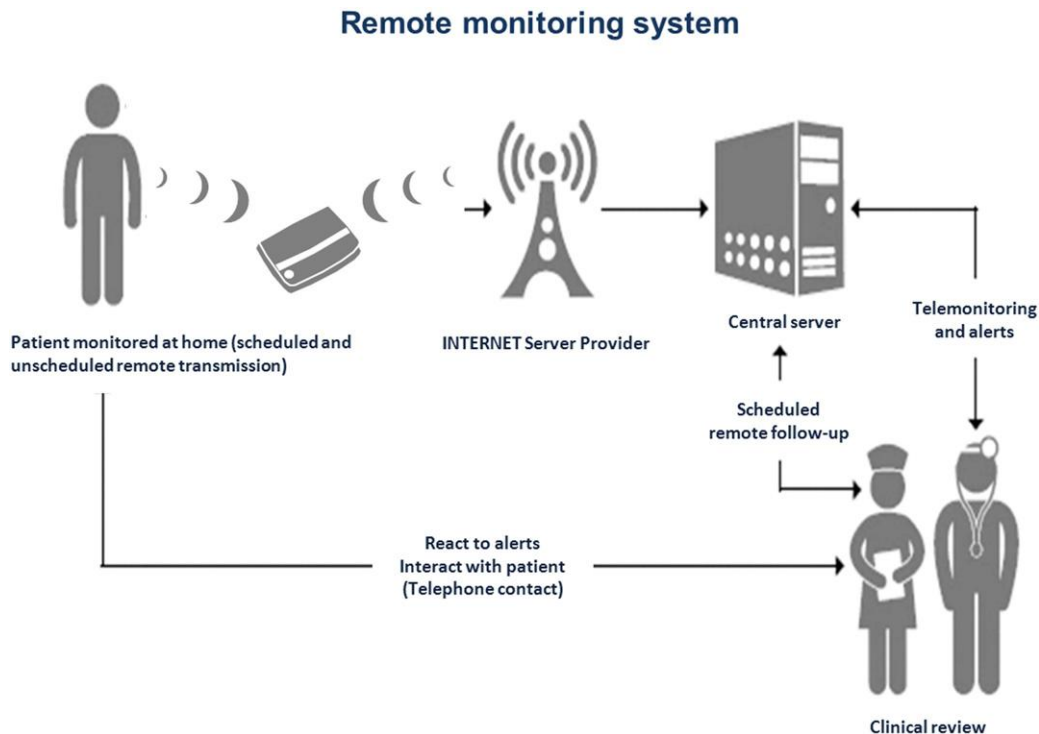


**Fig. 3.** Complex relationships between AF and stroke/systemic embolism. AF plays a dual role: (i) as a risk factor for cardioembolic stroke, with a cause–effect relationship and (ii) as a marker of risk, with a relationship of simple association between arrhythmia and stroke.

arteries or even from a calcified aortic stenosis or calcified mitral annulus [58–61] (Fig. 3). In this latter perspective, the complexity of the mechanisms of atherothrombosis and the number of factors modulating this process are well known [62–64]. Despite these data, indicating that AF may play a “dual role” with regard to stroke/thromboembolism, it is important to stress that independently on considerations and assessments of the actual role of AF (as a risk factor for cardioembolism or as a marker of vascular risk) prophylaxis with an oral anticoagulant

(apixaban) resulted superior to aspirin in preventing the end point of stroke (ischemic or hemorrhagic) or systemic embolism in a randomized double-blind trial [65]. In other terms, the current uncertainties on the actual role of AF should not minimize the crucial role played by oral anticoagulation in preventing the thromboembolic events associated with AF in patients at risk.

Whatever the case, the determinants of stroke are complex, and it is noteworthy that CHA<sub>2</sub>DS<sub>2</sub>–VASC and CHADS<sub>2</sub> scores predict risk of



**Fig. 4.** Organization of remote monitoring of cardiac implantable electronic device (CIEDs) to monitor the patient at home, with the flow of information becoming available to health-care professionals (physician, nurses), who can remotely interact with the patient.

stroke or death in elderly patients with implanted PMs even regardless of AF history [66].

## 8. Antithrombotic prophylaxis, AF burden, and type of AF

Risk stratification for stroke and choice of an appropriate oral anticoagulant, if indicated according to consensus guidelines, is a crucial step in AF management, much more important than the choice between rhythm and rate control strategies [2]. Traditionally, a gap in the prescription of oral anticoagulants has been reported, with many patients not being prescribed oral anticoagulants in consideration of an unfavorable risk–benefit profile, or perceived lack of safety [12,67,68]. The availability of non-vitamin K antagonist oral anticoagulants (NOACs), which do not require routine monitoring of their effects on coagulation have the potential to increase the proportion of patients with nonvalvular AF appropriately treated with oral anticoagulants, although this is not fully proved [67]. The propensity of clinicians to take appropriate clinical decisions based on device data on AF burden in case of subclinical AF is unknown. Some data indicate that providing physicians with specific data on the presence/duration of AF and atrial tachyarrhythmias may offer the basis for an improved approach to prescription of oral anticoagulants in AF compared with that based on the usual risk stratification. The ANGELS of AF project was a medical care program aimed at supporting adherence to oral anticoagulation guidelines for thromboprophylaxis using advanced diagnostics available in CIEDs [53]. In the ANGELS of AF centers, the proportion of patients on oral anticoagulant therapy according to guidelines increased during the follow-up from about 46% at the baseline up to approximately 73% at the end of the observation period, with more patients as anticoagulants than controls.

The increasing use of remote monitoring of CIEDs is an alternative to conventional in-office checking, and offers the possibility of a prompt notification to physicians and nurses of any episode of tachyarrhythmia detected by the CIED, even if asymptomatic. The clinical use of remote monitoring, with a flow process depicted in Fig. 4, makes it possible to shorten the notification of detected AF to a very short time (usually within 2 days) [69–71], in order to accelerate clinical decision making. Detection of previously unrecognized clinically silent AF is a typical condition where appropriate decision making may have important implications for patient outcome, when clinical risk factors suggest a substantial risk of stroke. The potential benefit of device-guided institution of antithrombotic agents for AF was evaluated in a modeling study by Ricci et al. [72], who calculated that prompt reaction to AF detection with the appropriate, evidence-based start of an antithrombotic treatment might result in an important reduction of stroke, in the range of 9–18% at 2 years. The actual effect of remote monitoring on the occurrence of stroke in real-world practice is still unknown, and trials and registries are ongoing in the complex scenario of heart failure patients.

Continuous monitoring through CIEDs has been proposed for not only initiating oral anticoagulants in patients at risk but also discontinuing them, if no AF is detected for a certain period of time. This strategy appears unsafe, as recently demonstrated by the IMPACT trial [55], and is contraindicated in patients whose clinical profile indicates a substantial risk of stroke ( $\text{CHA}_2\text{DS}_2\text{-VASc}$  score  $\geq 2$ ). At present, the risk of stroke associated with AF, as assessed by traditional risk scores, has to be considered irreversible, and anticoagulation, if indicated, should not be discontinued after a period of sinus rhythm maintenance if the clinical profile indicates a substantial risk.

The main question that arises from studies on AF burden in CIEDs is “What is the threshold of the asymptomatic, subclinical burden of atrial tachyarrhythmias and AF associated with a beneficial effect of oral anticoagulants in patients with a clinical profile at substantial risk based on traditional risk stratifiers for stroke ( $\text{CHA}_2\text{DS}_2\text{-VASc}$  and  $\text{CHADS}_2$ )?” The effect of anticoagulation therapy on stroke and thromboembolism, started based on device-detected AF, even with AF episodes of short duration, in combination with clinical risk stratification will be

prospectively addressed by ARTESiA (Apixaban for the Reduction of Thrombo-Embolic events in patients with Device-Detected Sub-Clinical Atrial fibrillation) and NOAH (Non-vitamin K Antagonist Oral Anticoagulants in Patients With AHRE) trials [73,74]. These randomized controlled studies will include patients with device-detected atrial tachyarrhythmia between 6 min and 24 h (ARTESiA trial) [73] or  $\geq 6$  min (NOAH trial) [74].

## 9. Practical considerations on the prescription of oral anticoagulants according to AF burden and AF type

Risk stratification for stroke is a crucial step in the clinical management of AF patients and is currently based on the evaluation of a series of factors included in user-friendly scores ( $\text{CHADS}_2$  and  $\text{CHA}_2\text{DS}_2\text{-VASc}$ ). Patients with a substantial clinical risk of stroke ( $\text{CHA}_2\text{DS}_2\text{-VASc}$  score  $\geq 2$ ) should be anticoagulated regardless of their AF pattern/type, which indicates that paroxysmal AF should not be an element to deny anticoagulation in patients at risk.

In deciding whether or not to offer anticoagulation to patients at lower risk (i.e.,  $\text{CHA}_2\text{DS}_2\text{-VASc}$  score = 1), for whom the risk–benefit ratio of anticoagulation is less clear, it may be useful to consider the pattern of AF occurrence (nonparoxysmal vs. paroxysmal AF) or, more simply, whether the patient is in sinus rhythm or not at the time of the clinical evaluation [49]. The latter pattern may help identify “truly low risk” patients.

In the case of asymptomatic AF, it is important to stress that for any episode of substantial duration, that is, at least 24 h, the risk of stroke/systemic embolism is the same as with symptomatic AF, and therefore decision making regarding oral anticoagulation should not be different from current recommendations, and be based on scores for risk stratification. In this regard, majority of the patients with asymptomatic AF of undefined but surely long duration may have complex clinical profiles in terms of comorbidities and risk of adverse outcomes that require specific clinical evaluation with regard to assessment of the potential hemorrhagic risk of anticoagulants and choice of the most appropriate anticoagulation agent and regimen.

For patients with subclinical AF detected by a CIED, validation of the arrhythmia through device diagnostics is indicated (by analysis of the EGMs stored in device memory) to rule out oversensing and confirm the diagnosis of the atrial tachyarrhythmia. Data from the literature indicate that, for device-detected atrial tachyarrhythmias, arrhythmia duration or AF burden of  $\geq 5$ –6 min is associated with a significant increase in the risk of stroke/systemic embolism. However, the specific cutoff of AF duration or AF burden at which initiation of oral anticoagulants is warranted for patients at risk, in terms of risk–benefit ratio, is not established, and controlled trials are ongoing. In general, the higher the clinical risk, as expressed by a  $\text{CHA}_2\text{DS}_2\text{-VASc}$  score  $\geq 3$ , the lower the threshold of AF burden that should be considered for initiating oral anticoagulants (i.e., 5–6 min or 1 h), but this is not well established by intervention trials and is still a matter of debate. Many physicians suggest that, if not contraindicated, oral anticoagulants should be prescribed in patients with a  $\text{CHA}_2\text{DS}_2\text{-VASc}$  score  $\geq 2$  whenever the AF burden is in the range of hours (i.e.,  $>5$ –12 h), although no specific intervention trial is in support of this reasonable choice. In patients with a  $\text{CHA}_2\text{DS}_2\text{-VASc}$  score of 1 and a clinically silent AF detected by a CIED with a variable AF burden (minutes to hours), individualized decision making is needed, considering that the current approach is more focused on appropriate identification of “truly low risk” patients (to be excluded from anticoagulation) rather than the identification of patients at higher risk, who anyway need prophylaxis with oral anticoagulants [2]. In the setting of patients with a  $\text{CHA}_2\text{DS}_2\text{-VASc}$  score of 1, where no controlled data are available, clinical decision making may benefit from a series of considerations on the favorable safety profile and high treatment adherence that can be achieved with NOACs.

Finally, it is important to stress that even at present, with the availability of advanced diagnostic tools, the approach to a patient with



documented AF remains primarily clinical, based on the evaluation of the underlying heart disease, correction of potential precipitating factors, and risk stratification for stroke. The most advanced technologies, including the diagnostic capabilities of CIEDs and remote monitoring, may be additional valuable clinical tools for detecting subclinical AF or precisely quantifying the AF burden, as further elements to improve the decision-making process.

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