Usefulness of Continuous Electrocardiographic Monitoring for Atrial Fibrillation

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The problem of early recognition of atrial fibrillation (AF) is greatly aggravated by the often silent nature of the rhythm disturbance. In about 1/3 of patients with this arrhythmia, patients are not aware of the so-called asymptomatic AF. In the past 15 years, the diagnostic data provided by implanted pacemakers and defibrillators have dramatically increased knowledge about silent AF. The unreliability of symptoms to estimate AF burden and to identify patients with and without AF has been pointed out not only by pacemaker trials but also in patients without implanted devices. The technology for continuous monitoring of AF has been largely validated. It is a powerful tool to detect silent paroxysmal AF in patients without previously documented arrhythmic episodes, such as those with cryptogenic stroke or other risk factors. Early diagnosis triggers earlier treatment for primary or secondary stroke prevention. Today, new devices are also available for pure electrocardiographic monitoring, implanted subcutaneously using a minimally invasive technique. In conclusion, this recent and promising technology adds relevant clinical and scientific information to improve risk stratification for stroke and may play an important role in testing and tailoring the therapies for rhythm and rate control. © 2012 Published by Elsevier Inc. (Am J Cardiol 2012;110:270–276)

The gold standard for diagnosing atrial fibrillation (AF) is the visual inspection of the electrocardiogram. An irregular pulse may raise suspicion for AF, but an electrocardiogram is necessary to diagnose AF.[1,2] The problem of early recognition of AF is greatly aggravated by the often silent nature of the rhythm disturbance.[3] In about 1/3 of patients with this arrhythmia, patients are not aware of the so-called asymptomatic AF. Much earlier detection of the arrhythmia might allow the timely introduction of therapies to protect patients not only from the consequences of the arrhythmia but also from progression of AF from an easily treated condition to an utterly refractory problem. Not surprisingly, silent AF is associated with at least the same risk for stroke as is symptomatic AF.[4] Patients with symptomatic AF are much more likely to be diagnosed early on and treated with stroke prevention therapy. Despite clinical evidence and guidelines,[1,2] many reports from the United States and Europe have shown that only 25% to 50% of patients with AF and thromboembolic risk factors are offered antithrombotic therapies, and those who do receive therapy often discontinue it within months or do not achieve the target range of international normalized ratio values.[5,6] With the advent of modern technologies in implantable cardiac devices, there is an opportunity to detect AF onset and accurately measure AF duration, frequency, burden, and ventricular rate. The availability of these new tools will open new frontiers in the scientific and clinical knowledge of AF and might have a relevant impact on patient management and risk stratification for stroke.

Limited Value of Symptoms and Intermittent Electrocardiographic Monitoring for Atrial Fibrillation Detection and Burden Assessment

The silent form of AF is noticed incidentally through a wide variety of methods, including routine physical examinations, office electrocardiography, preoperative assessments, or population surveys. In some cases, asymptomatic AF is revealed only after complications such as stroke or congestive heart failure have occurred.[3]

Many trials have confirmed that most paroxysmal AF (PAF) episodes are asymptomatic, many patients are completely asymptomatic, and electrocardiographic (ECG) monitoring with Holter devices has limited sensitivity.[7–18] The advent of the technology for continuous AF monitoring made possible to rigorously define the AF burden as the measured percentage of time spent in AF during the follow-up period. Similarly, it was possible to rigorously define the daily AF burden as the total amount of time spent in AF each day of the follow-up period. AF burden is a parameter that takes into account the frequency and duration of AF episodes during the overall follow-up period, and

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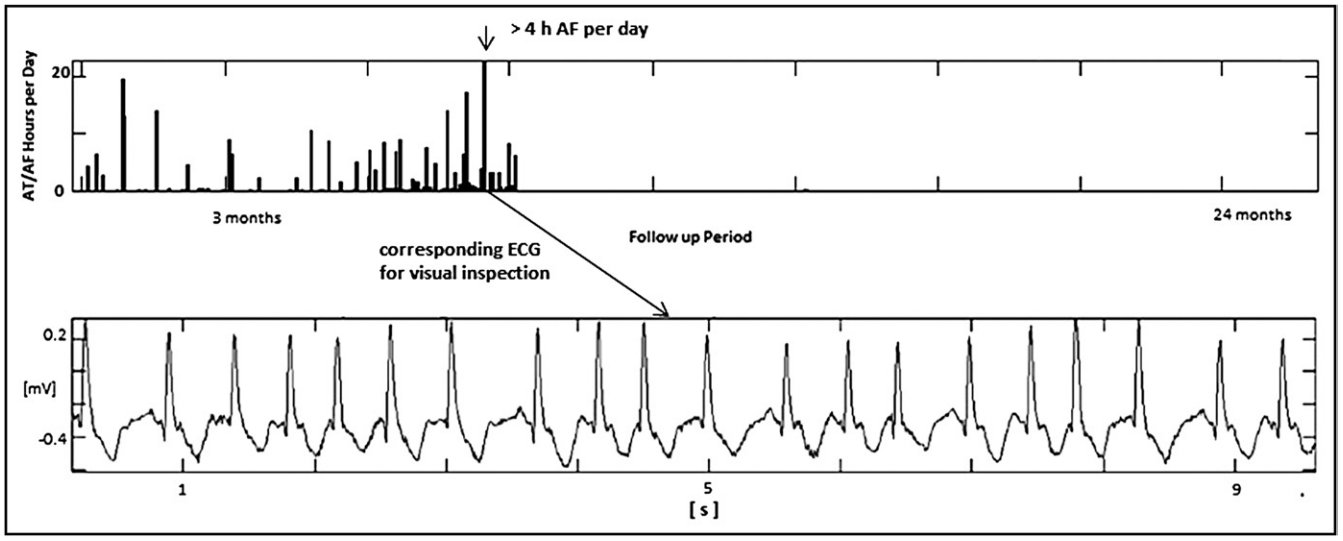

Figure 1. Example of Cardiac Compass (Medtronic, Inc., Minneapolis, Minnesota) in a patient with sporadic and asymptomatic episodes of PAF. The electrocardiogram (ECG) shows the cardiac rhythm during the longest episode stored by the device, confirming AF. The chance of detecting these episodes through standard Holter recording would be very low. The trend of the daily AF burden is a simple and efficient tool: it shows how long the AF episodes last and how frequently they occur. In addition, an ECG is available to validate the cardiac rhythm.

Table 1
Symptoms and ambulatory electrocardiographic monitoring versus continuous monitoring (studies including >40 patients)

Study	Device (n)	Sinus Rhythm, AT, AF
Defaye et al[19]	DDD (354)	SV arrhythmias were detected in 179 patients (50.6%), 104 of whom (65%) were asymptomatic and 117 of whom (65%) had no previous documentation.
Glotzer et al[16]	DDD (312)	When symptoms were assessed as an indicator of AT/AF, their sensitivity was 82.4%, but their specificity was 38.3%, with a PPV of 58.7%.
Israel et al[17]	DDD (110)	AF was documented in 51 patients (46%) by ECG recording and in 97 patients (88%) by a review of stored electrograms. AF duration >48 hours was totally asymptomatic in a significant proportion of patients.
Ziegler et al[7]	DDD (574)	Intermittent (annual, quarterly, monthly 24-hour Holter; 7- and 30-day annual long-term recordings) monitoring/symptoms was highly inaccurate for identifying patients with any AT/AF.
Israel et al[20]	DDD (254)	Symptoms were absent in 108 of 137 patients (79%) with device-documented AT but present in 70 of 117 patients (60%) without AT documentation.
Hanke et al[15]	ICM (45)	Sinus rhythm was documented in 53 readings of 24-hour Holter monitoring but in only 34 of these instances by the implanted device, reflecting a 24-hour Holter sensitivity of 0.60 and an NPV of 0.64.
Botto et al[12]	DDD (568)	The sensitivity for detecting AF episodes lasting ≥5 minutes was 44.4%, 50.4%, and 65.1% for 24-hour Holter, 1-week Holter, and 1-month Holter monitoring vs continuous monitoring.
Quirino et al[14]	DDD (102)	The sensitivity and PPV of symptoms to detect AF episodes were 19% and 21%.
Ziegler et al[21]	DDD (163)	Newly detected episodes of AT/AF were found on continuous monitoring in 28% of patients without previous documentation.
Pokushalov et al[18]	ICM (129)	After ablation, only 32% of the symptomatic episodes corresponded to genuine AF episodes.

AT = atrial tachycardia; ICM = subcutaneous insertable cardiac monitor; NPV = negative predictive value; PPV = positive predictive value; SV = supraventricular.

daily AF burden is an estimate of the overall duration of AF episodes in each day. The trend of daily AF burden during the follow-up period is an easy and efficient way to show the presence and evolution of the disease. Moreover, it provides relevant information about the duration of recurrences (Figure 1).

The Suppression of Paroxysmal Atrial Tachyarrhythmias (SOPAT) trial[8] showed that only 6,165 of 188,634 telephonic electrocardiograms (46%) recorded during the 1-year follow-up period were associated with specific symptoms. The remaining 54% were asymptomatic AF episodes. Similarly, the Prevention of Atrial Fibrillation After Cardioversion (PAFAC) trial[9] collected 191,103 recordings using daily telephonic ECG monitoring; 70% of all AF recurrences occurred completely asymptomatically.

Arya et al[13] used 7-day Holter recordings before ablation and documented AF in 92 of 114 patients (81%). All episodes were symptomatic in 35 patients (38%). In 52 patients (57%), symptomatic and asymptomatic episodes were recorded, whereas in 5 patients (5%), all documented AF episodes were asymptomatic. After ablation, the percentage of patients with only asymptomatic AF recurrences increased to 37%.

Senatore et al[11] showed that the absence of symptoms should not be interpreted as the absence of AF, because 50%

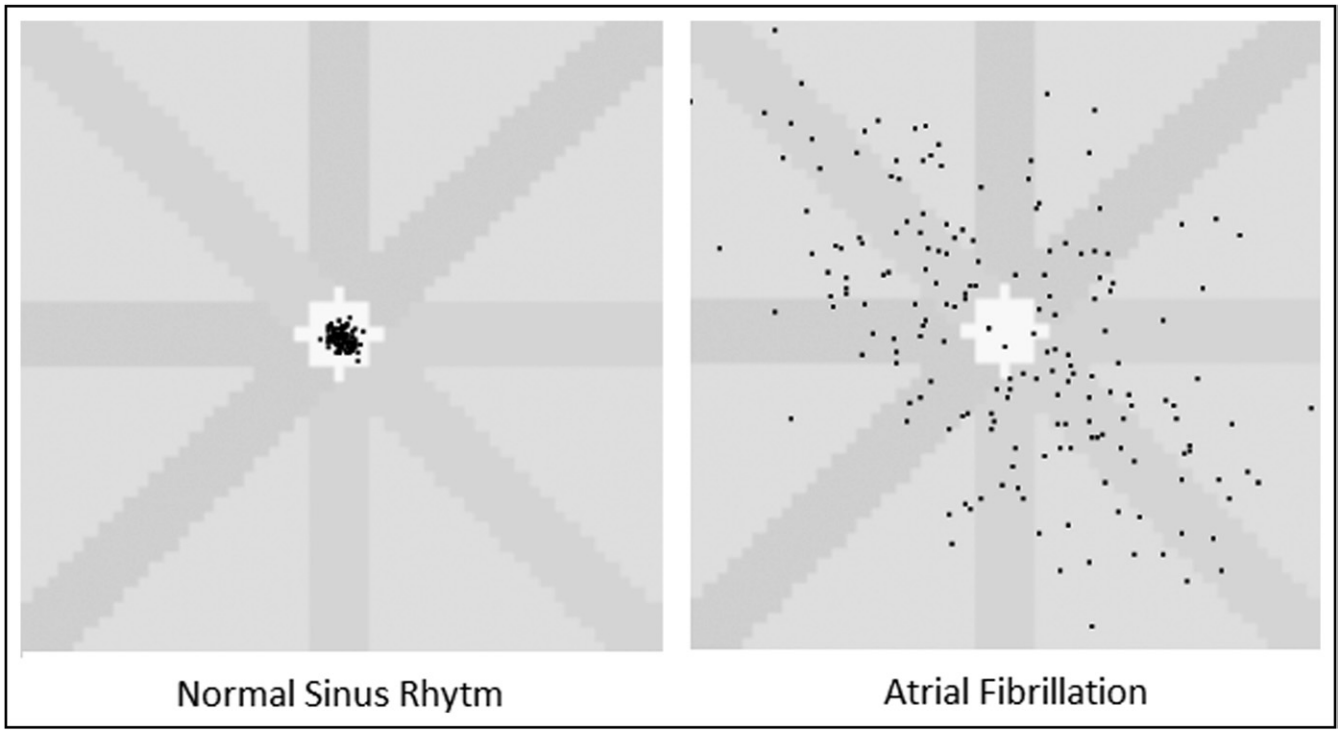

Figure 2. Examples of Lorentz plots with AF and sinus rhythm. The Lorentz plot is a graphic representation of the beat-to-beat variations of the cardiac cycles. Each dot in the plane corresponds to a couple of consecutive differences in cardiac cycles. Because AF is characterized by a higher cycle-to-cycle variability compared to sinus rhythm, the dots in the plane are significantly more scattered in the presence of AF. The current generation of implantable cardiac monitors uses a 2-minute time window to collect sufficient cardiac cycles for the analysis and rhythm classification.

of patients were asymptomatic during ≥1 AF episode after ablation, as detected by telephonic ECG transmission.

Ziegler et al[7] compared continuous monitoring with different strategies of intermittent ECG monitoring in pacemaker patients. All intermittent and symptom-based monitoring resulted in significantly lower sensitivity (range 31% to 71%) and negative predictive value (range 21% to 39%) for the identification of patients with AF and underestimated AF burden. These results were also confirmed by Botto et al[12] in a similar patient population. In patients submitted to ablation and not implanted with monitoring devices, Arya et al[13] showed that greater monitoring results in greater sensitivity for AF detection and burden estimation.

In pacemaker patients, Quirino et al[14] showed that the sensitivity and positive predictive value of symptoms to identify AF episodes were 19% and 21%, respectively. Hanke et al[15] used implantable subcutaneous cardiac monitors in patients submitted to surgical AF ablation and showed that sinus rhythm was documented in 53 readings of 24-hour Holter recordings but in only 34 of these instances by the implanted monitor in the time period before 24-hour Holter readings (64%), reflecting a 24-hour Holter sensitivity of 60% and a negative predictive value of only 64% for detecting AF recurrence.

In a subanalysis of the Mode Selection Trial (MOST) conducted in pacemaker patients, Glotzer et al[16] showed that when symptoms are assessed as an indicator of atrial arrhythmias, their sensitivity to identify patients with the arrhythmia is 82.4%, but their specificity is only 38.3%, with a positive predictive value of 58.7%, making symptoms useless for risk stratification and burden assessment. Israel et al[17] showed in pacemaker patients that AF was documented in 46% by office ECG recording compared to 88% by a review of the electrograms automatically stored by the implanted device. In addition, device interrogation revealed AF recurrences lasting >48 hours in 50 patients, 19 of whom (38%) were completely asymptomatic and in sinus rhythm at subsequent follow-up.

Pokushalov et al[18] collected data on AF recurrences after ablation. Only 32% of electrocardiograms stored during symptomatic events corresponded to genuine AF; 39% were sinus rhythm, 19% sinus rhythm with some premature contractions, 6% sinus bradycardia, and 4% sinus tachycardia. Table 1[7,12,14–21] shows the low reliability of symptoms and ambulatory methods for monitoring AF compared with continuous monitoring through implantable devices.

Evolution in the Technology of Continuous Atrial Fibrillation Monitoring

Dual-mode, dual-pacing, dual-sensing DDD devices: Several algorithms have been studied and tested to define the optimal method for AF detection. Several trials have been conducted to validate the diagnostic and monitoring features in implantable DDD pacemakers and implantable cardioverter-defibrillators.[16,19,22–28]

Pollak et al[23] showed that by minimizing the risk for detecting artifacts caused by myopotentials or other sources of electrical interference, the detection of atrial tachyarrhythmia episodes lasting ≥5 minutes correlated well with a proved diagnosis of AF.

Many clinical studies have been conducted using the diagnostic features of implanted DDD pacemakers

Table 2
Validation of atrial fibrillation monitoring features in implantable devices (studies including >40 patients)

Study	Device (n)	Setting	Major Findings
Defaye et al[19]	Chorus (617)	ED ≥1 minute	93.8% sensitivity, 94.2% specificity for AF episode detection
Swerdlow et al[22]	Jewel AF (80)	ED ≥32 VCs	100% sensitivity, 99% specificity for AT/AF episode detection
Pollak et al[23]	Thera (56)	AR ≥150 beats/min	ED ≥5 minutes had 88% correlation with true AF/AT episodes
Glotzer et al[16]	DDD PMs (312)	AR ≥220 beats/min	ED ≥5 minutes had 100% sensitivity and 97% specificity for AF detection
Purerfellner et al[24]	AT500 (409)	ED ≥24 VCs	100% of the sustained atrial arrhythmia episodes detected
Hoffmann et al[25]	Selection (98)	AR ≥200 beats/min, ED ≥6 VCs	Detailed analysis of rate and rhythm changes before AF onset
Pérez et al[26]	Selection (282)	AR ≥200 beats/min, ED ≥10 VCs	Time to the first AF recurrence was not a surrogate of AF burden
Nowak et al[27]	Pulsar M (351)	AR ≥170 beats/min, ED ≥4 VCs	Therapeutic decisions based on validated stored electrograms
Martinek et al[28]	AT500 (41)	AC <360 ms, ED ≥24 VCs	Continuous monitoring was significantly more sensitive than follow-up
Hanke et al[15]	Reveal XT (45)	2-minute Lorentz plot	Continuous monitoring was superior to any conventional strategy
Hindricks et al[41]	Reveal XT (247)	2-minute Lorentz plot	Overall accuracy of Reveal XT for detecting AF was 98.5%

AC = atrial cycle; AR = atrial rate; AT = atrial tachycardia; ED = episode duration; PM = pacemaker; VC = ventricular cycle.

or implantable cardioverter-defibrillators to measure AF burden and compare different therapeutic strategies.[25–26,29–36] Pacing algorithms for AF prevention have been studied using the diagnostic features of the implanted device itself.[25–26,29–33] In a similar way, AF diagnostics were used to monitor AF burden in patients treated with algorithms to minimize ventricular pacing.[34] Other studies were conducted in implanted patients to compare antiarrhythmic drug therapies[35] in patients with PAF, through the diagnostic features of the devices.

In patients with heart failure implanted with cardiac resynchronization therapy devices, AF diagnostics have been largely used to detect new-onset AF and its progression.[36–39]

Subcutaneous electrocardiographic monitors: With the advent of implantable loop recorders, a new method for detecting AF has been developed. Unlike DDD pacemakers and implantable cardioverter-defibrillators, these subcutaneous devices cannot sense endocardial atrial activity, and an analysis of consecutive RR intervals is used for the diagnosis of AF. The irregularity of the RR interval is now a proved parameter for AF detection,[40] and the mathematical tool for the assessment is the so-called Lorentz plot (Figure 2). In a Lorenz plot, each RR interval is plotted against the previous value of the RR interval, and this can be displayed graphically and used to discriminate between AF and sinus rhythm. A recent validation study, the Reveal XT Performance Trial (XPECT),[41] showed that a subcutaneous monitoring device equipped with an algorithm for AF detection can accurately measure AF burden (98.5%) and is very sensitive (96.4%) to identify patients with AF, independently of symptoms. The device automatically stores a 2-minute ECG strip corresponding to each of the 3 most recent episodes, thus allowing visual inspection and confirmation by the physician.

In the field of AF ablation, subcutaneous monitoring has recently been used to monitor patients after the procedure and elucidate the impact of ablation on arrhythmia recurrences.[18,42] This method has been very useful to collect day-by-day data independently of patient compliance and independently of symptomatic events. Table 2 summarizes the most important technical and scientific advances on AF diagnostics using implantable devices.

Continuous Atrial Fibrillation Monitoring and Risk Stratification for Stroke

Continuous monitoring is already used in ongoing trials in patients with cryptogenic stroke[43] to identify those with silent PAF and drive the most appropriate antithrombotic therapy. About 20% to 30% of patients hospitalized for ischemic stroke or transient ischemic attack are discharged with the diagnosis of cryptogenic stroke,[44,45] that is, without a defined cause of the clinical event. Jabaudon et al[45] showed that more intensive ECG monitoring leads to the detection of more patients with AF among those in sinus rhythm hospitalized for stroke.

Recently, data from a large-scale pacemaker trial, Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT),[46] have been published. Patients were classified with and without AF through the diagnostics of the implanted DDD pacemakers. Patients were defined as free of AF if they did not have any AF episodes lasting >6 minutes. At 3 months, 10% of ASSERT patients had ≥1 AF episode lasting >6 minutes. AF, as detected by the implanted device, was associated with a

Table 3
Atrial fibrillation detected by dual-chamber devices and risk for stroke

Study	n (Patient Population)	Major Findings
Glotzer et al[16]	312 (SSS)	AHRE identified patients that are >2 times as likely to die or have a stroke and 6 times as likely to develop AF as those without AHRE (median FU 27 months).
Capucci et al[35]	725 (history of PAF)	The risk for embolism was 3.1 times increased in patients with device-detected AT/AF episodes lasting >24 hours (median FU 22 months).
Botto et al[12]	568 (history of PAF)	Risk stratification can be improved by combining $CHADS_2$ score with data on AF presence and duration (1-year FU).
Glotzer et al[48]	2,486 (≥1 RFS)	Daily AF burden ≥5.5 hours on any of 30 previous days appeared to double the risk for stroke (mean FU 1.4 years).
Ziegler et al[21]	163 (PS, no history of PAF)	Newly detected episodes of AF were found via continuous monitoring in 28% of patients with previous stroke (mean FU 1.1 years).
Boriani et al[50]	568 (history of PAF)	The combination of data on AF burden with $CHADS_2$ or CHA_2DS_2VASc score improved risk stratification for stroke (1-year FU).
Healey et al[46]	2580 (age ≥65 years, HTN, no history of PAF)	Device-detected atrial tachyarrhythmias were associated with a 2.5-fold increased risk for ischemic stroke or systemic embolism (mean FU 2.5 years).
Shanmugam et al[49]	560 (CRT)	In a cohort of heart failure patients, daily AF burden >3.8 hours over 24 hours was associated with a significant increase in the event rate (median FU 370 days).

AHRE = atrial high-rate episodes; AT = atrial tachycardia; CRT = cardiac resynchronization therapy; FU = follow-up; HTN = hypertension; RFS = risk factors for stroke; SSS = sick sinus syndrome; PS = previous stroke.

2.5-fold increase in the risk for ischemic stroke and systemic embolism, confirming the clinical value of the diagnostics of implantable devices.

Interesting reports have been published on the clinical value of AF burden as accurately measured by implantable devices. Glotzer et al[16] showed that patients with atrial arrhythmias (defined as atrial arrhythmias lasting >5 minutes) had a 5.93 greater chance of developing clinical AF and a 2.79 greater risk for stroke or death. Capucci et al[47] showed that the risk for embolism, adjusted for known risk factors, was 3.1 times increased in patients with device-detected AF episodes >1 day during follow-up. The latter supports the hypothesis that not all PAF episodes are the same and that AF duration is probably an important clinical parameter when measured using a reliable technique. Botto et al[12] first showed that those patients with histories of PAF, but without any arrhythmias during 1-year follow-up, had a low risk for stroke: 0.6% ($CHADS_2$ scores of 0, 1, and 2). In contrast, those patients with AF recurrence had risk that depended on the duration of the AF episodes combined with the risk factors as summarized by the $CHADS_2$ score. However, the investigators did not try to identify a threshold AF duration to define when AF is potentially dangerous. The previously mentioned studies[12,16,46,47] classified patients with AF if they had AF episodes lasting >5 or 6 minutes or daily AF burden >5 minutes. Patients with shorter AF episodes were classified as free of AF. Thus, they showed that episodes <5 minutes may not have a significant impact on the risk for stroke. In contrast, these studies did not try to establish a cut-off episode duration to discriminate between clinically relevant and nonrelevant episodes. This was attempted by Glotzer et al[48] in the Relationship Between Daily Atrial Tachy-Arrhythmia Burden from Implantable Device Diagnostics and Stroke Risk (TRENDS) trial: the median daily AF burden was 5.5 hours in 1 of the 30 days preceding a stroke or transient ischemic attack. When the daily burden was >5.5 hours, the patient had a 2.4 greater risk for stroke compared to patients with lower daily burdens. A similar data analysis performed in a cohort of patients with heart failure, showed that device-detected atrial arrhythmias were associated with an increased incidence of thromboembolic events.[49] A cut-off point of 3.8 hours over 24 hours was associated with a significant increase in the event rate. Finally, Boriani et al[50] showed that adding data of daily AF burden can improve risk stratification for stroke when the $CHADS_2$ score or CHA_2DS_2VASc score is used. For the $CHADS_2$ score, the data on AF burden improve the balance between sensitivity and specificity. For the CHA_2DS_2VASc score, the data on AF burden increase specificity. Table 3 lists the most relevant data on risk stratification for stroke through implantable devices.

Clinical Perspective

Continuous monitoring is a powerful tool to detect silent PAF in patients without previously documented arrhythmic episodes, such as those with cryptogenic stroke or other risk factors. Early diagnosis would trigger early treatment for primary or secondary stroke prevention.

In clinical practice, there are several categories of patients at risk for silent PAF The major risk factors are hypertension, age, elevated body mass index, diabetes mellitus, cigarette smoking, and previous cardiac disease.[1,2]

At very high risk are patients with chronic kidney disease who share several common risk factors among those for AF,

such as hypertension, diabetes, previous cardiac disease, obesity, and metabolic syndrome.

AF monitoring may be attractive also in patients with documented histories of PAF treated with rhythm-control strategies, when the objective is treating AF for preventing stroke, not only symptoms.

Patients with heart failure and PAF might benefit from optimal rhythm control to prevent recurrences and optimal rate control to prevent hemodynamic impairment during AF episodes.

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