JAFIB
Featured Review
Journal of Atrial Fibrillation

www. jafib.com

Monitoring Atrial Fibrillation After Catheter Ablation

Giovanni B Forleo, MD, PhD[1], Michela Casella, MD, PhD[2], Antonio Dello Russo, MD, PhD[2], Massimo Moltrasio, MD[2], Gaetano Fassini, MD[2], Manfredi Tesauro, MD, PhD[1], Claudio Tondo, MD, PhD[2]

[1]Policlinico Universitario Tor Vergata, Rome, Italy. [2]Cardiac Arrhythmia Research Center, Centro Cardiologico Monzino IRCCS, Milan, Italy.

Abstract

Although catheter ablation is an effective treatment for recurrent atrial fibrillation (AF), there is no consensus on the definition of success or follow-up strategies. Symptoms are the major motivation for undergoing catheter ablation in patients with AF, however it is well known that reliance on perception of AF by patients after AF ablation results in an underestimation of recurrence of the arrhythmia. Because symptoms of AF occurrence may be misleading, a reliable assessment of rhythm outcome is essential for the definition of success in both clinical care and research trials.

Continuous rhythm monitoring over long periods of time is superior to intermittent recording using external monitors to detect the presence of AF episodes and to quantify the AF burden. Today, new devices implanted subcutaneously using a minimally invasive technique have been developed for continuous AF monitoring. Implantable devices keep detailed information about arrhythmia recurrences and might allow identification of very brief episodes of AF, the significance of which is still uncertain. In particular, it is not known whether there is any critical value of daily AF burden that has a prognostic significance. This issue remains an area of active discussion, debate and investigation. Further investigation is required to determine if continuous AF monitoring with implantable devices is effective in reducing stroke risk and facilitating maintenance of sinus rhythm after AF ablation.

Introduction

Atrial fibrillation (AF) is one of the major common and chronic disorders seen in clinical practice[1] and it is associated with a reduced quality of life and an increased long-term risk of stroke, heart failure and all cause mortality.[2-3] A number of controlled, and randomized clinical trials have consistently shown that catheter ablation is superior to antiarrhythmic pharmacological treatment in maintaining sinus rhythm among patients with symptomatic drug-refractory AF.[4-10] Remarkably there is no consensus on the definition of success or follow-up strategies after AF ablation. Even brief asymptomatic episodes can substantially raise the risk of stroke, therefore a reliable evaluation of AF recurrences is crucial after AF ablation and may be useful in making clinical decisions.

Irrespective of symptoms, assessment of rhythm can be conducted with the use of intermittent (noninvasive) or continuous (implanted devices) monitoring systems. Increased duration of monitoring appears to be associated with increased rates of detection of AF and, on the basis of different monitoring techniques,[11-12] sensitivity in detecting AF recurrences after catheter ablation is reported to range between 31% and 71% and negative predictive value between 21% and 65%.[13]

Non-Continuous Af Monitoring Systems

In addition to baseline ECG and symptom evaluation, several methods have been described to improve rhythm monitoring in AF patients. Intermittent monitoring includes periodical ECGs, Holter and event recorders with or without loop memory. The diagnostic accuracy of these methods is limited and it is well known that there is a clear relationship between the duration of monitoring and the diagnostic yield.

Follow-up evaluation after AF ablation has been traditionally performed by routine ECG recordings and ambulatory 24-hour Holter monitoring.[14-16] Recently, new extended monitoring methods have been introduced, including trans-telephonic ECG transmissions, event recorders and external loop recorders. Systems without a loop memory allow intermittent rhythm monitoring and are useful to confirm recurrences in patients with symptoms suggestive

Key Words:
AtrialFibrillation, Catheter Ablation; Continuous Monitoring; Implantable Cardiac Monitor; Loop Recorders; Remote Monitoring; Silent Atrial Fibrillation.

Disclosures:
Claudio Tondo consults for St Jude Medical, he has served as an expert witness for Medtronic and received lecture fees from St Jude Medical.

Corresponding Author:
Claudio Tondo,
Cardiac Arrhythmia Research Centre,
Centro Cardiologico Monzino,
IRCCS, Via Parea, 4, 21038

of AF. External loop recorder systems are ideal for capturing also asymptomatic AF recurrences; the ECG recording is triggered either automatically, according to the arrhythmia detection algorithm, or manually by the patient; besides device data can be stored on a memory card or sent through a telephone/internet connection.

The main drawback of these systems is that they are tolerated only by highly motivated patients over a short period of time (usually few months). Thus, non-implantable recording systems play a limited role for a reliable and continuous monitoring of post-ablation recurrences. Furthermore, patients with infrequent AF recurrences are the most difficult to identify with intermittent monitoring and face a significant thromboembolic (TE) risk in the absence of appropriate oral anticoagulation (OAC) therapy.

Continuous AF Monitoring Systems

Continuous AF monitoring can only be achieved through the diagnostics of implantable device, which can store significant information regarding heart rhythm. The first experience with continuous AF monitoring is derived from the analysis of data stored in dual-chamber pacemakers and implantable cardioverter-defibrillators (ICD) capable of arrhythmia monitoring. If the atrial rate exceeds a programmable value for a given period of time, an atrial arrhythmia will be detected allowing the assessment of AF episodes irrespective of associated symptoms.

The use of cardiac pacemaker as an implanted arrhythmia monitor has been first evaluated in the MOST trial.[17] In a population of 312 pacemaker patients, this study evaluated the correlation between the presence of atrial high rate events (AHRE) and clinical outcomes. The presence of AHRE longer than 5 min was found to be an independent predictor of total mortality and non-fatal stroke. Similarly, other large prospective multi-centric studies[17-22] have examined the relationship between AF episodes detected by implanted devices and patient outcomes (Table 1).

Dual-chamber pacemakers and implantable cardioverter-defibrillators allow direct recording of atrial electrograms, but those devices are clearly not the ideal arrhythmia surveillance method, mainly because of the presence of intracardiac leads. To provide continuous information on cardiac rhythm, implantable leadless cardiac monitoring systems (ICM) with specific AF detection algorithms have been developed. Automatic triggers with physician-programmable parameters allow AF episodes detection as well as AF burden quantification and batteries can last up to 5 to 6 years affording the possibility of prolonged continuous monitoring. The ICM memory can store both automatically detected AF episodes and a number of patient-activated episodes, which can be easily transmitted via telephone or internet to remotely and continuously evaluate a patient for AF recurrences after AF ablation.

The XPECT study[13] evaluated for the first time the performance of an implantable leadless cardiac monitor (Reveal XT; Medtronic Inc.) with dedicated AF detection capabilities. The study showed that the overall accuracy of the ICM for detecting AF was 98.5% and the ICM-measured AF burden was very well correlated (Pearson coefficient r = 0.97) with the reference value derived from Holter. Very recently, the CRYSTAL-AF study[23] demonstrated that this system is more effective than standard non-invasive monitoring methods to find an AF episode in patients with cryptogenic stroke. This study included 441 patients randomized to Reveal-XT or standard cardiac monitoring within 90 days of a cryptogenic stroke. At 12 months, AF was detected in 12.4% of patients in the Reveal arm versus 2.0% of those in the control arm [HR 7.3 (95% CI 2.6-20.8, p<0.0001)].

Implantable leadless device monitoring systems might override the problems related to the patient compliance and several data on continuous monitoring after AF ablation have recently been published. Verma et al. in a large multicentric prospective study evaluated the incidence of asymptomatic AF episodes before and after CA, as assessed by an implantable cardiac monitor with AF detection.[24] In this study, ICM detected 12% of patients with purely asymptomatic AF and the ratio of asymptomatic to symptomatic AF episodes increase from 1.1 before to 3.7 after catheter ablation. Consistent with the results of this study, we have recently demonstrated in 145 patients with paroxysmal or persistent AF, that continuous ECG monitoring is a valuable tool for long-term follow-up after AF catheter ablation facilitating reliable assessment of symptomatic and asymptomatic AF episodes.[25] Furthermore, Bogachev-Prokophiev et al.[26] confirmed the reliability of subcutaneous continuous monitoring also in patients who had undergone surgical AF ablation.

Is Procedural Success Truly Achieved Without Continuous AF Monitoring?

The definition of "long-term ablation success" remains controversial. Guidelines state that the primary indication of AF ablation is to reduce AF-related symptoms and to improve quality of life. Secondary endpoints might include elimination of symptomatic AF and control of AF with previously ineffective antiarrhythmic drugs (AAD). The poor correlation between symptoms and AF[27] should caution physicians against making clinical decisions depending on symptoms. Asymptomatic AF has been reported to be up to 12 times more frequent than symptomatic AF, even in patients with histories of symptomatic AF.[28] Although ablation significantly reduces the burden of AF, the proportion of asymptomatic AF episodes increases, consequently the procedural success is overestimated by patient

Table 1: Critical value of daily AT/AF burden: relationship with clinical events

Study, year	patients	Detection Methods	Follow-up	Endpoint	AT/AF burden cutoff	Hazard ratio and
MOST 2003	312	PM	27 months	Total mortality	> 5 minutes	HR 2.48 P=0.0092
				Death/non fatal stroke	> 5 minutes	HR 2.79 P= 0.0011
Capucci et al. 2005	725	PM	22 months	Arterial embolism	> 24 hours	HR 3.1
						p= 0.044
					> 5 min	P=NS
TRENDS 2009	2486	PM/ICD	1.4 years	Annualized TE rates	< 5.5 hours	HR 0.98 P= 0.97
					> 5.5 hours	HR 2.20 P= 0.06
ASSERT 2012	2580	PM/ICDor NSAIDs) or alcohol excess/ abuse	2.5 years	Ischemic stroke/ systemic embolism	> 6 minutes	HR 5.56 P<0.001
				Clinical atrial fibrillation	> 6 minutes	HR 5.56 P<0.001
SOS AF 2013	10016	PM-ICD	24 months	Ischaemic stroke	> 5 minutes	HR 1.76 P = 0.041
					> 1 hour	HR 2.11 P =.0.008

Abbreviations: AT/AF= atrial tachycardia/fibrillation; HR= Hazard Ratio; ICD= internal cardioverter defibrillator; PM= pacemaker; TE= thromboembolic..

symptoms[11] Silent AF is likely to be associated with morbidity and mortality rates not inferior to symptomatic AF,[21,29-30] therefore, a reliable rhythm outcome analysis after AF ablation has the potential to reduce that risk. Post-procedure arrhythmia monitoring is also useful because in a significant number of patients, palpitations may be misinterpreted as AF episodes; in one study , 40% of pacemaker patients reported symptoms suggestive of AF that were not confirmed neither by standard ECG recording nor device interrogation.[31]

Emerging evidence suggests that sinus rhythm restoration following AF ablation can provide clinical and prognostic benefits.[32-38] Winkle et al[39] have recently demonstrated that patients with prior stroke, who under successful AF ablation, have a low incidence of subsequent thromboembolic events, and most of those patients may be able to discontinue OAC. The consistency of these findings suggests that restoration of sinus rhythm by catheter ablation might result in lower rates of stroke and death. Of note, the Heart Rhythm Society's consensus document on AF ablation recommends that success can be defined as freedom from AF or atrial tachycardia, lasting 30 seconds 12 months after AF ablation.[40] Intermittent and symptom-based monitoring is highly inaccurate for identifying patients with AF recurrences[41,42] leaving untreated a vulnerable population. Thus, implantable devices are the most reliable method to precisely identify AF recurrences after AF ablation both in clinical care and in the setting of a clinical research study.

Estimating AF Burden: The Importance Of Cutoff Length

The unexpectedly high incidence of ICM-detected non-sustained atrial arrhythmias raises the question of whether there is any clinical significance to these, often asymptomatic, AF episodes. Quantitative AT/AF burden detected by implanted devices may be a thromboembolic (TE) risk element independent of standard stroke risk factors and absence of symptoms can even increase the thromboembolic risk if objective information on AF status is lacking.

Current guidelines do not specifically address any anticoagulation use in case of non-sustained device-detected AF episodes. Generally, it has been demonstrated that patients with AHREs, compared to those without AHREs, are more likely to have adverse clinical outcomes, including a higher incidence of stroke, death and subsequent AF. The adverse effects of paroxysmal AF have been correlated to the duration of the episodes and to the AF burden (Table 1). However, the amount of AF burden that conveys a substantial risk of stroke has been the object of debate. In particular, it is not clear whether very brief AF episodes are associated with a significant risk of stroke and deserve OAC therapy.

The ASSERT trial[21] suggests that subclinical atrial high-rate episodes (>190 bpm lasting more than 6 minutes) conferred a relative risk of 2.49 (p=0.007) for subsequent ischemic stroke or systemic embolism. These data strongly suggest that, if available, AHRE data should be collected and used to risk-stratify pacemaker patients. Other studies showed that even shorter AF episodes lasting < 30 seconds might be associated with the presence of stroke or TIA.[17,43,44] The relationship between the AF burden and stroke risk is uncertain and still an area of active investigation. Capucci et al, in a population of 788 pacemaker patients suffering from AF, demonstrated that only device-detected AF episodes lasting > 24 hours were independently associated with embolic events while shorter episodes (> 5min) did not increased the TE risk.[18] Furthermore, in a subanalysis of the TRENDS study[45] the majority of thromboembolic events did not occur proximal to recent device-detected AT/AF episodes, suggesting that TE events may also involve mechanisms other than cardioembolism due to atrial tachyarrhythmias. However, in this patient population short AF recurrences were very common, occurring in about 80% of patients; this might explain why device-detected AF episodes < 5 min were not associated with a higher embolic risk.

In a pooled analysis from three studies (TRENDS, PANORAMA and the Italian Clinical Service Registry), Boriani et al. assessed the association between the maximum daily AF burden and the risk of ischaemic stroke. This analysis on >10,000 patients without permanent AF[22] demonstrated that device-detected AF burden is an independent predictor of ischaemic stroke. Among the thresholds of AF burden evaluated, 1 h was associated with the highest hazard ratio (HR 2.11; P = 0.008) for ischaemic stroke. The threshold of ≥5 min was also statistically and significantly associated with the occurrence of ischaemic stroke, HR 1.76 (95% CI: 1.02–3.02, P . 0.041).

Taken together these data from large cohorts of implanted patients add to the current evidence that measuring daily AF burden may have an important clinical relevance. New technologies of continuous rhythm monitoring might allow identification of very brief episodes of AF but is not known whether there is a critical value of daily AF burden that has a prognostic significance. The main issue is that AF is responsible for an increased risk of stroke and death, and elimination of AF normalises that risk; therefore great attention should be paid to device-detected AF episodes and treatment should be delivered accordingly. A comprehensive evaluation should combine AF burden and TE risk.[18-20] Botto et al[20] demonstrated that risk stratification for thromboembolic events in device-detected AF patients can be improved by combining $CHADS_2$ score with AF presence and duration.

Continuous AF Monitoring: Impacting Patient Outcomes

Atrial fibrillation ablation has the potential to restore sinus rhythm, eliminating the need for AADs and potentially for long-term anticoagulation.[27,46] Because AF symptoms may be misleading, appropriate rhythm monitoring surveillance after AF ablation may help to guide clinical decision making in certain subsets of patients. The present evidence suggests that a highly accurate follow-up, as provided by implantable devices, may add significant information to current clinical risk stratification schemes.[42,47] The device-stored data can also be evaluated with remote monitoring systems, which can allow a prompt clinical reaction and may reduce hospitalizations and costs.

Optimal post-procedural anticoagulation strategy is essential for minimising bleeding and thromboembolic risk after AF ablation. Hemorrhagic risk can be lowered by reducing unnecessary and prolonged OAC administration while the patient is in sinus rhythm. In patients with CHADS score ≤2, OAC are frequently discontinued after AF ablation if no recurrences have been documented during follow-up. In a large reported experience on 831 patients after AF ablation , warfarin was stopped within 12 months in 76.5% of patients with no arrhythmia recurrence.[14] This approach is commonly performed despite the fact that patients are frequently followed-up with the use of limited temporal ECG monitoring duration. However, caution should be considered before OAC withdrawal because unrecognized recurrences might lead to devastating consequences, including death and thromboembolic stroke. If OAC are discontinued after AF ablation, the risk of asymptomatic AF recurrences cannot be ruled out without a continuous AF monitoring

system.

The routine use of cardiac monitoring to identify AF patients who will benefit from anticoagulation has been reported to be cost-effective.[48] Continuous AF monitoring with implanted devices increases sensitivity of AF detection when compared to conventional diagnostic methods[20] and data transmission allows a remote and continuous evaluation for AF recurrences. Recently, the ANGELS of AF project demonstrated the possibility to improve OAC use as thrombo-prophylaxis through the use of information from ICD AF-diagnostics as compared with standard care.[49]

Early diagnosis triggers earlier treatment and in this regard novel OAC (dabigratan, rivaroxaban and apixaban), which might be early self-administered without dose titration, allows for rapid onset anticoagulation with a single oral dose early after an AF episode. Current evidence suggests that a prothrombotic state is evident within minutes after the onset of an AF episode.[50-51] Since left atrial thrombi can develop early during AF episodes, an early AF detection afforded by ICM might increase the safety of discontinuing OAC after AF ablation. The ongoing IMPACT trial[52] has been designed to test the hypothesis that initiation or withdrawal of oral anticoagulant therapy guided by continuous ambulatory monitoring of the atrial intracardiac electrograms improves clinical outcomes. This study has the potential to provide some answers to this important question but it has been stopped early and remains unpublished.

Beyond implementation of appropriate anticoagulation, an early intervention following device-detected AF episodes has other potential benefits in improving the management of patients after AF ablation. It is likely that the benefits of sinus rhythm are in part counterbalanced by the potential adverse effects of long-term AAD use.[53] The detailed rhythm information obtained through continuous monitoring might allow an earlier AAD discontinuation reducing the potential side effects of medications.

Brief and predominantly asymptomatic AF episodes may remain undetected until the next scheduled evaluation delaying the appropriate management of AF recurrences. Early diagnosis, through continuous AF monitoring, triggers earlier treatment and might also facilitate the self-administration of a single oral dose of Ic drug (pill-in-the-pocket)[54] shortly after the onset of the AF recurrence. The prolonged duration of AF negatively effects electrical and structural atrial remodelling, therefore early restoration of sinus rhythm might have potential benefits over the long-term follow-up.

Optimal Time And Duration Of AF Monitoring

Limited data are available on the optimal time and duration of monitoring after AF ablation. Continuous AF monitoring might be useful both in the short-term and over the long-term follow-up after AF ablation. Early recurrences of AF are quite common in the so-called blanking period and are often asymptomatic.[55] However, appropriate surveillance during the early post-ablation period may identify patients who are at a higher risk of long term treatment failure since early recurrences strongly predict a lack of long-term success.[56-57]

Pokushalov et al. demonstrated in 286 patients continuously monitored through an implantable device after AF ablation, that this strategy might be useful for deciding whether to perform a second ablation or to implement drug therapy.[20] In this study patients were treated according to the onset mechanism of AF recurrences, as detected and stored by the implantable cardiac monitor. They observed that patients with recurrences after the first AF ablation are likely to respond to a second early ablation when AF is triggered by supraventricular arrhythmias or premature contractions.

Several clinical studies assessing the long-term efficacy of catheter ablation procedures have reported late AF recurrences in patients who were initially considered responders to catheter ablation.[58] Therefore, longer-term monitoring might identify AF episodes in patients in whom the OAC had been previously suspended. Because of the recognition of the late AF recurrences, the HRS/EHRA/ECAS consensus document on AF ablation concluded that a decision regarding OAC discontinuation should be based on the CHADS stroke risk score rather than the apparent efficacy of the AF ablation procedure.

False Positive Device-Detected Events

Long-term AF monitoring by implanted devices may be of substantial clinical value. However, its practical application may, in part, be limited by the prevalence of false-positive events. The risk of false-positives detections mainly generated by myopotential and motion artefacts still exists,[13,48] highlighting the importance of human revaluation of automatically detected episode. False-positive events might lead to unscheduled evaluations in patients with remote follow-up that significantly increase the physician work burden.[59,60] Unscheduled patient evaluation after ICM implantation has also a major impact on quality of life and cost-effectiveness in ICM recipients. Longer cutoff might result in a reduced number of false-positive events. An analysis from the ASSERT trial by using a cutoff of >6 minutes and >190 beats/min showed a 17.3% rate of false-positive AHREs, making physician review of electrograms essential.[61] For AHREs lasting >6 hours, the rate of false positives is 3.3%, making physician review less crucial.

New sensing and detection algorithms for ICM have been developed in order to substantially reduce the occurrence of inappropriately detected AT/AF episodes.[62] A higher specificity of the algorithm is necessary and would avoid unnecessary clinical evaluations once the alert system is activated. Future research will focus on optimal device programming that will offer maximal benefit, increasing the clinical utility of ICM algorithms.

Conclusions:

Because AF symptoms may be misleading, appropriate rhythm monitoring surveillance after AF ablation may help to guide clinical decision making in certain subsets of patients. The present evidence suggests that a highly accurate follow-up, as provided by implantable devices, may add significant information to current clinical risk stratification schemes.

Implantable devices keep detailed information about arrhythmia recurrences and might allow identification of very brief episodes of AF, the significance of which is still uncertain. In particular, it is not known whether there is a critical value of daily AF burden that has any prognostic significance. This issue remains an area of active discussion, debate and investigation. Further investigation is required to determine if continuous AF monitoring with implantable devices is effective in reducing stroke risk and facilitating maintenance of sinus rhythm after AF ablation.

References:

1. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. N Engl J Med 1982; 306: 1018-1022.

2. Vidaillet H, Granada JF, Chyou Po, Maassen K, Ortiz M, Pulido JN, Sharma P, Smith PN, Hayes J. A population-based study of mortality among patients with atrial fibrillation or flutter. Am J Med. 2002;113(5):365-70.
3. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation. 1998 Sep 8;98(10):946-52.
4. Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, Bash D, Schweikert R, Brachmann J, Gunther J, Gutleben K, Pisano E, Potenza D, Fanelli R, Raviele A, Themistoclakis S, Rossillo A, Bonso A, Natale A. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. JAMA 2005; 293: 2634-2640
5. Stabile G, Bertaglia E, Senatore G, De Simone A, Zoppo F, Donnici G, Turco P, Pascotto P, Fazzari M, Vitale DF. Catheter ablation treatment in patients with drug-refractory atrial fibrillation: a prospective, multi-centre, randomized, controlled study (Catheter Ablation For The Cure Of Atrial Fibrillation Study). Eur Heart J 2006; 27: 216-221
6. Pappone C, Augello G, Sala S, Gugliotta F, Vicedomini G, Gulletta S, Paglino G, Mazzone P, Sora N, Greiss I, Santagostino A, LiVolsi L, Pappone N, Radinovic A, Manguso F, Santinelli V. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study. J Am Coll Cardiol 2006; 48: 2340-2347
7. aïs P, Cauchemez B, Macle L, Daoud E, Khairy P, Subbiah R, Hocini M, Extramiana F, Sacher F, Bordachar P, Klein G, Weerasooriya R, Clémenty J, Haïssaguerre M. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. Circulation 2008; 118: 2498-2505
8. Forleo GB, Mantica M, De Luca L, Leo R, Santini L, Panigada S, De Sanctis V, Pappalardo A, Laurenzi F, Avella A, Casella M, Dello Russo A, Romeo F, Pelargonio G, Tondo C. Catheter ablation of atrial fibrillation in patients with diabetes mellitus type 2: results from a randomized study comparing pulmonary vein isolation versus antiarrhythmic drug therapy. J Cardiovasc Electrophysiol 2009; 20: 22-28
9. Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, Macle L, Daoud EG, Calkins H, Hall B, Reddy V, Augello G, Reynolds MR, Vinekar C, Liu CY, Berry SM, Berry DA; ThermoCool AF Trial Investigators. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. JAMA. 2010;303(4):333-40.
10. Mohanty S, Mohanty P, Di Biase L, Bai R, Santangeli P, Casella M, Dello Russo A, Tondo C, Themistoclakis S, Raviele A, Rossillo A, Corrado A, Pelargonio G, Forleo G, Natale A. Results from a single-blind, randomized study comparing the impact of different ablation approaches on long-term procedure outcome in coexistent atrial fibrillation and flutter (APPROVAL). Circulation. 2013 May 7;127(18):1853-60.
11. Hindricks G, Piorkowski C, Tanner H, Kobza R, Gerds-Li JH, Carbu- cicchio C, Kottkamp H: Perception of atrial fibrillation before and after radiofrequency catheter ablation: Relevance of asymptomatic arrhythmia recurrence. Circulation 2005;112:307-313.
12. Senatore G, Stabile G, Bertaglia E, Donnici G, De Sa, Zoppo F, Turco P, Pascotto P, Fazzari M: Role of transtelephonic electrocardiographic monitoring in detecting short-term arrhythmia recurrences after radiofrequency ablation in patients with atrial fibrillation. J Am Coll Cardiol 2005;45:873-876.
13. Hindricks G, Pokulashov E, Urban L, Taborsky M, Kuch KH, Lebedev D, Rieger G, Purerfellner H; on behalf of the XPECT Trial Investigators: Performance of a new implantable cardiac monitor in detecting and quantifying atrial fibrillation. Results of the XPECT Trial. Circ Arrhythm Electrophysiol 2010;3:141-147.
14. Hussein, A. A., Saliba, W. I., Martin, D. O., Bhargava, M., Sherman, M., Magnelli-Reyes, C., et al. Natural history and long-term outcomes of ablated atrial fibrillation. Circulation. Arrhythmia and Electrophysiology, 2011; 4, 271–278.
15. Forleo GB, De Martino G, Mantica M, Menardi E, Trevisi N, Faustino M, Muto C, Perna F, Santamaria M, Pandozi C, Pappalardo A, Mancusi C, Romano E, Della Bella P, Tondo C. Catheter ablation of atrial fibrillation guided by a 3D electroanatomical mapping system: a 2-year follow-up study from the Italian Registry On NavX Atrial Fibrillation ablation procedures (IRON-AF). J Interv Card Electrophysiol. 2013 Jun;37(1):87-95.
16. Arbelo E, Brugada J, Hindricks G, Maggioni AP, Tavazzi L, Vardas P, Laroche C, Anselme F, Inama G, Jais P, Kalarus Z, Kautzner J, Lewalter T, Mairesse GH, Perez-Villacastin J, Riahi S, Taborsky M, Theodorakis G, Trines SA; on the behalf of the Atrial Fibrillation Ablation Pilot Study Investigators. The Atrial Fibrillation Ablation Pilot Study: an European Survey on Methodology and Results of Catheter Ablation for Atrial Fibrillation: conducted by the European Heart Rhythm Association. Eur Heart J. 2014 Jan 31.
17. Glotzer, T. V., Hellkamp, A. S., Zimmerman, J., Sweeney, M. O., Yee, R., Marinchak, R., et al. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke. Circulation, 2003; 107, 1614–1619.
18. Capucci, A., Santini, M., Padeletti, L., Gulizia, M., Botto, G., Boriani, G., et al.. Monitored atrial fibrillation duration predicts arterial embolic events in patients suffering from bradycardia and atrial fibrillation implanted with antitachycardia pacemakers. Journal of the Am College of Cardiologiy, 2005; 46, 1913–1920.
19. Glotzer, T. V., Daoud, E. G., Wyse, D. G., Singer, D. E., Ezekowitz, M. D., Hilker, C., et al. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk. The TRENDS Study. Circulation: Arrhythmias and Electrophysiology. 2209; 2, 474–480.
20. Botto, G. L., Padeletti, L., Santini, M., Capucci, A., Gulizia, M., Zolezzi, F., et al. Presence and duration of atrial fibrillation detected by continuous monitoring: crucial implications for the risk of thromboembolic events. Journal of Cardiovascular Electrophysiology, 2009; 20, 241–248.
21. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH; ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med. 2012;366(2):120-129.
22. Boriani G, Glotzer TV, Santini M, West TM, De Melis M, Sepsi M, Gasparini M, Lewalter T, Camm JA, Singer DE. Device-detected atrial fibrillation and risk for stroke: an analysis of >10 000 patients from the SOS AF project (Stroke preventiOn Strategies based on Atrial Fibrillation information from implanted-devices). Eur Heart J. 2013 Dec 11. [Epub ahead of print] PubMed PMID: 24334432.
23. Bernstein RA, Di Lazzaro V, Rymer MM, Diener HC, Sanna T, Brachmann J, Passman RS, Morillo C, Thijs VN, Rogers TB, Beckers F, Lindborg K. Cryptogenic Stroke and Underlying Atrial Fibrillation (CRYSTAL AF). Late-Breaking Science Oral Abstracts presented at the INTERNATIONAL STROKE CONFERENCE 2014. Presentation Number: LB11. http://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm_460266.pdf.
24. Verma A, Champagne J, Sapp J, Essebag V, Novak P, Skanes A, Morillo CA, Khaykin Y, Birnie D. Discerning the incidence of symptomatic and asymptomatic episodes of atrial fibrillation before and after catheter ablation (DISCERN AF): a prospective, multicenter study. JAMA Intern Med. 2013 Jan 28;173:149-56.
25. Tondo C, Tritto M, Landolina M, DE Girolamo PG, Bencardino G, Moltrasio M, Russo AD, Bella PD, Bertaglia E, Proclemer A, DE Sanctis V, Mantica M. Rhythm-symptom Correlation in Patients on Continuous Monitoring after Catheter Ablation of Atrial Fibrillation. J Cardiovasc Electrophysiol. 2013 Sep 19. doi:10.1111/jce.12292. [Epub ahead of print]
26. Bogachev-Prokophiev A, Zheleznev S, Romanov A, Pokushalov E, Pivkin A, Corbucci G, Karaskov A. Ablation for atrial fibrillation during mitral valve surgery: 1-year results through continuous subcutaneous monitoring. Interact Cardiovasc Thorac Surg. 2012 Jul;15(1):37-41.

27. Forleo G, DI Biase L, Della Rocca D, Fassini G, Santini L, Natale A, Tondo C. Exploring the Potential Role of Catheter Ablation in Patients with Asymptomatic Atrial Fibrillation Should We Move away from Symptom Relief? Journal of Atrial Fibrillation. 2013; 6: 54-62
28. Page RL, Wilkinson WE, Clair WK, McCarthy EA, Pritchett EL. Asymptomatic arrhythmias in patients with symptomatic paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia. Circulation 1994;89:224 –227.
29. Flaker GC, Belew K, Beckman K, Vidaillet H, Kron J, Safford R, Mickel M, Barrell P; AFFIRM Investigators. 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(4):657-663.
30. 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 Aug 1. doi:pii: S0167-5273(13)01459-9.
31. srael CW, Grönefeld G, Ehrlich JR, Li YG, Hohnloser SH. Longterm risk of recurrent atrial fibrillation as documented by an implantable monitoring device: implications for optimal patient care. J Am Coll Cardiol 2004; 43(1): 47-52.
32. Pappone C, Rosanio S, Augello G, Gallus G, Vicedomini G, Mazzone P, Gulletta S, Gugliotta F, Pappone A, Santinelli V, Tortoriello V, Sala S, Zangrillo A, Crescenzi G, Benussi S, Alfieri O. Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation: outcomes from a controlled nonrandomized long-term study. J Am Coll Cardiol 2003;42:185e97.
33. Corley SD, Epstein AE, DiMarco JP, Domanski MJ, Geller N, Greene HL, Josephson RA, Kellen JC, Klein RC, Krahn AD, Mickel M, Mitchell LB, Nelson JD, Rosenberg Y, Schron E, Shemanski L, Waldo AL, Wyse DG, AFFIRM Investigators: Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. Circulation 2004, 109:1509–1513.
34. Bunch TJ, Asirvatham SJ, Friedman PA, Monahan KH, Bluhm CM, Hodge DO, Meverden RA, Munger TM, Shen VK, Packer DL. Mortality benefit and quality of life outcomes in patients undergoing curative ablation for atrial fibrillation: comparison with a disease-matched community population. Circulation. 2007;114:II_602
35. Sonne K, Patel D, Mohanty P, Armaganijan L, Riedlbauchova L, El-Ali M, Di Biase L, Venkatraman P, Shaheen M, Kozeluhova M, Schweikert R, Burkhardt JD, Canby R, Wazni O, Saliba W, Natale A. . Pulmonary vein antrum isolation, atrioventricular junction ablation, and antiarrhythmic drugs combined with direct current cardioversion: survival rates at 7 years follow-up. J Interv Card Electrophysiol 2009;26:121e6.
36. Bunch TJ, Crandall BG, Weiss JP, May HT, Bair TL, Osborn JS, Anderson JL, Muhlestein JB, Horne BD, Lappe DL, Day JD. Patients treated with catheter ablation for atrial fibrillation have long-term rates of death, stroke, and dementia similar to patients without atrial fibrillation. J Cardiovasc Electrophysiol 2011;22:839e45.
37. Hunter RJ, McCready J, Diab I, Page SP, Finlay M, Richmond L, French A, Earley MJ, Sporton S, Jones M, Joseph JP, Bashir Y, Betts TR, Thomas G, Staniforth A, Lee G, Kistler P, Rajappan K, Chow A, Schilling RJ. Maintenance of sinus rhythm with an ablation strategy in patients with atrial fibrillation is associated with a lower risk of stroke and death. Heart. 2012 Jan;98(1):48-53.
38. Lin YJ, Chao TF, Tsao HM, Chang SL, Lo LW, Chiang CE, Hu YF, Hsu PF, Chuang SY, Li CH, Chung FP, Chen YY, Wu TJ, Hsieh MH, Chen SA. Successful catheter ablation reduces the risk of cardiovascular events in atrial fibrillation patients with CHA2DS2-VASc risk score of 1 and higher. Europace. 2013 May;15(5):676-84.
39. Winkle RA, Mead RH, Engel G, Kong MH, Patrawala RA. Discontinuing anticoagulation following successful atrial fibrillation ablation in patients with prior strokes. J Interv Card Electrophysiol. 2013;38(3):147-53.
40. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, Crijns HJ, Damiano RJ Jr, Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim YH, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin JN, Shemin RJ, Tsao HM, Wilber D; Heart Rhythm Society Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. 2012 HRS/EHRA/ECAS expert consensus statement 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. Heart Rhythm. 2012;9(4):632-696.e21.
41. Ziegler PD, Koehler JL, Mehra R. Comparison of continuous versus intermittent monitoring of atrial arrhythmias. Heart Rhythm. 2006;3: 1445–1452.
42. Charitos EI, Stierle U, Ziegler PD, Baldewig M, Robinson DR, Sievers HH, Hanke T: A comprehensive evaluation of rhythm monitoring strategies for the detection of atrial fibrillation recurrence: Insights from 647 continuously monitored patients and implications for moni- toring after therapeutic interventions. Circulation 2012;126:806-814.
43. Tayal AH, Tian M, Kelly KM, Jones SC, Wright DG, Singh D, Jarouse J, Brillman J, Murali S, Gupta R. Atrial fibrillation detected by mobile cardiac outpatient telemetry in cryptogenic TIA or stroke. Neurology. 2008;71:1696 –1701.
44. Alhadramy O, Jeerakathil TJ, Majumdar SR, Najjar E, Choy J, Saqqur M. Prevalence and predictors of paroxysmal atrial fibrillation on Holter monitor in patients with stroke or transient ischemic attack. Stroke. 2010;41:2596 –2600
45. Daoud EG, Glotzer TV, Wyse DG, Ezekowitz MD, Hilker C, Koehler J, Ziegler PD; TRENDS Investigators. Temporal relationship of atrial tachyarrhythmias, cerebrovascular events, and systemic emboli based on stored device data: a subgroup analysis of TRENDS. Heart Rhythm. 2011;8(9):1416-23.
46. Forleo GB, De Martino G, Mantica M, Carreras G, Parisi Q, Zingarini G, Panigada S, Romano E, Dello Russo A, Di Biase L, Natale A, Tondo C. Clinical impact of catheter ablation in patients with asymptomatic atrial fibrillation: the IRON-AF (Italian registry on NavX atrial fibrillation ablation procedures) study. Int J Cardiol. 2013 Oct 9;168(4):3968-70.
47. Kapa S, Epstein AE, Callans DJ, Garcia FC, Lin D, Bala R, Riley MP, Hutchinson MD, Gerstenfeld EP, Tzou W, Marchlinski FE, Frankel DS, Cooper JM, Supple G, Deo R, Verdino RJ, Patel VV, Dixit S. Assessing arrhythmia burden after catheter ablation of atrial fibrillation using an implantable loop recorder: the ABACUS study. J Cardiovasc Electrophysiol. 2013;24(8):875-81.
48. Kamel H, Hegde M, Johnson DR, Gage BF, Johnston SC. Cost-effectiveness of outpatient cardiac monitoring to detect atrial fibrillation after ischemic stroke. Stroke. 2010;41:1514 –1520.
49. Boriani G, Santini M, Lunati M, Gasparini M, Proclemer A, Landolina M, Padeletti L, Botto GL, Capucci A, Bianchi S, Biffi M, Ricci RP, Vimercati M, Grammatico A, Lip GY; Italian ClinicalService Project. Improving thromboprophylaxis using atrial fibrillation diagnostic capabilities in implantable cardioverter-defibrillators: the multicentre Italian ANGELS of AF Project. Circ Cardiovasc Qual Outcomes. 2012 Mar 1;5(2):182-8.
50. Lim HS, Willoughby SR, Schultz C, Gan C, Alasady M, Lau DH, Leong DP, Brooks AG, Young GD, Kistler PM, Kalman JM, Worthley MI, Sanders P. Effect of atrial fibrillation on atrial thrombogenesis in humans: impact of rate and rhythm. J Am Coll Cardiol. 2013 Feb 26;61(8):852-60.
51. Akar JG, Jeske W, Wilber DJ. Acute onset human atrial fibrillation is associated with local cardiac platelet activation and endothelial dysfunction. J Am Coll Cardiol. 2008 May 6;51(18):1790-3.
52. Ip J, Waldo AL, Lip GY, Rothwell PM, Martin DT, Bersohn MM, Choucair WK, Akar JG, Wathen MS, Rohani P, Halperin JL; IMPACT Investigators. Multicenter randomized study of anticoagulation guided by remote rhythm

monitoring in patients with implantable cardioverter-defibrillator and CRT-D devices: Rationale, design, and clinical characteristics of the initially enrolled cohort The IMPACT study. Am Heart J. 2009 Sep;158(3):364-370.

53. Forleo GB, Tondo C. Atrial fibrillation: cure or treat? Ther Adv Cardiovasc Dis. 2009 Jun;3(3):187-96.
54. Alboni P, Botto GL, Baldi N, et al. Outpatient treatment of recent-onset atrial fibrillation with the "pill-in-the-pocket" approach. N Engl J Med. 2004;351:2384 –91.
55. Joshi S, Choi AD, Kamath GS, Raiszadeh F, Marrero D, Badheka A, Mittal S, Steinberg JS. Prevalence, predictors, and prognosis of atrial fibrillation early after pulmonary vein isolation: findings from 3 months of continuous automatic ECG loop recordings. J Cardiovasc Electrophysiol. 2009 Oct;20(10):1089-94.
56. Andrade JG, Macle L, Khairy P, Khaykin Y, Mantovan R, De Martino G, Chen J, Morillo CA, Novak P, Guerra PG, Nair G, Torrecilla EG, Verma A. Incidence and significance of early recurrences associated with different ablation strategies for AF: a STAR-AF substudy. J Cardiovasc Electrophysiol. 2012;23:1295-301.
57. Lellouche N, Jaïs P, Nault I, Wright M, Bevilacqua M, Knecht S, Matsuo S, Lim KT, Sacher F, Deplagne A, Bordachar P, Hocini M, Haïssaguerre M. Early recurrences after atrial fibrillation ablation: prognostic value and effect of early reablation. J Cardiovasc Electrophysiol. 2008;19: 599–605
58. Bertaglia E, Tondo C, De Simone A, Zoppo F, Mantica M, Turco P, Iuliano A, Forleo G, La Rocca V, Stabile G. Does catheter ablation cure atrial fibrillation? Single-procedure outcome of drug-refractory atrial fibrillation ablation: a 6-year multicentre experience. Europace. 2010;12(2):181-7.
59. Forleo GB, Tesauro M, Panattoni G, Della Rocca DG, Papavasileiou LP, Sergi D, Di Molfetta A, Santini L, Romeo F. Impact of continuous intracardiac ST-segment monitoring on mid-term outcomes of ICD-implanted patients with coronary artery disease. Early results of a prospective comparison with conventional ICD outcomes. Heart. 2012 Mar;98(5):402-7.
60. Papavasileiou LP, Forleo GB, Panattoni G, Schirripa V, Minni V, Magliano G, Bellos K, Santini L, Romeo F. Work burden with remote monitoring of implantable cardioverter defibrillator: is it time for reimbursement policies? J Cardiovasc Med (Hagerstown). 2013 Feb;14(2):114-9.
61. Kaufman ES, Israel CW, Nair GM, Armaganijan L, Divakaramenon S, Mairesse GH, Brandes A, Crystal E, Costantini O, Sandhu RK, Parkash R, Connolly SJ, Hohnloser SH, Healey JS; 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.
62. Brignole M, Bellardine Black CL, Thomsen PE, Sutton R, Moya A, Stadler RW, Cao J, Messier M, Huikuri HV. Improved Arrhythmia Detection in Implantable Loop Recorders. J Cardiovasc Electrophysiol. 2008;19(9):928-34.