



Extended ECG monitoring with an implantable loop recorder in patients with cryptogenic stroke: time schedule, reasons for explantation and incidental findings (results from the TRACK-AF trial)

Markus Bettin¹ · Dirk Dechering¹ · Simon Kochhäuser¹ · Niklas Bode¹ · Lars Eckardt¹ · Gerrit Frommeyer¹  · Florian Reinke¹

Received: 18 May 2018 / Accepted: 20 August 2018 / Published online: 22 August 2018
© Springer-Verlag GmbH Germany, part of Springer Nature 2018

Abstract

Background Implantable loop recorders (ILR) may be used to detect occult atrial fibrillation (AF) in patients with cryptogenic stroke. At present, there has been no description on the incidental findings of stored episodes in these patients. Furthermore, no standard practice has been established with respect to the duration of continued ECG monitoring in these patients.

Materials and methods In the prospective monocentric study (TRACK-AF), a total of 173 patients with cryptogenic stroke received an ILR for detection of AF between November 2010 and December 2014. Before implantation all patients had undergone recommended protocols for detection of stroke causes.

Results During a mean follow-up of 24.8 ± 11.5 months, atrial tachyarrhythmias were detected in $n = 33$ pts (19.1%). Diagnosis of AF was made after a mean of 10.7 ± 11.4 months, time to first AF detection ranged between 0.2 and 39.8 months. In 15 patients (8.7%), other incidental findings were stored in the ILR memory. Short episodes of sinus arrest at night not requiring a permanent pacemaker were present in 8 pts (4.6%). DDD-pacemaker implantation due to sinus arrest or symptomatic bradyarrhythmias occurred in 5 patients (2.9%) after a median monitoring period of 23.1 ± 7.4 months. Further incidental findings were atrial flutter and an AV-nodal-reentry tachycardia in one patient, respectively. Both patients underwent successful catheter ablation. So far, ILR were explanted in 111 pts, and 71 ILR were explanted before end of service status of the battery. Main reason for ILR explantation was patients' preference (51%), followed by battery depletion (24%) and diagnosis of AF (15%).

Conclusion The present study revealed a significant number of ECG findings during continued ECG monitoring for AF in patients with cryptogenic stroke. Apart from AF (17.5% during the first 1.5 years), other clinical relevant arrhythmias requiring, e.g., pacemaker implantations, were observed. With respect to these findings, we recommend to extend ILR monitoring to the end of battery life. However, acceptance of continued ECG monitoring until battery depletion was poor; in 71 patients (64%), the ILR were explanted before the end of battery life.

Trial registration Registered at ClinicalTrials.gov: NCT02641678.

Keywords Implantable loop recorder · Atrial fibrillation · Stroke

Abbreviations

| | |
|-----|---------------------------|
| AF | Atrial fibrillation |
| ILR | Implantable loop recorder |
| NPV | Negative predictive value |
| PPV | Positive predictive value |

Gerrit Frommeyer and Florian Reinke contributed equally to this work.

✉ Gerrit Frommeyer
gerrit.frommeyer@ukmuenster.de

¹ Department of Cardiology II-Electrophysiology, University Hospital of Muenster, Albert-Schweitzer-Campus 1, Building A1, 48149 Muenster, Germany

Introduction

Implantable loop recorders have become a valuable option to detect silent atrial fibrillation in patients with cryptogenic stroke. Detection rates vary between 4.2 and 33.7% [1, 2]. According to the TOAST criteria [3], strokes are defined as cryptogenic when the etiology remains undeterminable. Atrial fibrillation has a significant impact on the risk of stroke [4] and has been suggested as a major cause of many cryptogenic strokes. However, due to its often paroxysmal and asymptomatic character, atrial fibrillation is difficult to detect.

Increased monitoring times improve the detection rate of atrial fibrillation in patients with cryptogenic stroke [5]. However, as of yet, it has not been determined which time interval of monitoring after an ischemic event seems reasonable. No data exist describing the reasons for ILR explantation in a collective with cryptogenic stroke. Furthermore, there has been no description on the incidental findings of stored episodes in these patients besides the diagnosis of atrial fibrillation. We, therefore, retrospectively analyzed all patients of our prospective, monocentric head-to-head TRACK-AF study (Thorough Evaluation by online Rhythm evaluation, extended Holter Monitoring And implantable Cardiac monitor of Patients with Cryptogenic stroke to detect Atrial Fibrillation) [6], and our pilot study for detecting atrial fibrillation after cryptogenic stroke [7].

Materials and methods

Between November 2010 and December 2014, a total of 2263 patients were admitted to our stroke unit with diagnosis of transient ischemic attack or ischemic stroke. Complete diagnostic workup has been described elsewhere [6, 7] and is summarized briefly. Patients underwent complete evaluation to exclude other causes of stroke. All patients received cerebral imaging (MRI or CT), a 12-lead ECG recording upon admission, a 24-h-Holter ECG, a duplex and Doppler ultrasound of the carotid and vertebral arteries and a transesophageal echocardiography. All patients included in this study had imaging proven ischemic stroke. Patients with lacunar infarcts, incomplete workup, or competing sources of embolism were excluded. If there was no determining pathology, the stroke was classified as cryptogenic according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [3].

In total, 173 out of 622 patients with stroke of undetermined etiology (cryptogenic stroke, TOAST 5b) provided informed consent to participate in this study. All

included patients received a subcutaneously implanted loop recorder (Reveal XT; Medtronic, Minneapolis, MN, USA) [8]. Scheduled monitoring time for all patients was 12 months (minimum prospective monitoring time), but patients were offered to continue ILR monitoring until battery depletion if desired. Patients were instructed to report daily ECGs of 7.5-min duration via telephone-based CareLink® (Medtronic) interface. Transmissions of these patient-activated episodes as well all automatically saved episodes were analyzed independently by three experienced cardiologists for the presence of paroxysmal AF. All patients were seen in our hospital every 3 months for clinical events. The primary endpoint was the detection of atrial fibrillation with a duration > 30 s according to the guidelines of the European Society of Cardiology for the management of atrial fibrillation [9]. After diagnosis of atrial fibrillation, all patients received an effective oral anticoagulation. Patients with patent foramen ovale were also excluded and transferred for feasibility of percutaneous closure of PFO [10]. Furthermore, we analyzed age and the CHA₂DS₂-VASc Score as known predictors of atrial fibrillation as well for prediction of additional findings [11, 12]. Both studies were approved by the local ethics committee and the TRACK-AF trial was registered at ClinicalTrials.gov (TRACK-AF; Clinical Trials.gov number: NCT02641678).

Statistical analysis

Categorical data are presented as frequencies; continuous variables are expressed as mean and standard deviation (SD). The Kaplan–Meier method was used to estimate the time of first occurrence atrial fibrillation. A univariate regression was used to identify predictors of incidental findings. Data transformation and all statistical analyses were performed using the IBM SPSS Statistics 20.0 for Windows (IBM Corporation, Somers, NY, USA).

Results

A total of 173 patients with cryptogenic stroke were included in this study. Median time from stroke event to ILR implantation was 35.5 ± 47.5 days. Baseline characteristics are summarized in Table 1. A total of 33 (19.1%) patients were diagnosed with AF after a mean monitoring period of 10.7 ± 11.4 months. Since all patients had at least a CHA₂DS₂-VASc Score of 2 or more, all patients received an effective oral anticoagulation after AF diagnosis.

The mean follow-up was 24.8 ± 11.5 months. So far, the ILR were explanted in 111 pts. In 13 cases, the ILR were explanted within the first year of arrhythmia monitoring. Main reason for explantation was patient's preference in

Table 1 Baseline characteristics

| Parameter | Total (n = 173) |
|--|-----------------|
| Age (years) | 61.4 ± 12.8 |
| Range (years) | 30.2–85.0 |
| Female (n) | 73 (42.2%) |
| Time | |
| To implant (days) | 35.5 ± 47.5 |
| Until AF detection (months) | 10.7 ± 11.4 |
| Median follow-up duration (months) | 24.8 ± 11.5 |
| To pacemaker indication (months) | 23.1 ± 7.4 |
| Risk factors | |
| Congestive heart failure (n) | 7 (4.1%) |
| Arterial hypertension (n) | 123 (71.1%) |
| Diabetes mellitus (n) | 31 (17.9%) |
| Vascular disease (n) | 21 (12.1%) |
| CHA ₂ DS ₂ -VASc Score | 4.0 ± 1.4 |
| CHA ₂ DS ₂ -VASc Score 2 (n) | 20 (11.6%) |
| CHA ₂ DS ₂ -VASc Score 3 (n) | 54 (31.2%) |
| CHA ₂ DS ₂ -VASc Score 4 (n) | 40 (23.1%) |
| CHA ₂ DS ₂ -VASc Score 5 (n) | 25 (14.5%) |
| CHA ₂ DS ₂ -VASc Score 6 (n) | 26 (15.0%) |
| CHA ₂ DS ₂ -VASc Score 7 (n) | 7 (4.1%) |
| CHA ₂ DS ₂ -VASc Score 8 (n) | 1 (0.6%) |

N number of patients

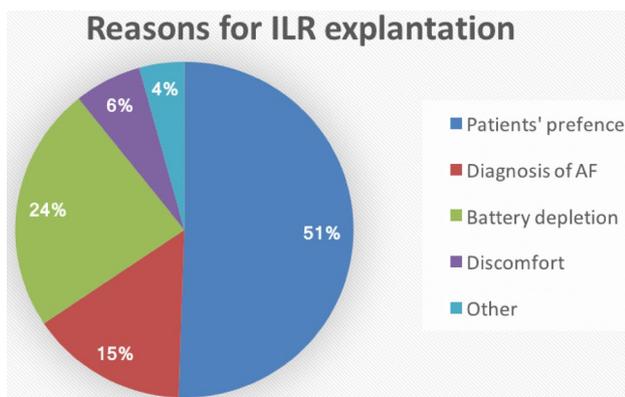


Fig. 1 Reasons for ILR explantation. So far, 111 patients underwent ILR explantation. Main reason for explantation was patients' preference in 51% of all cases

47 patients (51%) (Fig. 1). In 71 patients (64%), ILR were explanted before end of life of the battery. After the diagnosis of AF, the ILR were explanted in 14 patients.

The first documented AF episode in the ILR occurred after a median of 10.7 ± 11.4 months after ILR implantation (Fig. 2). Besides the diagnosis of atrial fibrillation, 15 patients (8.7%) had incidental findings in ILR memory. Most of them were asymptomatic and had no therapeutic implications. Short episodes of sinus arrest at night, not requiring a

Time to diagnosis of atrial fibrillation

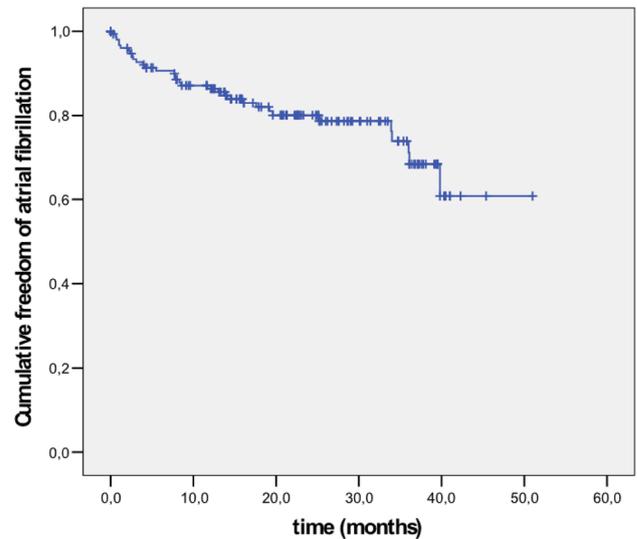


Fig. 2 Time to diagnosis of atrial fibrillation. Atrial fibrillation was detected in 33 patients (19.1%). 17.5% of AF diagnosis were made within the first 1.5 years of monitoring. All patients received an effective oral anticoagulation after AF diagnosis

Table 2 Results and major findings of ILR monitoring after cryptogenic stroke

| Parameter | Total (n = 173) (%) |
|---|---------------------|
| Diagnosis of atrial fibrillation (n) | 33 (19.1) |
| Explantation | 111 (64.2) |
| Within first year (n) | 13 (7.5) |
| Within third year (n) | 72 (41.6) |
| After third year (n) | 26 (15.0) |
| Incidental findings (n) | 15 (8.7) |
| Short episode of sinus arrest at night (n) | 8 (4.6) |
| Symptomatic sinus arrest or bradyarrhythmia requiring pacemaker (n) | 5 (2.9) |
| Atrial flutter (n) | 1 (0.6) |
| AV-nodal-reentry tachycardia (AVNRT) (n) | 1 (0.6) |

permanent pacemaker stimulation were present in 8 patients (4.6%). In five patients (2.9%), symptomatic sinus arrest was documented and followed by DDD-pacemaker implantation. In one patient, atrial flutter was found after the diagnosis of atrial fibrillation. In another patient with history of palpitations, a typical AV-nodal-reentry tachycardia was found. In both patients, an EP study with successful ablation of the arrhythmia was performed. Results of ILR monitoring are summarized in Table 2.

Serious additional findings which required pacemaker insertion were detected mainly in the long-term follow-up (median time 23.1 ± 7.4 months). Median age of patients

with pacemaker implantation was 75.2 ± 7.6 years. Four of these patients had the previous diagnosis of atrial fibrillation after a median follow-up time of 6.0 ± 5.6 months. We did not find an independent predictor for incidental findings on our study, but higher age was a significant independent predictor of atrial fibrillation (odds ratio 1.06, 95% confidence interval 1.02–1.11, $p < 0.05$) (Table 3).

Discussion

Implantable loop recorders (ILR) have been evolved as an adjuvant tool in the diagnostics of AF in patients with history of cryptogenic stroke. ILR allow continuous rhythm monitoring with high sensitivity for detecting paroxysmal AF. The XPECT trial [8] showed a sensitivity of 96.1%, a specificity of 85.4%, a PPV of 79.3%, and an NPV of 97.4% for detection of paroxysmal AF. Although implantation of an ILR is a secure procedure and problems with the implanted device are rare, the question arises if it is reasonable to continue ILR monitoring in patients even when the initial indication no longer persists (i.e., diagnosis of AF).

In the present study, the detection rate of paroxysmal atrial fibrillation was 19.1%. Therefore, our study underlines the use of ILR in the detection of atrial fibrillation in cryptogenic stroke. It is well known that longer duration of monitoring increases the diagnosis of atrial fibrillation [5]. In our study, median time to AF diagnosis was made after 10.7 ± 11.4 months. Besides the diagnosis of atrial fibrillation, in 2.9% of patients, significant arrhythmias were detected which required the implantation of a pacemaker. Interestingly, in four patients, the indication for pacemaker insertion was made after the diagnosis of atrial fibrillation (median time until pacemaker indication 23.1 ± 7.4 months).

On the other hand, median time until explantation of the ILR was 24.8 ± 11.5 months. Main reason for explantation was patient's choice in 51%. The crystal AF trial [13] investigated ILR monitoring versus conventional AF in patients with cryptogenic stroke. After 6 months, there was a highly significant difference between detection of atrial fibrillation

with an ILR in 8.9% of patients versus 1.4% of patients in the control group. After 36 months, the detection rate of atrial fibrillation had been increased to 30.0% of patients in the ILR group versus 3.0% of patients in the control group. Therefore, continued monitoring with an ILR was superior to conventional follow-up for detecting AF following cryptogenic stroke. The authors concluded that monitoring for AF with an ILR should be performed for a longer time. However, 88 out of 221 patients completed the 24-month visit in the ILR group and only 24 patients completed the 36-month visit [14]. These results are consistent with our observation that the ILR is explanted before battery depletion in most cases.

Long-time monitoring after cryptogenic stroke with an implantable loop recorder has a significant detection rate of atrial fibrillation [7, 15, 16]. At present, there is no standard practice with respect to length of continued ECG monitoring in these patients. However, in the present study, 17.5% of all patients received AF diagnosis within the first 1.5 years of monitoring. In clinical practice, many patients wish to explant the device after successful diagnosis of atrial fibrillation. According to an expert opinion paper [17], prolonged ECG monitoring should be based on risk estimation for atrial fibrillation. In our study, many ILR are explanted before full lifetime of battery, which is predicted about 3 years by the manufacturer. In other studies, premature explantation of the ILR was lower. For example, in the SURPRISE study [18], in only 5.3% of patients, the device was explanted prematurely due to skin reaction or to discomfort. However, most studies did not intend to extend the monitoring until battery depletion even after the diagnosis of AF.

There may be other reasons to continue monitoring even after the diagnosis of atrial fibrillation in cryptogenic stroke: In our study, diagnosis of AF was made when the episode lasted longer than 30 s. This definition was chosen according to the current guidelines of the European Society of Cardiology (ESC) for the management of atrial fibrillation [9] and was as well used in the CRYSTAL AF study [13]. This definition may be controversial. In the ASSERT trial

Table 3 Predictors of incidental findings and atrial fibrillation

| | Incidental findings | | Atrial fibrillation | |
|-------------------|---------------------|----------------|---------------------|----------------|
| | Odds ratio (95% CI) | <i>p</i> value | Odds ratio (95% CI) | <i>p</i> value |
| Age | 1.13 (0.97–1.30) | 0.111 | 1.06 (1.02–1.11) | 0.002 |
| Male | 0.68 (0.22–2.08) | 0.405 | 1.31 (0.59–2.94) | 0.510 |
| Hypertension | 0.16 (0.02–1.24) | 0.342 | 0.96 (0.33–2.75) | 0.938 |
| Diabetes mellitus | 0.57 (0.17–1.91) | 0.361 | 1.55 (0.53–4.52) | 0.419 |
| CAD | 0.89 (0.19–4.25) | 0.882 | 2.23 (0.58–8.53) | 0.240 |

There was no statistical significant independent predictor for incidental findings. However, higher age was a significant independent predictor for detection of atrial fibrillation

CI confidence interval, CAD coronary artery disease

[19], the authors showed that in patients with implantable devices, a duration of longer than 6 min of AF was associated with an increased stroke risk. In line with these results, the MOST study [20] found a similar result with an AF duration longer than 5 min. In the SOS AF trial [21], the duration of atrial fibrillation episodes influenced the treating physician to decide for an oral anticoagulation: In patients with at least one long-lasting AF episode (> 1 h), all patients received oral anticoagulation. In contrast, patients with episodes lasting shorter than 1 h no more than 70% received an anticoagulant. Based on the aforementioned studies, with continued monitoring after diagnosis of AF, the burden of atrial fibrillation could be determined and maintain the decision for an oral anticoagulation.

Furthermore, in symptomatic AF patients, rhythm- or frequency control can be supervised with the data of the ILR recordings. Our study shows that in some cases, clinical relevant arrhythmias requiring, e.g., pacemaker implantations, can be observed after the diagnosis of AF. For this reason, once an arrhythmia monitoring with an implantable loop recorder has been initiated, it should be continued until battery depletion.

Limitations

There are some limitations due to the design of this study: because the study was co-funded by industry, only one ILR system was used for detection of atrial fibrillation. It is a single-center study with a moderate sample size compared to the number of patients in the recruiting period. This may have led to a significant selection bias. However, only patients with a complete diagnostic setup were included in this trial. Most patients with cryptogenic stroke did not consent in the recruiting period. Due to the non-randomized design, it is not feasible to draw final conclusions on the optimal length of ECG monitoring after cryptogenic stroke. The minimum prospective monitoring time was 12 months, but patients were offered to continue ILR monitoring until battery depletion if desired. Patients were informed before implantation that monitoring period could be prolonged until battery depletion. This may have impacted on the patients' preference to explant the ILR before the end of battery lifetime. Although the TRACK-AF trial was a prospective study, the present analysis was only a retrospective analysis of the TRACK-AF data.

Conclusions

The present study revealed a significant number of ECG findings during continued ECG monitoring for AF in patients with cryptogenic stroke. Apart from AF (17.5% during the

first 1.5 years), other clinical relevant arrhythmias requiring, e.g., pacemaker implantations, were observed. With respect to these findings, it should be recommended to extend ILR monitoring to the end of battery life. However, acceptance of continued ECG monitoring until battery depletion was poor; in 71 patients (64%), the ILR were explanted before the end of battery life.

Funding Funded by the European Union, support code: 005-GW02-021A.

Compliance with ethical standards

Conflict of interest D.D., L.E., G.F., and F.R. received lecture honoraria and travel grants by Medtronic, Biotronik, Boston Scientific, and Abbott. The study was co-funded by grants of Medtronic.

References

1. Dion F, Saudeau D, Bonnaud I et al (2010) Unexpected low prevalence of atrial fibrillation in cryptogenic ischemic stroke: a prospective study. *J Interv Card Electrophysiol* 28:101–107
2. Rojo-Martinez E, Sandín-Fuentes M, Calleja-Sanz AI et al (2013) High performance of an implantable Holter monitor in the detection of concealed paroxysmal atrial fibrillation in patients with cryptogenic stroke and a suspected embolic mechanism. *Rev Neurol* 57:251–257
3. Adams HP Jr, Bendixen BH, Kappelle LJ et al (1993) Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 24(1):35–41
4. Lip GY, Beavers DG (1995) ABC of atrial fibrillation. History, epidemiology, and importance of atrial fibrillation. *BMJ* 311:1361–1363
5. Ziegler PD, Rogers JD, Ferreira SW et al (2015) Real-world experience with insertable cardiac monitors to find atrial fibrillation in cryptogenic stroke. *Cerebrovasc Dis* 40:175–181
6. Reinke F, Bettin M, Ross LS et al (2017) Refinement of detecting atrial fibrillation in stroke patients: results from the TRACK-AF study. *Eur J Neurol* 45(1–2):54–60
7. Ritter MA, Kochhäuser S, Duning T et al (2013) Occult atrial fibrillation in cryptogenic stroke: detection by 7-day electrocardiogram versus implantable cardiac monitors. *Stroke* 44:1449–1452
8. Hindricks G, Pokushalov E, Urban L, XPECT Trial Investigators et al (2010) Performance of a new leadless implantable cardiac monitor in detecting and quantifying atrial fibrillation: results of the XPECT trial. *Circ Arrhythm Electrophysiol* 3:141–147
9. Kirchhof P, Benussi S, Kotecha D et al (2016) 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 37:2893–2962
10. Alushi B, Lauten A, Cassese S et al (2018) Patent foramen ovale closure versus medical therapy for prevention of recurrent cryptogenic embolism: an updated meta-analysis of randomized clinical trials. *Clin Res Cardiol*. <https://doi.org/10.1007/s00392-018-1246-y> (Epub ahead of print)
11. Liu D, Hu K, Schmidt M et al (2018) Value of the CHA₂DS₂-VASc score and Fabry-specific score for predicting new-onset or recurrent stroke/TIA in Fabry disease patients without atrial fibrillation. *Clin Res Cardiol*. <https://doi.org/10.1007/s00392-018-1285-4>. (Epub ahead of print)

12. Müller P, Ivanov V, Kara K et al (2017) Total atrial conduction time to predict occult atrial fibrillation after cryptogenic stroke. *Clin Res Cardiol* 106:113–119
13. Sanna T, Diener H-C, Passman RS et al (2014) Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 370:2478–2486
14. Brachmann J, Morillo CA, Sanna T et al (2016) Uncovering atrial fibrillation beyond short-term monitoring in cryptogenic stroke patients: three-year results from the cryptogenic stroke and underlying atrial fibrillation trial. *Circ Arrhythm Electrophysiol* 9:e003333
15. Gladstone DJ, Spring M, Dorian P et al (2014) Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 370:2467–2477
16. Cotter PE, Martin PJ, Ring L et al (2013) Incidence of atrial fibrillation detected by implantable loop recorders in unexplained stroke. *Neurology* 80:1546–1550
17. Haeusler KG, Gröschel K, Köhrmann M et al (2018) Expert opinion paper on atrial fibrillation detection after ischemic stroke. *Clin Res Cardiol*. <https://doi.org/10.1007/s00392-018-1256-9>. (**Epub ahead of print**)
18. Christensen LM, Krieger DW, Højberg S, Pedersen OD et al (2014) Paroxysmal atrial fibrillation occurs often in cryptogenic ischaemic stroke. Final results from the SURPRISE study. *Eur J Neurol* 21:884–889
19. Healey JS, Connolly SJ, Gold MR et al (2012) Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 366:120–129
20. Glotzer TV, Hellkamp AS, Zimmermann J et al (2003) Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the MOde Selection Trial (MOST). *Circulation* 107:1614–1619
21. Boriani G, Glotzer TV, Santini M et al (2014) 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* 35:508–516