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(Article begins on next page)
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)

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Objective
The aim of this study was to assess the association between maximum daily atrial fibrillation (AF) burden and risk of ischaemic stroke.

Background
Cardiac implanted electronic devices (CIEDs) enhance detection of AF, providing a comprehensive measure of AF burden.

Design, setting, and patients
A pooled analysis of individual patient data from five prospective studies was performed. Patients without permanent AF, previously implanted with CIEDs, were included if they had at least 3 months of follow-up. A total of 10 016 patients (median age 70 years) met these criteria. The risk of ischaemic stroke associated with pre-specified cut-off points of AF burden (5 min, 1, 6, 12, and 23 h, respectively) was assessed.

Results
During a median follow-up of 24 months, 43% of 10 016 patients experienced at least 1 day with at least 5 min of AF burden and for them the median time to the maximum AF burden was 6 months (inter-quartile range: 1.3–14). A Cox regression analysis adjusted for the CHADS2 score and anticoagulants at baseline demonstrated that AF burden was an independent predictor of ischaemic stroke. Among the thresholds of AF burden that we evaluated, 1 h was associated with the highest hazard ratio (HR) for ischaemic stroke, i.e. 2.11 (95% CI: 1.22–3.64, P = 0.008).

Conclusions
Device-detected AF burden is associated with an increased risk of ischaemic stroke in a relatively unselected population of CIEDs patients. This finding may add to the basis for timely and clinically appropriate decision-making on anticoagulation treatment.

Keywords
Atrial fibrillation • Anticoagulation • Implantable defibrillator • Pacemaker • Stroke
Device-detected atrial fibrillation and risk for stroke

Introduction

Atrial fibrillation (AF)-associated ischaemic stroke can be devastating and a major contributor to healthcare spending. Fortunately, it is largely preventable by anticoagulant therapy. Current guidelines recommend risk-based use of anticoagulant therapy in patients with AF. Such guidelines apply to patients with paroxysmal as well as persistent AF.1 However, among patients with paroxysmal AF, the frequency and length of episodes of AF are highly variable. Further, many episodes of AF are clinically ‘silent’, being detected incidentally through routine physical examinations, pre-operative assessments, diagnostic logs of implanted devices, or population surveys.2 Current guidelines do not specifically address anticoagulation use in cases of ‘silent’ AF. Indeed, in some cases, asymptomatic AF is revealed only after complications such as ischaemic stroke or congestive heart failure have occurred.3

The relationship between the duration and frequency of AF and stroke risk is uncertain and an area of active investigation. Moreover, the definition of a clinically useful measure that accurately reflects an individual risk from an intermittent and progressive disease is a challenge.4–10 Modern implanted devices such as defibrillators, pacemakers, or implantable loop recorders now allow precise, continuous long-term monitoring of heart rhythms, such as AF.11 Implanted devices with an atrial lead can measure the total time spent in AF each day, i.e. the daily atrial tachycardia/AF burden or ‘daily AF burden’. We pooled data from three studies of patients with a broad spectrum of such devices to assess the association between the maximum daily AF burden and the risk of ischaemic stroke in order to provide a large patient population to be evaluated for this scope.

Methods

Patient population and study design

A pooled analysis of individual patient data from three large prospective observational studies was performed. Patients were eligible for the pooled database if they were implanted with a device capable of measuring atrial tachyarrhythmia, had at least 3 months of follow-up and device diagnostic data available, and did not have permanent AF. Among the 22,433 patients enrolled in the three studies, 10,016 (45%) patients fulfilled the inclusion criteria. Reasons for patients exclusions were a follow-up shorter than 3 months in 32%, incomplete diagnostic data coverage of the follow-up period in 32%, implant of a single-chamber device in 30%, and permanent AF in 6%. Overall, health status at 1-year follow-up was known for 8515 patients (85% of patients included in this analysis).

The current analysis included results from the TRENDS and PANORAMA studies and the Italian ClinicalService® Project. TRENDS (ClinicalTrials.gov identifier: NCT00279981) was a prospective, observational study designed to assess the relationship between device-detected atrial tachyarrhythmias and thrombo-embolic events with 3045 patients enrolled from 116 sites in USA, Canada, and Australia. PANORAMA (ClinicalTrials.gov identifier: NCT00382525) is a prospective, observational study designed to investigate the long-term operation and clinical outcomes of cardiac rhythm management devices. A total of 8522 patients were enrolled between January 2005 and July 2011, with the majority of the patients coming from emerging or developing economies. The Italian ClinicalService® Project (ClinicalTrials.gov identifier: NCT01007474) is a national cardiovascular data repository and medical care project aimed at describing and improving the use of implantable cardiac devices in 150 Italian cardiology centres. Patient recruitment and follow-up is on-going with 10,866 patients included between January 2004 and July 2011.

PANORAMA and the Italian ClinicalService® Project are observational studies of clinical care where all treatment decisions (including device settings, use of concomitant therapies, and medication) are made by treating physicians. Clinical follow-ups and device interrogations were performed according to the routine practice of the participating centres.10 TRENDS was an observational cohort study with patient eligibility criteria and specified follow-up visits. TRENDS study patients had to have at least one stroke risk factor (including a history of congestive heart failure, hypertension, age ≥ 65 years, diabetes mellitus, or prior stroke/transient ischaemic attack); patients with replacement devices or long-standing permanent AF were excluded. TRENDS patients were followed with device interrogations every 3 months and clinic visits every 6 months for 2 years.7 Patients with a history of paroxysmal and persistent AF were kept in the analysis cohort to reflect the spectrum of patients encountered in daily routine practice and to explore in depth the association between device-detected AF and ischaemic stroke.

Device-detection of atrial fibrillation burden

Patients had been previously implanted with devices (Medtronic, Inc., Minneapolis, MN, USA) capable of continuous AF detection and monitoring by means of atrial lead and rate detection algorithms. In TRENDS, the protocol specified that AF detection be programmed to nominal settings (atrial rate >175 b.p.m. lasting ≥ 20 s). In the ClinicalService and PANORAMA studies, nominal device settings were usually applied. The sensitivity and specificity of device detection of AF burden in Medtronic devices has been established in previous studies and has been shown to exceed 95% for both measures.12 The number of minutes of AF recorded in a day (i.e. daily AF burden) was used for analysis and in every patient the maximum daily AF burden experienced during the follow-up was analysed. To investigate the prognostic value of AF burden (i.e. maximum daily AF burden), a range of cut-off points were defined a priori as 5 min, 1, 6, 12, and 23 h. Cut-off points were based on previously reported thresholds (5 min, 6 and 23 h)6,7,9 with additional cut-off points added to have a more complete characterization of the consequences of AF burden. Patients with no AF burden or <5 min of AF burden were categorized as not having AF. A minimum threshold of 5 min of AF burden was previously found to carry clinical relevance6,8 and recently the ASSERT trial found that >6 min of AF were associated with an increased risk of ischaemic stroke and systemic embolism.13 The analysis of AF burden continued through our sequence of thresholds to a threshold of 23 h where patients with at least 1 day with
at least 23 h of AF burden detected were compared with patients who
experienced 0 to 23 h of AF burden as their maximum daily AF burden.

Statistical methods
Data are reported as median and inter-quartile range (IQR) or as number
and percentage, as appropriate. Person-years rates of ischaemic stroke and
ischaemic stroke plus TIA were calculated for categories of AF burden.
Analyses were restricted to patients with at least one follow-up visit and
at least 3 months of continuous device monitoring. Multivariable modelling
of ischaemic stroke risk was done using Cox regression models with time-
dependent covariates. In the first analyses, AF burden was entered as a
continuous time-dependent covariate. In this analysis, a patient’s AF
burden could increase but not decrease during the follow-up period.
This assumption is clinically justified by the prevalent concept that AF
carries a risk of ischaemic stroke independent on its reduction in fre-
quency/duration or its potential disappearance for some time. The
results are expressed as hazard ratios (HRs) with 95% confidence intervals
(95% CI), which can be interpreted as the increase in risk for each additional
hour of AF burden experienced. In the second analysis, we used separate
Cox regression models where AF burden was entered as a dichotomized
time-dependent covariate where the status of the time-dependent indica-
tor variable changed at the moment the patient crossed the AF threshold
value. Once a patient has crossed the AF threshold being evaluated they
were considered exposed for the remainder of the follow-up period.
For each cut-off, ischaemic stroke and TIA events were compared
between patients with AF burden below that threshold and patients
with AF at or above that threshold. This approach diminishes the relative
increase in risk at higher thresholds but reflects the difference in event
takes that are reported for the CHADS2 score, oral anticoagulation use at baseline;
both adjusted and unadjusted results are reported. Additionally, we also
adjusted for the CHADS2 score, oral anticoagulation use at baseline and
study cohort. Patients were censored at the last day of device data available.

Results

Baseline characteristics
At entry to the study, the median age was 70 years, and 31% were
female. A history of prior stroke was present in 6% of the patients
and 59% had a CHADS2 score of two or more. Additional baseline
characteristics in the aggregate and by individual study are presented
in Table 1.

Atrial fibrillation burden during
the follow-up
The median duration of follow-up was 24 months (IQR: 14–40
months). During the follow-up, 43% of patients experienced at
least 1 day with at least 5 min of AF burden detected. Among these
patients, the median time to the first day with at least 5 min of AF
was 2 months (IQR: 0.2–9.5) (Figure 1). Within the first 3 months,
24% of patients experienced at least 1 day with 5 min of AF, 18% at
least 1 h, 13% at least 6 h, 10% at least 12 h, and 6% experienced at
least 1 day with at least 23 h of AF.

Among patients experiencing at least 1 day of AF burden during
the follow-up, the median time to the maximum AF burden was 6 months
(IQR: 1.3–14). Figure 2 shows the cumulative proportion over time of
patients reaching the day with the maximum observed daily AF
burden value during the follow-up. The characteristics of patients
at baseline according to the maximum daily AF burden experienced
during the follow-up are shown in Table 2.

Table 1 Baseline characteristics by study

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 10 016)</th>
<th>PANORAMA (n = 3556)</th>
<th>TRENDS (n = 2553)</th>
<th>ClinicalService (n = 3907)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median years (IQR)</td>
<td>70 (61, 76)</td>
<td>69 (60, 76)</td>
<td>73 (64, 79)</td>
<td>68 (60, 74)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>6859 (69)</td>
<td>2096 (39)</td>
<td>1694 (66)</td>
<td>3069 (79)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>2537 (25)</td>
<td>896 (25)</td>
<td>817 (32)</td>
<td>824 (21)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>5896 (59)</td>
<td>2116 (60)</td>
<td>1940 (76)</td>
<td>1840 (47)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>1923 (19)</td>
<td>784 (22)</td>
<td>678 (27)</td>
<td>461 (12)</td>
</tr>
<tr>
<td>Persistent</td>
<td>478 (5)</td>
<td>91 (3)</td>
<td>48 (2)</td>
<td>339 (9)</td>
</tr>
<tr>
<td>Oral anticoagulation, n (%)</td>
<td>1822 (18)</td>
<td>631 (18)</td>
<td>526 (21)</td>
<td>665 (17)</td>
</tr>
<tr>
<td>CHADS2 group, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHADS2 0–1</td>
<td>4133 (41)</td>
<td>1684 (47)</td>
<td>722 (28)</td>
<td>1727 (44)</td>
</tr>
<tr>
<td>CHADS2 2–6</td>
<td>5883 (59)</td>
<td>1872 (53)</td>
<td>1831 (72)</td>
<td>2180 (56)</td>
</tr>
<tr>
<td>Prior stroke, n (%)</td>
<td>589 (6)</td>
<td>89 (3)</td>
<td>345 (14)</td>
<td>155 (4)</td>
</tr>
<tr>
<td>Device type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM</td>
<td>4277 (43)</td>
<td>2726 (77)</td>
<td>1238 (49)</td>
<td>313 (8)</td>
</tr>
<tr>
<td>ICD</td>
<td>2004 (20)</td>
<td>404 (11)</td>
<td>822 (32)</td>
<td>778 (20)</td>
</tr>
<tr>
<td>CRT</td>
<td>3735 (37)</td>
<td>426 (12)</td>
<td>493 (19)</td>
<td>2816 (72)</td>
</tr>
</tbody>
</table>

IQR, inter-quartile range; PM, pacemaker; ICD, implantable cardiac defibrillator; CRT, cardiac resynchronization therapy.
Risk of ischaemic stroke and transient ischaemic attack events associated with atrial fibrillation burden: continuous analysis

We sought to define the HR for ischaemic stroke at any given maximum AF burden. To this end, we modelled ischaemic stroke risk with AF burden entered as a continuous variable. After adjustment for the CHADS2 score and oral anticoagulation at baseline, there was a significant association between daily AF burden modelled for risk of ischaemic stroke at any given maximum AF burden. To this end, we modelled ischaemic stroke risk with AF burden entered as a continuous variable. After adjustment for the CHADS2 score and oral anticoagulation at baseline, there was a significant association between daily AF burden modelled for risk of ischaemic stroke at any given maximum AF burden. To this end, we modelled ischaemic stroke risk with AF burden entered as a continuous variable. After adjustment for the CHADS2 score and oral anticoagulation at baseline, there was a significant association between daily AF burden modelled.
as a continuous variable and ischaemic stroke events with an HR = 1.03 per h (95% CI: 1.00–1.05, P = 0.040). To calculate the HR for any given increase the following formula can be applied:

\[
\text{Hazard ratio} = \text{Exponential}(0.0263 \times AF\ burden\ daily\ maximum\ hours).
\]

This result implies that the HR for a maximum AF burden of 6 h was 1.17 (95% CI: 1.01–1.36) and for 12 h the HR was 1.37 (95% CI: 1.01–1.85).

The results were similar for ischaemic stroke and TIA events with an expected HR, for a 6 h AF burden = 1.14 (95% CI: 1.02–1.28) and for a 12 h AF burden = 1.30 (95% CI: 1.03–1.65).

**Risk of ischaemic stroke and transient ischaemic attack events associated with atrial fibrillation burden: analysis by dichotomized cut-off thresholds of atrial fibrillation burden**

By means of a series of Cox regression models, we explored the association of pre-defined thresholds of AF burden and ischaemic stroke, controlling for the CHADS2 score and anticoagulation use at baseline. The ischaemic stroke HR point estimates were similar for all the thresholds examined, but the highest point estimate was observed for a threshold ≥ 1 h with an HR of 2.11 (95% CI: 1.22–3.64, P = 0.008). The threshold of ≥ 5 min was also statistically significantly associated with the occurrence of ischaemic stroke, HR = 1.76 (95% CI: 1.02–3.02, P = 0.041). Atrial fibrillation burden experienced prior to event occurrence.

**Figure 3** Distribution of patients according to maximum atrial fibrillation burden experienced during the follow-up. Stroke and transient ischaemic attack events and event rates are given in the table below the figure. Events were classified according to maximum atrial fibrillation burden experienced prior to event occurrence.
Figure 4 The Forest plot of unadjusted hazard ratios for (A) stroke events and (B) stroke or transient ischaemic attack events. Dotted line indicates line of unity (HR = 1.0) with dots above the line showing increased risk of stroke or (stroke or TIA); bars represent 95% CIs.
burden may have important clinical relevance \(^13\) and support the finding, our study provides an analysis of the clinical implications of device-detected AF burden with a wider clinical perspective compared with ASSERT\(^13\), where the focus was on the implications of AF burden detected in the first 3 months of observation.

With the advent of CIEDs that have improved arrhythmia detection algorithms and memory capabilities, as well as the advent of remote monitoring, there is frequent detection of episodes of AF of variable duration, usually silent in device clinics.\(^2\) The diagnostic accuracy of pacemaker and ICDs with an atrial lead is very high, with appropriate detection of 95% of AF episodes,\(^12\) while for implantable loop recorders, not included in this data set, the specificity is \(\sim 85\%\).\(^16\) A recent editorial commenting on the clinical implications of device-detected AF according to ASSERT findings\(^15\) pointed out that there is need to identify precise thresholds of AF burden associated with clinically relevant increases in the risk of stroke. The assessment of AF burden thresholds associated with increasing risks of stroke is important and our study provides a contribution in the field.

Clinical decisions regarding the prescription of antithrombotic prophylaxis are based on risk stratification, frequently using the CHADS\(_2\) score and an assessment of the individual’s bleeding risk, as well as patient preferences.\(^17\)–\(^19\) Our continuous analysis helps to assess the additional impact of quantified AF burden on stroke risk in patients with AF. Moreover, quantified AF burden provided by implanted devices may be clinically important, since it has been observed that providing physicians with timely information on AF burden may result in an increased prescription of appropriate antithrombotic prophylaxis.\(^20\) Our dichotomized analysis shows that after adjustment for the CHADS\(_2\) score and oral anticoagulants use, device-detected AF burden is associated with an increased risk of stroke; of the several cut-points evaluated, the 1 h threshold appears to be the most robust with a doubling in the risk of stroke. Choice of a potential threshold of AF burden associated with an increased risk of stroke remains problematic. As a matter of fact, when increasing the duration of AF burden (i.e. to 12 or 23 h) the discriminatory capability is lost, probably because the risk is consistent also below the proposed threshold. The prognostic implications of AF burden \(< 5\) min are at present unknown for patients carrying a pacemaker or an implantable defibrillator.

We recognize that our study has limitations. There may be confounding factors associated with AF burden that we have not accounted for in our analyses, for example, the differences in follow-up timing between the three studies. In our study, the absolute event rate of ischaemic stroke was low, perhaps reflecting a general trend towards lower rates of ischaemic strokes in comparison with what predicted by CHADS\(_2\), a score validated \(> 10\) years ago in a group of patients with a mean age of 81 years derived from the National

### Table 3
Cox regression analysis performed on 8122 patients without oral anticoagulation at baseline, adjusted for the CHADS\(_2\) score

<table>
<thead>
<tr>
<th>Total</th>
<th>Events</th>
<th>HR for AF burden (\geq 1) h vs. (&lt; 1) h (95% CI)</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>8122</td>
<td>44</td>
<td>2.09 (1.10, 3.96)</td>
</tr>
<tr>
<td>Stroke + TIA</td>
<td>8122</td>
<td>69</td>
<td>2.05 (1.24, 3.39)</td>
</tr>
</tbody>
</table>

Adjusting for CHADS\(_2\) score

Stroke | 8122 | 44  | 1.90 (1.00, 3.61) | 0.0487 |
Stroke + TIA | 8122 | 69  | 1.89 (1.14, 3.12) | 0.0135 |

TIA, transient ischaemic attack; HR, hazard ratio; CI, confidence interval.
Registry of Atrial Fibrillation, with a high prevalence of heart failure.\textsuperscript{21} It is noteworthy that also in ASSERT,\textsuperscript{14} the actual risk of stroke in patients with device-detected AF was much lower than that expected by the CHADS\textsubscript{2} score, possibly reflecting a general temporal trend towards a progressive reduction incidence of stroke in developed countries.\textsuperscript{22,23} Moreover, the low rate of ischaemic strokes observed even among patients experiencing sizable AF burdens may reflect the long periods of sinus rhythm experienced by our patients and better treatment of stroke risk factors. In addition, some degree of under-reporting of ischaemic stroke and TIA events cannot be ruled out with the study designs used and this has to be considered in the clinical interpretation of the rather low stroke rates.

Stroke risk can also be reduced by use of anticoagulants, whose implementation is more common in higher CHADS\textsubscript{2} categories. We accounted for the use of anticoagulants in our multivariable models and also by excluding patients on anticoagulants in a secondary analysis. In these additional analyses, performed by excluding patients on anticoagulants at baseline, as well as by excluding patients on OAC at baseline and adjusting for the CHADS\textsubscript{2} score, the significantly increased risk of stroke and stroke + TIA for a device-detected AF burden ≥ 1 h vs. a device-detected AF burden < 1 h was confirmed, with H\textsubscript{R} between 1.89 and 2.09.

In summary, our results show that monitoring AF burden continuously (made possible by the information from an implanted device) may allow timely evaluation of the risk of ischaemic stroke faced by patients with AF. Its comprehensive nature avoids the problem of missed episodes of AF inherent in intermittent monitoring for detecting clinically silent AF. It is noteworthy that in our population of over 10,000 patients the day with the maximum AF duration occurred after a mean of 6 months of monitoring. On-going and future studies, also using remote transmission of data on AF burden, will allow more precise assessment of the ways to integrate information on specific levels of AF burden (i.e. ≥ 1 h) into clinical decision-making tailored to reduce stroke risk.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

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**References**

CARDIOVASCULAR FLASHLIGHT

Twiddler syndrome causing an inappropriate implantable cardioverter-defibrillator shock

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A 72-year-old man was implanted with a dual-chamber cardioverter-defibrillator (Lumax 540-HFT, Biotronik, Germany, Berlin) in secondary prevention. An atrial active fixation lead (Biotronik Solia S53) and a ventricular active fixation lead (Biotronik Linox S65) were used. Predischarge an X-ray showed a good position of both leads (Panel A) and the internal cardioverter-defibrillator was checked and functioned correctly. The patient was followed on remote monitoring (Home Monitoring network, Biotronik SE & Co. KG). Before the first planned in-clinic follow up, we received an alert due to the delivery of a shock for a ventricular arrhythmia and an episode of atrial fibrillation. All atrial and ventricular leads parameters seemed stable. Analysing the electrogram (EGM) (Panel B), we recognized an episode of atrial fibrillation on the atrial EGM. The ventricular EGM showed intermittent irregular rapid activity, with obvious similarity to the atrial rhythm. This could be explained by either intermittent 1:1 conduction of AF or by intermittent cross-talk with oversensing of the atrial signal on the ventricular lead. The patient was admitted and a chest X-ray confirmed intermittent cross-talk with oversensing of the atrial signal on the ventricular lead. The patient denied conscious manipulation of the device pocket, but reported ‘spontaneous’ rotation of the device. A second intervention was consequently performed, electrodes were completely twisted (Panels D and E) and the ventricular lead showed signs of insulation break. Both leads were extracted and replaced. The generator was fixed in the pocket with a ligature.

(A) Chest X-ray at before discharge. (B) Stored EGM of the episode. From top to bottom are atrial and ventricular marker channel, atrial EGM, and ventricular EGM. Correct detection of an episode of atrial fibrillation (black circle—AF onset) and inappropriate detection of ventricular fibrillation leading to inappropriate therapy. (C) Chest X-ray showing displacement of the ventricular lead in the right atrium and twisted leads. (D and E) Twisted leads during repositioning.

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