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Detection of new atrial fibrillation in patients with cardiac implanted electronic devices and factors associated with transition to higher device-detected atrial fibrillation burden

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Abstract

Background: *In patients with cardiac implanted electronic devices (CIEDs) detection of new atrial fibrillation (AF) is associated with an increased risk of stroke.*

Objective*: To characterize daily AF burden at first detection and the rate of temporal transition to higher device detected AF burden.*

Methods*: A pooled analysis of data from three prospective studies was analyzed and 6580 patients (mean age 68±12 years, 72% male) with no history of AF and no anticoagulants at baseline were identified. Various thresholds of daily AF burden (5 minutes, 1, 6, 12 and 23 hours) were analyzed.*

Results: *Among the study population of 6580 patients, a new AF, with a AF burden of at least 5 min, was detected in 2244 patients (34%) during a follow up of 2.4±1.7 years. Among these patients 1091 (49.8%) transitioned to a higher AF burden threshold during follow-up. A higher duration of daily AF burden manifest at first detection, as well as $CHADS_2$ score ≥2, were associated with faster transition to a subsequent higher burden. Approximately 24% of patients transitioned from a lower threshold to a daily AF burden ≥23 hours during follow-up.*

Conclusion*: More than one third of patients with no history of AF develop device-detected AF, with attainment of different thresholds of daily AF burden over time. Continuous long-term monitoring, especially when the initial detection corresponds to a higher daily AF burden and the CHADS2 score is 2 or more, could support timely clinical decisions on anticoagulation by capturing transitions to higher AF burden thresholds.*

Key words*: anticoagulants, atrial fibrillation; atrial fibrillation burden; cardioverter-defibrillator; pacemaker; stroke.*

Introduction

The extensive monitoring capabilities of cardiac implanted electrical devices (CIEDs) with sensing of atrial activity currently allow the detection of episodes of atrial high rate events (AHRE) episodes also known as subclinical atrial fibrillation (SCAF)[1–3] .The relationship between the duration of AHREs and the risk of stroke is complex and is an area of active investigation[4–6] Device-detected AF is associated with an increased risk of stroke,[1,3,7,8] but the precise threshold of device-detected AF that may justify initiation of oral anticoagulation (OAC) in patients with a clinical profile at risk, is not yet understood.[3,9]

Current guidelines recommend risk-based prescription of OAC in patients with clinically documented AF.[10] However, the guidelines do not account for AF burden, i.e., the length and frequency of AF episodes which vary greatly across and within patients. Further, many episodes of AF are clinically 'silent'. In patients with CIEDs, episodes of AHRE may occur, with a duration of minutes to hours leading to the concept of "subclinical AF".[1–3] In patients with CIED and no history of AF, detection of new AF is of potential importance and requires appropriate clinical management and decision making. Several different thresholds of daily AF burden (for example, 5-6 minutes, 1, 6, 12 and 23 hours) have been investigated in patients with CIEDs and an association with an increased risk of stroke has been demonstrated.[11,12] No controlled study has defined the specific threshold of AF burden that justifies initiation of OAC in patients at risk.

A comprehensive, accurate definition of the dynamics of device-detected AF, and of the factors influencing the transition from shorter to longer maximum daily AF burden could be helpful in clinical decision-making with regard to patient monitoring and surveillance, as well as for prescription of OAC. In this regard it is noteworthy that subclinical AF predicts the occurrence of clinical AF, as well as the risk of ischemic stroke/systemic embolism[1,3] but no data are currently available on the transition from a lower to a higher AF burden of device detected AHREs. The importance of investigating the transition to AF of long duration (longer than 23-24 hours) is stressed by a recent analysis from ASSERT showing that patients in whom

the longest episode of silent AF exceeded 24 hours had a significantly increased risk of stroke during follow up [15] .

The aim of the current work is to characterize the daily AF burden at first detection and the rate of temporal transition to a higher device detected AF burden from a large dataset that quantified the incidence of device-detected AF during follow up.

Methods

A pooled analysis of individual patient data from three prospective studies (TRENDS, Italian Clinical Service, and PANORAMA), part of the SOS AF project,[8] was performed. The details of the methods are in the Supplementary web-only Appendix.

Results

Patient characteristics and occurrence of device detected AF burden during follow up

A group of 6580 patients implanted with a CIED (mean age 67±12 years, 69% male) without history of AF and no OAC use at baseline were identified and followed for 2.4±1.7 years. The clinical characteristics of these patients are shown in Table 1 for the entire cohort, while the breakdown by every specific study is presented in the Supplementary on-line Appendix (Table S1).

During the follow up, 2244 of 6580 patients (34.1%) had detection of a daily AF burden of at least 5 minutes. In the competing risk analysis, the cumulative incidence of a daily AF burden ≥5 minutes at 36 months was 40.4% (95%CI: 38.9-41.9%, Figure 1), similarly to the finding of the Kaplan-Meier approach (Figure S1 in the Supplementary Appendix).

The patients with device-detection of AF during follow-up differed from those without AF in terms of a slightly higher age and a slightly higher prevalence of male gender, as well as a lower prevalence of diabetes (Table 1). As shown in Table S2

(Supplementary Appendix), only age ≥ 75 years was an independent predictor of new AF in the cohort (HR 1.32, 95%CI: 1.20-1.45, p<0.001).

As shown in Figure 2, in more than half of the cases the first detected AF burden was of limited duration (between 5 min and less than 1 hour) and in about one-fourth of patients it was between 1 and 6 hours. First device detected AF episodes exceeding 6 hours occurred in less than 20% of patients.

Transition to a higher device-detected AF burden during follow up

The transition to a higher daily AF burden over time was assessed in the 2189 patients available for the transition analysis (Figure S2 in the Supplementary Appendix). This group included the patients with a device-detected AF burden of at least 5 minutes after exclusion of 27 patients with a first AF burden of at least 23 hours and 28 patients with the first AF episode occurring on the last day of follow up. One thousand and ninety-one patients (49.8%) had at least one transition from a lower to a higher category of daily AF burden during follow-up. The proportion of patients who had a transition to a higher daily burden on the day immediately following their first-detected AF burden was 17.5% of the whole group (382/2189) and 35.0% (382/1091) of those with a transition from a lower to a higher AF burden (Figure 3, Panel A). Overall the cumulative incidence of transition to a higher device-detected daily AF burden, as estimated in the competitive risk analysis, was 57.5% (95%CI: 54.8-60.1%) at 36 months and 41.0% (95%CI: 38.8-43.1%) in the first 6 months. Similar results were found using the Kaplan Meier approach. (Figure S3 in the Supplementary Appendix).

As shown in Table 2, multivariable analysis indicated that male gender and a $CHADS_2$ score ≥2 were significant independent predictors of a transition to a higher AF burden following a first device-detected AF event with a daily AF burden of at least 5 min (HR 1.21, 95%CI: 1.06-1.39, p=0.006 and HR 1.22, 95%CI: 1.08-1.37, p=0.002, respectively). In this analysis the variables that were components of $CHADS_2$ score were not included in the model, taking into account collinearity. Another model, that instead excluded $CHADS_2$ score from the analysis, found that male gender, age ≥75 and hypertension were significant independent predictors of transition to a higher AF burden (Table S3 in the Supplementary Appendix).

The time course and incidence of transition to higher AF burden thresholds is shown in Table 3 for every category of AF burden at first detection. As shown, transition to higher AF burdens was common and a higher threshold of daily AF burden at first detection was associated with a faster transition to a subsequent higher burden. For patients with new AF having a first detection in the category between 5 min and less than 1 hour, the transition to upper thresholds occurred after a median time of 1.5-7.0 months. In contrast, the average time of transition decreased when upper AF burden categories were analyzed, becoming less than 1 month, on average, for the category of AF burden at first detection from 6 hours to <12 hours, and even shorter for the highest categories of AF burden.

The transition to a higher threshold of AF burden occurred in variable proportions on the day after the first device-detected AF burden. Furthermore, these early transitions were more common when the first AF event was in a high category of first-detected daily AF burden.

In Figures S4-S7 (Supplementary Appendix), the time to transition to specific thresholds of higher AF burden is shown for every specific category of AF burden at first detection.

In the same cohort of 2189 patients, 520 subjects (23.8%) experienced a transition of daily AF burden from a lower threshold to a daily AF burden of at least 23 hours. The proportion of patients who had a transition to a burden of at least 23 hours on the day immediately following their first-detected AF burden was 8.6% of the whole group (188/2189) and 36.2% (188/520) of those with a transition from a lower burden to a burden of at least 23 hours. Overall, the probability of transition from a lower AF burden to a daily AF burden of at least 23 hours was 29.6% (95%CI: 27.0 – 32.2%) at 36 months (Figure 3, panel B) according to the competing risk analysis. Similar results were found using the Kaplan Meier approach (Figure S8 in the Supplementary Appendix).

The incidence and time course of transition from a lower device-detected daily AF burden to a daily AF burden ≥23 hours differed at the competing risk analysis

according to the category of first device-detected AF burden (Figure 4). The results using the Kaplan Meier approach are shown in Figure S9. As shown in Table 3, 10.1% of patients with an initial AF burden from 5 min to < 1 hour had a transition to a burden ≥ 23 hours (in 0.8% occurring the day following the first detection), 24.5% of patients with an initial AF burden from 1 hour to < 6 hours had a transition to a burden ≥ 23 hours (in 5.3% occurring the day following the first detection), 49% of patients with an initial AF burden from 6 hours to < 12 hours had a transition to a burden ≥ 23 hours (in 20.9% occurring the day following the first detection), and 70.8% of patients with an initial AF burden from 12 hours to < 23 hours had a transition to a burden ≥ 23 hours (in 49% occurring the day following the first detection).

As shown in Table 4, multivariable analysis indicated that male gender and a $CHADS_2$ score ≥2 were significant independent predictors of transition to an AF burden ≥23 hours among patients with a first device detected AF with an AF burden of at least 5 min and <23 hours (HR 1.77, 95%CI: 1.41-2.21 p<0.001, and HR 1.44, 95% CI: 1.20-1.72, p<0.001, respectively). In this analysis the variables that were components of $CHADS_2$ score were not included in the model, taking into account collinearity. Another model, that alternatively excluded $CHADS_2$ score from the analysis, found that male gender and age ≥ 75 were significant independent predictors of transition to an AF burden ≥23 hours (Table S4 in the Supplementary Appendix).

Discussion

The present study shows that in patients implanted with a CIED and no clinical history of AF, device-detected atrial tachyarrhythmias, often reported as atrial high rate episodes or subclinical AF, are common, occurring in more than one-third of patients over a period of 2.4±1.7 years. Our study also shows that, in patients with no clinical history of previous AF, the first occurrence of device-detected tachyarrhythmias is usually an AF burden of short duration, from 5 minutes to few hours. Age was the only significant predictor of detection of new AF (with at least 5 minutes of AF burden). It is noteworthy that $CHADS_2$, while predicting new AF in univariate analysis, did not independently predict new AF at the multivariable analysis.

Our study identifies several predictors of transition to a higher device-detected AF burden, more relevantly to an AF burden of at least 23 hours. Male gender and $CHADS_2$ score (or, alternatively, age ≥ 75 years in another model) were independent predictors of transition from a lower AF burden to an AF burden ≥23 hours. In the literature, different durations of AF burden have been found to be associated with an increased risk of stroke[7,8,18–21] but the threshold at which it is appropriate to initiate OAC in patients at risk is poorly understood and is not defined. Two randomized trials are currently exploring the potential benefits of non-vitamin K antagonists in subclinical AF[13,14]. In the meantime, it appears that the risk of stroke is markedly increased when the duration of the longest episode of AF is more than 24 hours' as shown by the recent analysis of ASSERT data[15], in agreement with previous findings[19].

The findings of the present study provide further elements for clinical judgment in individual cases. A higher threshold of daily AF burden at first detection was associated with faster transition to a subsequent higher category. Moreover, patients with higher $CHADS_2$ scores (2-6 vs. 0-1) experienced a faster transition to a higher AF burden category. In patients with a first device-detected AF burden of at least 6 hours, the median time for transition to an AF burden ≥23 hours was less than 1 month.

This information could guide recommendations for the frequency of monitoring or the frequency of device interrogations for patients presenting with CIED detected AHREs, in order to make appropriate considerations for oral anticoagulation. Through remote monitoring, physicians could be promptly notified of attainment of specific pre-defined thresholds of AF burden, according to physician's choice, on the basis of individual patient considerations. An individualized approach to device-detected AF could thus be considered by integrating baseline risk factors for stroke with timely quantification of AF burden.[11]

Our observation that patients with a first device-detected AF burden of at least 6 hours have a faster transition to ≥ 23hour AF burden may warrant more intensive monitoring in this select group of patients, thereby differentiating this subgroup of patients from those with a lower first device-detected AF burden.

In our study we analyzed device-detected daily AF burden similarly to previous studies that estimated the risk of stroke associated with maximum daily AF burden[8,11,12] . In other studies, the duration of individual AF episodes was analyzed, but this requires careful analysis of every episode in order to correct the consequences of transient phases of under-sensing of the atrial channel that can minimally affect AF burden, but may result in substantial changes in the estimate of individual AF episode duration.[22–24]

A careful review of each stored atrial electrogram for AHRE episodes lasting many minutes to hours is not sustainable in daily practice due to limitations of device storage capability and dedicated personnel. Therefore in order to mimic what happens in daily practice, we considered only the measure of AF burden reported by device diagnostics, the accuracy of which has been previously validated..[23] Of course, as a consequence of using simple device diagnostics for measuring AF burden, a single episode of atrial tachyarrhythmia straddling midnight may be split into AF burden recorded on two consecutive days [8,11,12].

The assessment of each specific daily burden category and of its transition to subsequent higher categories allows the use of a strictly device-specific analysis of atrial tachyarrhythmias. Our study shows that the burdens of device-detected atrial tachyarrhythmias are not homogeneous with transitions from lower to higher AF burden categories depending on the AF burden at first detection, gender, and $CHADS_2$ score. Currently clinical decision making regarding the need for anticoagulation remains uncertain, but if the profile is known to be at risk ($CHADS_2$ score ≥ 2) considerations of the probability of transition to an AF burden ≥ 23 hours can offer further elements to take into account.[15,19]

Our study has some limitations, reported in the Supplementary web-only Appendix.

Conclusions

Patients implanted with a pacemaker, ICD, or CRT device and no previous clinical history of AF, have episodes of device detected atrial tachyarrhythmias $\geq$ 5 min frequently, occurring in around one-third of patients at 2 years of follow up and age is an independent predictor. These device-detected atrial tachyarrhythmias can be

classified in categories of daily AF burden. The transition from lower to higher AF burden categories depends on the AF burden at first detection, and $CHADS_2$ score. The longer the duration of AF burden, the higher the probability of a faster transition to a AF burden $\geq$ 23 hours, a threshold that is associated with an increase in the risk of stroke. The independent predictors of transition from a lower to a higher AF burden are male gender, and $CHADS_2$ score and this may help in individualizing monitoring and clinical surveillance. Continuous long-term EKG monitoring, by capturing transitions to higher AF burden thresholds could support timely anticoagulation decisions in patients with increased risk of stroke and no history of AF.

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Tables

Table 1. Clinical characteristics of the cohort and of patients with and without AF detected during follow up.

	Total (n=6580)	**No AF Detected (n=4336)**	**AF Detected (n=2244)**	**p-value**
Baseline and Demographic Characteristics				
Age (years), mean ± SD	67 ± 12	67 ± 12	68 ± 12	<0.001
Male, n (%)	4569 (69.5%)	2958 (68.3%)	1611 (71.9%)	0.003
Diabetes, n (%)	1734 (28.3%)	1188 (29.2%)	546 (26.4%)	0.019
Hypertension, n (%)	3754 (61.6%)	2527 (62.5%)	1227 (60.0%)	0.060
Heart failure, n (%)	6465 (56.6%)	2399 (56.3%)	1257 (57.0%)	0.615
***CHADS* ≥ *2*, n (%)**	3735 (56.8%)	2475 (57.1%)	1260 (56.1%)	0.470
Prior stroke, n (%)	293 (4.7%)	207 (5.0%)	86 (4.1%)	0.125
Implanted device				
Pacemaker, n (%)	2555 (38.8%)	1672 (38.6%)	883 (39.3%)	0.100
ICD, n (%)	1401 (21.3%)	960 (22.1%)	441 (19.7%)	
CRT, n (%)	2586 (39.3%)	1677 (38.7%)	909 (40.5%)	

Table 2. Predictors of transition to a higher AF burden following first device-detected AF with an AF burden of at least 5 min (excluding from the multivariable analysis the individual components of $CHADS_2$ score).

	Univariate		**Multivariate**	
Parameter	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**
Male Gender*	**1.22 (1.06 - 1.40)**	**0.006**	1.21 (1.06-1.39)	0.006
Age ≥ 75	**1.18 (1.04 - 1.34)**	**0.009**		
Diabetes	1.08 (0.94 - 1.24)	0.281		
Prior Stroke	1.00 (0.73 - 1.38)	0.982		
Hypertension	**1.24 (1.09 - 1.41)**	**0.001**		
Heart Failure	1.07 (0.95 - 1.21)	0.253		
$CHADS_2$ ≥ 2*	**1.22 (1.08 - 1.38)**	**0.001**	1.22 (1.08 - 1.37)	0.002
CRT	1.04 (0.92 - 1.17)	0.514		

*Included in the stepwise multivariable method.

Table 3. Transition to a specific category of higher device-detected daily AF burden for patients presenting specific categories of AF burden at first detection.

Patients (N= 1165) with first AF burden from 5 Minutes to < 1hour.					
	Patients with transition (%)	Median time of transition, months (95% CI)	Patients of this AF burden subgroup with transition occurring the day after the first device-detected AF burden (%)	6-Months Incidence of transition to a higher AF burden (95% CI)	36-Months Incidence of transition to a higher AF burden (95% CI)
Transition to an AF burden ≥ 1 hour	497 (42.7%)	1.4 (0.1-6)	96 (8.2%)	33.5% (30.7-36.3%)	50.5% (46.8-54.1%)
Transition to an AF burden ≥ 6 hours	267 (22.9%)	3.1 (0.3-10.6)	35 (3%)	15.3% (13.2-17.5%)	29.9% (26.4-33.5%)
Transition to an AF burden ≥ 12 hours	178 (15.3%)	3.8 (0.4-13.4)	20 (1.7%)	8.9% (7.3-10.7%)	21.3% (18.0-24.7%)
Transition to an AF burden ≥ 23 hours	118 (10.1%)	6.9 (0.8-14.9)	9 (0.8%)	5.1% (3.9-6.5%)	14.5% (11.7-17.6%)

Patients (N= 588) with first AF burden from 1 hour to <6 hours					
	Patients with transition (%)	Median time of transition, months (95% CI)	Patients of this AF burden subgroup with transition occurring the day after the first device-detected AF burden (%)	6-Months Incidence of transition to a higher AF burden (95% CI)	36-Months Incidence of transition to a higher AF burden (95% CI)
Transition to an AF burden ≥ 6 hours	307 (52.2%)	0.6 (0.1-4.3)	103 (17.5%)	42.2% (38.1-46.3%)	61.8% (56.2-66.9%)
Transition to an AF burden ≥ 12 hours	222 (37.8%)	1.2 (0.1-9.5)	68 (11.6%)	27.5% (23.9-31.3%)	45.3% (39.9-50.6%)
Transition to an AF burden ≥ 23 hours	144 (24.5%)	2.9 (0.1-14.7)	31 (5.3%)	16.0% (13.1-19.2%)	29.6% (26.7-34.6%)

Patients (N= 234) with first AF burden from 6 hours to <12 hours					
	Patients with transition (%)	Median time of transition, months (95% CI)	Patients of this AF burden subgroup with transition occurring the day after the first device-detected AF burden (%)	6-Months Incidence of transition to a higher AF burden (95% CI)	36-Months Incidence of transition to a higher AF burden (95% CI)
Transition to an AF burden ≥ 12 hours	144 (61.5%)	0.03 (0.03-2)	84 (35.9%)	55.8% (49.1-62.0%)	65.1% (57.5-71.7%)
Transition to an AF burden ≥ 23 hours	115 (49.1%)	0.07 (0.03-2.6)	49 (20.9%)	40.6% (34.2-46.8%)	56.4% (47.9-64.0%)

Patients (N= 202) with first AF burden from 12 hours to <23 hours					
	Patients with transition (%)	Median time of transition, months (95% CI)	Patients of this AF burden subgroup with transition occurring the day after the first device-detected AF burden (%)	6-Months Incidence of transition to a higher AF burden (95% CI)	36-Months Incidence of transition to a higher AF burden (95% CI)
Transition to an AF burden ≥ 23 hours	143 (70.8%)	0.03 (0.03-0.16)	99 (49%)	63.1% (56.0-69.4%)	78.2% (67.0-86.0%)

Table 4. Predictors of transition to a AF burden ≥23 hours following first device detected AF with a AF burden of at least 5 min (excluding from the multivariable analysis the individual components of $CHADS_2$ score).

	Univariate		**Multivariate**	
Parameter	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**
Male Gender *	**1.78 (1.42 - 2.22)**	**<0.001**	1.77 (1.41 - 2.21)	<0.001
Age ≥ 75	**1.32 (1.10 - 1.58)**	**0.003**		
Diabetes	1.09 (0.88 - 1.33)	0.430		
Prior Stroke	1.13 (0.73 - 1.75)	0.586		
Hypertension	**1.26 (1.04 - 1.52)**	**0.017**		
Heart Failure	**1.19 (0.99 - 1.42)**	**0.060**		
$CHADS_2$ ≥ 2 *	**1.45 (1.21 - 1.73)**	**<0.001**	1.44 (1.20 - 1.72)	<0.001
CRT	**1.26 (1.06 - 1.50)**	**0.008**		

***Included **in** the stepwise multivariable method

Figure legends

Figure 1. Incidence of first device-detected AF, considered as daily AF burden ≥ 5 min, taking into account the competing risk of death.

Figure 2. Distribution of AF daily burden for first device-detected AF.

Figure 3. panel A. Incidence of transition from a lower to a higher category of daily AF burden in patients with a first device detected AF burden of at least 5 min, taking into account the competing risk of death**.**

Figure 3, panel B. Incidence of transition from a lower daily AF burden to a daily AF burden ≥23 hours in patients with a first device detected AF of at least 5 min, taking into account the competing risk of death.

Figure 4. Incidence of transition to AF burden ≥ 23 hours for patients characterized by different AF burden categories at first AF detection, taking into account the competing risk of death.

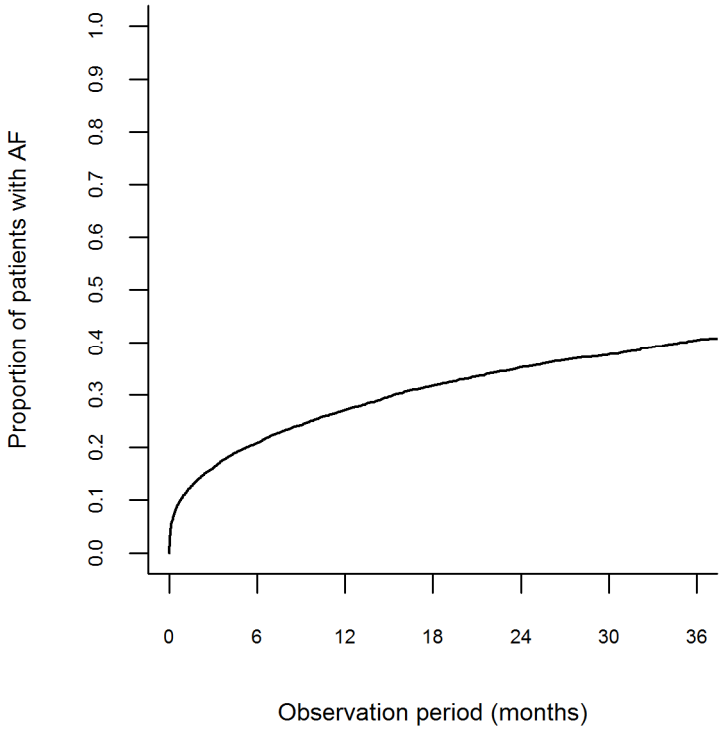


Figure 1. Incidence of first device-detected AF, considered as daily AF burden ≥ 5 min, taking into account the competing risk of death.

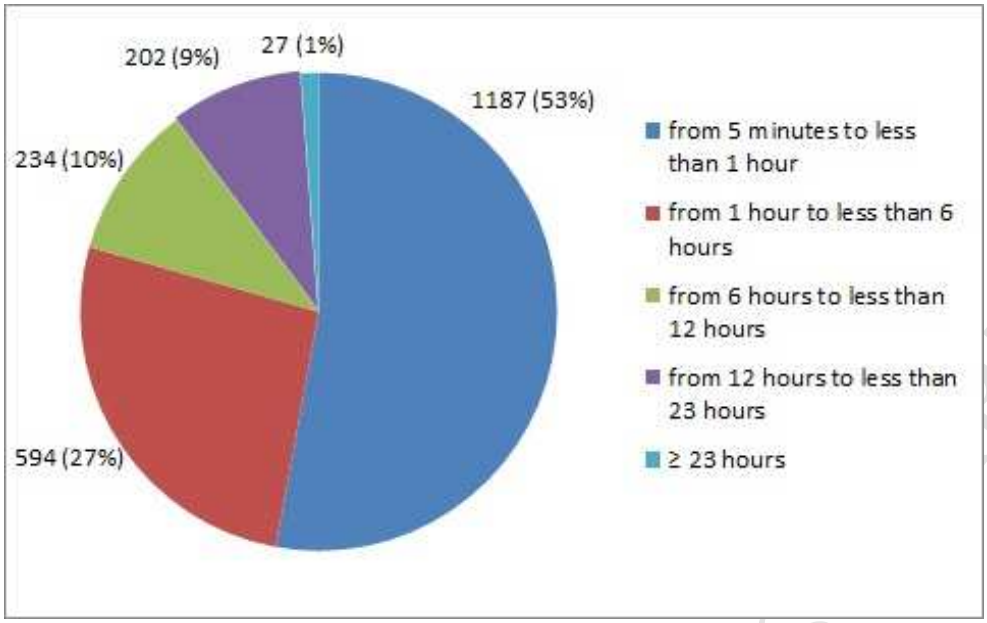


Figure 2. Distribution of AF daily burden for first device-detected AF.

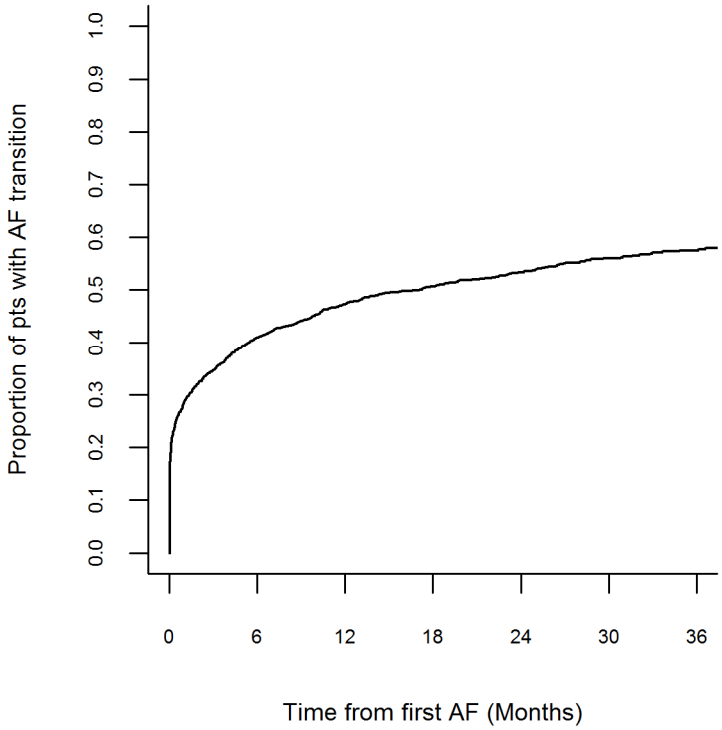


Figure 3. panel A. Incidence of transition from a lower to a higher category of daily AF burden in patients with a first device detected AF burden of at least 5 min, taking into account the competing risk of death.

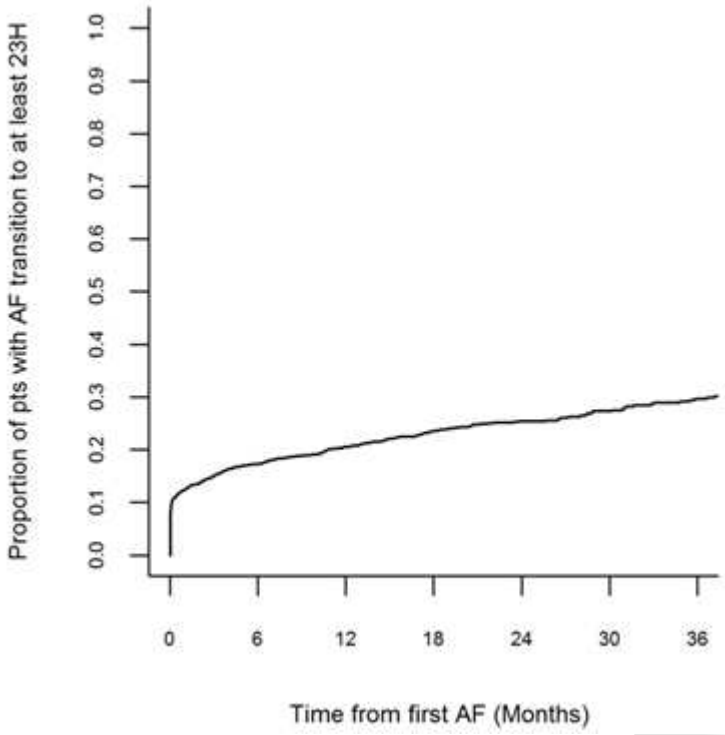


Figure 3, panel B. Incidence of transition from a lower daily AF burden to a daily AF burden ≥23 hours in patients with a first device detected AF of at least 5 min, taking into account the competing risk of death.

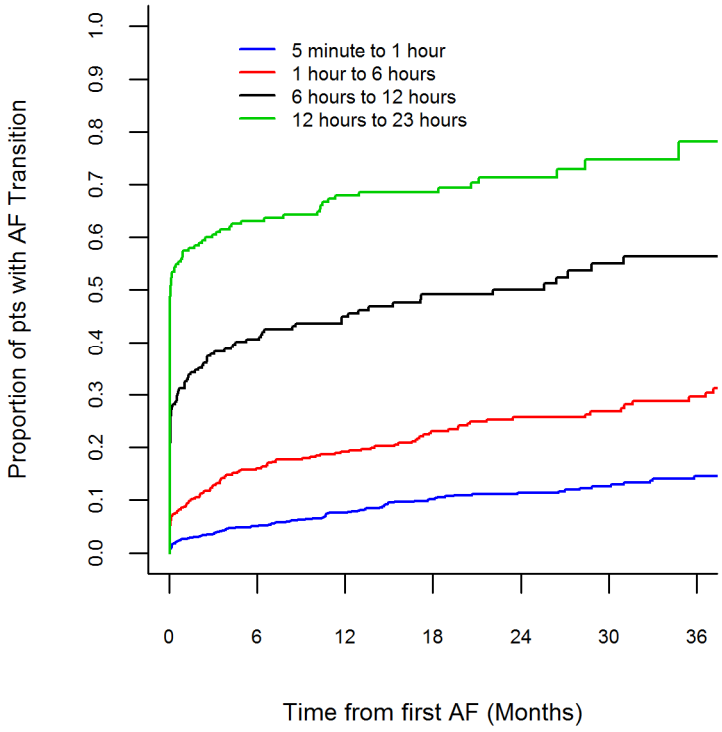
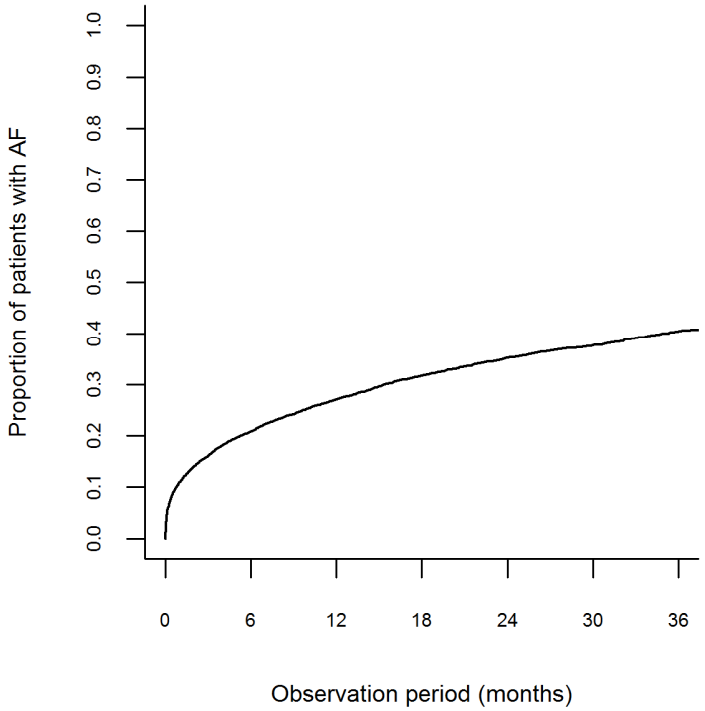
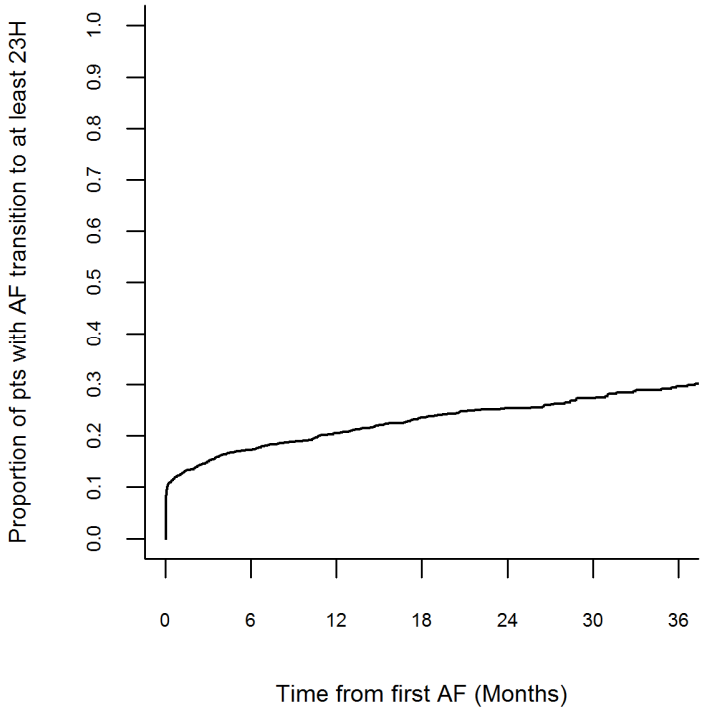
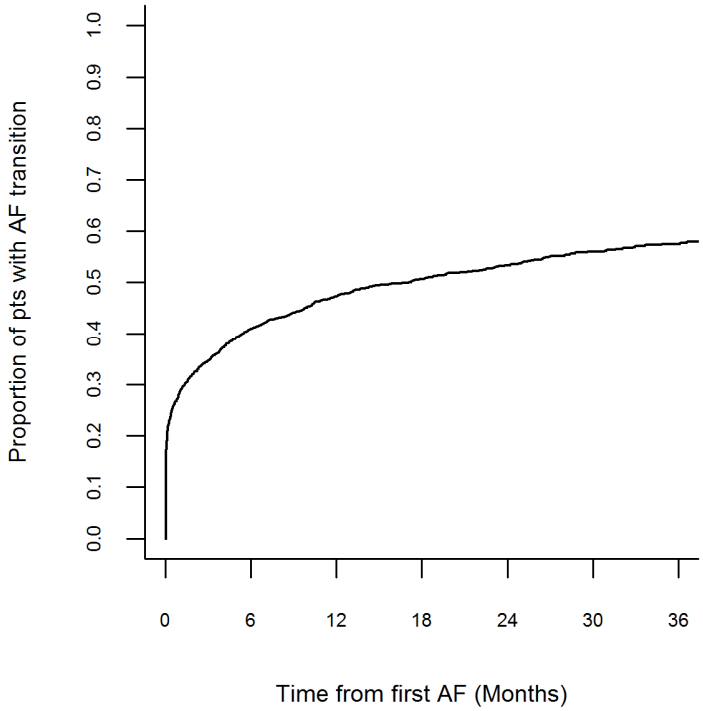
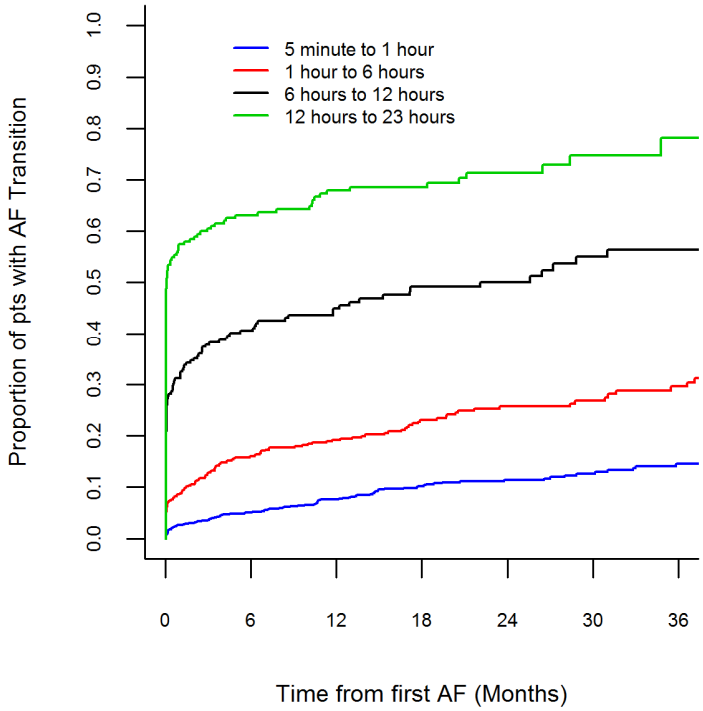


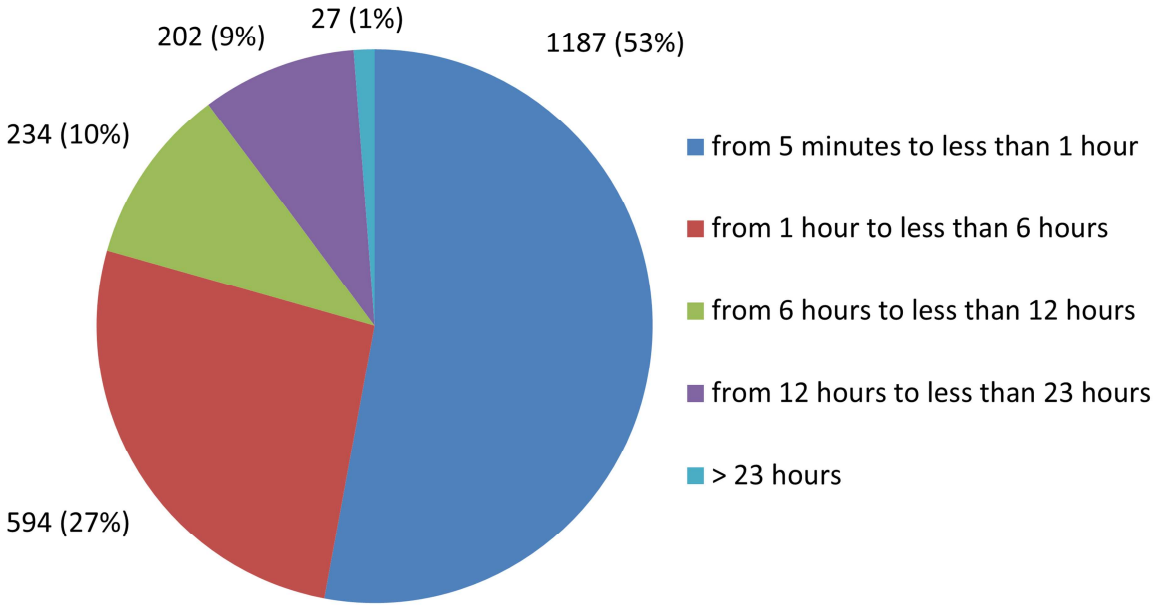
Figure 4. Incidence of transition to AF burden ≥ 23 hours for patients characterized by different AF burden categories at first AF detection, taking into account the competing risk of death.










27 (1%)
202 (9%)
1187 (53%)
234 (10%)
594 (27%)
from 5 minutes to less than 1 hour
from 1 hour to less than 6 hours
from 6 hours to less than 12 hours
from 12 hours to less than 23 hours
> 23 hours