Journal Pre-proof

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PII: S1547-5271(22)00035-2

DOI: https://doi.org/10.1016/j.hrthm.2022.01.020

Reference: HRTHM 9120

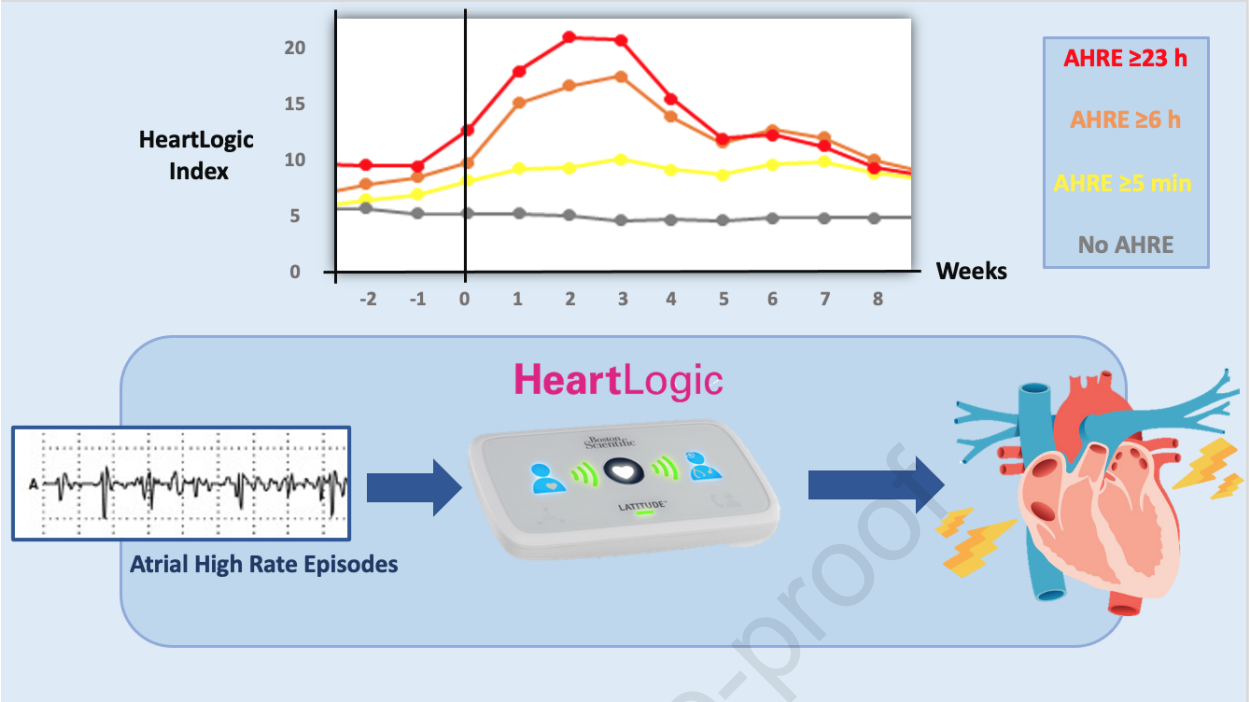
To appear in: *Heart Rhythm*

Received Date: 27 November 2021

Revised Date: 6 January 2022

Accepted Date: 12 January 2022

Please cite this article as: Bertini M, Vitali F, Santini L, Tavoletta V, Giano A, Savarese G, Dello Russo A, Santobuono VE, Mattera A, Lavalle C, Amellone C, Pecora D, Calvanese R, Rapacciuolo A, Campari M, Valsecchi S, Calò L, Implantable defibrillator-detected heart failure status predicts atrial fibrillation occurrence, *Heart Rhythm* (2022), doi: https://doi.org/10.1016/j.hrthm.2022.01.020.



Implantable defibrillator-detected heart failure status predicts atrial fibrillation occurrence

Bertini: Heart Failure Status predicts atrial fibrillation.

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TOTAL WORD COUNT: 2636

KEYWORDS: *ICD; CRT; atrial fibrillation; heart failure; risk stratification.*

CONFLICT OF INTEREST: M. Campari and S. Valsecchi are employees of Boston Scientific.

The other authors report no conflicts.

ABSTRACT

*Background:*In heart failure(HF) patients, atrial fibrillation(AF) is associated with a worse prognosis. Implantable defibrillator(ICD) diagnostics allow continuous monitoring of AF, and are equipped with algorithms for HF monitoring.

*Objective:*We evaluated the association between the values of the multisensor HF HeartLogic Index and the incidence of AF, and assessed the performance of the Index in detecting follow-up periods of significantly increased AF risk.

*Methods:*The HeartLogic feature was activated in 568 ICD patients. The median follow-up was 25 months[25th–75th percentile:15-35]. The HeartLogic algorithm calculates a daily HF index and identifies periods IN the alert state on the basis of a configurable threshold. The endpoints were: daily AF burden of ≥5minutes, ≥6hours and ≥23hours.ClinicalTrials.gov(identifier:NCT02275637).

*Results:*The HeartLogic index crossed the threshold value 1200 times. AF burden of ≥5 minutes/day was documented in 183(32%) patients, ≥6 hours/day in 118(21%) patients, and ≥23 hours/day in 89(16%). The weekly time IN the alert state was independently associated with an AF burden of ≥5 minutes/day (HR:1.95, 95%CI:1.22-3.13, p=0.005), ≥6 hours/day (HR:2.66, 95%CI:1.60-4.44, p<0.001), and ≥23 hours/day (HR:3.32, 95%CI:1.83-6.02, p<0.001), after correction for baseline confounders. Comparison of the episode rates in the IN-alert state with those in the OUT-of-alert state yielded HRs ranging from 1.57 to 3.11 for AF burden from ≥5 minutes to ≥23 hours.

*Conclusions:*The HeartLogic alert state was independently associated with AF occurrence. The intervals of time defined by the algorithm as periods of increased risk of HF allow risk stratification of AF according to various thresholds of daily burden.

INTRODUCTION

In heart failure (HF) patients, atrial fibrillation (AF) is a common comorbidity and is associated with a worse prognosis (1-3). The use of implantable defibrillators (ICD) and defibrillators for resynchronization therapy (CRT-D) has been demonstrated to improve the outcome of selected HF patients, and is currently recommended for the management of chronic HF (4). Device diagnostics allow continuous monitoring of cardiac arrhythmias and accurate evaluation of the occurrence atrial of high-rate events (AHRE) as a surrogate of AF (5). Moreover, some modern devices are equipped with automated algorithms that provide detailed information on the HF condition, concurrently with AF progression, on a daily basis. In the Multisensor Chronic Evaluation in Ambulatory Heart Failure Patients (MultiSENSE) study (6), a novel algorithm for HF monitoring was implemented: the HeartLogic (Boston Scientific, St. Paul, Minnesota) index, which combines data from multiple ICD- and CRT-D-based sensors. This proved to be a sensitive and timely predictor of impending HF decompensation. In the present study, we sought to evaluate the association between the Index values and the incidence of AF, and to assess the performance of the Index in detecting follow-up periods of significantly increased AF risk.

METHODS

At 26 study centers (full list of participating centers in Supplemental Material section) HeartLogic was activated in all HF patients with reduced left ventricular ejection fraction (≤35% at the time of implantation) who had received a HeartLogic-enabled ICD or CRT-D device (RESONATE family, Boston Scientific) in accordance with standard indications (4), and were enrolled in the LATITUDE (Boston Scientific) remote monitoring platform. Patients were followed up in accordance with the standard practice of the participating centers, based on current international recommendations (7). Clinics periodically checked the remote monitoring website for transmissions. Data on the clinical events that occurred during follow-up were collected at the study centers in the framework of a prospective registry. The Institutional Review Boards approved the study, and all patients provided written informed consent for data storage and analysis. This project is registered on

ClinicalTrials.gov (identifier: NCT02275637).

Association between HeartLogic alert state and atrial fibrillation occurrence

The objective of the study was to investigate the association between the HeartLogic Index values calculated by the ICD algorithm and the incidence of AHRE during the post-enrollment follow-up period, and to evaluate the performance of the HeartLogic Index in detecting follow-up periods of significantly increased AHRE risk. Current guidelines for the diagnosis and management of AF consider AHRE to be an expression of subclinical AF (8). The incidence and duration of AHRE were derived from device data, which comprise the total time spent by the patient in AHRE on each day of the follow-up period. As recommended, AHRE were visually inspected by a local expert electrophysiologist for excluding artefacts or other causes of inappropriate detection (8). In the present study, patients were considered to have experienced AHRE episodes as surrogate of AF episodes if the device detected a cumulative daily duration ≥5 minutes, ≥6 hours, ≥23 hours, in agreement with previous studies (9).

HeartLogic algorithm

The details of the HeartLogic algorithm have been reported previously (6). Briefly, the algorithm combines data from multiple sensors: accelerometer-based first and third heart sounds, intrathoracic impedance, respiration rate, the ratio of respiration rate to tidal volume, night heart rate, and patient activity. Each day, the device calculates the degree of worsening in sensors from their moving baseline and computes a composite index. An alert is issued when the index crosses a programmable threshold (nominal value 16). When the index enters into an alert state, the "exit-alert" threshold is automatically dropped to a recovery value (nominal value 6).

Statistical analysis

Descriptive statistics are reported as means±SD for normally distributed continuous variables, or medians with 25th to 75th percentiles in the case of skewed distribution. Normality of distribution was tested by means of the nonparametric Kolmogorov–Smirnov test. Categorical data are expressed as percentages. Analysis of the time to the first episode was made by means of the

Kaplan-Meier method. Cox proportional hazards models were used to determine the association between the occurrence of AHRE episodes during the follow-up period and baseline characteristics, and to estimate the hazard ratios (HRs) and the 95% confidence intervals (CIs) of an episode. The weekly value of IN- or OUT-of-alert state was also treated as a time-varying covariate by means of time-dependent Cox models. All variables displaying statistical significance (p-value <0.05) were entered into a multivariate regression analysis. To evaluate the performance of the Index in detecting follow-up periods of significantly increased AHRE risk, we compared the IN- and OUT-of-alert periods in terms of time to the first AHRE episode by means of the Anderson–Gill model, an extension of the Cox proportional hazards model that takes into account multiple evaluations in patients. The model was adjusted for those baseline variables that proved to be associated with the occurrence of AHRE on univariate analysis. IN-alert periods started when the HeartLogic index crossed the threshold, and ended at the time of the first AHRE episode, or were censored when the index decreased to below the recovery threshold (or at the end of follow-up). OUT-of-alert periods started on the day of HeartLogic activation (at the end of the initialization period) or at the end of a previous IN-alert period, and ended at the time of the first AHRE episode, or were censored when the index rose above the threshold (or at the end of follow-up). The time-course of HeartLogic index and sensor changes surrounding the AHRE episode was described by recording average weekly values over the weeks before and after the first AHRE occurrence. For control purposes, averaged sensor data were calculated in patients who did not have AHRE episodes during clinical follow-up. All statistical analyses were performed by means of R: a language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

From December 2017 to June 2021, HeartLogic was activated in 568 patients who had received an ICD or CRT-D. Table 1 shows the baseline clinical variables of all patients in analysis.

Follow-up

The median follow-up was 25 months [25th-75th percentile: 15-35] (a total of 1159 patient-years).

The HeartLogic index crossed the threshold value 1200 times (0.71 alerts/patient-year) in 370 patients. Overall, the time IN the alert state was 151 years (13% of the total observation period). The median time IN the alert state was 7% [25th-75th percentile: 0%-21%]. During the observation period, 36 patients died of any cause. An AF burden of ≥5 minutes/day was documented in 183 (32%) patients, ≥6 hours/day in 118 (21%) patients, and ≥23 hours/day in 89 (16%) patients. AF episodes that occurred during the algorithm initialization period (59 episodes ≥5 minutes, 39 episodes ≥6 hours and 29 episodes ≥23 hours) were excluded from the analysis of the association between episodes and weekly Index values.

Association between HeartLogic alert state and atrial fibrillation occurrence

Figure 1 shows the Kaplan–Meier analysis of time from the implantation to the first episode of AF burden ≥5 minutes, ≥6 hours and ≥23 hours. Patients are stratified according to the occurrence of at least one HeartLogic alert. The results of the regression analysis of baseline variables associated with AHRE occurrence, according to various thresholds of daily AF burden, are shown in Table 2. On using a time-dependent Cox model, the weekly IN-alert state was independently associated with an AF burden of ≥5 minutes/day (HR:1.95, 95%CI:1.22-3.13, p=0.005), ≥6 hours/day (HR:2.66, 95%CI:1.60-4.44, p<0.001), and ≥23 hours/day (HR:3.32, 95%CI:1.83-6.02, p<0.001), after correction for age, history of AF, chronic kidney disease, and pulmonary disease (Figure 2).

Figure 3 shows the Kaplan–Meier plot of the time to the first AHRE episode, according to various thresholds of daily AF burden (≥5 minutes, ≥6 hours, ≥23 hours), in the IN- and OUT-of-alert states. Comparison of the episode rates in the IN-alert state with those in the OUT-of-alert state yielded HRs of: 1.57, 95% CI: 1.04-2.50, p=0.042 for AF burden ≥5 minutes; 2.06, 95% CI: 1.22-3.47, p=0.007 for AF burden ≥6 hours, and 3.11, 95% CI: 1.73-5.57, p<0.001 for AF burden ≥23 hours, in models adjusted for those baseline clinical variables that had proved to be associated with the occurrence of episodes on univariate analysis (Table 2).

Figure 4 shows the Kaplan–Meier plot of the time to first HeartLogic alert after the detection of AF burden ≥5 minutes, ≥6 hours, ≥23 hours. For comparison it is reported the group of patients who did not have AHRE during follow-up (overall log-rank test, p<0.001).

Sensor data findings

The trends in the average HeartLogic index and sensor values surrounding the first AHRE episode, according to various thresholds of daily AF burden, are reported in Figure 5 and in Supplemental Figure 1. Average sensor data from clinically stable periods (from patients who did not have AF events during follow-up) are reported for comparison.

DISCUSSION

In the present study, we described the association between the patient's HF status, as evaluated by the HeartLogic algorithm, and the incidence of AF, and we assessed the performance of the HeartLogic Index in detecting follow-up periods of significantly increased AF risk. The main findings were: 1) the HeartLogic alert state was independently associated with an AF burden of ≥5 minutes/day (HR: 1.95), ≥6 hours/day (HR: 2.66), and ≥23 hours/day (HR: 3.32); 2) the intervals of time defined by the algorithm as periods of increased risk of HF also allow risk stratification of AF according to various thresholds of daily burden (≥5 minutes/day, ≥6 hours/day and ≥23 hours/day). Atrial fibrillation is a frequent comorbidity in HF patients, and is associated with a significantly increased risk of mortality, morbidity and HF progression (1-3, 10). Electronic implantable cardiac devices allow long-term continuous monitoring of atrial arrhythmias. Very short device-detected AHRE are usually considered clinically irrelevant, but longer episodes (≥5 minutes/day) are associated with an increased risk of clinical AF, ischemic stroke, major adverse cardiovascular events and cardiovascular death (11,12). Modern algorithms for HF monitoring are based on the combination of multiple ICD-measured clinically relevant physiological variables, and allow accurate continuous, automatic HF diagnosis. They have been proposed as predictors of impending HF decompensation (6) that can trigger timely interventions and identify periods of increased risk of HF, in order to better triage resources to the most vulnerable population (13). Such tools not only

enable the association between HF status and the onset of AF to be analyzed; they can also shed light on the reciprocal causal mechanisms of HF and AF and identify predisposing factors that could be targets of specific therapies.

In the present study, we enrolled one of the largest populations of patients with devices (not only CRT-D) equipped with the HeartLogic algorithm, and followed them up over the longest period reported to date (median 25 months). We confirmed the rate of HeartLogic alerts and the amount of time IN the alert state that had previously been measured during algorithm validation (6) and in initial experiences in clinical practice (14,15).

In our analysis, patients who experienced at least one ICD-diagnosed HF event were those at greatest risk of having AHRE occurrence, according to various thresholds of daily AF burden. The clinical relevance of shorter versus longer AHRE episodes differs according to the clinical outcome observed. Indeed, although the risk of stroke is markedly increased when the duration of the longest episode of AF is >24 hours (16), the risk of HF hospitalization seems higher in the case of new-onset AF than in longer-lasting AF (17). Nonetheless, recent findings suggest that the transition from shorter to longer AHRE is common (9) and that progression to longer maximum daily AF burden is associated with an increased risk of HF hospitalization (18). In our study, apart from identifying patients at higher risk of AF on the basis of the occurrence of HF alerts during follow-up, we showed the association between AF and the continuously measured weekly HeartLogic Index by using a time-dependent model. Thus, we demonstrated the ability of the algorithm to dynamically stratify patients during follow-up. In this study, the weekly IN-alert state during follow-up identified patients who were from two- to more than three-fold more likely to experience an AHRE episode, according to various thresholds of daily AF burden (≥5 minutes, ≥6 hours, ≥23 hours). Moreover, the consequences of AF on HF progression are also evident. Indeed, detection of AHRE was significantly associated with subsequent HeartLogic alerts, i.e. a surrogate of HF decompensation. Therefore, we observed a robust association between the HeartLogic alert state and AF, and this association was even stronger when the AF burden was higher. The association

between the IN-alert state and AF was confirmed even after correction for risk factors assessed during baseline evaluation (i.e. age, history of AF, chronic kidney disease and pulmonary disease), which, by contrast, seemed to lose their significance when included in multivariate models that included a predictor analyzed over time. In our analysis, we found that chronic kidney disease was independently related only with longer AF episodes. Indeed, the extensive structural and electrical atrial remodeling in patients with chronic kidney disease creates the substrate for potentially longer AF episodes and exposes these patients to a higher risk of thromboembolic-related adverse events (19). More than simple risk stratification, the dynamic nature of the association between HF status and AF seems to confirm the causal mechanisms that have been proposed to explain the link between HF and AF (20,21), i.e. structural cardiac remodeling, activation of neurohormonal systems, and rate-related left ventricular impairment.

With the HeartLogic algorithm, an alert is issued when the index crosses a programmable threshold, in order to promptly identify patients at higher HF risk (6). Recently, it has been demonstrated that the time to the first HF event is significantly shorter in the IN-alert state than in the OUT-of-alert state (15). In the present study, we showed that the same applies to the onset of AF, which occurs earlier when a patient enters an IN-alert state period. From a practical point of view, this could have important implications. Moreover, it has recently been shown that the rate of HF events is lower when the HeartLogic alerts prompt clinical actions (15); and the same could apply to the onset of AF. Early HF intervention might reduce the risk of AF. Indeed, diuretics for congestion relief may reduce sympathetic drive, thereby reducing AF incidence or increasing the chance of spontaneous return to sinus rhythm. Similarly, other treatments for HF, such as ACE-inhibitors (8) and optimal CRT (22), may reduce the risk of developing AF. Moreover, treatments for AF, such as cardioversion, amiodarone (23) and catheter ablation (24), may, in turn, improve HF outcomes. Overall, it is exciting to think that these findings could lead to the construction of management flowcharts that include decongestive treatments, antiarrhythmic therapies and stroke prevention strategies, in response to the automatic sensors of implanted devices. The availability of multiple

ICD-measured physiological variables can further facilitate the identification of targeted interventions. Indeed, our analysis of pre-event trends confirmed the sensitivity of the sensors and their ability to suggest the mechanism that triggers the arrhythmia. For example, a high third heart sound amplitude is suggestive of elevated filling pressure (25), low thoracic impedance is indicative of more severe congestion (26), and a high respiratory rate is associated with elevated pulmonary venous pressure, loss of contraction and abnormal compliance of the left atrium (27). Continuous multi-parameter monitoring also facilitates the evaluation of the post-AF onset phase. Indeed, as commented before, detection of AHRE was significantly associated with subsequent HeartLogic alerts according to the Kaplan-Meier analysis. Moreover, the analysis of trends showed that, even in the case of AHRE of shorter duration, the consequences of the AF occurrence persist, in terms of deviations of the global index and of the contributing sensors. Initial experiences have shown that timely HF treatment in response to HeartLogic alerts can be effective in reducing the rate of HF events and may shorten IN-alert periods (28); plausibly, it may also result in a lower rate of AF events.

Limitations

Our study has some limitations. First, its observational design may have introduced an inherent bias. Second, device-detected AHRE are a surrogate of subclinical - and not clinical - AF, which has different clinical implications.

Third, AF occurrence may directly affect some of the contributing sensors (e.g. increased heart rate), determining an increase in the index not associated with worsened HF. However, for an alert to be generated, the algorithm requires the occurrence of several conditions, which depend also on other sensors (e.g. thoracic impedance, respiration), less sensitive to the immediate changes induced by the onset of AF. Moreover, this bias could have affected the analysis of the time between the onset of AF and the HF alert, but not the analysis of the risk of AF during periods IN the alert state, in which the alert had to precede the AF onset. Finally, larger studies targeting stroke risk and HF progression are needed in order to confirm these results and assess the clinical consequences of our

findings.

Conclusions

In the present study, patients who experienced ICD-diagnosed HF events were at greatest risk of AF occurrence and viceversa. The HeartLogic IN-alert state during follow-up identified patients who were from two- to more than three-fold more likely to experience an AHRE episode, according to various thresholds of daily AF burden.

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FIGURE LEGENDS

Figure 1. Kaplan–Meier analysis of time to first event of AF burden ≥5 minutes, ≥6 hours, ≥23 hours. Patients are stratified according to the occurrence of at least one HeartLogic alert.

Figure 2. Results of the time-dependent Cox model. Association between weekly IN-alert state and AF burden ≥5 minutes/day, ≥6 hours/day and ≥23 hours/day, after adjusting for clinical variables.

Figure 3. Kaplan–Meier plot of the time to the first AHRE event, according to various thresholds of daily AF burden (≥5 minutes, ≥6 hours, ≥23 hours), in the IN- and OUT-of-alert states.

Figure 4. Kaplan–Meier analysis of time to first HeartLogic alert after the detection of AF burden ≥5 minutes, ≥6 hours, ≥23 hours. For comparison it is reported the no AF group: patients who did not have AHRE during follow-up (for them, day 0 is a random day during the observation period).

Figure 5. Average HeartLogic index surrounding the first AHRE event, according to various thresholds of daily AF burden (**yellow trend:** ≥5 minutes, **orange trend:** ≥6 hours, **red trend:** ≥23 hours). Average sensor data from clinically stable periods (**gray trend:** from patients who did not have AHRE events during follow-up) were aligned on a random day during the observation period and are reported for comparison. (week 0 is the week of the AHRE event).

Table 1. Demographics and baseline clinical parameters of the study population.

Parameter	Total N=568
Male gender, n (%)	453 (80)
Age, years	69±10
Ischemic etiology, n (%)	285 (50)
NYHA class	
– Class I, n (%)	36 (6)
– Class II, n (%)	351 (62)
– Class III, n (%)	171 (30)
– Class IV, n (%)	10 (2)
LV ejection fraction, %	32±9
AF history, n (%)	196 (35)
Diabetes, n (%)	167 (29)
COPD, n (%)	89 (16)
Chronic kidney disease, n (%)	153 (27)
Hypertension, n (%)	334 (59)
β-Blocker use, n (%)	520 (92)
ACE-inhibitor, ARB or ARNI use, n (%)	536 (94)
Diuretic use, n (%)	506 (89)
Antiarrhythmic use, n (%)	116 (20)
Ivabradine use, n (%)	37 (7)
CRT device, n (%)	410 (72)
Primary prevention, n (%)	500 (88)

NYHA = New York Heart Association; LV = Left ventricular; AF = Atrial fibrillation; COPD = Chronic obstructive pulmonary disease; ACE = Angiotensin-converting enzyme; ARB = Angiotensin II receptor blockers; ARNI = Angiotensin receptor-neprilysin inhibitor; CRT = Cardiac resynchronization therapy.

Table 2. Univariate analysis of baseline variables associated with AF occurrence.

	AF burden of ≥5 minutes			AF burden of ≥6 hours			AF burden of ≥23 hours		
	HR	**95% CI**	**p**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**p**
Age	1.02	1.01-1.04	0.005	1.04	1.02-1.06	<0.001	1.04	1.01 - 1.06	0.002
Male gender	0.80	0.56-1.14	0.226	0.87	0.55-1.35	0.532	0.87	0.52-1.46	0.613
NYHA Class	0.98	0.77-1.24	0.865	1.14	0.85-1.53	0.374	1.06	0.76-1.50	0.720
Ischemic Heart Disease	1.14	0.85-1.52	0.373	0.98	0.69-1.41	0.985	1.00	0.66-1.51	1.000
Ejection fraction	0.99	0.98-1.01	0.663	1.01	0.99-1.03	0.565	1.00	0.98-1.03	0.821
History of AF	1.69	1.26-2.26	<0.001	3.26	2.26-4.71	<0.001	4.14	2.67-6.41	<0.001
Hypertension	0.79	0.59-1.06	0.120	0.90	0.62-1.29	0.559	0.96	0.63-1.46	0.841
Pulmonary disease	1.29	0.89-1.86	0.185	1.60	1.04-2.47	0.033	1.73	1.06-2.81	0.029
Diabetes	0.78	0.56-1.08	0.143	0.83	0.55-1.24	0.368	0.88	0.55-1.39	0.584
Chronic kidney disease	1.26	0.92-1.71	0.155	2.03	1.41-2.92	<0.001	1.95	1.28-2.97	0.002
≥1 HeartLogic alert	1.43	1.03-1.99	0.035	2.40	1.49-3.87	<0.001	3.14	1.71-5.75	<0.001

NYHA = New York Heart Association; AF = Atrial fibrillation.

Figure 1.

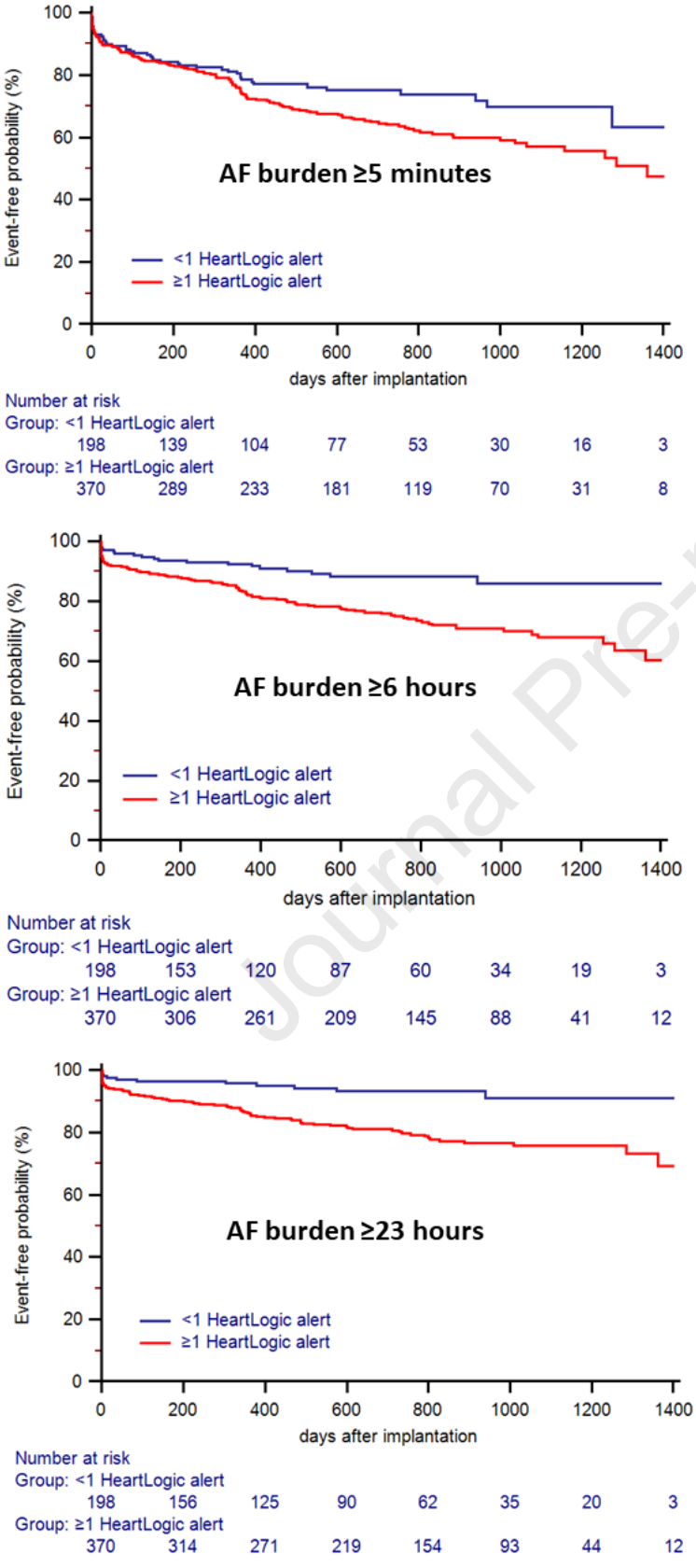
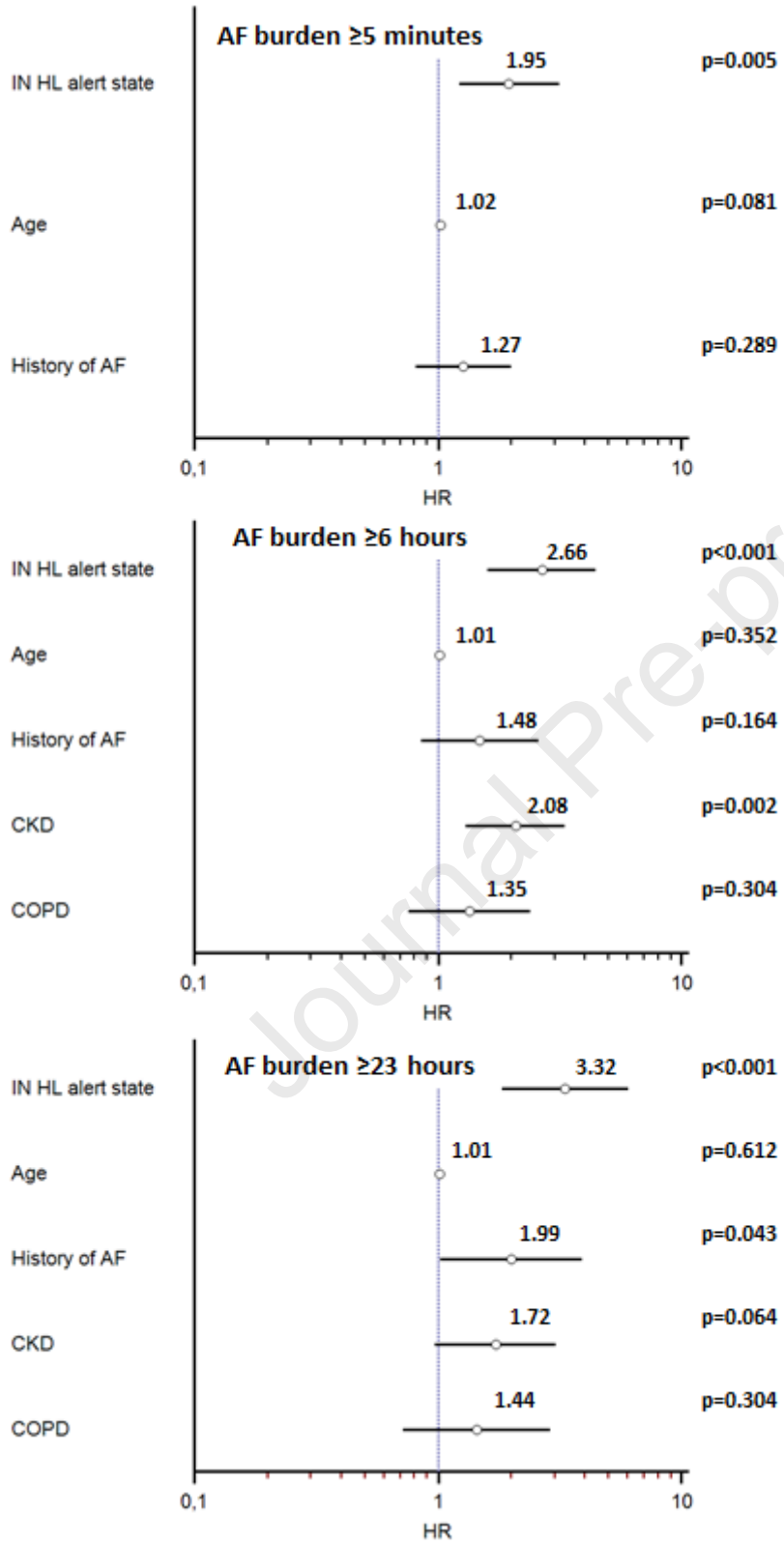


Figure 2.



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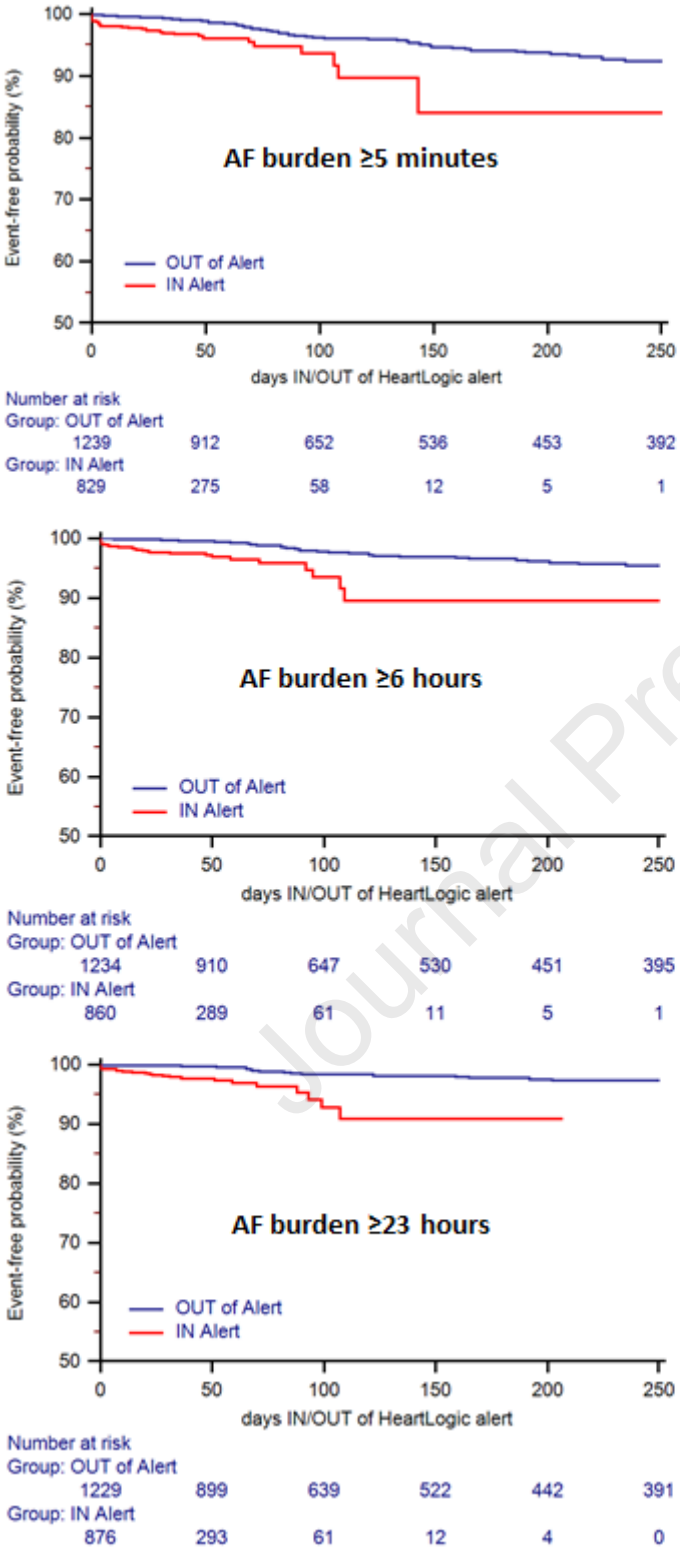
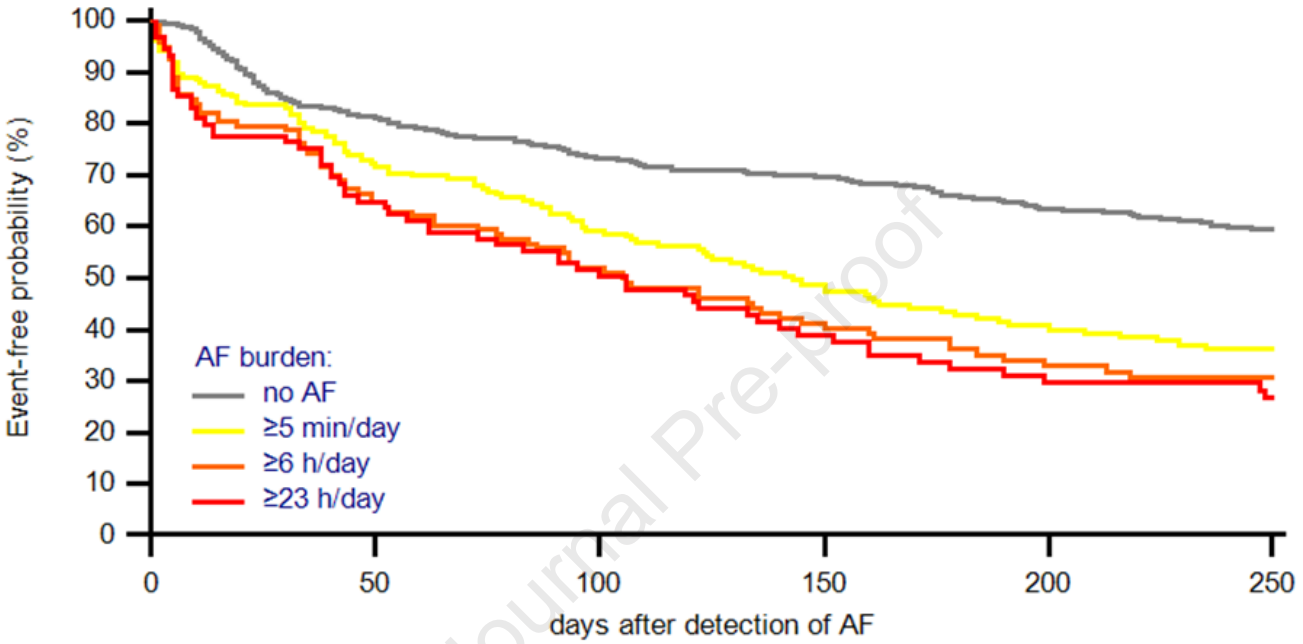
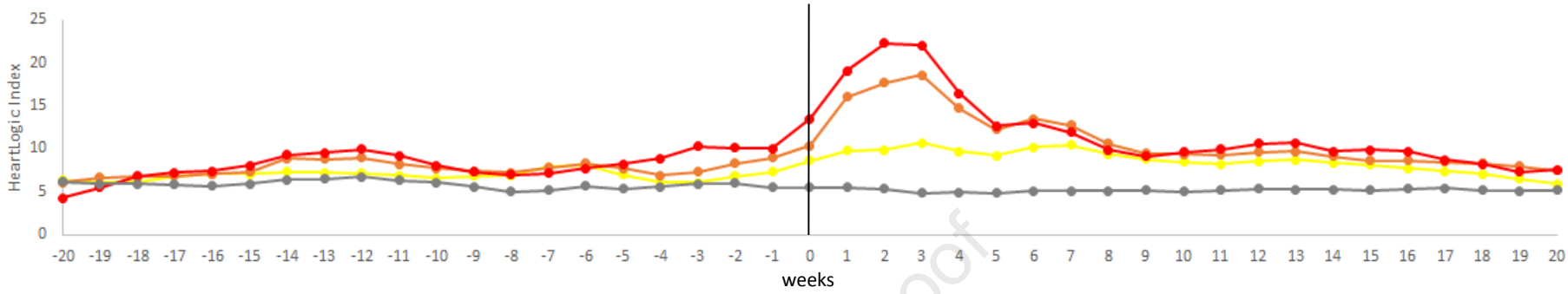


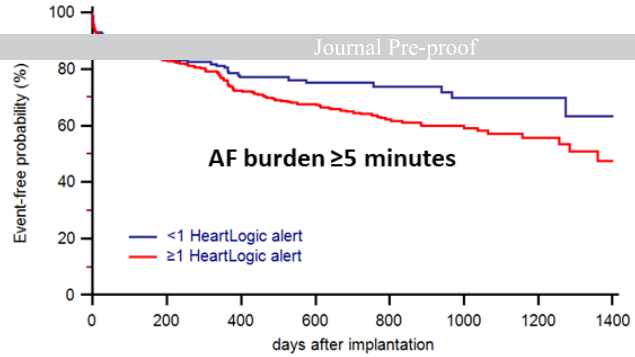
Figure 4.



Number at risk					
Group: no AF					
531	393	340	310	277	254
Group: ≥5 min/day					
183	123	93	71	56	47
Group: ≥6 h/day					
118	73	55	40	30	26
Group: ≥23 h/day					
89	55	41	30	22	17

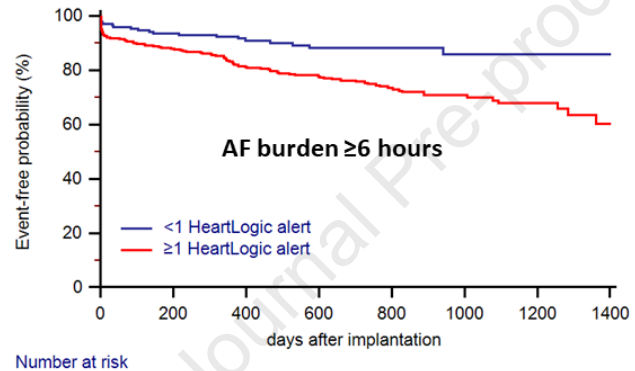
Figure 5.





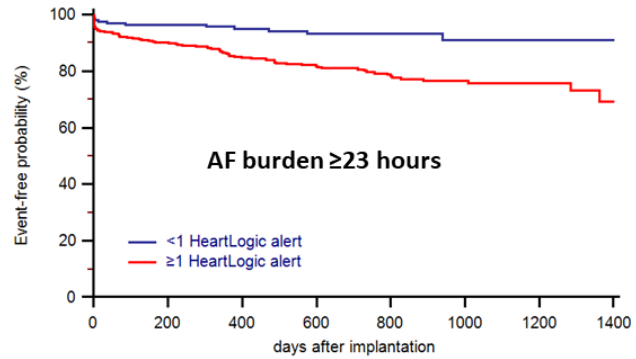
Number at risk

Group: <1 HeartLogic alert	198	139	104	77	53	30	16	3
Group: ≥1 HeartLogic alert	370	289	233	181	119	70	31	8



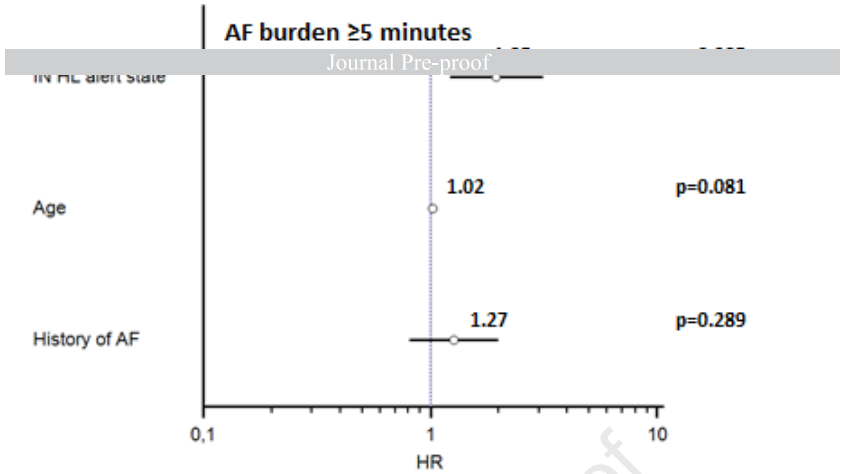
Number at risk

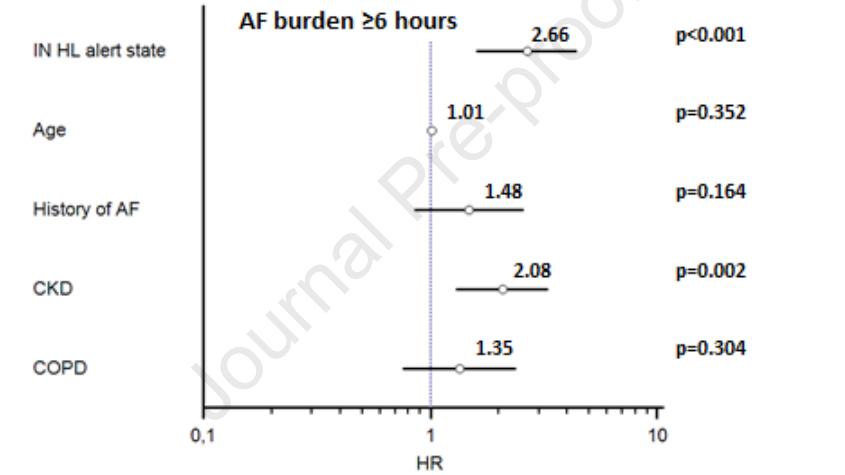
Group: <1 HeartLogic alert	198	153	120	87	60	34	19	3
Group: ≥1 HeartLogic alert	370	306	261	209	145	88	41	12

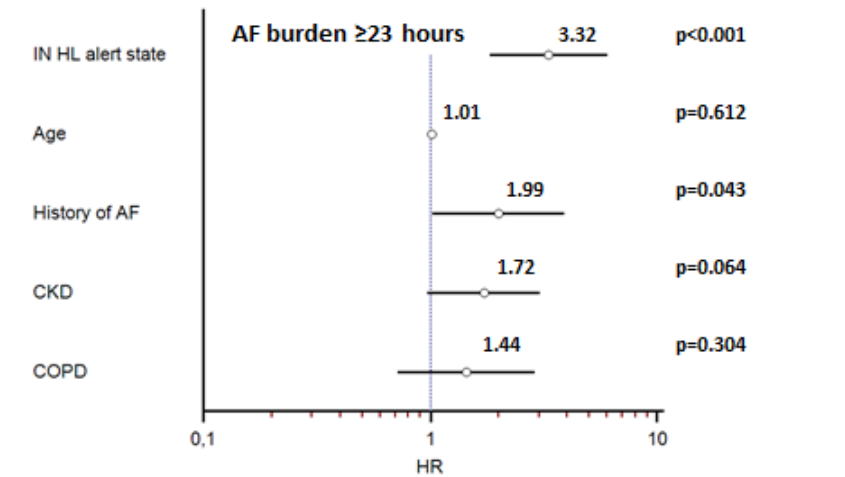


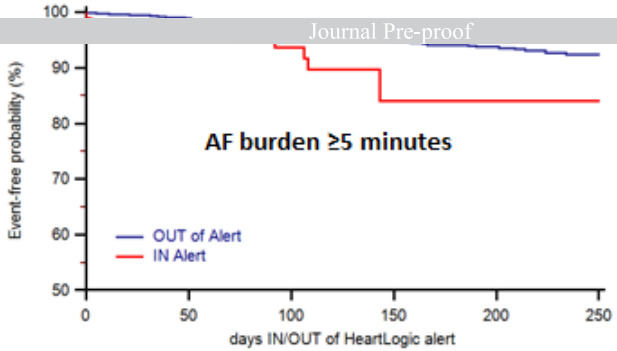
Number at risk

Group: <1 HeartLogic alert	198	156	125	90	62	35	20	3
Group: ≥1 HeartLogic alert	370	314	271	219	154	93	44	12

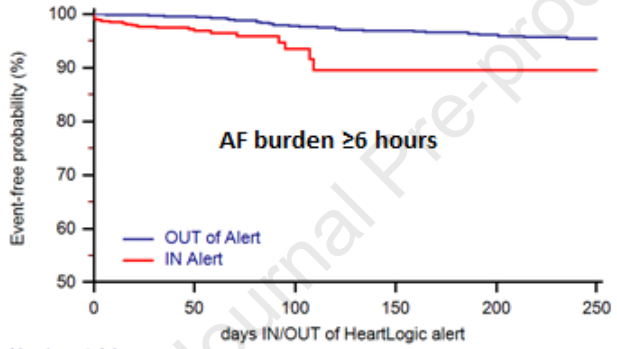




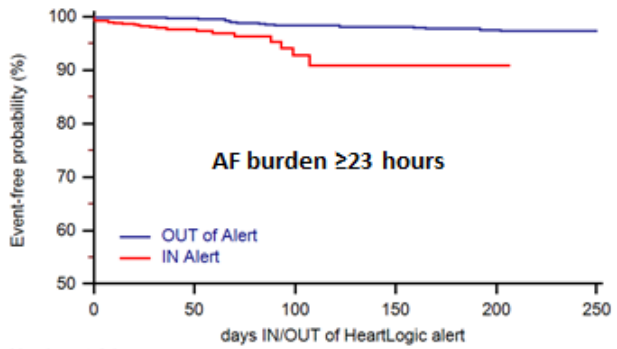




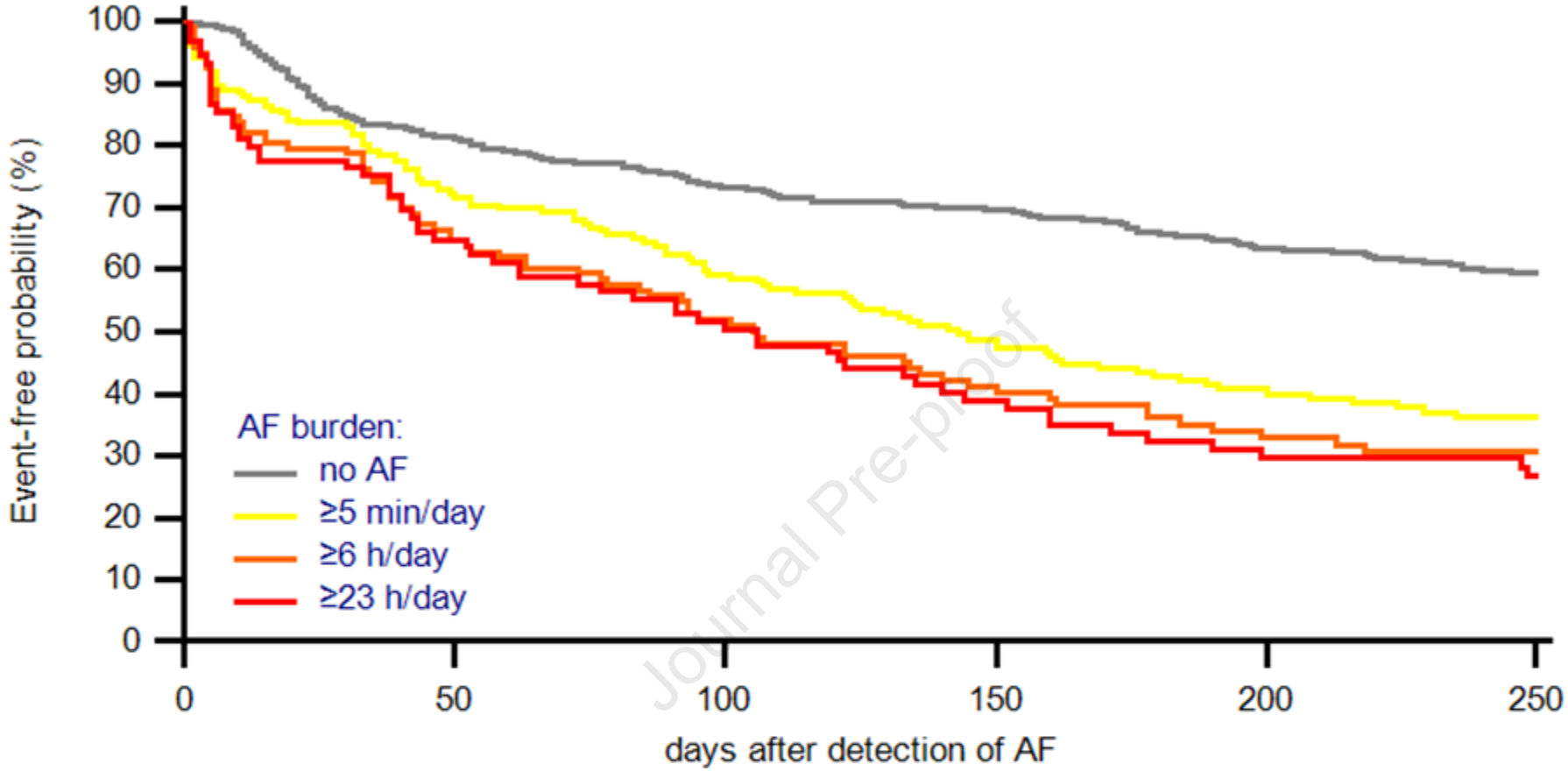
Number at risk						
Group: OUT of Alert	1239	912	652	536	453	392
Group: IN Alert	829	275	58	12	5	1



Number at risk						
Group: OUT of Alert	1234	910	647	530	451	395
Group: IN Alert	860	289	61	11	5	1



Number at risk						
Group: OUT of Alert	1229	899	639	522	442	391
Group: IN Alert	876	293	61	12	4	0



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