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Properly quantifiying outcomes of AF Ablation - Is a 30-second recurrence an evidence-based endpoint?

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ABSTRACT

Background: Although atrial fibrillation (**AF**) ablation is a well-established treatment, the classical **definition of recurrence** and therefore success is **not evidence-based**. Additionally, the frequency of asymptomatic patients whose episodes are not noticed on routine electrocardiogram (ECG) may compromise the actual success rate.

Objectives: This study aimed to assess the characteristics of AF burden after atrial fibrillation ablation and its **influence on patients' symptoms** in the setting of **continuous remote monitoring**. It also sought to investigate a **relevant cutoff** as a new definition for recurrence.

Methods: 141 consecutive patients with **symptomatic paroxysmal or persistent** AF underwent an AF ablation and then were followed by continuous rhythm monitoring. The AF/atrial tachycardia (AT) burden, duration of episodes and symptoms where registered systematically.

Results: After the blanking period, **freedom from AF/AT >30sec. was 59%.** Considering an **AF-Burden <1%**, the **success rate was 80%**. The incidence of **asymptomatic episodes** in the group of patients with **conventional recurrence** was **24% (14/58) and 20% (8/41)** when a **cut-off of 1%** of AF/AT burden was considered. **Asymptomatic** patients had an AF **burden of 1.87 ± 4.6%** during follow-up, **compared to 4.0 ± 7.2% in symptomatic patients (p=0.02**). There was no statistical difference between AF type (paroxysmal vs. persistent) and the frequency of asymptomatic episodes.

Conclusions: Patients with **asymptomatic AF Episodes** represent a **significant proportion** after AF ablation. These patients could be easily overlooked without a proper monitoring technique. A **burden cutoff of 1% and freedom from symptom should be considered as an ablation endpoint.**

INTRODUCTION

Atrial Fibrillation (AF) is an epidemic that affects 1-1.5% of the developed world's population and its prevalence is supposed to triple by 2050 (1). It is the most common arrhythmia in everyday clinical practice (2, 3) and incurs on expressive morbidity and mortality (4). Its health-related costs may add to 8 billion dollars each year just in the United States (5).

Ablation is a well-established approach to treat atrial fibrillation (3), but the **success rates are incongruent** between the various published papers, ranging from 50 to almost 90% (6). The reasons might vary to the **diverse definitions of recurrence** after ablation, as well as from the **ability to really document asymptomatic recurrences** (7). The established period of **30 seconds** for considering an AF recurrence has **questionable clinical significance**. The ASSERT study (8) showed that AF episodes shorter than 5 minutes had no prognostic effect, i.e., showed no higher risk of originating embolic events compared to no recurrence. **30 seconds is an arbitrarily given amount of time, not derived from research**. How much fibrillation is really atrial fibrillation is an important topic that requires more investigation.

Although it has long been known that silent AF occurs (9), the magnitude of this problem is only beginning to be appreciated. The AFFIRM study (10) brought some light to the fact that **asymptomatic patients may have thromboembolic events**. Since **asymptomatic recurrences can still originate strokes** (11), precise documentation is fundamental to take the right decision about anticoagulation therapy duration and the need for further anti-arrhythmic drugs. Asymptomatic AF was detected in 17% within 6 months in a group of 1380 individuals (12) in routine trans-telephonic ECG monitoring (4, 13). Particularly after AF ablation, 37% of ablated patients become asymptomatic recurrences during follow-up, as shown by Holter monitoring studies (14). **Cardiovascular implantable devices offer better accuracy** in detecting AF

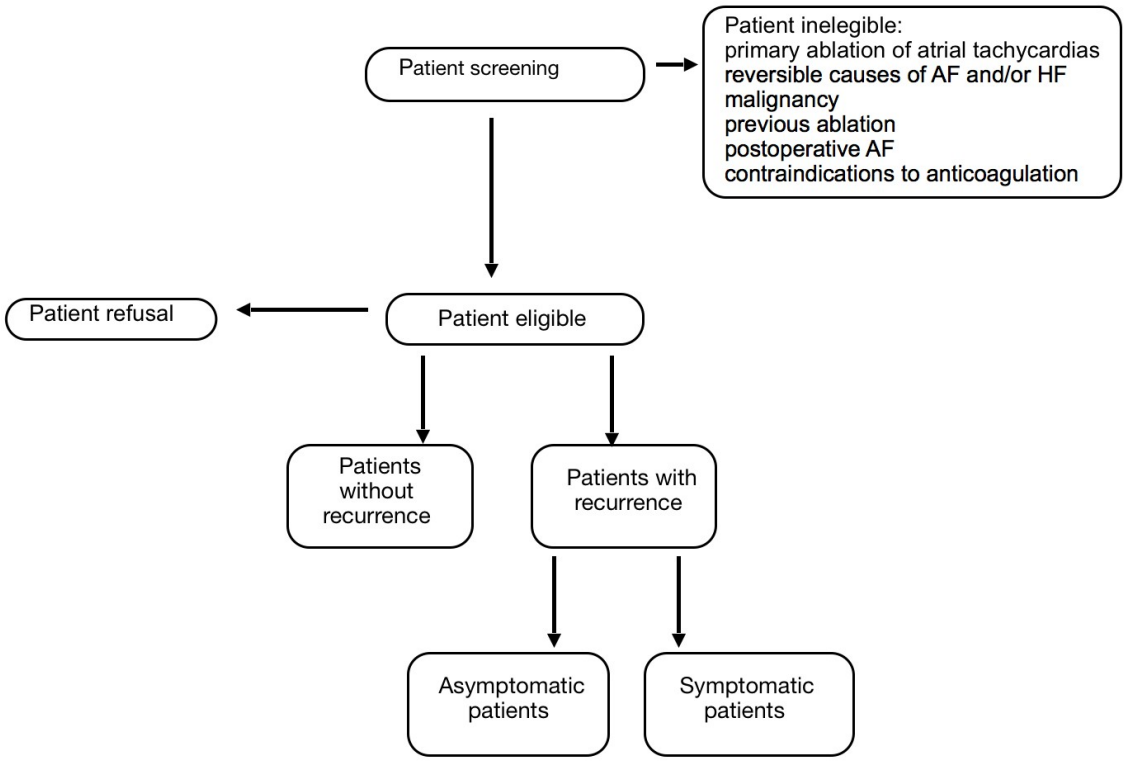
recurrences (9). In post-ablation patients, implantable loop recorders (ILR) have the advantage of their small size, low complication rates and reliable online monitoring (15).

This study investigated **AF recurrence after AF ablation** using **continuous ECG monitoring** via telemedicine and, when needed, ambulatory follow-up. The goals of this study were to assess the **characteristics of AF burden after atrial fibrillation ablation** and its **influence on patients' symptoms,** as well as to **propose a clinically relevant cutoff** as a new definition for recurrence

METHODS

Patient population

The study included **consecutive** patients **above 18 years** old, who underwent **catheter ablation of documented, symptomatic** (European Heart Rhythm Association [EHRA] class II to IV) **AF** (including paroxysmal and persistent AF) between **April 2016 and**



September 2017. All patients willed to undergo an **ILR implantation** after ablation. In addition to common contraindications to AF ablation (left atrial thrombus, reversible

Figure 1. Flowchart of study design

causes of AF, malignancy, contraindications to anticoagulation, post-operative AF), we excluded patients with primary ablation of atrial tachycardia (AT) or previous left atrial (LA) ablation. All patients provided **written informed consent both for ablation and then separately for ILR implant**.

Patients were sequentially enrolled in AF ablation **according to EHRA guidelines** (16). A total of **141 consecutive patients** were included for a **minimum follow-up of 12 months**. AF/AT recurrences were documented by **remote monitoring**. In the recurrence group, the pattern of **symptomatic and asymptomatic** recurrences was also analyzed.

Baseline assessments

All patients underwent a **baseline assessment** of medical history (coronary heart disease, cardiomyopathy, hypertension, COPD, sleep apnea and diabetes), demographic and clinical data, physical examination, ECG, echocardiography and MRI results, glomerular filtration levels and medications. CHA2DS2VASC Score was calculated. Basic metabolic panel and complete blood count with white blood cell differential, as well as INR and pro-BNP, were measured. Left atrial diameter (LAD) and left ventricular ejection fraction (LVEF) were recorded for further analysis.

Catheter ablation

Ablation was performed according to the 2017 HRS/EHRA/ECAS/APHRS/ SOLAECE Expert Consensus Statement on Catheter Ablation (16). Patients underwent a PVI using **radiofrequency** (RF) **or cryoenergy**. Radiofrequency ablation procedure was performed as follows: After access to the femoral vein(s) was obtained, a decapolar electrode was placed in the coronary sinus for recording and pacing. Transseptal catheterization was performed under fluoroscopic guidance. Two long vascular sheaths were introduced into the LA. After the transseptal puncture, Heparin was administered and repeated doses of heparin were given to maintain an activated clotting time of 300-350 seconds to prevent thromboembolic events.

Three-dimensional maps of the left atrium were constructed with the use of a non-fluoroscopic navigation system (CARTO, Biosense Webster or EnSite, Abbott). Circumferential lesions were created encircling the antrum of the right and left pulmonary veins (PV) guided by PV angiography and electro-anatomical mapping. An irrigated RF ablation catheter was used (Smart touch surround flow, Biosense Webster or Flexability, Abbott), with an irrigation rate of 17ml/min., a maximum temperature of 40°C and a power of 30-35 W anteriorly and 28W on the posterior wall. Complete isolation of all PVs was demonstrated using a circular mapping catheter.

PVI using cryoenergy was performed using the Arctic Front Advance Cardiac Cryoablation Catheter System (Medtronic). Occlusion Grade III/IV or IV on PV angiography was attempted. Complete PV isolation was confirmed using the Achieve catheter. A Freeze of maximal 240 seconds and -55 °C was performed. A second freeze was added if no isolation was shown within 45 seconds.

In **persistent AF**, **additional substrate modification** was performed in case of **extensive LA low-voltage areas and/or no AF cycle length prolongation** after PVI, using linear ablation or defragmentation as described before (17). If AF persisted after ablation a direct current conversion was performed.

ILR Implantation

An ILR (Reveal LINQ, Medtronic) was implanted in the left parasternal region in the conventional technique, 24 to 72 hours after the ablation procedure. The patients were instructed to use the trigger and record the onset time and features when symptoms occurred.

Follow up

The automated Medtronic Carelink algorithm was used for diagnostic and verified individually (Figure 2).

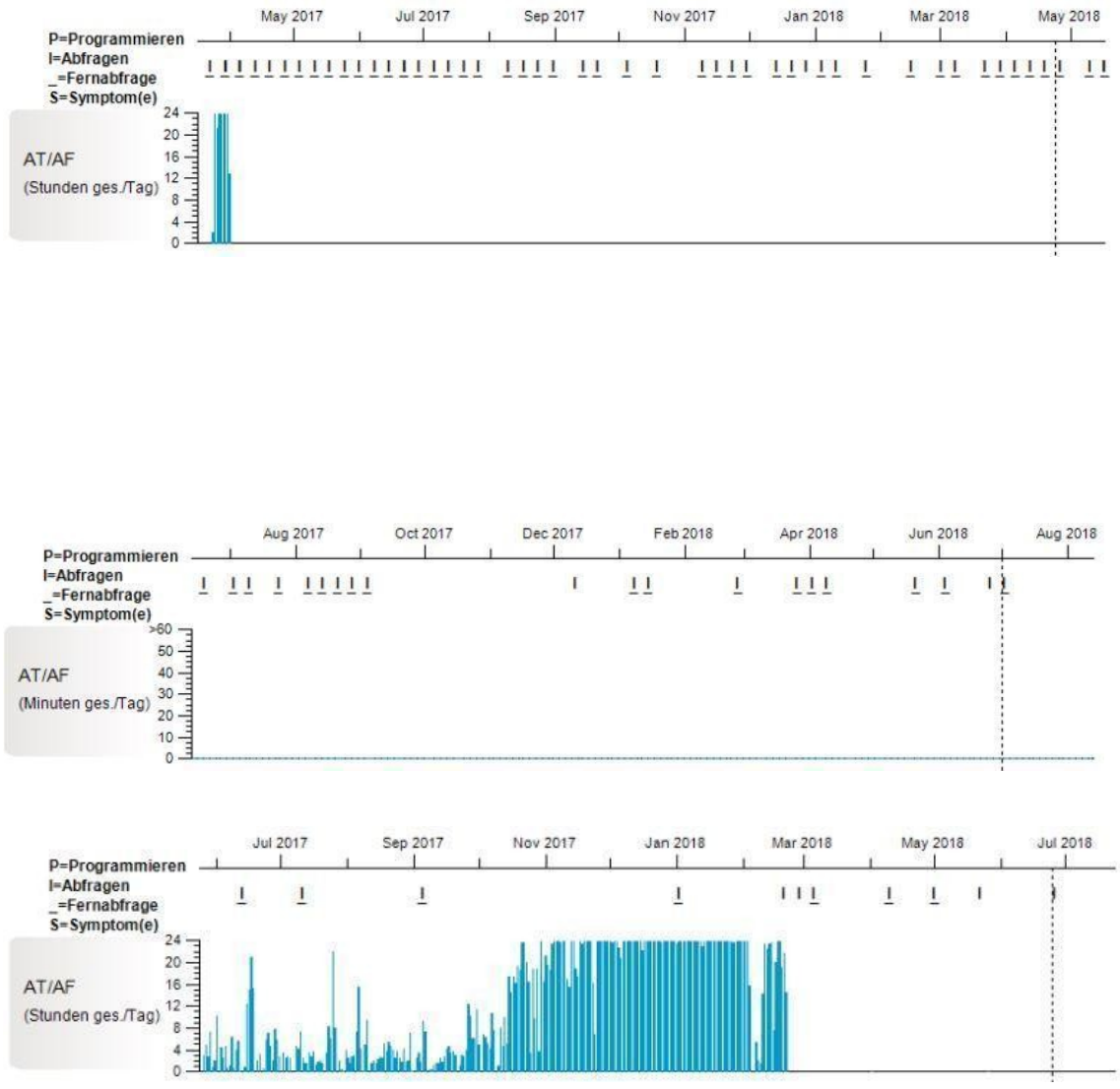


Figure 2. A. Responder (or success of the first ablation)to the first ablation. Recurrence in the 3-month blanking period, but no recurrences afterward. B. Responder to the first ablation. No recurrence in the 3-month blanking period and no recurrence afterward. C. Nonresponder to the first ablation. Responder after the second ablation.

Cases of oversensing were corrected and the AF burden adjusted if necessary. Trained nurses made monitoring of the episodes online daily in workdays. The alerts were discussed with the attending electrophysiologist. The patient was contacted if he triggered the symptom activator and/or in case of documented episodes. The AF/AT burden, duration of episodes and symptoms were registered **systematically at 3, 6, 9 and 12 months**. An ambulatory visit took place systematically at the end of the blanking period (90 days) or in case of symptoms. Otherwise, the patient was followed every 6 months by the referring cardiologist.

Definitions and study endpoints

A **conventional recurrence** was defined as an AF/AT episode with a duration longer than **30 seconds**. A recurrence was considered **symptomatic** when the patient-**reported symptoms or the trigger was activated**. Otherwise, the episode was classified as asymptomatic. The blanking period was considered the first 3 months after ablation. According to the definition of ESC guidelines (16), persistent AF implied on a duration longer than 7 days. A patient with at least one symptomatic episode was counted as symptomatic.

The **primary endpoint** was defined as the presence of **symptomatic AT/AF longer than 30 seconds** during the first year of follow up.

Secondary endpoints were (1) the presence of **asymptomatic AT/AF** longer than 30 seconds during the first year of follow up (2) assessment of the **predictors of asymptomatic AT/AF**, including the type of ablation (RF vs. Cryo), AF type (paroxysmal vs. persistent), duration of episodes and AT/AF Burden.

Statistical analysis

Ordinal and nominal variables were reported as count and percentages if normally distributed and as median with an interquartile range if asymmetrically distributed. Quantitative variables were reported as mean and standard deviation. A comparison of quantitative data was performed using a student's *t*-test if symmetrically distributed; otherwise, the Mann-Whitney test was used. For qualitative variables, the $\chi 2$ test was used. Kaplan–Meier curves were reported for reablation during follow-up**.** To assess the statistically significant point where a clinical significant event occurred (AF with indication to reablation) a ROC curve was used for different AF recurrence criteria (>30 seconds, burden > 1%, burden > 2%). The point on the ROC curve associated with the greatest

discriminatory potential for AF burden was 0.96% (sensitivity 72.7%, specificity 71% based on the Youden Index). The discriminated burden value was rounded to 1% for practical purposes.

Statistics were obtained using IBM Corp. Released in 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. A p-Value < 0.05 was considered as statistically significant.

RESULTS

Study population

The patients' population included 141 consecutive patients [70 (50%) with paroxysmal AF] followed by continuous rhythm monitoring for 19 ± 5 months. Baseline characteristics are shown in Table 1.

Table 1. Baseline characteristics of patients submitted to AF Ablation

	Total	Paroxysmal AF	Persistent AF	p
Age (years)	64 ± 10	64 ± 9	63 ± 11	0.640
Female (n, %)	54 (38%)	32 (46%)	22 (31%)	0.072
BMI (kg/m2)	30.7 ± 5.0	29.9 ± 4.8	31.5 ± 5.3	0.058
Diabetes mellitus (n, %)	21 (15%)	8 (11%)	13 (18%)	0.251
Arterial hypertension (n,	116 (82%)	54 (77%)	62 (87%)	0.114
Sleep Apnea (n, %)	7 (5%)	2 (3%)	5 (7%)	0.253
Ischemic cardiomyopathy	4 (3%)	1 (1%)	3 (4.2%)	0.317
CAD (n, %)	42 (30%)	17 (24%)	25 (35%)	0.156
Previous Stroke or TIA (n,	12 (9%)	1 (1%)	3 (4.3%)	0.317
COPD (n, %)	9 (6%)	10 (14%)	2 (3%)	0.015
Cryoablation (n, %)	9 (6%)	2 (3%)	7 (10%)	0.089
LVEF (%)	59 ± 8	61 ± 7	58 ± 10	0.057
LA diameter (cm)	48 ± 6	46 ± 4	47 ± 3	0.068
CHA2DS2-VASc score	2.65 ± 1.50	2.67 ± 1.56	2.64 ± 1.44	0.895

CRP (mg/dl)	1.9 ± 1.0	1.7 ± 1.0	2.1 ± 1.6	0.845
Creatinine (mg/dl)	1.0 ± 0.2	0.9 ± 0.2	1.0 ± 0.3	0.105
GFR (ml/min)	76 ± 20	77 ± 19	76 ± 21	0.886
TSH (mIU/L)	1.68 ± 1.03	1.55 ± 0.96	1.81 ± 1.00	0.141
PAP (mmHg)	34 ± 7	33 ± 6	35 ± 8	0.177
Pro-BNP (pg/ml)	1422 ± 221	1068 ± 217	1628 ± 221	0.038
Troponin (ng/ml)	0.023 ± 0.081	0.025 ± 0.079	0.022 ± 0.94	0.265

Adverse events

Ablation related complications included peripheral puncture related complications (n=8, 5.5%), cardiac tamponade (n=1, 0.7%) and transitory ischemic attack (n=1, 0.7%).

No implantable cardiac monitor related complications occurred.

Long term outcome

After the blanking period, freedom from any atrial arrhythmia recurrence (AF/AT, >30sec.) evaluated by continuous monitoring was 59% (n=83) (Figure 3). Considering an **AF-Burden <1%, the success rate was 80%**. If an AF-Burden <2% was considered, the success rate was 83%.

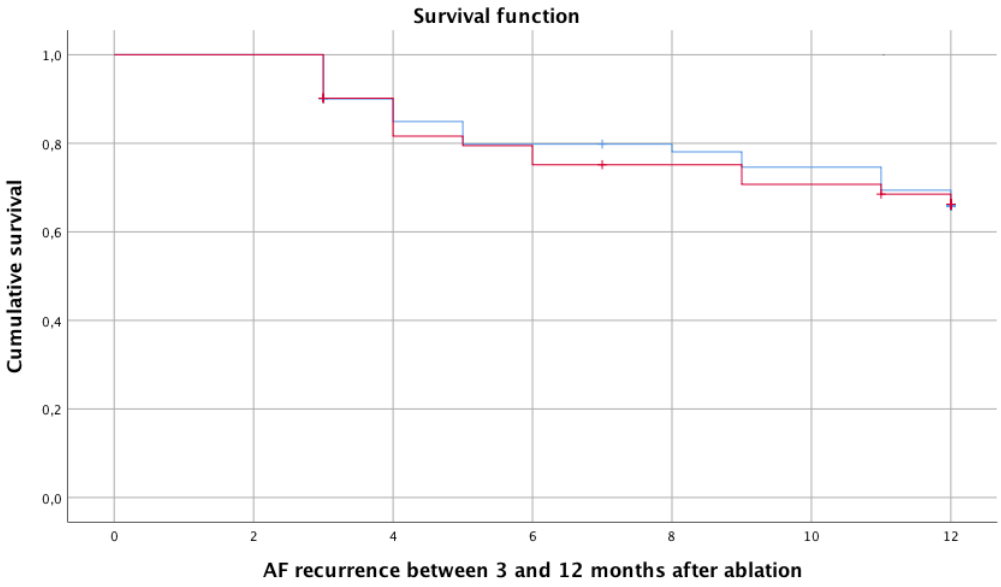


Figure 3. Kaplan-Meier survival curves (**Survival free from AF/AT recurrence)** showing the freedom from any atrial arrhythmia recurrence (AF/AT) >30sec without antiarrhythmic drugs during follow-up.

The study showed a tendency toward **longer recurrence episodes in persistent AF**, with a mean difference of 2667 minutes (p=0.175). The **mean burden** during blanking was **2.9 ± 7.8% in paroxysmal and 9.3 ± 20.8% in persistent AF (p=0.022)**. A difference in AF burden at 12 months was also present, with 1.9 ± 4.6 in paroxysmal and 4.0 ± 7.2 in persistent AF (p=0.002).

To assess the statistically significant point where a clinical significant event occurred (AF with indication to reablation) a ROC curve was used (see supplemental material). The point on the ROC curve associated with the greatest discriminatory potential for AF burden was 0.96% (sensitivity 72.7%, specificity 71% based on the Youden Index). The discriminated burden value was rounded to 1% for practical purposes.

Outcome stratified by symptoms

The incidence of **asymptomatic episodes was 50%** (41/82) **during the blanking** period **and 17%** (n=24) **during remained follow-up**.

The baseline characteristics of asymptomatic and symptomatic patients are shown in Table 2.

Table 2. Baseline characteristics of patients with asymptomatic and symptomatic AF recurrences

	Asymptomatic	Symptomatic	p
Age (years)	68 ± 8	62 ± 12	0.132
Female (n, %)	9 (64%)	14 (32%)	0.031
BMI	29.9 ± 4.8	31.5 ± 5.3	0.800
Diabetes mellitus (n, %)	0 (0%)	9 (21%)	0.066
Arterial hypertension (n, %)	11 (79%)	37 (84%)	0.634
Sleep Apnea (n, %)	0 (0%)	2 (5%)	0.417

Ischemic cardiomyopathy (n, %)	0 (0%)	2 (4.5%)	0.417
CAD (n, %)	3 (21%)	12 (27%)	0.664
Previous Stroke or TIA (n, %)	2 (14%)	4 (9%)	0.578
COPD (n, %)	0 (0%)	3 (7%)	0.316
Paroxysmal AF (n, %)	8 (57%)	20 (45%)	0.446
LVEF (%)	61 ± 8	58 ± 10	0.326
LA diameter (cm)	46 ± 7	48 ± 4	0.311
CHA2DS2-VASc score	2.69 ± 1.60	2.55 ± 1.39	0.747
CRP (mg/dl)	1.7 ± 1.0	2.1 ± 1.6	0.101
Creatinine (mg/dl)	0.9 ± 0.2	1.0 ± 0.3	0.588
GFR (ml/min)	72 ± 23	76 ± 21	0.576
TSH (mIU/L)	1.61 ± 0.83	1.99 ± 1.31	0.338
Pro-BNP (pg/ml)	542 ± 779	850 ± 913	0.035
Troponin (ng/ml)	0.036 ± 0.099	0.028 ± 0.12	0.818

BMI = Body max index, CAD = coronary artery disease, COPD = chronic obstructive pulmonary disease, LVEF = left ventricular ejection function, CRP = C reactive protein, GFR = glomerular filtration rate, TSH = thyroid-stimulating hormone, Pro-BNP = Pro Brain natriuretic Peptide

Significantly, **more females were asymptomatic**.

The mean **pro-BNP was significantly higher in symptomatic patients**. No other statistical significance was found between the groups.

	Asymptomatic	Symptomatic	p
Early recurrence (n, %)	3 (21%)	37 (84%)	< 0.001
First recurrence (days)	19 ± 24	20 ± 26	0.383
Last recurrence in blanking period	50 ± 32	59 ± 32	< 0.001
AF burden at 3 months (%)	0.1 ± 0.3	14.5 ± 23.3	0.026
Longest episode (minutes)	233 ± 404	3065 ± 9432	0.307
AF burden at 12 months (%)	1.87 ± 4.6	4.0 ± 7.2	0.002

Table 3. Follow up characteristics of patients with asymptomatic and symptomatic episodes

The incidence of **asymptomatic episodes** in the group of patients with **conventional recurrence** was **24%** (14/58). If the **burden cut-off of 1%** is used, there was an incidence of asymptomatic episodes of **20%** (8/41).

Asymptomatic patients had an AF burden of 0.2% during follow-up, **compared to 6.9% in symptomatic patients (p=0.014).** Asymptomatic episodes occurred **equally after persistent** (20.8%) **than paroxysmal AF** ablation (20%).

As assessed by continuous cardiac rhythm monitoring, AF ablation showed an **arrhythmia free rate of 59%**, with a total **symptom-free rate of 64%**.

DISCUSSION

The **main finding** of our study is that about **25% of AF/AT recurrences after ablation are asymptomatic and might not be detected in routine ECG follow-up**.

We also propose to **redefine the endpoint of AF ablation.** Instead of the arbitrary 30 sec. success criteria, we propose **evidenced-based criteria** (based on statistical analysis) but also **combined with clinical data**. As most of the patients with AF burden <1% are asymptomatic, a cut-off of 1% per year appears to be useful.

Recurrence after Ablation

According to Ritter et. al, the incidence of detected AF events with the use of ILR in the general population is more than 2 times higher than the generally used 7-day Holter (18). Therefore, it is to expect that **the recurrence** rate after ablation with **ILR assessment will be higher than** the one described with the use of **ECG or Holter alone**. Using the conventional definition of AF relapse, recurrence rates in our study were 41%, compatible with the described

recurrence rate assessed by the Linq AF study, which analyzed the same population with continuous monitoring. (19).

We found a striking difference between AF recurrences depending on the recurrence criteria. Indeed, the continuous monitoring showed an **AT/AF recurrence > 30 sec. of 41%, compared to 20% when the burden < 1% was the cut-off criteria and 17% when a burden < 2% was used**. Since atrial fibrillation **ablation indication is strongly linked to symptoms**, it makes sense to propose a **cut-off that takes symptoms into account**.

After statistical analysis (ROC-curve) and based on clinical significance, we propose a **burden cut-off of 1%** as a definition of success after ablation. A **classical recurrence could not be well correlated with the need for reablation, as opposed to the burden criteria**, which should be taken into account for the definition of success.

The persistent AF group showed a median AF burden more than 2 times higher than the paroxysmal group and that could explain the higher prevalence of symptomatic episodes in the persistent AF group, as well as the higher indication for reablation and cardioversion in that population.

Asymptomatic atrial fibrillation

Our study is the first with a primary focus on the clinical issue of asymptomatic patients after atrial fibrillation ablation with ICM monitoring.

In our study, the female gender was found to be a statistically significant predictor of asymptomatic episodes. In a comprehensive register of the European population with 3119 patients, Boriani et al. (20) described that asymptomatic episodes were linked often to the male gender. The differences in our findings may be explained by the diagnostic method, i.e., we diagnosed

actual asymptomatic episodes with ILR and the above-mentioned register identified patients with AF in ECG that then were characterized as symptomatic or not. Although such registers are essential for strategic planning, this is an example of how the **real characteristics of AF may be underestimated with ECG as a diagnostic tool.**

There is sufficient evidence that the outcome of **silent AF might be as severe as non-silent AF** (21). Also, the mere existence of a **symptomatic episode does not exclude** the occurrence of other episodes that may be **asymptomatic**. Furthermore, a history of symptomatic AF in the past in no way guarantees that recurrence will be symptomatic. (22)

Atrial fibrillation burden

Most published studies evaluated **AF in a dichotomous fashion** (presence or absence of AF) and have not investigated the AF burden. This **binary concept** - absence or presence of AF, whether paroxysmal, persistent or permanent - is the one that permeates almost every clinical research that we have conducted so far. **What would be considered as minimal AF** and even if its concept should be based on the burden or in duration, **still needs to be determined**. Therefore, the impact of minimal AF after ablation still needs further investigation.

The average atrial fibrillation burden after ablation in our research was 6.2% in the blanking period and 2.9% in the 12 months' period. Among patients with recurrence, the burden was 10.9% in the blanking period and 5.4% in the 12 months' period. Three other studies evaluated arrhythmia characteristics with ILR in a population submitted to RF and Cryoablation. The Linq AF Study (15) found that **burden analysis was the more accurate** diagnosis pattern for AF

recurrences, which is in line with our data. They propose a cut-off of 6 minutes or AF burden > 0.1% as recurrence criteria, but their recommendations are not directly based on clinical relevance as this actual paper is. Another study (23) included 113 patients submitted to AF ablation and ILR Implant and detected the mean burden to be 35.1 ± 30.6, but **also didn't make a correlation between burden and symptoms to assess an adequate cut-off for recurrences**. Similarly, a study (24) with 143 patients in the same population found 46% of recurrences to be asymptomatic but **didn't propose a burden cut-off.** Other studies evaluated AF recurrence in terms of **minutes in pacemaker and ICD patients**, but those patients represent just a **small fraction of the everyday AF ablation patient** (25).

Future developments

It may come a day where continuous - or almost continuous ECG monitoring will be broadly available, and this day is not so far away. In fact, today we are already able to continuously monitor blood pressure, glucose, heart frequency, with a device that doesn't need to be implanted - it can be bought online and delivered in the comfort of your home. We may still see the point where **anticoagulation may be individually tailored**, based on the certainty of recent AF episodes or can be skipped if the episodes don't happen at all.

The b**ehavioral characteristics of the asymptomatic recurrences in the long-term are still unknown**. It is also not clear if the patients with asymptomatic recurrences in the first year would always have asymptomatic episodes. A longer follow-up of at least 5 years would be necessary to determine that.

Limitations

Ours is an observational, non-randomized study. The data collection was made in patients treated with specific ablation techniques, i.e. PVI and Cryoablation. Therefore, our findings may not be extended to other populations of AF patients. The relatively small size of the Cryoablation group makes it hard to determine the validity of our findings in this group.

Since patients were not implanted before ablation, we weren´t able to assess the difference in burden characteristics before and after the procedure. However, all patients were symptomatic before ablation and had at least two documented AF episodes in the last year.

CONCLUSIONS

Asymptomatic patients represent a **significant proportion of recurrences** after AF ablation. These patients could be **easily overlooked without a proper monitoring technique**. Clearly, the importance of those findings cannot be underestimated. **AF may not be considered** "**cured" in the lack of continuous monitoring.**

The burden is a reliable cutoff linked to the clinical outcome and/or therapeutic decisions. **We propose a new cut-off of 1% to define a recurrence and indicate reablation.**

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