

# Progressive reduction of AF burden after cryoablation in patients with early persistent AF evaluated by continuous cardiac rhythm monitoring: COOL-PER trial

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# Disclosure

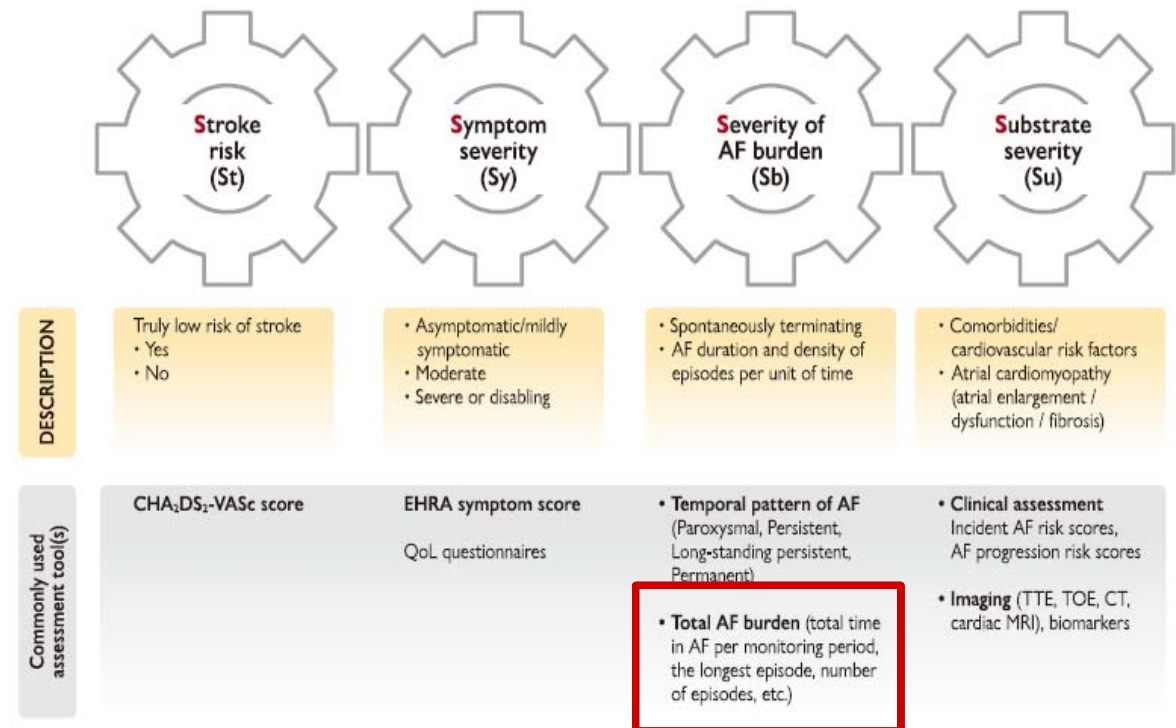
- **Relationships with commercial interests:**

- **Grants/Research Support:** Abbott, Bayer, BMS/Pfizer, Biosense Webster, Chong Kun Dang, Daewoong Pharmaceutical Co., Daiichi-Sankyo, DeepQure, Dreamtech Co., Ltd., Jeil Pharmaceutical Co. Ltd, Medtronic, Samjinpharm, Seers Technology, and Skylabs.
- **Speakers Bureau/Honoraria:** Abbott, Bayer, BMS/Pfizer, Biosense Webster, Chong Kun Dang, Daewoong Pharmaceutical Co., Daiichi-Sankyo, Dreamtech Co., Ltd., Jeil Pharmaceutical Co. Ltd, Medtronic, Samjinpharm, Seers Technology, and Skylabs.

# Classification of AF

AF pattern	Definition
First diagnosed	AF not diagnosed before.
Paroxysmal	AF that terminates spontaneously or with intervention within 7 days of onset.
<b>Persistent</b>	AF that is continuously sustained beyond 7 days, including episodes that are terminated by cardioversion after 7 days or more.
Long-standing persistent	Continuous AF of >12 months duration when decided to adopt a rhythm control strategy.
<b>Permanent</b>	AF that is accepted by the patient and physician, and no further attempts to restore/maintain sinus rhythm will be undertaken.  Permanent AF represents a therapeutic attitude of the patient and physician rather than an inherent pathophysiological attribute of AF, and the term <u>should not be used in the context of a rhythm control strategy</u> with antiarrhythmic drug therapy or AF ablation.

## 4S-AF scheme as an example of structured characterization of AF



# Assessment of AF/AT recurrence: 30-sec rule

## 2017 HRS AF guideline

### Early Recurrence After Ablation Definition and Incidence

Early recurrences of AF after AF ablation has been defined as any recurrence of AF >30 seconds during the first 3 months of follow-up. Late recurrence has been defined as any recurrence of AF >30 seconds between 3 and 12 months after AF.<sup>141,142,143</sup> In using the term *early recurrence of AF*

Continuous ECG monitoring for longer periods (1–3 years)

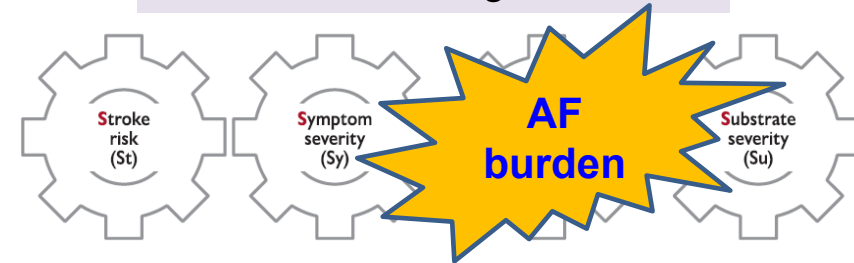
can be facilitated with the use of implantable devices. Long-term subcutaneous implantable loop monitors can facilitate continuous AF monitoring based on R-R interval analysis over a time period of up to 3 years.<sup>952,953</sup> These types of continuous ECG monitoring devices have been used in several studies to evaluate the results of surgical or catheter AF ablation.<sup>127,607,938,953,954,955,956,957,958,959,960,961</sup> Although implantable subcutaneous monitors hold promise for the

determination of AF burden in the long term, AF detection algorithms are primarily based on R-R interval regularity, and important limitations include reduced specificity due to undersensing of beats, oversensing of myopotentials, and irregular atrial and ventricular premature beats, as well as limited memory resulting in electrograms not being retrievable to verify the correct rhythm diagnosis.<sup>941,944,962</sup>

Nevertheless, implantable continuous monitors can ameliorate patient compliance issues and provide an assessment of long-term AF burden and late recurrences, including asymptomatic episodes that might have implications for continuation of anticoagulation. In one study after concomitant surgical ablation, ILRs compared with conventional Holter monitoring facilitated more follow-up antiarrhythmic management, including cardioversions and catheter ablation procedures, which were associated with a trend toward higher sinus rhythm rates at 1 year.<sup>942</sup>

SEOU

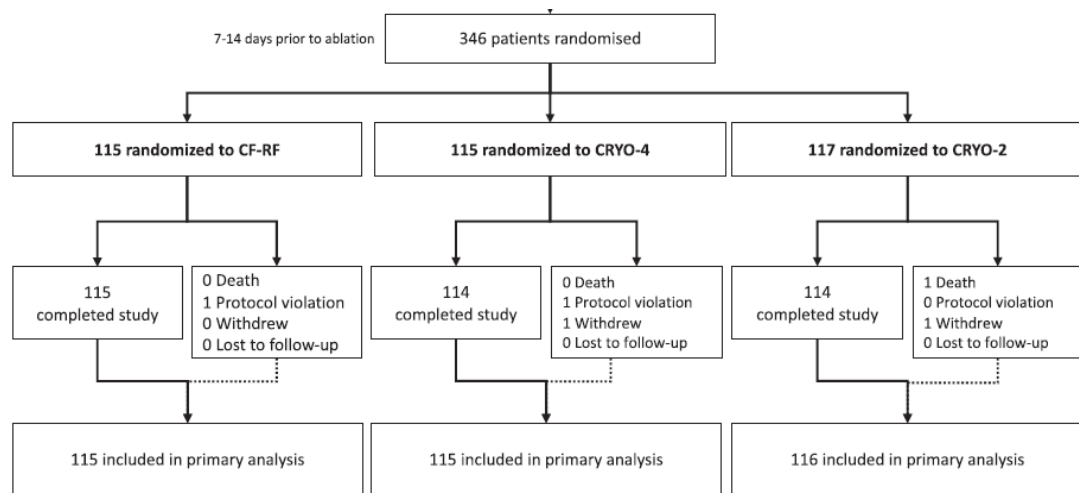
## 2020 ESC AF guideline



Clinical AF burden is routinely determined by AF temporal pattern<sup>146</sup> (Table 4) and intermittent ECG monitoring,<sup>153</sup> neither corresponding well to the long-term ECG monitoring. The relationship of clinical AF burden with specific outcomes is not well characterized,<sup>154</sup> but may be associated with higher risk of incident HF<sup>155</sup> and all-cause mortality,<sup>156</sup> while the association with quality of life (QoL) is complex and data about cognitive impairment/dementia are lacking.<sup>86</sup> Recent randomized controlled trial (RCT) data consistently showed significantly lower residual thrombo-embolic risk among anticoagulated patients with paroxysmal vs. persistent AF,<sup>156–159</sup> whereas earlier trial-based<sup>160</sup> and observational data<sup>161,162</sup> are contradictory. Among non-anticoagulated patients, stroke risk was lower with paroxysmal than non-paroxysmal AF,<sup>156</sup> and a greater total AF burden (but not the longest AF episode) was independently associated with higher thrombo-embolic event rates.<sup>163</sup> Clinical AF burden may influence the response to rhythm control therapy.<sup>164,165</sup> The presence of >6 h of AF per week (especially when progressing to >24 h weekly) was associated with increased mortality, especially in women.<sup>166</sup>

# Cryoballoon or Radiofrequency Ablation for Atrial Fibrillation Assessed by Continuous Monitoring

## CIRCA-DOSE Study



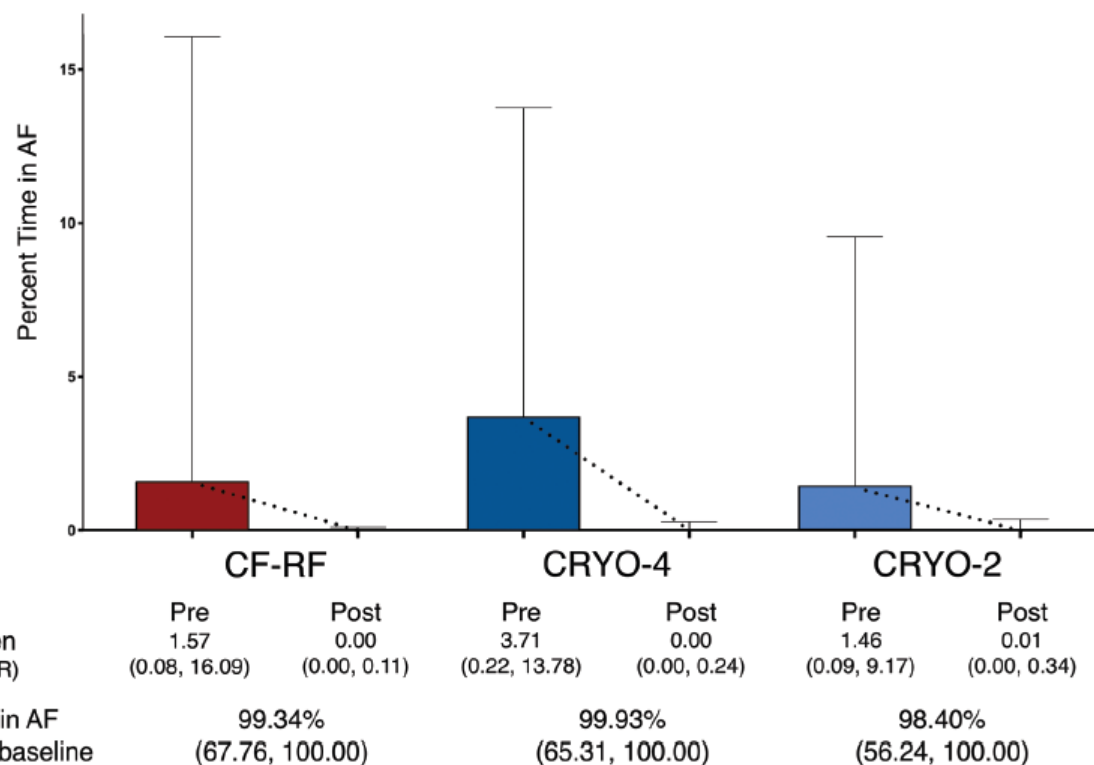
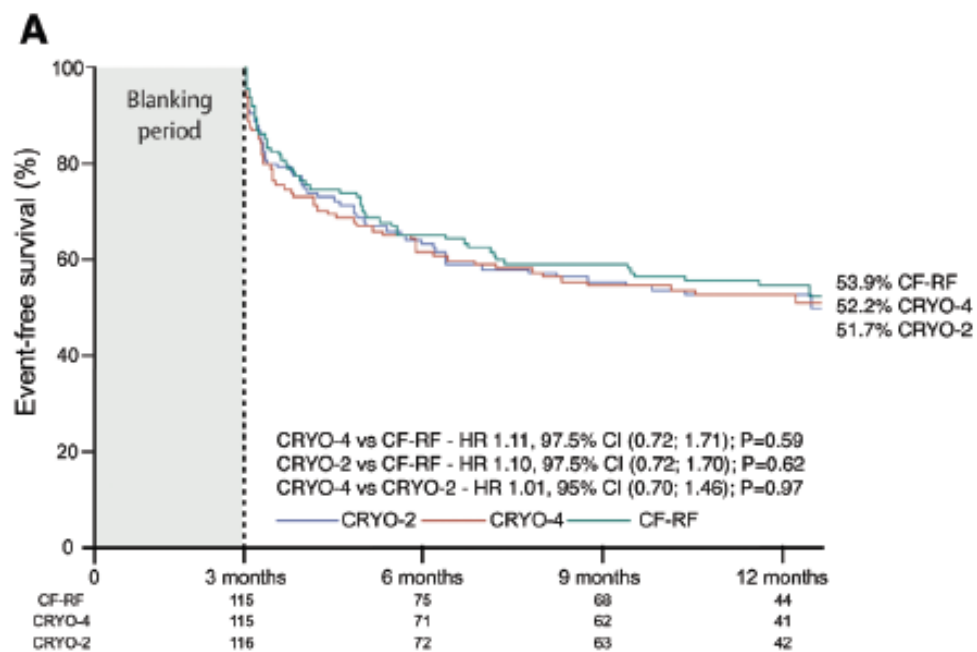
symptomatic **paroxysmal AF**  
refractory to at least 1 Class I or  
Class III AAD

**The primary end point** was time to first recurrence of symptomatic or asymptomatic atrial tachyarrhythmia (AF, atrial flutter, or atrial tachycardia) documented by any form of monitoring, including ILR, between days 91 and 365 after ablation, or a repeat ablation procedure between days 0 and 365 after ablation



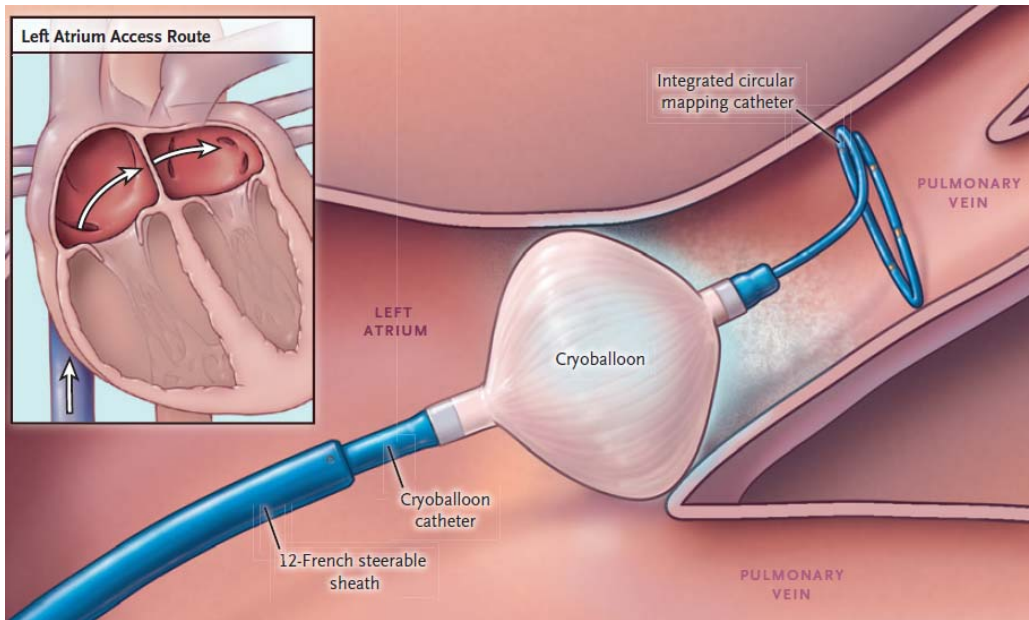
# Cryoballoon or Radiofrequency Ablation for Atrial Fibrillation Assessed by Continuous Monitoring

## AF burden change

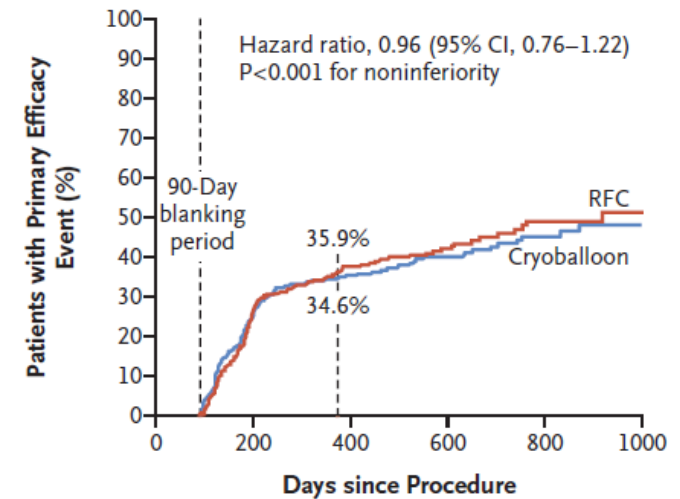




# Cryoballoon ablation for Paroxysmal AF (FIRE AND ICE Investigators)



A Primary Efficacy End Point



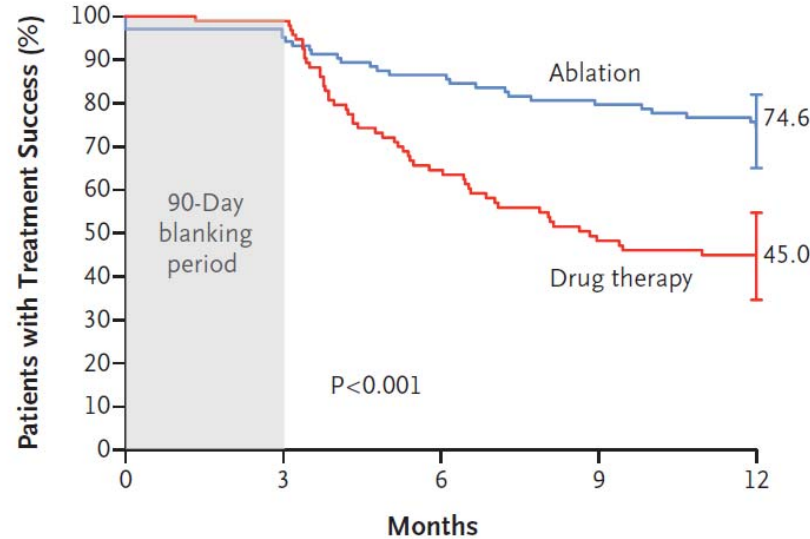
No. at Risk  
Cryoballoon  
RFC

374	338	242	194	165	132	107	70	57	34	12
376	350	243	191	149	118	93	58	44	25	12

- Cryoballoon ablation was noninferior to RFCA with respect to efficacy for the treatment of patients with drug-refractory paroxysmal AF,
- no significant difference between the two methods with regard to overall safety.

# Cryoballoon Ablation as Initial Therapy for Atrial Fibrillation

Oussama M. Wazni, M.D., Gopi Dandamudi, M.D., Nitesh Sood, M.D., Robert Hoyt, M.D., Jaret Tyler, M.D., Sarfraz Durrani, M.D., Mark Niebauer, M.D., Kevin Makati, M.D., Blair Halperin, M.D., Andre Gauri, M.D., Gustavo Morales, M.D., Mingyuan Shao, Ph.D., Jeffrey Cerkenik, M.S., Rachelle E. Kaplon, Ph.D., and Steven E. Nissen, M.D., for the **STOP AF First** Trial Investigators\*

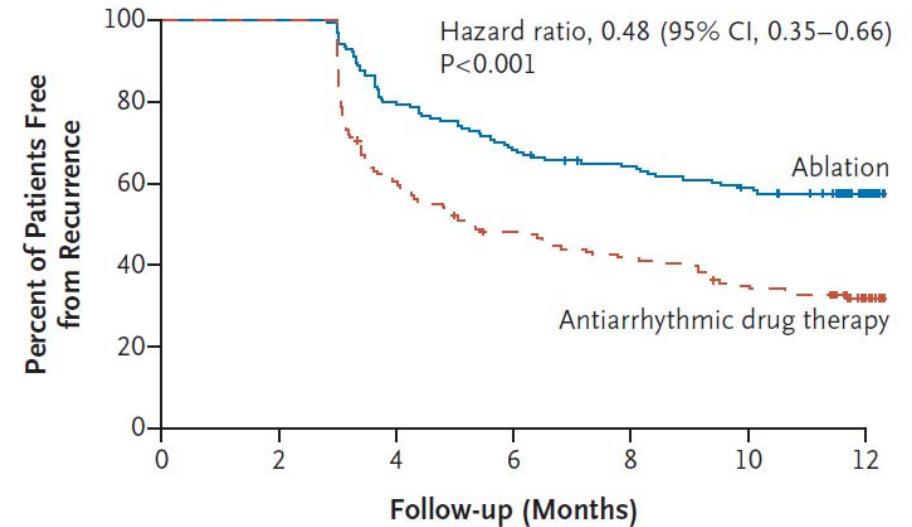


**No. at Risk**  
 Ablation  
 Drug therapy

	0	3	6	9	12
Ablation	104	99	88	81	70
Drug therapy	99	93	60	44	39

# Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation


Jason G. Andrade, M.D., George A. Wells, Ph.D., Marc W. Deyell, M.D., Matthew Bennett, M.D., Vidal Essebag, M.D., Ph.D., Jean Champagne, M.D., Jean-Francois Roux, M.D., Derek Yung, M.D., Allan Skanes, M.D., Yaariv Khaykin, M.D., Carlos Morillo, M.D., Umjeet Jolly, M.D., Paul Novak, M.D., Evan Lockwood, M.D., Guy Amit, M.D., Paul Angaran, M.D., John Sapp, M.D., Stephan Wardell, M.D., Sandra Lauck, Ph.D., Laurent Macle, M.D., and Atul Verma, M.D., for the **EARLY-AF** Investigators\*



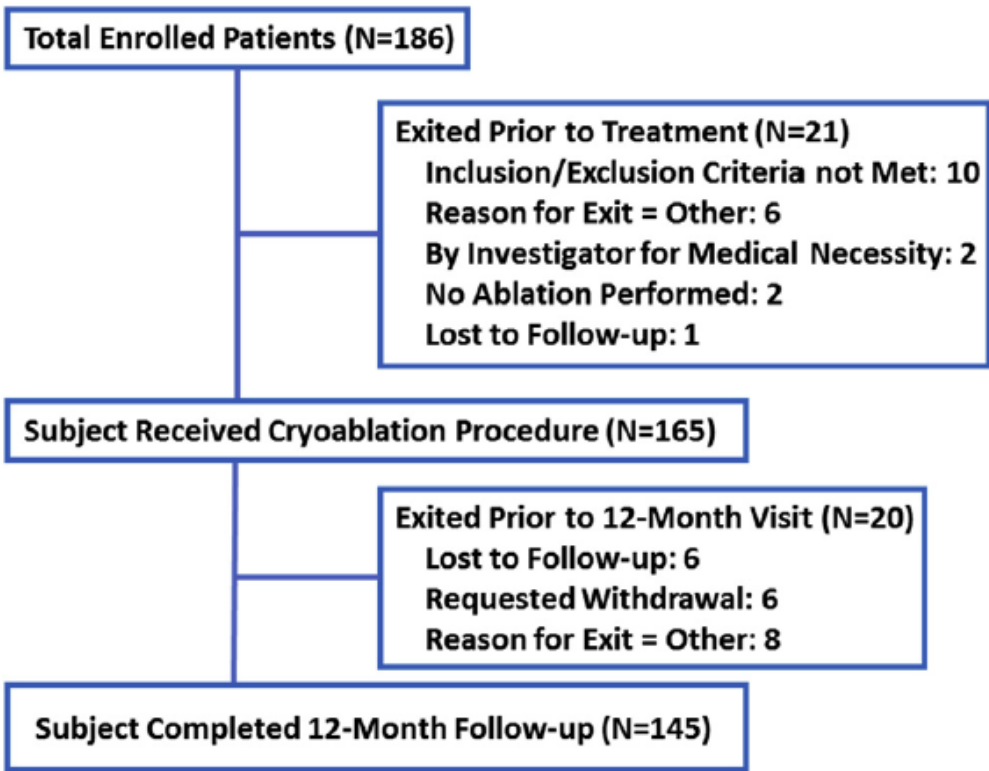
**No. at Risk**

	0	3	6	9	12		
Ablation	154	154	123	105	96	86	55
Antiarrhythmic drug therapy	149	149	89	69	60	49	27



**Cryoballoon ablation of pulmonary veins for persistent atrial fibrillation: Results from the multicenter STOP Persistent AF trial** 

# STOP PerAF trial



**Table 1** Baseline patient characteristics (N = 165)

Male sex	116 (70.3%)
Age (y)	65 ± 9
Left atrial diameter (cm)	4.2 ± 0.6
Left ventricular ejection fraction (%)	57 ± 7
AF at baseline visit	134 (81.2%)
Years since paroxysmal AF onset	5.1 ± 6.5
Years since persistent AF onset	0.6 ± 1.3
Duration of most recent AF episode (d)	60.5 ± 46.5
Duration of longest AF episode (d)	71.6 ± 48.9
No. of failed antiarrhythmic drugs	1.2 ± 0.5
Cardioversion before enrollment	121 (73.3%)
Cardioversions/patient before enrollment	1.9 ± 2.3
History of atrial flutter	28 (17.0%)
Body mass index (kg/m <sup>2</sup> )	31 ± 6
Systolic blood pressure (mm Hg)	129 ± 18
Diastolic blood pressure (mm Hg)	79 ± 12

# Cryoballoon ablation of pulmonary veins for persistent atrial fibrillation: Results from the multicenter STOP Persistent AF trial

## Procedural characteristics and outcomes

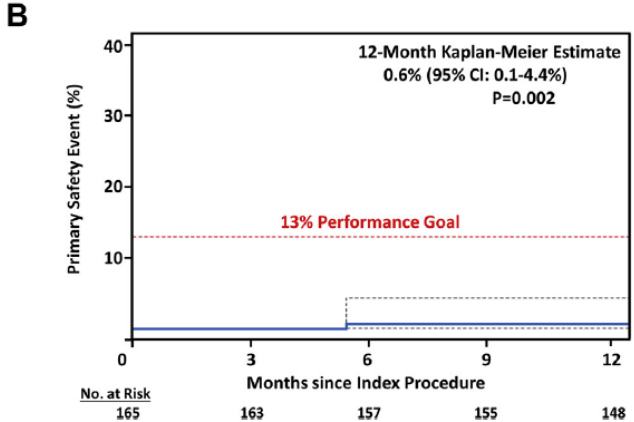
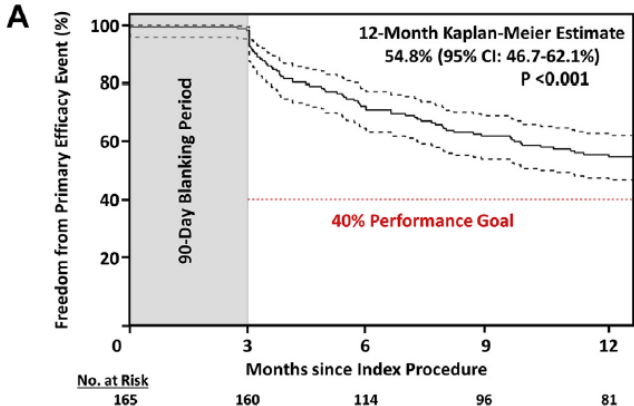
**Table 2** Index procedural characteristics (N = 165)

Total procedure time (min)	121±46
Left atrial dwell (min)	102±41
Study device left atrial dwell (min)	66±25
Total fluoroscopy time (min)	19±16
Cryoapplication duration (min)	24±8
Cavotricuspid isthmus line	50 (30.3%)
Acute success*	164 (99.4%)
PVI success by cryoballoon only	156
PVI touchup with focal cryocatheter	8
Cryoballoon applications	
No. of applications per vein	2.3±1.4
PVs treated with single cryoapplication	141/648 (21.8%)
Duration of cryoapplication (sec)	154±47
Median (interquartile range)	180 (120, 180)
Isoproterenol and/or adenosine used to assess PVI	24 (14.5%)

Values are given as mean ± SD, n (%), or n unless otherwise indicated.

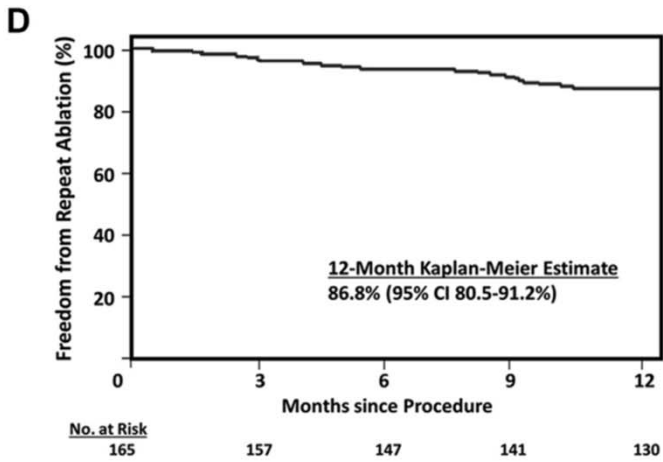
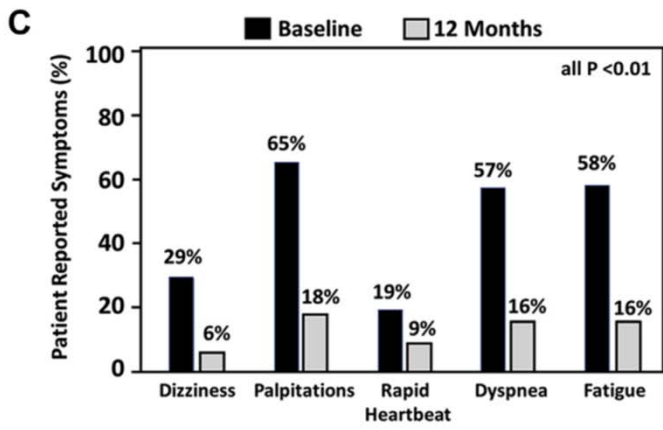
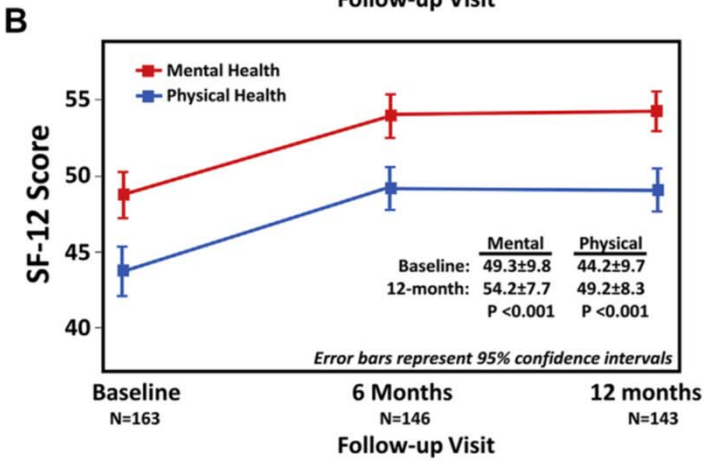
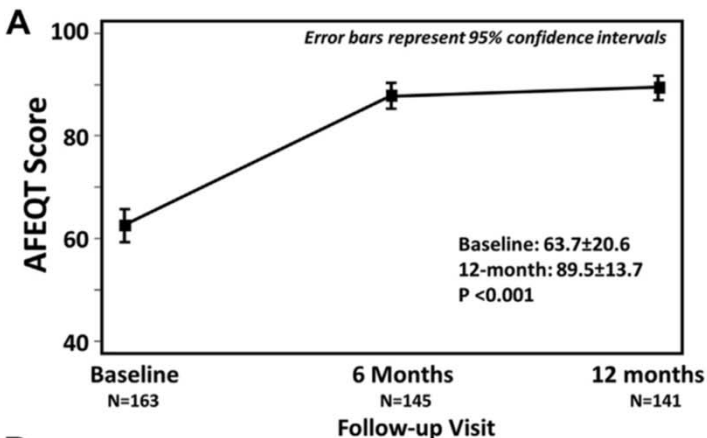
PV = pulmonary vein; PVI = pulmonary vein isolation.

\*Acute procedural failure in 1 subject resulted from radiofrequency ablation to complete PVI.



**Cryoballoon ablation of pulmonary veins for persistent atrial fibrillation: Results from the multicenter STOP Persistent AF trial**

**Secondary outcomes**

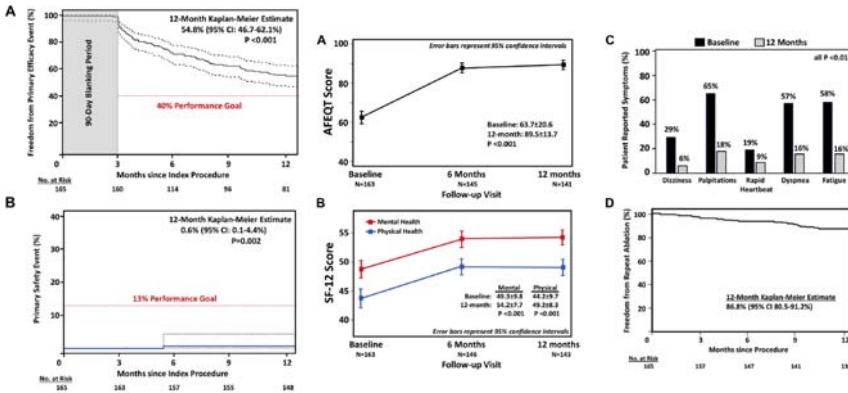


Is PVAI using cryoablation

an effective and safe option

for patients with (early) persistent AF?

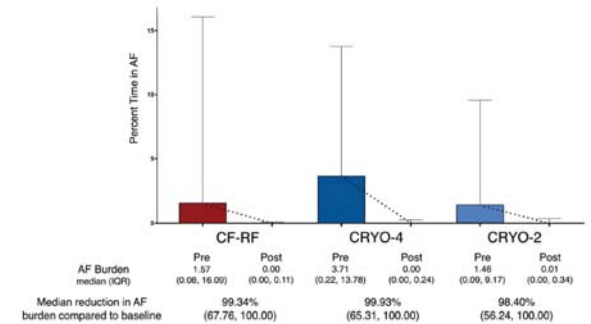
STOP Persistent AF



CIRCA-DOSE like rhythm assessment

ILR for Continuous Arrhythmia Monitoring

After enrollment, an ILR was inserted in all patients for the purpose of arrhythmia monitoring (Reveal LINQ; Medtronic, Minneapolis, MN). The ILR has an AF detection algorithm that continuously analyzes beat-to-beat variability of cardiac cycles, leading to an accurate determination of the timing of arrhythmia recurrence as well as an accurate quantification of AF burden (hours in AF per day and percentage of overall



AF burden assessed by ILR?

(Early) persistent AF?

COOL-PER study

# **CyrOablatiOn for puLmonary vein isolation alone in patients with early PERsistent AF assessed by continuous monitoring (COOL-PER)**

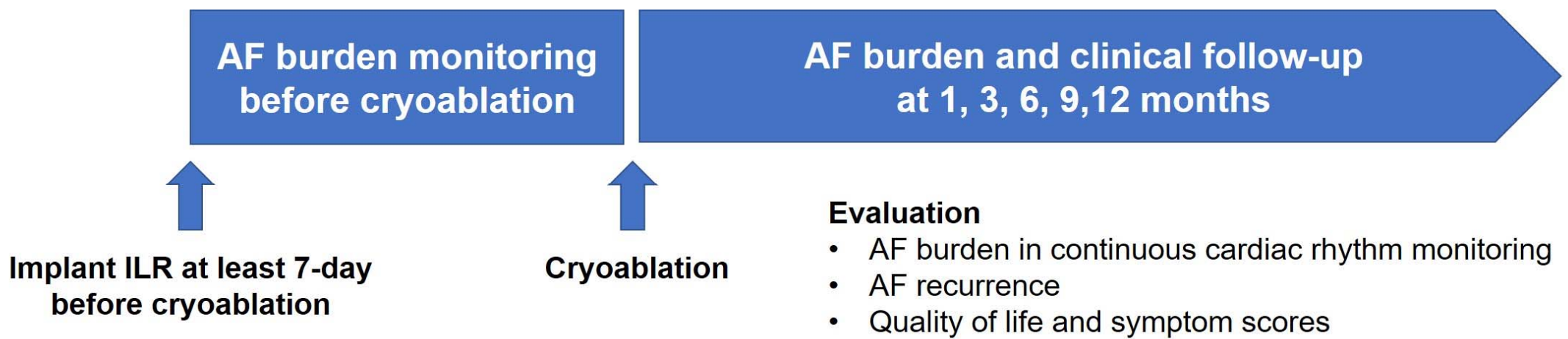
- Prospective, multicenter, single-arm, observational registry
- 6 centers in the Republic of Korea
  - Seoul National University Hospital
  - Seoul National University Bundang Hospital
  - Samsung Medical Center
  - Asan Medical Center
  - Hallym University Sacred Heart Hospital
  - Sejong General Hospital
- Product
  - Arctic Front Advance cardiac cryoablation catheter (Medtronic, Minneapolis, MN)
  - Reveal LINQ Insertable Cardiac Monitor system (Medtronic, Minneapolis, MN)

# Study Population

- Patients with non-valvular persistent AF having less than 3 years of AF duration
- Inclusion criteria
  - Age  $\geq 20$  years,  $< 80$  years
  - Drug refractory **symptomatic persistent AF diagnosed within 3 years**
  - Either two conditions
    - 1) **AF episode lasting longer than 7 days**, but less than 3 years documented by consecutive ECG recordings of **100% AF greater than 7 days apart** or
    - 2) AF episode requiring **electrical or pharmacological cardioversion** after 24 hours of AF documented by continuous recording



# Study flow



# Cryoablation protocol

The need for the coordinating centers to use a consistent dosing strategy (duration of freeze and # of freeze) so the results will be transferable. It does not have to be the same for every patient at every site; it should just be similar – and similar to what others around the world are doing.

**STOP Persistent AF** : “Recommended cryoballoon application time was **3 minutes per ablation**; however, the number and duration of cryoapplications were left to physician discretion.”

**CRYO4PERSISTENT**: “For PVI, the protocol recommended **240-s cryoapplications using a freeze-thaw-freeze** technique, with a bonus freeze after PVI which, at the time of the trial, was the current operator consensus for cryoablation application duration.”

**ICE-T trial**: Control: **empiric 240 sec freeze** vs. **ICE-T, 240 sec freeze** (TTI<75 sec, no further freeze, TTI>75 sec, **1 bonus freeze [240 seconds]** was delivered).

**ICE Re-Map Study**: Target freeze 180 sec vs. **240 sec freeze** (TTI<75 sec, no further freeze, TTI>75 sec, **1 bonus freeze** was delivered)\_ 240 was associated with significantly increased lesion durability

**CIRCA-DOSE**: RF vs. **2 min freeze** vs. **4 min freeze**

**(Minimum) 240 sec per PV and other things are left to physician discretion.**

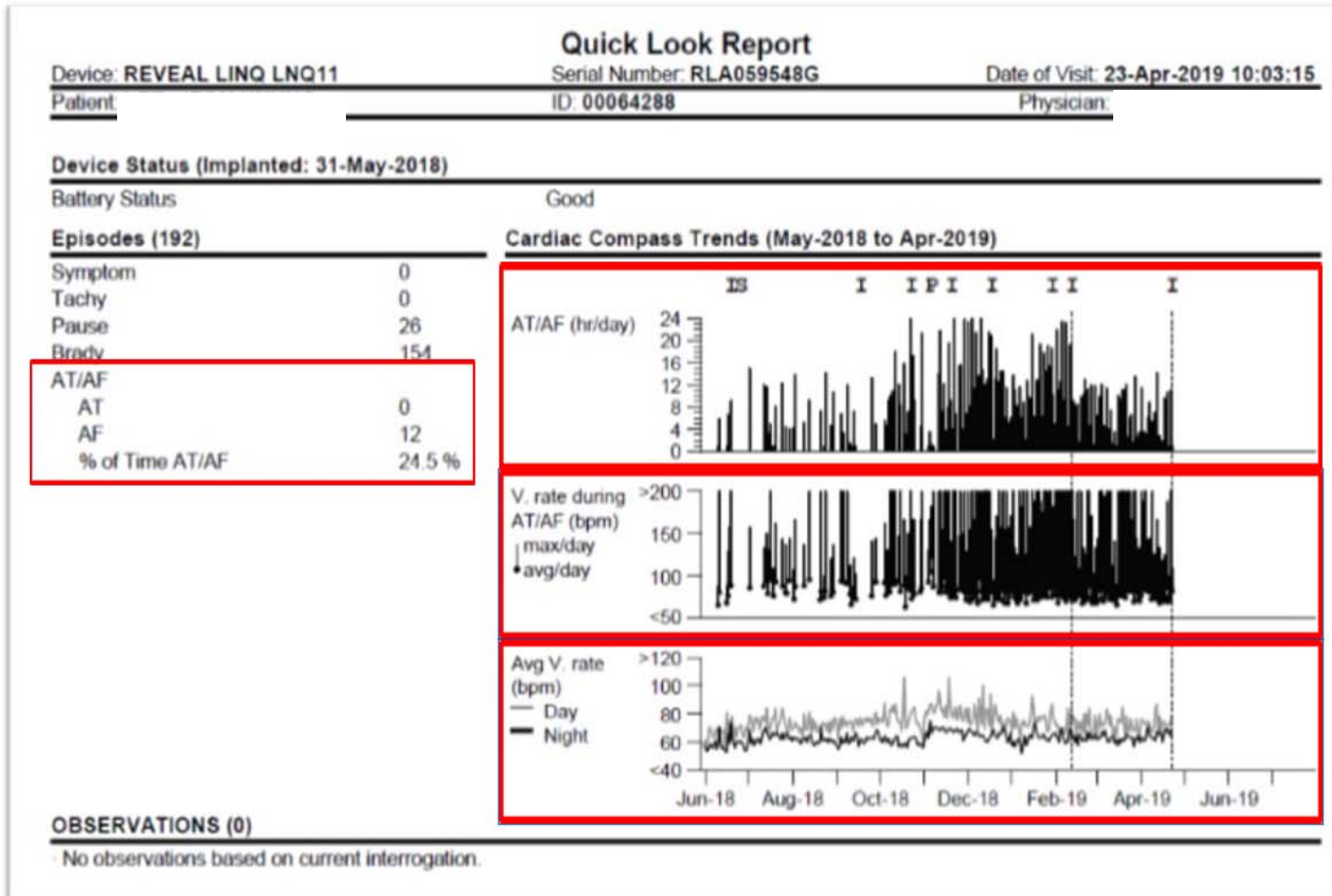
## Post cryoballoon ablation follow-up

- Scheduled follow-up visits will occur at 3, 6, 9 and 12 months from the first ablation procedure (within a 4-week margin)
- ILR monitoring and a 12-lead ECG will be performed at 3, 6, 9 and 12 months
- Arrhythmia recurrence during the first three months post-ablation could be treated with cardioversion and/or AADs.
- After 3-month of window period, AADs would be recommended to continue. However, this decision would be based on the discretion of the operator

# Post cryoballoon ablation follow-up

- Primary endpoint
  - Change of **ICM-detected AF/AT burden**, which was defined as the % of time spent in AF (hours of AF/hours of monitoring) during the first year after PVI (excluding a 3-month window) compared to pre-ablation AF/AT burden
  - Four types of records related to AF/AT: i) the number of AF/AT episode, ii) % of the time in AF/AT (from last patient session), iii) daily AF/AT burden (hours/day), and iv) AF/AFT episode list. We will evaluate "% of the time in AF/AT" to calculate the burden of AF/AT (between 3-month and) 1-year after cryoablation

# AF burden on ILR



# Clinical characteristics

Variable	Total (n=130)
Age (years)	59.9±9.2
Men	99 (76.2%)
BMI (kg/m <sup>2</sup> )	25.9±2.7
Persistent AF	130 (100%)
Persistent AF duration (month)	6.1±6.8
Paroxysmal AF history	43 (33.1%)
Paroxysmal to PeAF duration (month)*	29.5±29.1
DCC history	44 (33.8%)
DCC fail	6 (4.6%)
Hypertension	70 (53.8%)
Diabetes	24 (18.5%)
Heart failure	21 (16.2%)
Coronary artery disease	8 (6.2%)

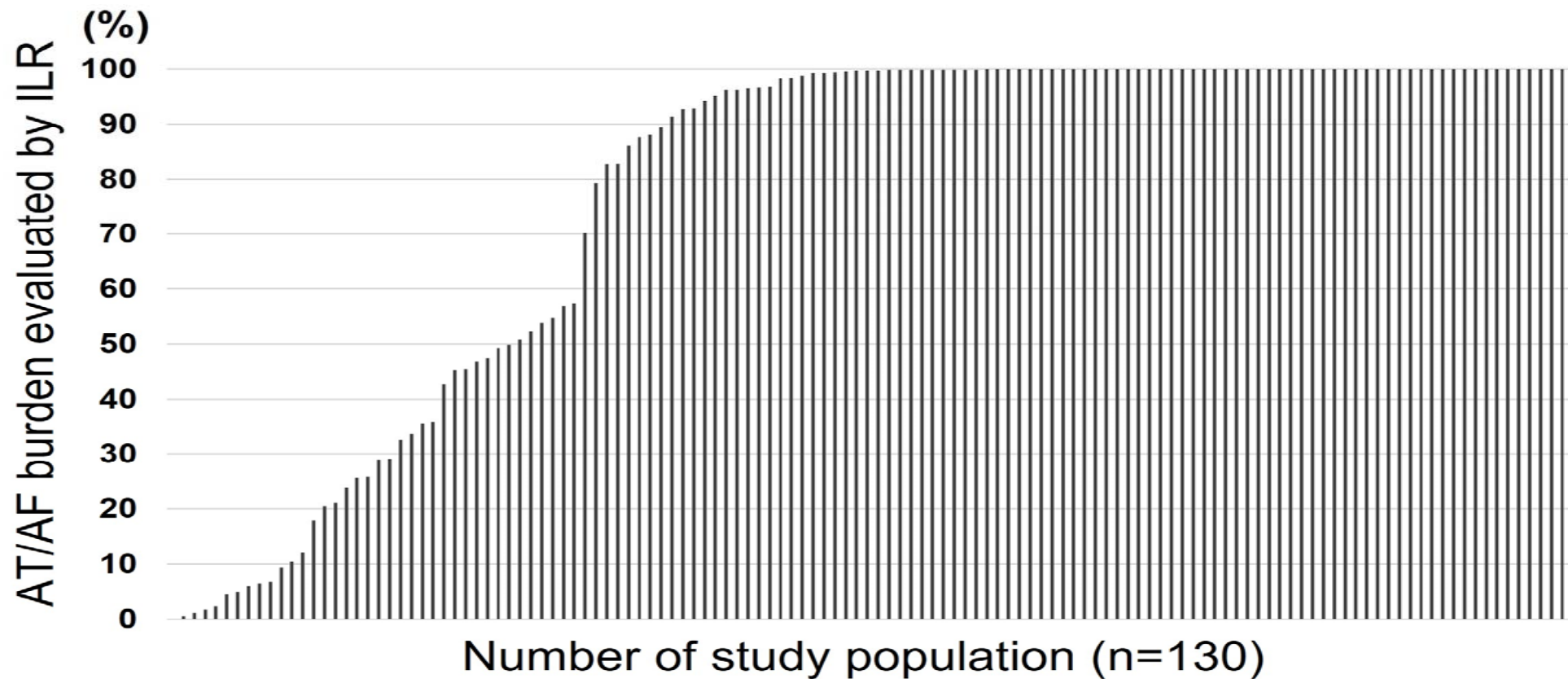
Variable	Total (n=130)
Peripheral artery disease	1 (0.8%)
Myocardial infarction	2 (1.5%)
Stroke/TIA	11 (8.5%)
Structural heart disease	9 (6.9%)
<b>Medication</b>	
Beta-blocker	58 (44.6%)
Calcium channel blocker	22 (16.9%)
Class Ic	59 (45.4%)
Sotalol	0 (0%)
Dronedarone	8 (6.2%)
Amiodarone	59 (45.4%)
RAS blocker	39 (30.0%)
Statin	38 (29.2%)
NOAC	125 (96.2%)
Warfarin	1 (0.8%)
Antiplatelet agent	2 (1.5%)



# Clinical characteristics

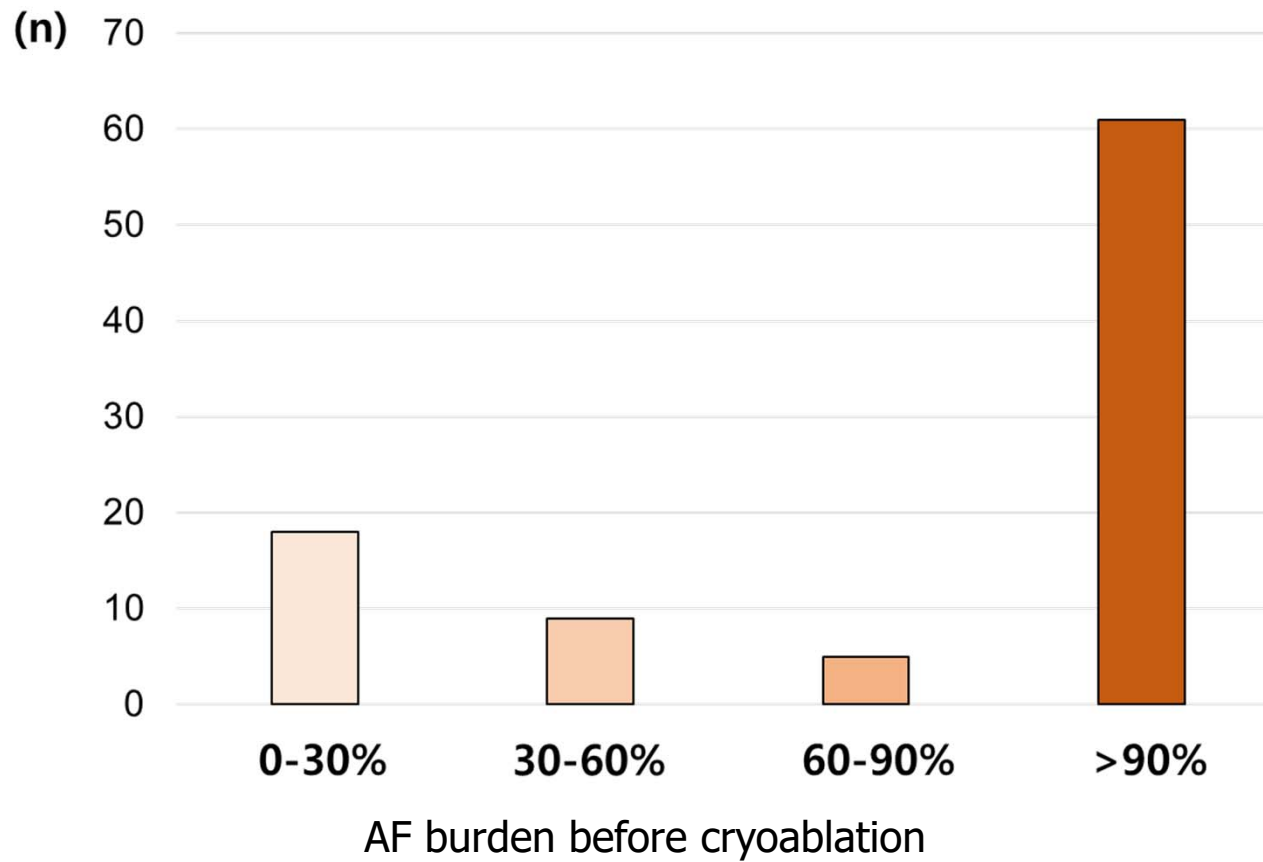
Variable	Total n=93
EHRA symptom score	
1	4 (3.1%)
2a	58 (44.6%)
2b	47 (36.2%)
3	21 (16.2%)
SF 63 score	138.6±34.6
LA AP diameter (mm)	43.8±3.9
LA volume (ml)	81.7±21.1
LA volume index	49.1±34.5
ILR to Cryo (days)	54.0±50.7
ILR baseline burden (%)	77.3±34.0
<b>Cryo procedure</b>	
Procedure time (min)	75.8±21.3
Ablation time (sec)	1235±426
Fluoro time (min)	18.9±11.1

# Baseline ILR burden



AF burden	0~<10%	10~<20 %	20~<30 %	30~<40 %	40~<50 %	50~<60 %	60~<70 %	70~<80 %	80~<90 %	90~<99.9 %	99.9~100%
N (%)	11 (8.5%)	3 (2.3%)	7 (5.4%)	4 (3.1%)	7 (5.4%)	6 (4.6%)	0 (0%)	2 (1.5%)	6 (4.6%)	20 (15.4%)	64 (49.2%)

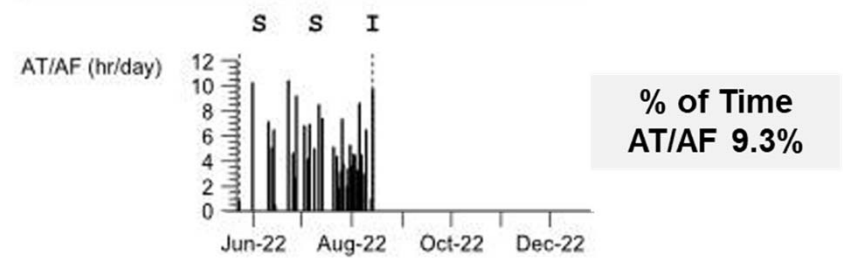
# Baseline ILR burden



# Patterns of persistent AF

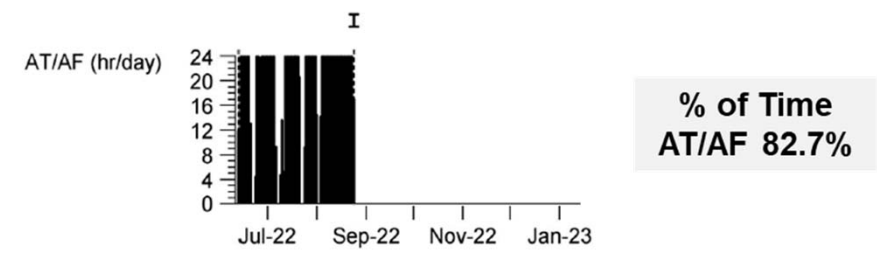
## High-burden paroxysmal AF (Type 1)

Cardiac Compass Trends (May-2022 to Aug-2022)

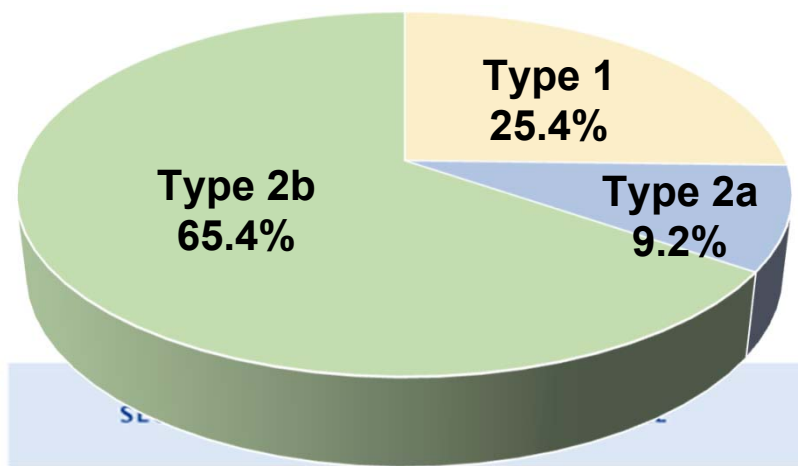


## PeAF with spontaneous termination (Type 2a)

Cardiac Compass Trends (Jun-2022 to Aug-2022)

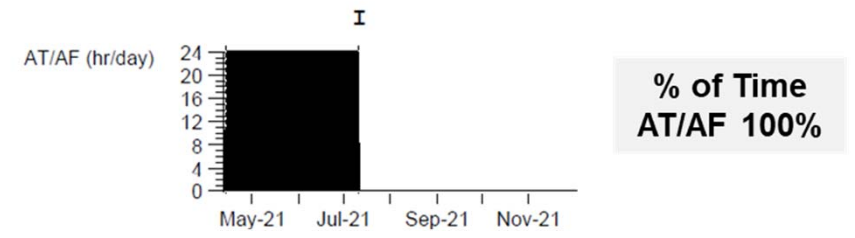


**Actual AF type evaluated by ILR monitor (n=130)**

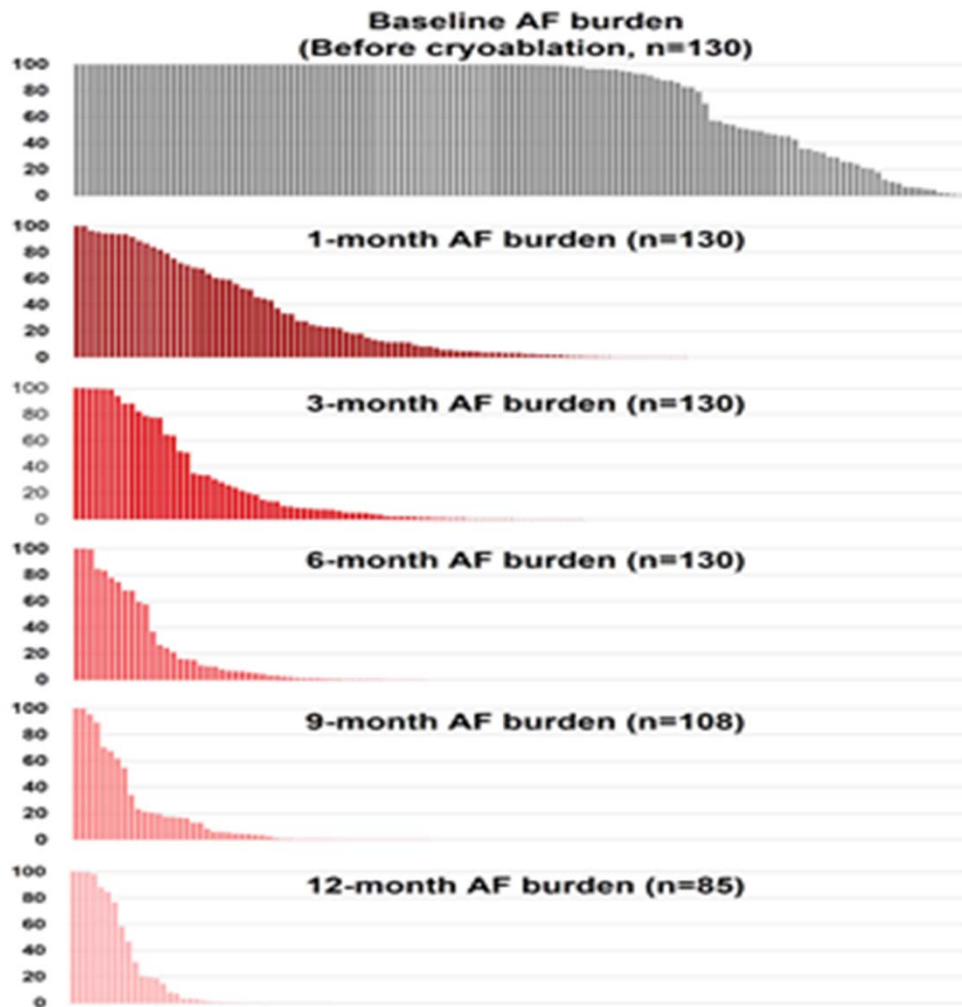


## PeAF without spontaneous termination (Type 2b)

Cardiac Compass Trends (Apr-2021 to Jul-2021)

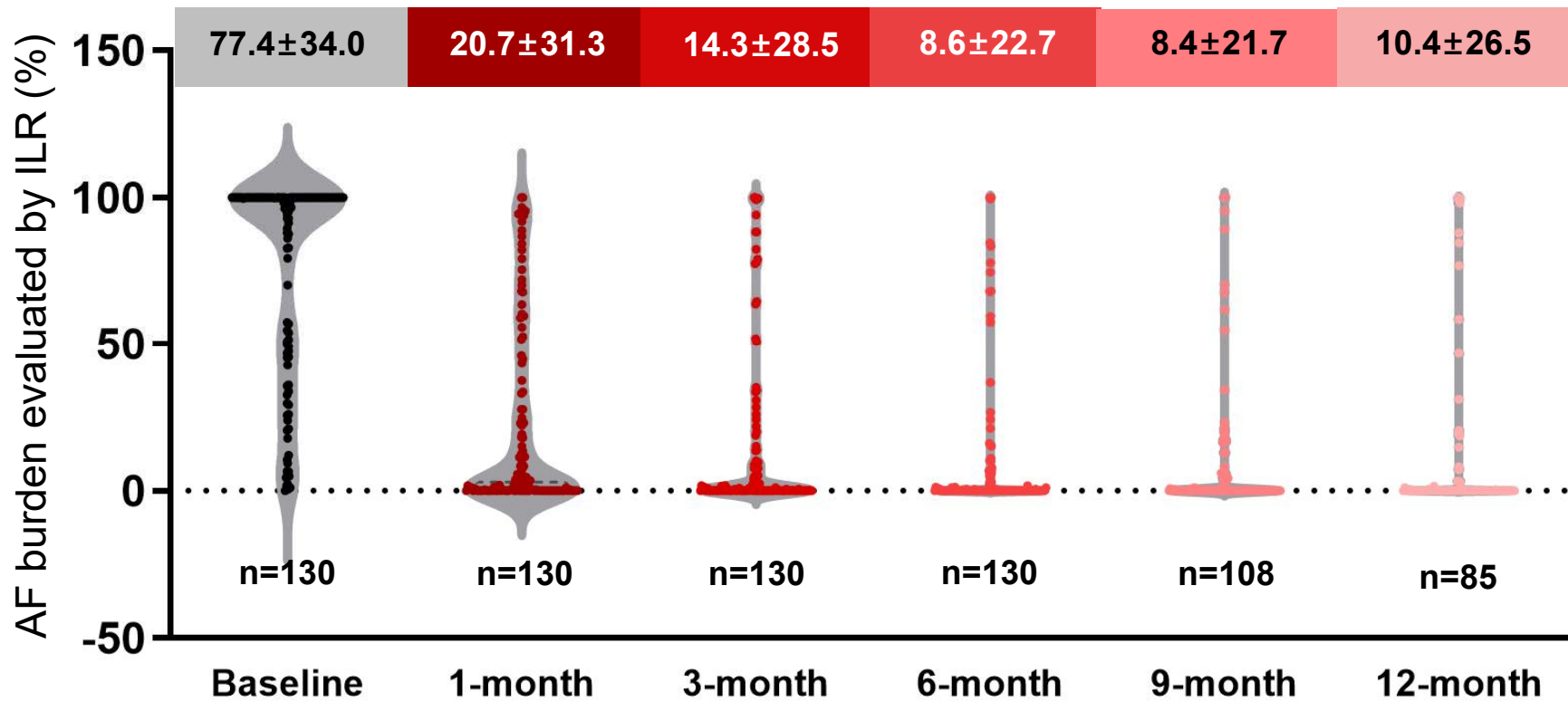


# Distribution of AF burden of study patients at each follow-up



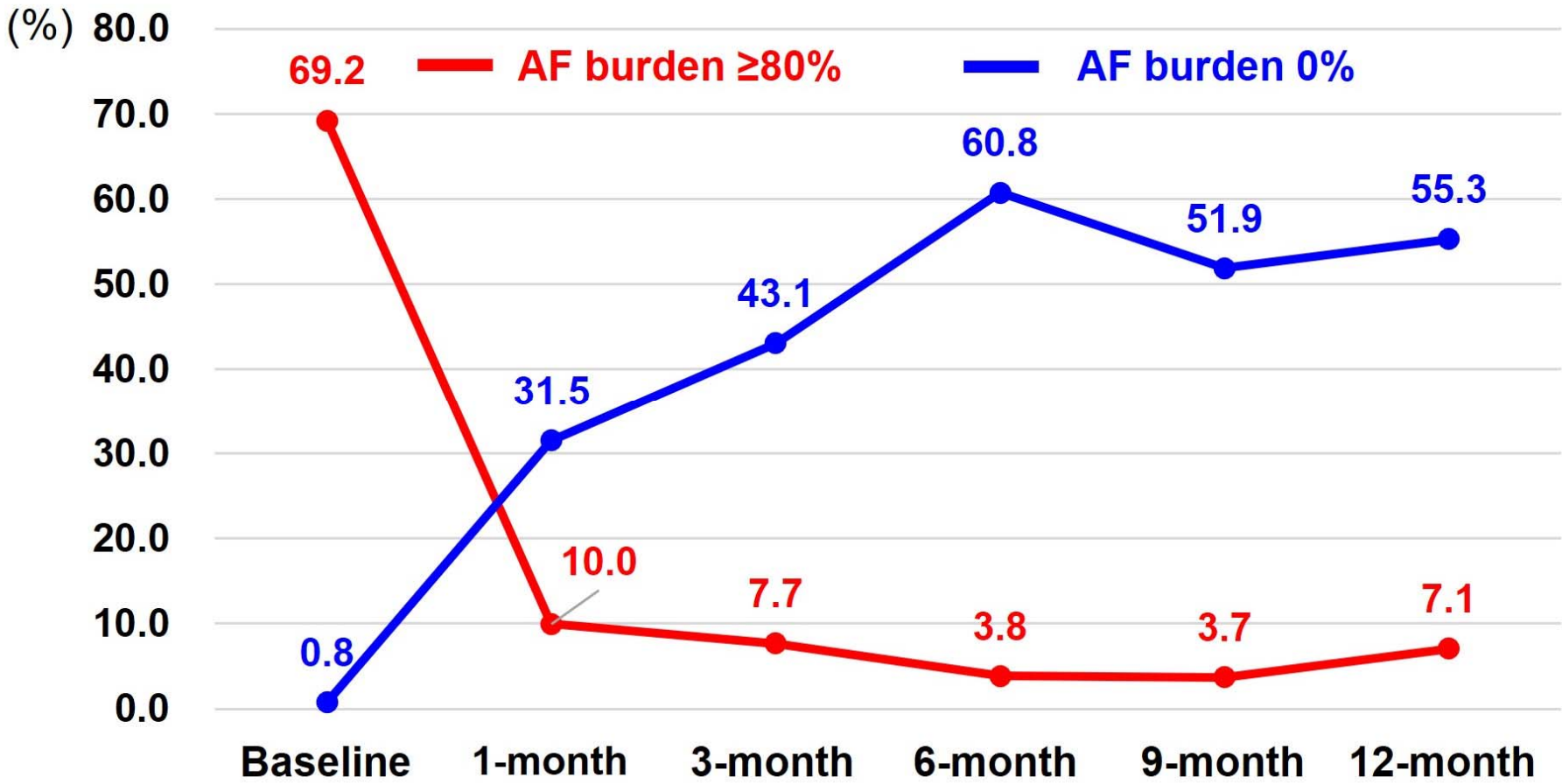
- Compared to the baseline, **the AF burden reduced substantially after index cryoablation.**
- The mean AF burden significantly decreased ( $77.4 \pm 34.0\%$  at baseline vs.  $20.7 \pm 31.3\%$  at 1-month vs.  $14.3 \pm 28.5\%$  at 3-month vs.  $8.6 \pm 22.7\%$  at 6-month,  $8.4 \pm 21.7$  at 9-month, and  $10.4 \pm 26.5$  at 12-month follow-up, p for trend  $< 0.001$ ).
- During **mean  $11 \pm 2$  month of follow-up, 45% (n=59) of patients showed "AF burden 0%"** in ILR monitor across the follow-up.

# Progressive reduction of mean AF burden during follow-up

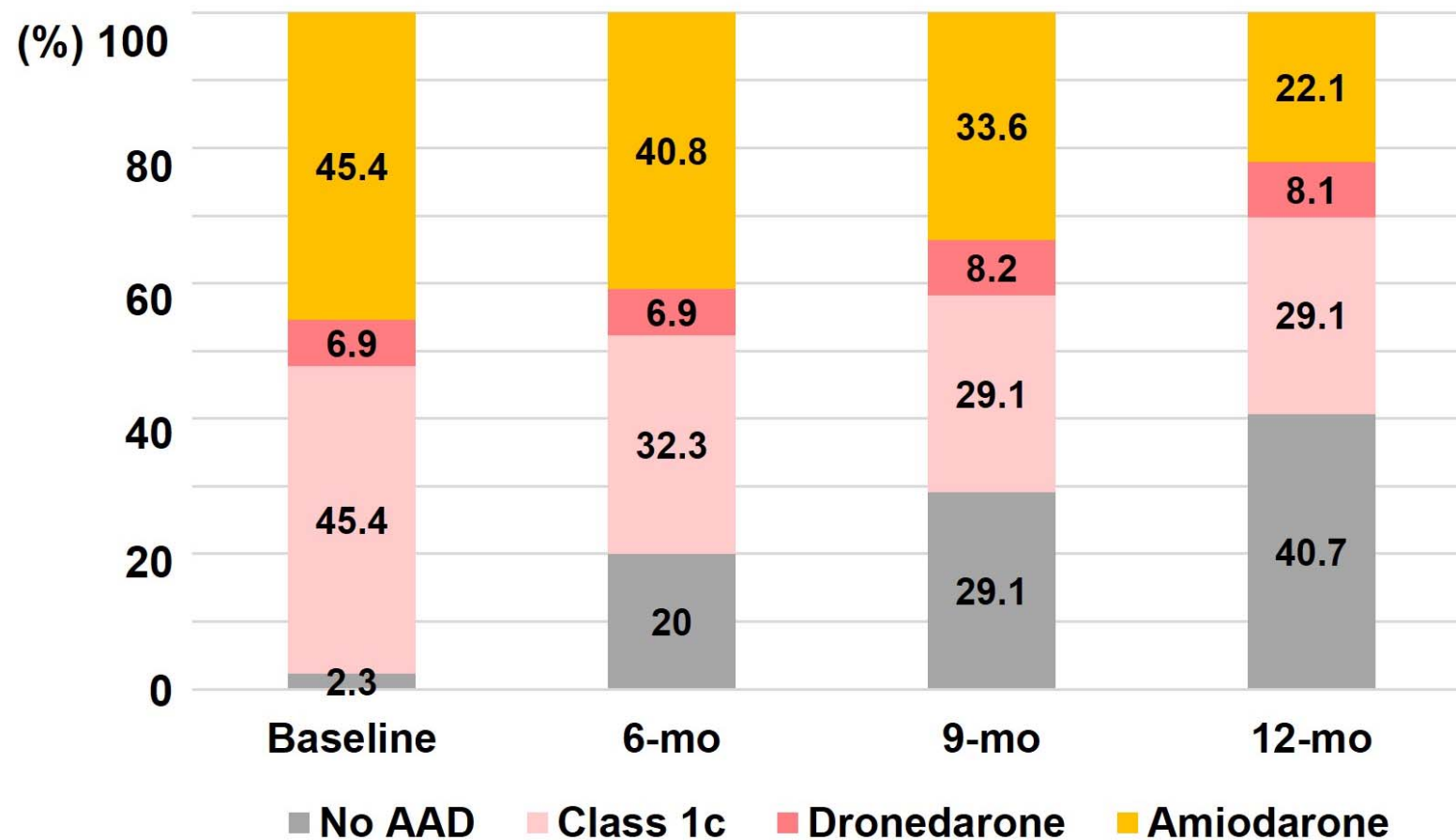




# Proportion of pts with AF burden $\geq 80\%$ and 0%



# Changes in antiarrhythmic drug prescription



# Case 1. M/63

- 2020/12 AF detected at local clinic (routine check-up)
- EHRA 2b
- HTN/DM
- 2021/10/12 ILR (REVEAL LINQ, Medtronic)
- 2021/10/26 PVAI (cryo)
- Mx: apixaban, propafenone, fimasartan

# Quick Look Report

Device: REVEAL LINQ LNQ11

Serial Number: RLA309123G

Date of Visit: 03-Nov-2022 13:49:48

Patient:

ID: 55366926

Physician: Prof. Choi, E K - - -

## Device Status (Implanted: 12-Oct-2021)

Battery Status

Good

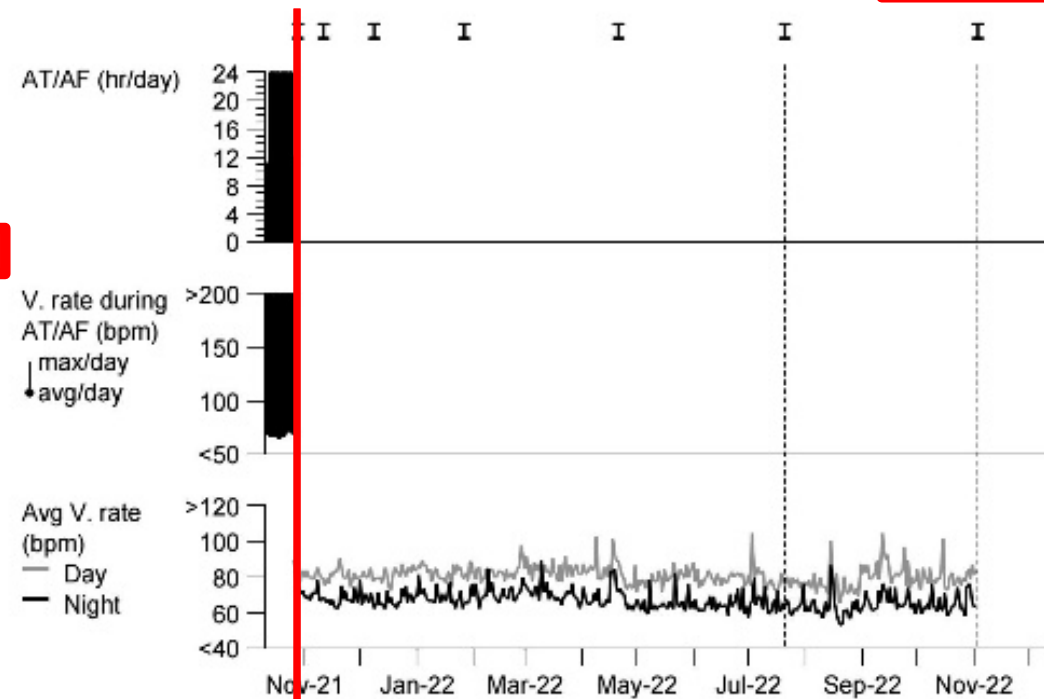
### Episodes (0)

Symptom	0
Tachy	0
Pause	0
Brady	0
AT/AF	0
AT	0
AF	0

**% of Time AT/AF 0.0 %**

### Cardiac Compass Trends (Oct-2021 to Nov-2022)

**1 YR**



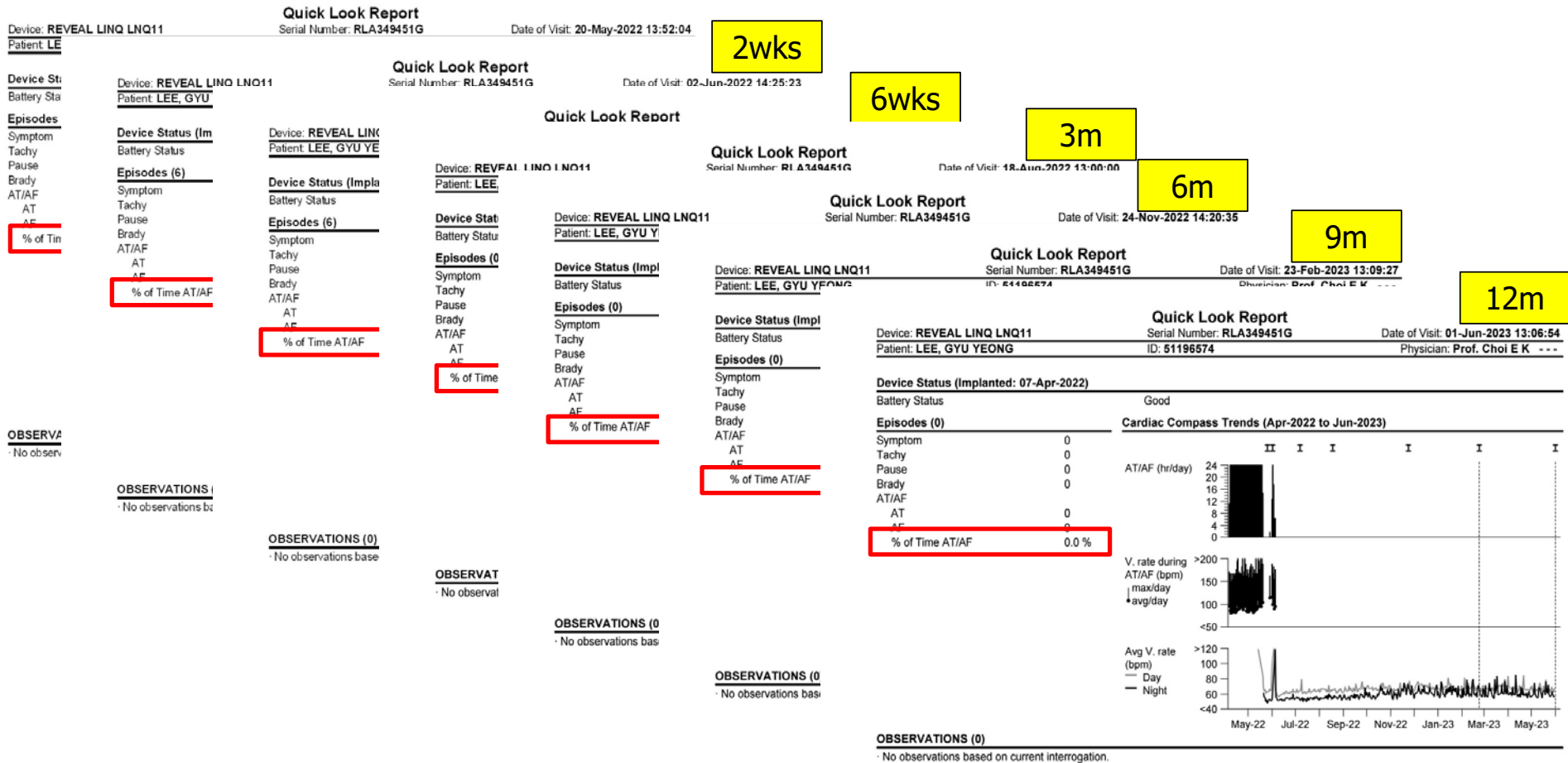
### OBSERVATIONS (0)

· No observations based on current interrogation.

**CryoABL**

## Case 2. M/51

- 2020/11 Routine health check-up, AF detected
- 2021/12/20 Echo-EF49%, LA48mm, global HK Holter-AF (100%)
- EHRA 2a
- HTN
- Mx: apixaban, dronedarone, fimasartan
- 2022/4/7 ILR (REVEAL LINQ, Medtronic)
- 2022/5/20 PVAI (cryo)



AF burden 100% → 9.6% → 4.7% → 0% → 0% → 0% → 0%

## Case 3. F/67

- 2021/5/3 ECG-AF → AMO → AF → DCC (2021/5/27) → AF
- HTN
- EHRA 2b
- Mx: edoxaban, amiodarone, carvedilol, telmisartan
- 2021/6/10 ILR (REVEAL LINQ, Medtronic)
- 2021/9/9 PVAI (cryo)



**Before CryoABL**

**6-wk**

**3-month**

**6-month**

**9-month**

**12-month**

### Quick Look Report

Device: REVEAL LINQ LNQ11

Serial Number: RLA261308G

Date of Visit: 30-Jun-2022 13:43:49

Patient: JEON, AE SOON

ID: 46234157

Physician: Prof. CHOI E K ---

#### Device Status (Implanted: 10-Jun-2021)

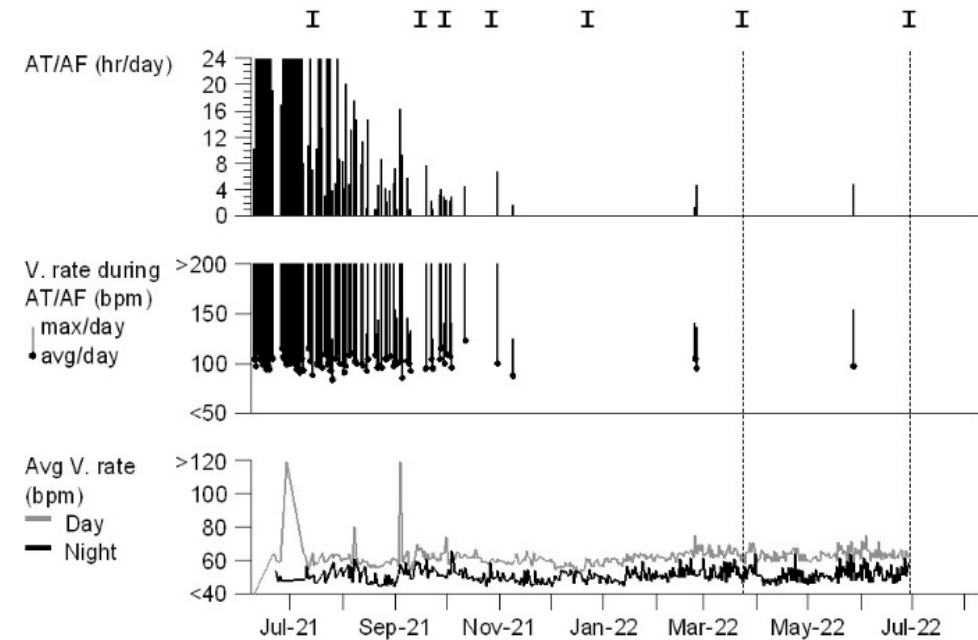
Battery Status

Good

#### Episodes (3)

Symptom	0
Tachy	0
Pause	0
Brady	0
AT/AF	0
AT	0
AF	3
% of Time AT/AF	0.2%

#### Cardiac Compass Trends (Jun-2021 to Jul-2022)



#### OBSERVATIONS (0)

No observations based on current interrogation.

AF burden 76.1% → 3.8% → 2.2% → 0.6% → 0.3% → 0.2%

## Case 4. M/66

- 2017/10 PAF → flecaide → AMO → multaq → PeAF (2019/12) → DCC → AF
- EHRA 2a
- Bicuspid AV
- Thyroid Ca op (2020/4)
- Mx: Apixaban (D-code), propafenone, indenol
- 2021/10/24 ILR (REVEAL LINQ, Medtronic)
- 2021/11/23 PVAI (cryo)

# Quick Look Report

Device: REVEAL LINQ LNQ11

Serial Number: RLA309109G

Date of Visit: 14-Nov-2022 13:48:22

Patient: [REDACTED]

ID: 50642973

Physician: Prof. Choi E K - - -

## Device Status (Implanted: 21-Oct-2021)

Battery Status

Good

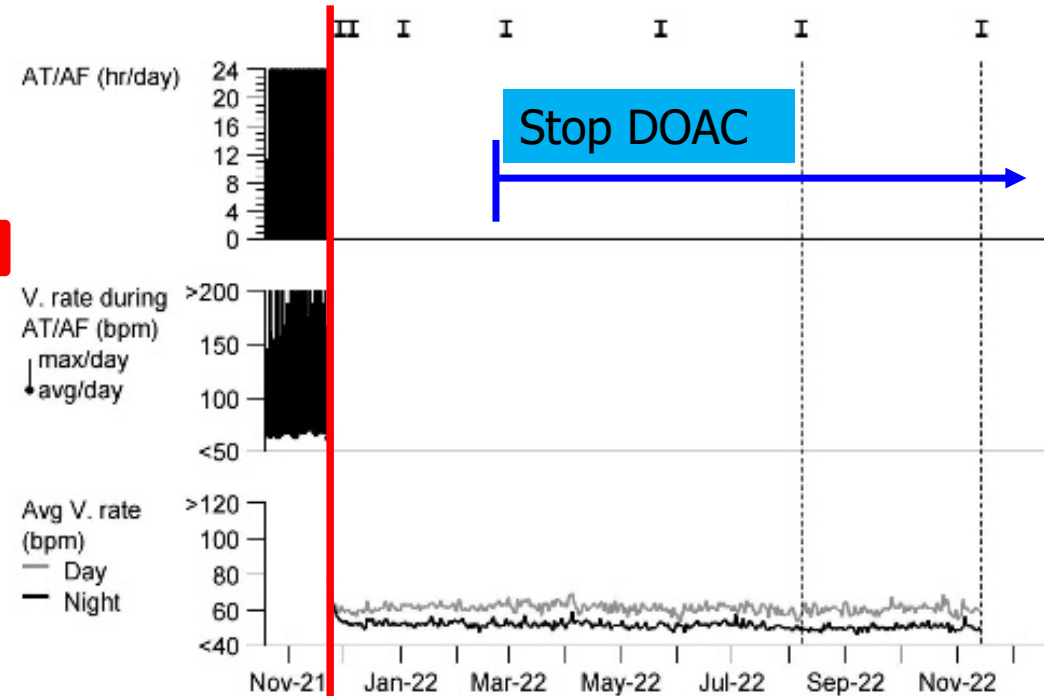
### Episodes (0)

Symptom	0
Tachy	0
Pause	0
Brady	0
AT/AF	0
AT	0
AF	0

**% of Time AT/AF 0.0 %**

### Cardiac Compass Trends (Oct-2021 to Nov-2022)

**1 YR**



### OBSERVATIONS (0)

· No observations based on current interrogation.

**CryoABL**

**Comparison between  
continuous oral anticoagulation versus  
pill-in-POCKET Oral AntiCoagulation strategy  
guided by continuous rhythm monitoring using ILR  
after AF catheter ablation  
(POCKET OAC study)**

# Take home message

- AF burden of **clinically persistent AF is diverse**
- Cryoballoon ablation resulted in a **significant AF burden reduction** as assessed by continuous cardiac rhythm monitoring
- Cryoballoon ablation to be safe and effective in treating patients with drug-refractory **early persistent AF** characterized by continuous AF episodes of less than 3 years
- More follow-up data regarding change in AF burden, symptom score and quality of life would be analyzed

# Seoul National University Hospital Cardiac Arrhythmia Laboratory

## **SNUH EP lab**

Seil Oh, MD, PhD  
Eue-Keun Choi, MD, PhD  
So-Ryoung Lee, MD, PhD  
Soonil Kwon, MD  
Hyo-Jeong Ahn, MD  
JungMin Choi, MD  
Kyung-Yeon Lee, MD

## **Animal Lab**

Moo-Kang Kim  
Ae-Sun Yoon  
Hae-Deun Kim

## **Clinical Research**

Ji-Hee Min  
Hye-Jin Song  
So-Hee Kim  
Eun-Keung Song  
Ji-In Hong  
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## **University of Liverpool and Liverpool Chest & Heart Hospital**

Gregory Y. H. Lip, MD

## **Soongsil University**

Kyung-Do Han, PhD

**Thank you for your attention**