What is the real recurrence rate after cryoballoon-based pulmonary vein isolation? Lessons from rhythm follow-up based on implanted cardiac devices with continuous atrial monitoring

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BACKGROUND Second-generation cryoballoon (CB2)-based pulmonary vein isolation (PVI) has demonstrated encouraging clinical results for the treatment of paroxysmal atrial fibrillation (AF) and persistent AF. However, rhythm follow-up after PVI is mainly based on Holter electrocardiography of limited duration.

OBJECTIVE The purpose of this study was to assess the real AF burden following CB2-based PVI in patients with implanted cardiac devices.

METHODS A total of 670 consecutive patients underwent CB2-based PVI at 3 electrophysiology centers. In 66 patients (9.9%), an implantable cardiac device with continuous monitor function was independently implanted before the procedure (device group). This patient cohort was compared to propensity score-matched patients without cardiac devices (n = 66; control group).

RESULTS A total of 254 of 258 PVs (98.4%0 in the device group were successfully isolated using only CB2. Postprocedural device interrogation found no device or lead malfunction related to the procedure. Periprocedural complications were registered in 7 of 66 patients (11%) in the device group and in 6 of 66 patients (9%) in the control group ($P = .770$). Phrenic nerve palsy occurred in 6 of 66 patients (9%) in the device group) and in 2 of 66 patients (3%) in the control group) ($P = .274$). Clinical success in terms of freedom from AF recurrence after a 1-year follow-up period was 63.8% (95% confidence interval 53–77) in the device group and 77.3% (95% confidence interval 68–88) in the control group ($P = .038$). In the device group, AF/AT burden decreased from 41.8% ± 35.0% before the procedure to 10.2% ± 22.4% after 1 year ($P < .0001$).

CONCLUSION CB2-PVI seems safe and feasible in patients with an implanted cardiac device. A significantly higher AF/AT burden was seen in patients with an implanted cardiac device compared to a control group.

KEYWORDS Atrial fibrillation; Cardiac resynchronization therapy; Cryoballoon; Implantable cardioverter-defibrillator; Implantable

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Introduction

The second-generation cryoballoon (CB2; Arctic Front Advance, Medtronic Inc, Minneapolis, MN) has demonstrated high procedural success rates and convincing long-term clinical outcome data for paroxysmal atrial fibrillation (PAF) and persistent atrial fibrillation (PersAF).[1–4] The FIRE AND ICE Trial proved the noninferiority of CB2- to radiofrequency (RF)-based pulmonary vein isolation (PVI) in patients with PAF.[5] As a consequence, the latest AF guidelines state that PVI should be performed using either RF or CB catheters.[6] Rhythm follow-up after PVI is mainly based on Holter electrocardiography (ECG), resting ECG, tele-ECG, or patient's symptoms. However, in particular for PAF, the most appropriate assessment of the real AF burden after PVI remains a subject of discussion. Implanted cardiac dual-chamber devices with implemented continuous atrial monitoring are assumed to have high appropriate detection rates of atrial high rate episodes.[7,8] Data on the impact of cardiac devices on acute efficacy, safety, and clinical outcomes in CB2-based PVI are not available yet.

Methods

Patient characteristics and study design

All patients referred to 3 highly experienced electrophysiology centers in Germany (Asklepios Klinik St. Georg, Hamburg; Asklepios Klinik Harburg, Hamburg; Charité Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin) were analyzed retrospectively. Patients with symptomatic PAF or PersAF scheduled for CB2-based PVI and a previously implanted cardiac device (implantable cardioverter-defibrillator [ICD], cardiac resynchronization therapy device [CRT], dual-chamber pacemaker [PM], or implantable loop recorder [ILR]) were extracted. Exclusion criteria were prior left atrial (LA) ablation, LA diameter >60 mm, severe valvular heart disease, long-standing PersAF, or contraindications to postinterventional oral anticoagulation. Transesophageal echocardiography was performed before ablation to assess LA diameter and to rule out intracardiac thrombi. No additional preprocedural imaging was performed. Follow-up and procedural data of patients who underwent CB2-based PVI with a cardiac device (device group) were compared to matched patients without cardiac devices (control group). All patients gave written informed consent, and all patient information was anonymized. The study was approved by the local ethics boards and was performed in accordance with the ethical standards given in the 1964 Declaration of Helsinki and its later amendments.

The primary endpoint was defined as recurrence of AF/AT during 1-year follow-up including a blanking period of 90 days. Secondary endpoints were defined as procedure-related lead dislocation, device malfunction, and periprocedural complications.

Intraprocedural management

Principles of CB2-based PVI have been described previously.[4,9] In brief, all procedures were performed with patients under deep sedation using midazolam, fentanyl, and propofol. Single transseptal puncture was performed using a modified Brockenbrough technique and an 8.5F transseptal sheath (SL1, St. Jude Medical, St. Paul, MN). The transseptal sheath was exchanged over a wire for a 12F steerable transseptal sheath (Flexcath Advance, Medtronic). After transseptal puncture, heparin was administered targeting an activated clotting time >300 seconds. Selective PV angiographies were performed to identify the individual PV ostia. A temperature probe (Sensitherm, St. Jude Medical; or Circa S-Cath, Circa Scientific, Englewood) was placed within the esophagus to monitor esophageal temperatures during freeze cycles. The intraluminal esophageal temperature cutoff was set at 15°C.[10]

During CB2 applications along the septal PVs, continuous pacing of the phrenic nerve (PN) was performed via a 7F diagnostic catheter positioned within the superior vena cava (Webster, Biosense Webster, Diamond Bar, CA).[11] Pacing was set at maximum output and pulse width, and cycle length of 1000 ms. Monitoring of the PN was based on tactile feedback of diaphragmatic contraction and assessment of the right diaphragmatic compound motor action potential.[12,13] Energy delivery was interrupted immediately if weakening or loss of diaphragmatic contraction was noted or a decrease of the compound motor action potential amplitude ≥30% was observed. In case of phrenic nerve palsy (PNP), no further cryoenergy was delivered along the septal PVs.[14]

PVI using the CB2

The CB2 was advanced into the LA over a spiral mapping-catheter (Achieve, Medtronic). Only the size 28-mm CB2 in conjunction with the 20-mm Achieve was used. The CB2 was inflated proximal to the PV ostium, followed by gentle push aiming for complete sealing at the antral aspect of the PV. Complete PV occlusion was verified by contrast medium injection through the central lumen of the CB2. Total PV occlusion was considered if no backflow of contrast to the LA was documented. Different ablation protocols were applied. The first 16 consecutive patients were treated by a "bonus-freeze" protocol (freeze-cycle duration 240 seconds, followed by 1 additional freeze cycle of 240-second duration after PVI).[4] Another 28 consecutive patients were treated with a "no bonus-freeze" protocol (freeze-cycle duration 240 seconds without an additional freeze cycle after PVI).[15] The last 22 consecutive patients were treated based on a "time-to-effect" guided ablation protocol (after real-time PVI, another 120 seconds were applied without an additional freeze cycle).[16,17] In the control group, the following

protocols were used: bonus freeze in 14, no bonus freeze in 28, and time-to-effect in 24.

Postprocedural care

After PVI, all patients underwent transthoracic echocardiography to rule out pericardial effusion. All patients were treated with proton pump inhibitors twice daily for 6 weeks. Low-molecular-weight heparin was administered in patients taking vitamin K antagonists and with an international normalized ratio <2.0 until a therapeutic international normalized ratio of 2–3 was reached. Novel oral anticoagulants were reinitiated 6 hours postablation at half dose, followed by standard dose the next day. Anticoagulation was continued for at least 3 months and thereafter based on the individual CHA_2DS_2-VASc score. Previously ineffective antiarrhythmic drugs were continued for at least 3 months.[9]

Follow-up

Patients completed outpatient clinic visits at 3, 6, 12, months and in 6-month intervals thereafter, including anamnestic survey, 12-lead surface ECG, and interrogation of the implanted cardiac device. In addition, regular telephonic interviews were performed. Additional outpatient clinic visits were immediately initiated in case of symptoms suggestive of recurrent AF/AT.[3,4,11] The stored atrial high rate episodes were analyzed, and the AF burden calculated by the device was obtained. The data then were reset to avoid data overlap.[7] High atrial rate episodes of at least 180 bpm lasting >30 seconds were assumed to be an episode of AF. AF burden was defined as the overall percentage of AF during the observed period.

Statistical analysis

Continuous data are given as mean ± SD for variables that were normally distributed; otherwise, the median, minimum, first and third quartiles, and maximum are reported. Categorical data are given as absolute and relative frequencies. Differences of metric variables between the 2 groups were analyzed with the Student *t* test if the data were normally distributed and with the Wilcoxon Mann–Whitney test otherwise. Differences between categorical variables were evaluated using the χ^2 test or the Fisher exact test in case of small expected cell frequencies. For the matched control group, propensity score matching was performed. It was based on a logistic regression model including age, gender, AF type, hypertension, LA size, and follow-up duration. Recurrence-free survival was estimated by the Kaplan–Meier method. Follow-up between the 2 groups was compared using the Wilcoxon test. All statistical tests were 2-sided, and $P \leq .05$ was considered significant. All calculations were performed using R version 3.3.1 (www.r-project.org).[3,4,11]

Table 1 Baseline characteristics

	All	Device group	Control group
No. of patients	132	66	66
Age (y)	67.4 ± 9	68.4 ± 10	66.4 ± 8
Female	64 (48)	31 (47)	33 (50)
Paroxysmal AF	85 (64)	40 (61)	45 (68)
Persistent AF	47 (36)	26 (39)	21 (32)
LA diameter (mm)	45 ± 6	46 ± 7	44 ± 5
Arterial hypertension	98 (74)	50 (76)	48 (73)
Congestive heart failure	14 (11)	10 (15)	4 (6)
Diabetes mellitus type II	12 (9)	6 (9)	6 (9)
Coronary artery disease	23 (17)	13 (20)	10 (15)
Prior stroke	13 (10)	8 (12)	5 (8)
CHA_2DS_2-VASc score	3 (2, 4)	3 (2, 4)	3 (2, 4)
NOAC	90	47	43
Phenprocoumon	42	19	23

Values are given as n, mean ± SD, n (%), or median (1st, 3rd quartile).

The χ^2 test of no regression predicting device group presented no statistical differences compared to the control group ($P = .486$).

AF = atrial fibrillation; LA = left atrium; NOAC = novel oral anticoagulant.

Results

Baseline characteristics

Between June 2012 and June 2016, a total of 670 consecutive patients underwent CB2-based PVI. In 66 of 670 patients (9.9%), previously implanted cardiac devices with implemented continuous atrial monitoring function (12 ICD, 3 CRT-D, 1 CRT-P, 45 PM, 5 ILR) were identified. In the control group without such devices,[4,11,15–17] no differences in patient baseline characteristics were detected (Table 1). A total of 42 of 66 patients (63.6%) in the device group and 36 of 66 patients (54.5%) in the control group reported previously failed antiarrhythmic drug therapy ($P = .288$).

Procedural characteristics

Procedural parameters are listed in Table 2. In the device group 254 of 258 PVs (98%) and in the control group 255 of 256 PVs (99%) were successfully isolated. A total of 5 right superior pulmonary veins (RSPVs) were not targeted because of PNP that occurred during treatment of the right inferior pulmonary veins (RIPV) (4 in device group, 1 in control group). No differences were observed between the groups with regard to procedural and fluoroscopy times or the amount of contrast medium.

Complications

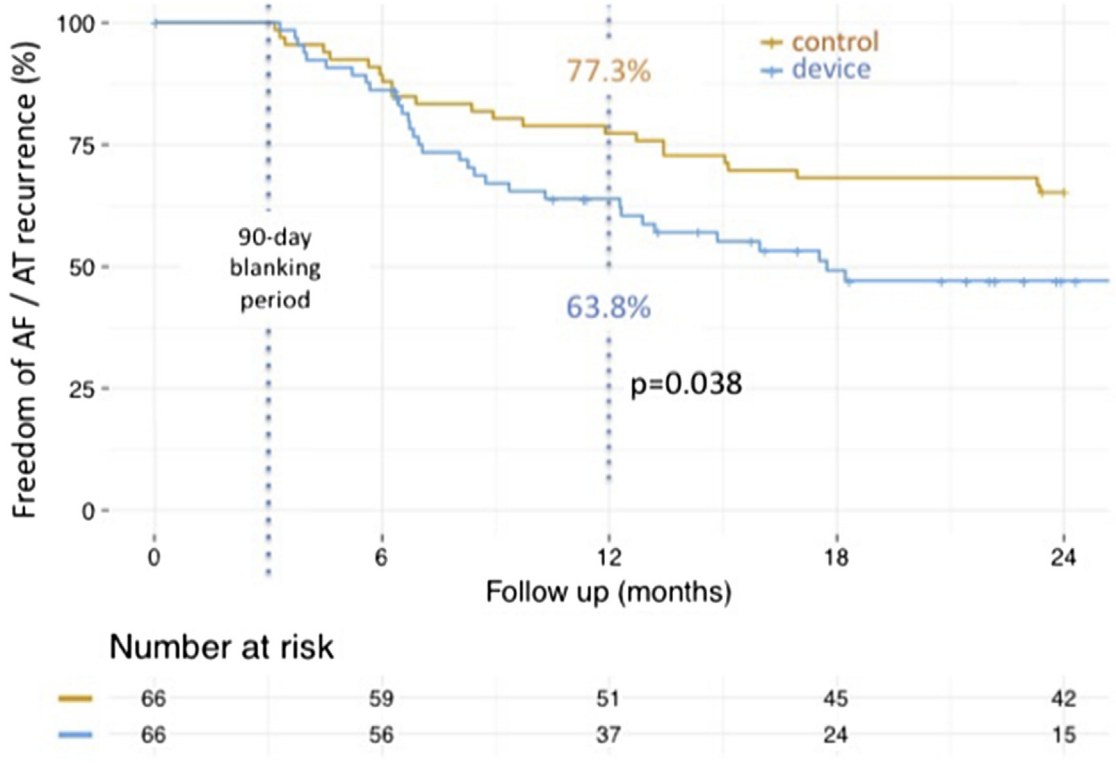
Periprocedural complications are listed in Table 2. PNP occurred in 6 of 66 patients (9%) in the device group and in 2 of 66 patients (3%) in the control group ($P = .274$). In the device group, PNP occurred during ablation along the RSPV in 4 patients and RIPV in 2 patients. In the control group, PNP occurred during ablation along the RSPV in 1 patient and along the RIPV in 1 patient. All PNPs recovered within a maximum of 6 months postablation. A total of 3 of 132 cases (2%) of pericardial effusion occurred (1 in the device group and 2 in the control group). In all

Table 2 Procedural data

	All	Control group	Device group	*P* value
No. of PVs	514	256	258	
Total freeze cycles per PV	1 (1, 2)	1 (1, 2)	1 (1, 2)	.999
Total freeze cycles per PV until PVI	1 (1, 2)	1 (1, 1)	1 (1, 1)	.999
No. of isolated PVs	509/514 (99)	255/256 (99)	254/258 (98)	.180
Procedure time (min)	130 (107, 147)	130 (106, 149)	128 (108, 147)	.489
Fluoroscopy time (min)	22 (17, 29)	22 (18, 27)	23 (17, 36)	.489
Amount of contrast medium (mL)	100 (70,150)	100 (88,150)	100 (64,153)	.160
Phrenic nerve palsy	8 (6)	2 (3)	6 (9)	.274
Pericardial effusion	3 (2)	2 (3)	1 (2)	.999
Pericardial tamponade	0 (0)	0 (0)	0 (0)	.999
Aneurysm spurium	2 (1.5)	2 (3.0)	0 (0)	.496
Periprocedural stroke/TIA	0 (0)	0 (0)	0 (0)	.999

Values are given as median (1st, 3rd quartile), or n (%).
PV = pulmonary vein; PVI = pulmonary vein isolation; TIA = transient ischemic attack.

mentioned cases, pericardial effusion did not result in pericardial tamponade, and no pericardiocentesis was necessary. All patients recovered without sequelae. No statistical differences have been observed between the groups. Bleeding complications or groin complications might be influenced by the anticoagulation regimen.[18] In



	Device group		Control group	
	Point estimate (%)	95% confidence interval (%)	Point estimate (%)	95% confidence interval (%)
0.5 years	86.2	78 - 95	89.4	82 - 97
1 year	63.8	53 - 77	77.3	68 - 88
1.5 years	49.1	38 - 64	68.2	58 - 80
2 years	47.1	36 - 62	65.2	55 - 78

Figure 1 Clinical success. Kaplan–Meier estimates demonstrate the relative proportion of patients in stable sinus rhythm after index pulmonary vein isolation using the second-generation 28-mm cryoballoon. A log-rank test was used to compare the AF/AT-free survival between groups (P = .038). AF = atrial fibrillation; AT = atrial tachycardia.

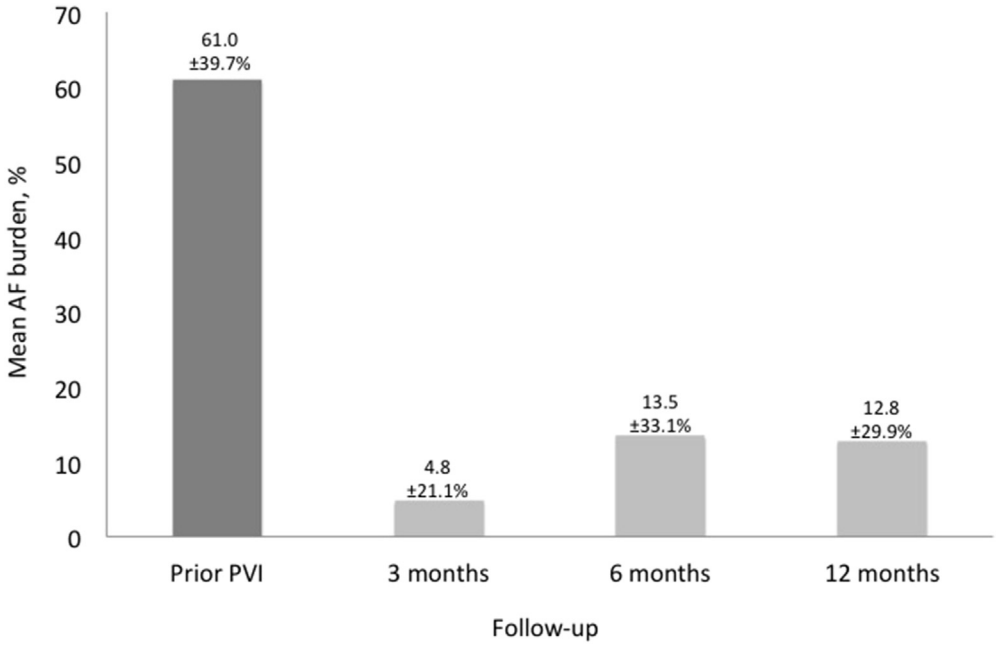


Figure 2 AF burden before and after PVI. Time course of AF burden (in percent) during follow-up (after 3, 6, and 12 months) in patients with implanted cardiac devices. After 12-month follow-up, a significant reduction of AF burden was observed ($P < .0001$). AF = atrial fibrillation; PVI = pulmonary vein isolation.

the present study population, no differences between anticoagulation regimens were observed.

Rhythm outcomes postablation

The median monitoring time before the procedure was 75 (interquartile range [IQR] 39, 280) days, 74.5 (IQR 51, 87) days at 3 months, 70 (IQR 38, 90) days at 6 months, and 152 (IQR 123, 202) days at 12-month follow-up. Kaplan–Meier estimates demonstrate the relative proportion of patients in stable sinus rhythm after CB2-based PVI (Figure 1). A log-rank test was used to compare AF-free survival between the groups. During 1-year follow-up, 63.8% of the device group patients remained in stable sinus rhythm (95% confidence interval 53–77), whereas 77.3% of the control group patients presented in stable sinus rhythm (95% confidence interval 68–88). These results achieved statistical significance ($P = .038$).

In patients with implanted devices, mean AF burden before the ablation procedure was 41.8% ± 35.0% and decreased to 10.2% ± 22.4% at 12-month follow-up ($P < .0001$) (Figure 2). For patients with PAF (n = 40), mean AF burden before the procedure was 18.6% ± 20.8% and decreased to 5.3% ± 18.6% at 12-month follow-up ($P = .011$). For patients with PersAF, mean AF burden before the procedure was 70.5% ± 26.6% and decreased to 17.2% ± 25.7% at 12-month follow-up ($P < .0001$). Antiarrhythmic drug therapy at 12 months after ablation was administered to 23 of 66 in the device group (35%) and 20 of 66 in the control group (30%) ($P = .577$).

Discussion

The current study is the first to report on acute safety and AF burden of CB2-based PVI in patients with previously implanted cardiac devices with continuous rhythm monitoring. When compared to a matched control group without such devices and conventional follow-up, the study demonstrated equally high acute success rates and procedural safety. However, there was a significant difference in 1-year clinical success to the disadvantage of the device group.

Medical cardiac devices (eg, PM, ICD, CRT) are increasingly being implanted to treat patients with different cardiac disorders. However, these cardiac devices require intracardiac leads, which harbor potential risks of dislodgment and interference during catheter ablation procedures. However, these devices provide the opportunity for continuous cardiac rhythm monitoring after catheter ablation.

Clinical success of AF ablation

Most clinical trials and studies reporting on clinical success rates after catheter ablation for AF are based on conventional follow-up by 12-lead ECG or 24- to 72-hour Holter ECG.[15,19–22] These follow-up strategies share the limitation of noncontinuous atrial rhythm monitoring, which might overestimate the overall clinical success rate, particularly in patients with PAF. In the FIRE AND ICE Trial, follow-up was based on 12-lead ECG and 24-hour Holter monitor recordings at 3, 6, and 12 months plus additional weekly transtelephonic ECG recordings. Furthermore, the patients were asked to transmit transtelephonic ECG recordings whenever symptoms of arrhythmia were felt. Because this follow-up strategy covers a much longer follow-up period, the 1-year clinical success was lower (65.4%) compared to many other studies that focused on 1-year outcomes after CB2-based PVI applying conventional follow-up strategies (80%–88%).[4,11,22–24] Because AF episodes after initial PVI might be asymptomatic in up to 36% of cases,[25,26]

conventional follow-up may miss such episodes. Therefore, the reported success rates of AF ablation procedures that are based on conventional rhythm monitoring might be overestimated. In our study cohort of patients having a cardiac device with continuous rhythm monitoring, the clinical success rate was significantly lower than in a matched control group with conventional follow-up, thus supporting this hypothesis.

Previous studies using continuous atrial monitoring by PMs for follow-up after AF ablation have also proven a significant reduction of AF burden. However, these single-center studies focused on RF-based PVI only and were limited by the small number of included patients.[7,27,28] Steven et al[7] have reported the largest study to date of patients with cardiac devices (n = 37). In this study, PVI was performed only with RF. No periprocedural device malfunctions or lead dislodgments were observed, and AF burden was reduced from 33.7% before the ablation procedure to 6.3% after 1-year follow-up. With a significant reduction of AF burden from 41.8% to 10.2%, these findings are in line with our multicenter CB2-based study.

Periprocedural complications

All procedures were performed without occurrence of lead dislodgments, and postprocedural device interrogations found no device or lead malfunction related to the procedure. Although no statistical differences were observed between the groups, a high rate of PNP (9%) was detected for patients with implanted cardiac devices. Because of the relatively small number of patients, a random variation of PNP might be the most likely explanation for this observation. We can only speculate on other potential reasons for our findings. (1) During CB2 ablation, the CB is pushed against the RSPV, which changes the anatomic proportions of the LA and right atrium. The right PN might be pushed against the leads crossing the right atrium, which potentially might cause a mechanical injury of the PN. (2) The close proximity of metal objects such as PM and ICD leads to the CB2 might lead to cooling of the surrounding tissue including the PN, resulting in compromise of the PN, as was observed for heating during RF procedures.[29] However, further validation of this hypothesis is necessary.

Study limitations

The current study is a retrospective analysis. However, it is a multicenter analysis, and patients with implanted cardiac devices were compared with a propensity score-matched control group. Although only patients with cardiac devices with implemented monitoring function were analyzed, it was not possible to achieve follow-up continuity of 100%. Different ablation protocols were used in the patient cohort. Noteworthy, it must be emphasized that in recent studies no differences were found in clinical outcomes when different CB2-based ablation protocols were applied.[15] A potential limitation might be electrode undersensing, which could cause arrhythmogenic episodes to be missed.

Conclusion

CB2-based PVI seems to be a safe and feasible treatment strategy in patients with previously implanted cardiac devices. Follow-up based on continuous atrial monitoring revealed a higher AF burden compared to conventional follow-up after CB2-based PVI.

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