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CLINICAL RESEARCH

# HIgh Power short duration radiofrequency ablation or cryoballoon ablation for paroxysmal Atrial Fibrillation (HIPAF trial)

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**Aims**

Pulmonary vein isolation (PVI) is a first-line treatment option for paroxysmal atrial fibrillation (PAF). Radiofrequency ablation (RFA) or cryoballoon ablation (CBA) are commonly used modalities. Recent studies demonstrated the superiority and potential benefits of very high-power short-duration (vHPSD) RFA using 70 W compared to conventional RFA (<50 W). Prospective randomized data comparing vHPSD RFA with 70 W with the frequently used CBA in the setting of PAF are lacking.

**Methods and results**

We conducted a randomized non-inferiority trial involving 170 patients undergoing *de novo* PVI for PAF. Patients were randomly assigned in a 1:1 ratio to undergo vHPSD RFA or to receive CBA. The composite primary endpoint consisted of (i) any atrial arrhythmia, (ii) new antiarrhythmic drug (AAD) onset, and (iii) re-ablation during 1 year after index procedure. The non-inferiority margin was predefined as a 10% lower 1-year event-free survival rate in vHPSD compared to CBA (delta = −0.1). A total of 170 patients with symptomatic PAF were enrolled and assigned to undergo *de novo* PVI, with 84 receiving vHPSD and 86 undergoing CBA. The overall study population had a mean age of 65 ± 11 years and included 50.6% women. For vHPSD PVI a 70 W/7 s anterior and 70 W/5 s posterior protocol including 3D mapping was used. Cryoballoon ablation was performed as usual. Successful PVI was achieved in all patients. Overall procedure time for vHPSD was significantly longer (81.1 ± 20.0 vs. 67.7 ± 17.2 min; $P < 0.001$). However, the mere ablation time was comparable (39.3 ± 15.5 vs. 36.7 ± 14.5 min; $P = 0.285$). Fluoroscopy time and amount of contrast medium were significantly lower for vHPSD PVI (9.2 ± 3.6 vs. 10.5 ± 4.3 min; $P = 0.031$; 15.5 ± 5.8 vs. 43.1 ± 30.0 mL; $P < 0.001$). Complication rates were comparable between groups. One pulmonary vein stenosis occurred after vHPSD. Three pericardial effusions and two transient ischaemic attack were reported after CBA. After a median follow-up of 367 days, 73.8% [$n = 62$, 95% confidence interval (CI): 63.1–82.8%] of patients in the vHPSD PVI group and 81.4% ($n = 70$, 95% CI: 71.6–89.0%) in the CBA group remained free of any event. Non-inferiority of vHPSD PVI compared to CBA PVI could not be demonstrated, with a difference of −0.076 [95% CI: (−0.201 to 0.049)] in event-free survival rates off AADs, as the 95% CI includes the delta of −0.1.

**Conclusion**

In this randomized non-inferiority trial comparing vHPSD RFA to CBA for PVI in patients with PAF, non-inferiority of vHPSD RFA could not be shown. Both methods showed comparable safety outcome with a shorter procedure time for CBA.

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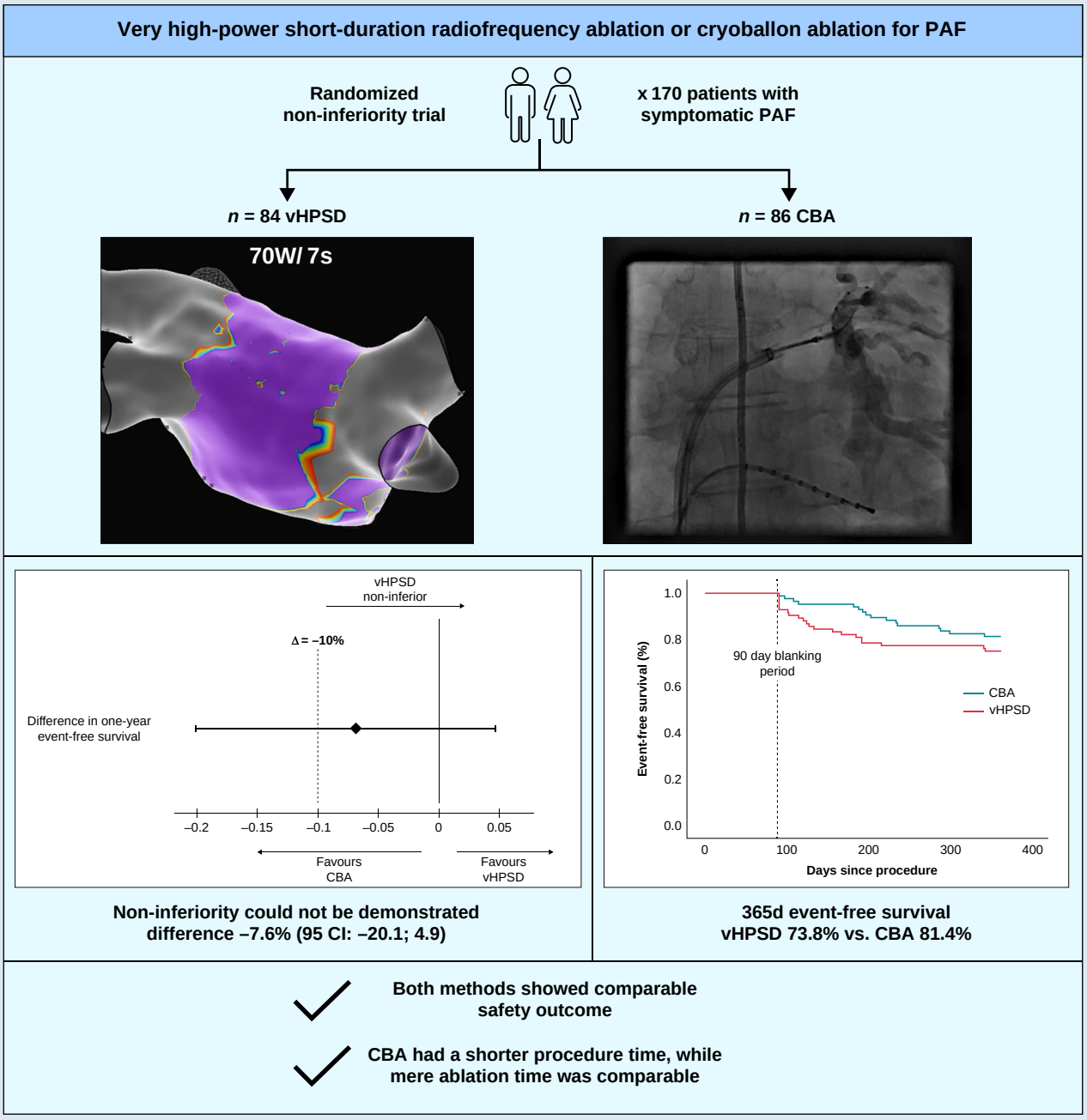
## Graphical Abstract




**Keywords** Trial testing non-inferiority of vHPSD vs Cryo in PAF patients

## What's new?

- This randomized non-inferiority trial compared very high-power short-duration (vHPSD) (70 W/7 s) radiofrequency ablation (RFA) with cryoballoon ablation for pulmonary vein isolation (PVI) in patients with paroxysmal atrial fibrillation
- Non-inferiority of vHPSD RFA could not be demonstrated
- Comparable safety was observed between the two techniques
- Cryoballoon ablation had a shorter total procedure time, while vHPSD RFA resulted in lower fluoroscopy time and contrast use
- Comparable mere PVI time with potential voltage information using vHPSD

# Introduction

Atrial fibrillation (AF) is the most common clinically significant arrhythmia, associated with increased mortality and morbidity.[1,2] Its incidence is anticipated to substantially rise in Europe, primarily attributed to the aging population and their comorbidities.[3] To reduce AF related clinical endpoints such as mortality, hospitalization, and worsening of heart failure, early implementation of rhythm control has shown to be effective.[4] Current guidelines support a first-line pulmonary vein isolation (PVI) for paroxysmal and persistent atrial fibrillation (PAF and persAF) in patients with intolerance or resistance to antiarrhythmic drugs (AADs) or even without previous AADs.[2,5]

Aside from the more recently introduced pulsed field ablation the two primary, established ablation techniques for PVI consisted of cryoballoon ablation (CBA) and radiofrequency ablation (RFA). Several studies demonstrated similar outcomes in terms of efficacy and safety.[6,7] Single-shot devices such as CBA potentially expedite PVI with a faster learning curve as compared to conventional RFA.[8,9] Regardless of the method used, pulmonary vein (PV) reconnection remains one of the leading causes of AF recurrence after PVI.[10,11]

Modification of the RFA technique, such as the high-power short-duration (HPSD) radiofrequency ablation using higher energy settings, are more frequently used. By applying more resistive than conductive heating to the tissue possibly advantageous lesion metrics are obtained in comparison to RFA with longer duration and lower energy application.[12,13] This could result in more continuous ablation lines, less PV reconnection and therefore a decrease of AF recurrence.

Recent studies investigating on various HPSD energy settings are demonstrating strong outcomes, emphasizing the potential of HPSD as a promising and effective RFA technique.[14,15] Very HPSD (vHPSD) ablation using 70 W, has been shown to be equally safe as conventional RFA with shorter procedure durations, and superior long-term outcomes.[16–18]

However, clinical data comparing HPSD ablation to CBA for PVI are sparse. Therefore, this prospective, randomized, clinical trial aimed to evaluate the safety and efficacy of vHPSD ablation with 70 W compared to the CBA for *de novo* PVI in patients with PAF.

# Methods

## Trial design

The HIPAF trial (high-power short-duration radiofrequency ablation or cryoballoon ablation for PAF) is a prospective, single-center, randomized, open label non-inferiority trial comparing vHPSD to CBA for PVI in the setting of PAF. The primary endpoint was a composite of freedom from any atrial arrhythmia, new antiarrhythmic drug (AAD) onset or re-ablation during 1 year after index procedure, tested for non-inferiority of vHPSD. All participants granted written informed consent for the procedure and data analysis during follow-up (FU). Data acquisition was performed using an electronic case report form (RedCap Database, Nashville, TN, USA). The study was approved by the local ethics committee at the University Hospital Cologne Germany and was conducted in accordance with the principles of the Declaration of Helsinki. This study is registered at clinicaltrials.gov (NCT04855890).

## Trial population

All enrolled adults (>18 years of age) had symptomatic atrial fibrillation and at least one episode of atrial fibrillation detected on electrocardiography before randomization.

Between April 2021 and August 2023, a total of 170 patients with PAF were enrolled in the study. The participants were randomized in a 1:1 ratio to either undergo vHPSD ablation ($n = 84$) or CBA ($n = 86$) PVI.

Patients with previous ablation, persistent atrial fibrillation (according to the ESC 2020 guidelines), severe obesity or other comorbidities (*Table 1*) were excluded from the trial.[19]

**Table 1** Further exclusion criteria

| |
|---|
| Contraindications for left atrial ablation |
| History of interventional or surgical AF-ablation |
| History of stroke in the past 12 months |
| BMI >40 kg/m$^2$ |
| History of mitral valve surgery |
| Severe mitral valve regurgitation |
| Inability to be treated with oral anticoagulation |
| Contraindication or absolute indication for one of the two strategies |
| Pregnancy |
| Participation in other clinical studies |
| Unwilling to follow the study protocol and to attend follow-up visits |

AF, atrial fibrillation; BMI, body mass index.

## Ablation procedure

Oral anticoagulation was discontinued the day before the procedure in both groups. For patients taking vitamin K antagonists, the target international normalized ratio (INR) was set between 2 and 3. During the procedure, heparin was administered to obtain an activated clotting time of >300 s. All procedures were performed under analgo-sedation using propofol, midazolam, and fentanyl. All physicians performing vHPSD PVI or CBA were fully trained and well experienced in each ablation technique performing a minimum case number of >300 RF and/or CBA procedures. Furthermore, physicians were properly trained in performing PVI ablation using non-contact force (CF) catheters. Prior to ablation procedures, presence of intracardiac thrombi was ruled out through transoesophageal echocardiography.

After access through the right femoral vein (double groin access for CBA and triple for vHPSD), a multipolar diagnostic catheter was placed in the coronary sinus (Dynamic XT™, large curve 4.0/Decapolar, Boston Scientific, Marlborough, MA, USA). After single transseptal puncture using the TSX™ fixed curve transseptal sheath and TSX™ transseptal needle (Boston Scientific, Marlborough, MA, USA), an 8.5 F transseptal sheath or 12F Cryo-Sheath (FlexCath Advance™, Medtronic, Minneapolis, MN, USA) was advanced into the left atrium.

Procedure duration was defined as the time from groin puncture to sheath removal (skin-to-skin time).

To provide comparable data on mere ablation time, PVI duration was measured by excluding the time taken for three-dimensional mapping (first burn or freeze to complete electrical isolation of the PVs).

Throughout all ablation procedures, we continuously monitored the oesophageal temperature using a temperature probe (S-Cath, Esophageal Temperature Probe, Circa Scientific Inc., Englewood, CO, USA). If the oesophageal-probe temperatures surpassed 40°C (vHPSD) or dropped below 16°C (CBA), ablation was interrupted to minimize the risk of atrio-oesophageal fistula formation or oesophageal erosion.

After completion of the procedure, a figure-of-eight-suture combined with compression bandage was used in both groups to prevent groin complications.[20,21]

To rule out pericardial effusion, all patients underwent transthoracic echocardiography (TTE) after the PVI. Oral anticoagulation was continued the same day. All patients were ECG monitored for 48 h after the procedure using telemetry.

## Very high-power short-duration radiofrequency ablation

For vHPSD, a detailed electroanatomical map of the left atrium during sinus rhythm was acquired using a three-dimensional mapping system (Ensite Precision™ or Ensite X™, Abbott, St. Paul, MN, USA) and a circumferential decapolar catheter (Advisor FL™ Sensor Enabled, Abbott, St. Paul, MN, USA). For vHPSD application an enhanced irrigated non-CT ablation catheter (Flexability Curve, Abbott, St. Paul, MN, USA) was used.

Pulmonary vein isolation was performed using a point-by-point ablation technique, ensuring isolation of both pairs of PVs while avoiding overlapping ablation lesions. For anterior ablation of the ipsilateral PVs a power setting of 70 W for 7 s was used. For the posterior ablation of the PVs a setting of 70 W for 5 s was applied.

Successful PVI in the vHPSD group was confirmed by either entrance- and/or exit block of PVs using a circular mapping catheter. In addition, as an institutional standard in RF-PVI, unexcitability of the ablation line was tested via the ablation catheter.[22] A potential influence of lacking CF information, which was not suitable for vHPSD at that time, might be mitigated by this approach.

## Cryoballoon ablation

In all CBA, a 28 mm balloon (ArcticFront Advance Pro™ CB, Medtronic, Minneapolis, MN, USA) was advanced into the left atrium and navigated to the PVs using an inner-lumen circular mapping catheter (Achieve Advance™, Medtronic, Minneapolis, MN, USA). After confirmation of complete PV sealing by the CB using occlusion angiograms, cryothermal energy was applied. The optimal duration for freeze applications was determined by either the time to isolation or the nadir temperature achieved during the application, both of which serve as predictors for optimal freeze duration.[23,24] The right PVs were isolated under constant pacing of the phrenic nerve to reduce risk of phrenic nerve palsies.[25]

Successful isolation of the PVs was confirmed using an inner-lumen circular mapping catheter. Pacing along the isolated area after CBA was not performed due to the different technology compared to vHPSD. Based on the balloon technology pacing along the isolated area potentially would have required a second catheter and is not routinely performed in CBA.

## Follow-up

Upon discharge, patients received another TTE and a 12-lead electrocardiogram (ECG) to exclude pericardial effusion and to exclude early relapse.

Follow-up visits were scheduled at 3 and 12 months as outpatient visits or in cooperation with referring physicians. All patients required a 12-lead ECG, TTE, and 24-h Holter-ECG. If, an outpatient visit was not possible, a telephone FU with transmission of the Holter-ECG was carried out.

## Endpoints

The primary endpoint was the recurrence of any atrial arrhythmia, onset of new AADs, or the necessity for re-ablation within 365 days after successful PVI. Events occurring during the first 90 days (referred to as the 'blanking period') were not considered as clinical failure of PVI and were not counted.

Secondary endpoints consisted of procedural parameters, the incidence of procedure associated complications, necessity of rehospitalizations and electrical cardioversions.

## Statistical analysis

Sample size and power calculation for statistical analysis acknowledged previous trials, with estimated 1-year event-free rates of 78% for vHPSD ablation and 71% for CBA according to previous landmark studies and real-world data.[6,7,16]

To achieve a statistical power of 80%, with a prespecified non-inferiority margin of 10% (delta = −0.1), allowing for a potential dropout of 5%, we estimated a total sample size of 170 participants. The non-inferiority margin was predefined at −10% based on clinical relevance and prior studies,[16] reflecting the preserved fraction. To assess non-inferiority, cumulative event-free rates at 365 days were calculated using the Kaplan–Meier estimator, and corresponding standard errors were derived. The difference in event-free rates between vHPSD and CBA was then computed, and a 95% confidence interval (CI) for this difference was calculated using the pooled standard error. Non-inferiority was evaluated by comparing this CI to the predefined margin. The results are displayed as Kaplan–Meier curve and a forest plot.

Continuous or ordinal scaled data were described as mean ± standard deviation, and an independent samples *t*-test was used to test for between-group differences. Categorical data are presented as frequencies and percentages and groups were compared by using the Fisher's exact test.

All statistical analyses were conducted at a two-sided alpha level of 5%. The analyses were carried out using SPSS version 29.0.2.0 for Mac and Excel version 16.93. for Mac and supported by the local Institute of Medical Statistics and Computational Biology.

# Results

## Patient population

A total of 170 ppatients were analysed (vHPSD group $n = 84$, CB group $n = 86$) with a mean age of 66 ± 11 years in vHPSD group and 64 ± 12 years in CBA and a history of PAF for at least 24 months.

Baseline characteristics were comparable between the two groups, as shown in *Table 2*.

**Table 2** Baseline characteristics

| | vHPSD ($n = 84$) | CBA ($n = 86$) | *P*-value |
|---|---|---|---|
| Age, years | 66 ± 11.0 | 64 ± 12 | 0.281 |
| Age >65, *n* (%) | 45 (53.6) | 44 (51.2) | 0.761 |
| Woman, *n* (%) | 40 (47.6) | 46 (53.5) | 0.540 |
| Body mass index (kg/m$^2$) | 27.5 ± 4.3 | 27.4 ± 3.9 | 0.883 |
| LVEF (%) | 60.8 ± 3.0 | 59.5 ± 3.9 | 0.019 |
| LA-diameter (mm) | 36.1 ± 4.2 | 35.9 ± 5.1 | 0.830 |
| Comorbidities, *n* (%) | | | |
| Hypertension | 53 (64.6) | 67 (77.9) | 0.062 |
| Coronary artery disease | 13 (15.5) | 24 (27.9) | 0.095 |
| CHF | 5 (6.0) | 3 (3.5) | 0.493 |
| Hyperlipoproteinaemia | 30 (39.0) | 36 (42.9) | 0.634 |
| Chronic kidney disease | 3 (3.6) | 0 (0.0) | 0.118 |
| Diabetes | 7 (8.4) | 9 (10.4) | 0.794 |
| COPD | 3 (3.6) | 5 (5.8) | 0.720 |
| Metabolic syndrome | 14 (16.7) | 20 (23.3) | 0.339 |
| $CHA_2DS_2$-VASc score | 2.5 ± 1.7 | 2.5 ± 1.5 | 0.849 |
| Previous stroke | 11 (13.1) | 5 (5.8) | 0.121 |
| Previous arterial thromboembolism | 3 (3.7) | 1 (1.3) | 0.621 |
| Medication use pre ablation, *n* (%) | | | |
| Flecainide | 8 (9.5) | 10 (11.6) | 0.804 |
| Amiodarone | 3 (3.6) | 2 (2.3) | 0.680 |
| ß-Blocker, *n* (%) | 54 (64.3) | 69 (80.2) | 0.026 |
| Oral anticoagulant, *n* (%) | 70 (83.3) | 72 (83.7) | 1.000 |
| Antiplatelet drugs, *n* (%) | 3 (3.6) | 2 (2.3) | 0.680 |

CBA, cryoballoon ablation; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; LA, left atrial; LVEF, left ventricular ejection fraction; PAF, paroxysmal atrial fibrillation; vHPSD, very high-power short-duration.

## Primary outcome

The median follow-up time of all participants was 367 days (IQR: 361–445). After 1-year FU, 22 of the 84 (26.2%) participants in the vHPSD experienced recurrence of atrial arrhythmia, new onset of AADs or underwent re-ablation, resulting in a 1-year event-free survival rate of 73.8% (95% CI: 63.1–82.8%) compared to 16 of the 86 (18.6%) participants in the CB Group resulting in an event-free survival rate of 81.4% (95% CI: 71.6–89.0%) (*Table 3* and *Figure 1*). As the CI includes the predefined non-inferiority margin of −0.1, non-inferiority for vHPSD compared to CBA was not shown, with a difference of −0.076 (−7.6%) and a 95% CI of −0.201 to 0.049 (−20.1% to +4.9%) (*Figure 2*).

The rate of consecutive atrial tachycardia was comparable between groups ($P = 0.632$). Nineteen of the 38 (50%) participants with recurrent atrial arrhythmias underwent re-ablation, with 9 in the vHPSD group (42.9%) and 10 in the CB group (62.5%) ($P = 0.325$).

## Procedural data

The vHPSD group had a significantly longer overall procedural duration (81.1 ± 20 min) compared to the CB group (67.7 ± 17.2 min) ($P < 0.001$). However, there was no significant difference in mere ablation time between the groups ($P = 0.285$). The fluoroscopy duration was

**Table 3** Primary outcome data

| | vHPSD ($n = 84$) | CBA ($n = 86$) | *P*-value |
|---|---|---|---|
| Total events after 1 year, *n* (%) | 22 (26.2) | 16 (18.6) | |
| Primary endpoint reached (components) | | | |
| Recurrence of any atrial arrhythmia, *n* (% of events) | 21 (95.5) | 16 (100) | 1.000 |
| Recurrence type, AF, *n* (% of recurrence) | 19 (90.5) | 13 (81.2) | 0.634 |
| Recurrence type, AT, *n* (% of recurrence) | 2 (9.5) | 3 (18.8) | 0.634 |
| Re-ablation, *n* (% of recurrence) | 9 (42.9) | 10 (62.5) | 0.325 |
| New onset of AAD, *n* (% of events) | 1 (4.5) | 0 (0) | 0.494 |
| Medical treatment | | | |
| AAD after 3 months, *n* (%) | 8 (9.5) | 8 (9.3) | 1.000 |
| AAD after 1 year, *n* (%) | 4 (4.8) | 4 (4.7) | 1.000 |
| ß-Blocker after 3 months, *n* (%) | 58 (69.0) | 64 (74.4) | 0.497 |
| ß-Blocker after 1 year, *n* (%) | 60 (71.4) | 62 (72.1) | 1.000 |

AAD, antiarrhythmic drug; AT, atrial tachycardia; CBA, cryoballoon ablation; vHPSD, very high-power short-duration.

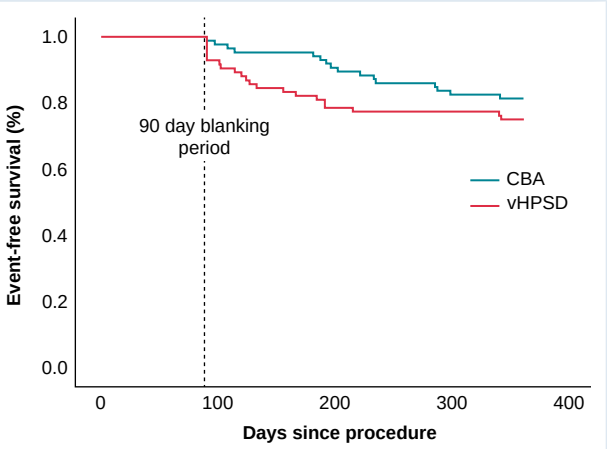



**Figure 1** Kaplan–Meier curve showing 1-year event-free survival using vHPSD ablation compared to CBA. CBA, cryoballoon ablation; vHPSD, very high-power short-duration.

significantly shorter in the vHPSD group (9.2 ± 3.6 min) than in the CB group (10.5 ± 4.3 min) ($P = 0.031$). Additionally, the vHPSD group had a significantly lower administration of contrast agent (15.5 ± 5.8 mL) than the CB group (43.1 ± 30.0 mL) ($P < 0.001$) (*Table 4*). Of note, obtained left atrial voltage-maps did not reveal any low voltage areas in this population of patients suffering from PAF.

## Safety endpoints

*Table 5* presents the safety endpoints observed during the study. Rehospitalization rate including electrical cardioversions, did not differ between groups.

Safety profiles of both ablation techniques were comparable, with no significant difference found in periprocedural or during FU complications.

Two cases of transient ischaemic attack (TIA) and three pericardial effusions were reported after CBA, all without residuals. One case of transient phrenic nerve palsy was reported in the CBA group. Groin haematomas occurred in both groups (five in vHPSD vs. two in CBA).

In the vHPSD group, one PV stenosis was reported and one participant died 7 months after the ablation procedure from causes unrelated to the procedure.

# Discussion

## Main findings

To the best of our knowledge, this is the first prospective randomized clinical trial comparing vHPSD ablation at 70 W using an enhanced irrigated single tip RF catheter to cryoballoon ablation for PVI in the setting of PAF. For the combined primary endpoint (1-year event-free survival), the non-inferiority of vHPSD compared to CBA for PVI could not be shown. Both methods showed comparable safety outcomes with acceptable complication rates.

## Outcome

This prospective randomized study was designed to evaluate the difference in clinical outcome between vHPSD and CBA. In the past, various clinical trials and retrospective studies have suggested, that PVI with vHPSD provides a clinical benefit. The present data now offer a robust foundation for assessing the method in clinical practice.

A key influence of this trial was a retrospective analysis by Woermann *et al.*, which found comparable safety and efficacy outcome between vHPSD and CBA. They found an event-free survival rate of 82.6% after 1 year opposed to 73.8% (off AADs) in the present trial. Notably, Woermann *et al.*'s reported success rate included patients on AADs (one third).[26]

Pak *et al.*[27] conducted a prospective clinical trial in 2021 comparing HPSD with 50–60 W to CBA. With a 1-year event-free rate of 73.4% for HPSD, they found comparable efficacy and safety outcomes. In contrast to our trial, a 'moderate' HPSD settings with 50–60 W was used, and most of the patients (98.1%) received an additional cavotricuspid isthmus ablation (CTI). Due to the different energy settings and the additional CTI ablation, their data are only comparable to some extend to our results.

In the Fast Power III trial, Castrejón-Castrejón *et al.*[28] compared vHPSD (70 W/9–10 s) with conventional RFA with 25–40 W that was guided either by lesion index or ablation index. They reported a 1-year event-free survival rate of only 67.1% for vHPSD despite rigorous testing for dormant conduction using adenosine.

The differences in outcome in the present study compared to Kottmaier *et al.*[16] for vHPSD PVI, using the same power setting, are potentially explicable by a very thorough ablation protocol. Kottmaier *et al.* implemented pacing along the line acutely and after a 20 min waiting time and furthermore tested for dormant conduction using adenosine. Although, such a thorough approach is favourable it might not reflect daily clinical routine as it was chosen per protocol in the present trial.

A more recent trial, the POWER PLUS Trial,[29] compared vHPSD using 90 W/4 s to a lower power setting of 35–50 W for PVI in the setting of PAF and persistent AF.

The lower energy setting was guided by ablation index. The event-free survival rate after 6 months was 83.3%. These results, indicate, that vHPSD ablation using 90/4 s potentially creates broader lesions resulting in a more contiguous ablation line as compared to other energy settings.[30] However, the first pass isolation rate was numerically lower. Of note, catheter designs and irrigation play an important role in lesion creation. Therefore, comprising data in the setting of vHPSD (70–90 W) is challenging.[12]

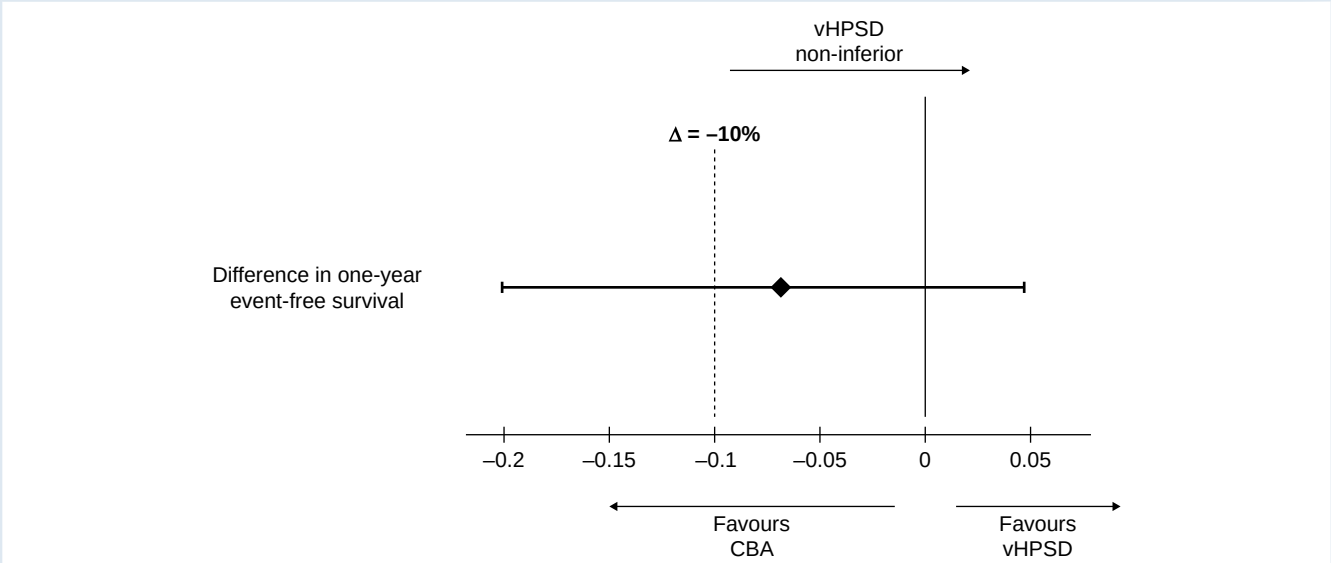



**Figure 2** Difference in 1-year event-free survival after vHPSD ablation compared to CBA, ranging from −0.201 to 0.049, with a point estimate of −0.076, including the prespecified non-inferiority margin of −0.1. CBA, cryoballoon ablation; vHPSD, very high-power short-duration.

**Table 4** Procedural data

| | vHPSD ($n = 84$) | CBA ($n = 86$) | *P*-value |
|---|---|---|---|
| Procedural duration (min) | 81.1 ± 20.0 | 67.7 ± 17.2 | <0.001 |
| Ablation time (min) | 39.3 ± 15.5 | 36.7 ± 14.5 | 0.285 |
| Fluoroscopy duration (min) | 9.2 ± 3.6 | 10.5 ± 4.3 | 0.031 |
| Contrast agent (ml) | 15.5 ± 5.8 | 43.1 ± 30.0 | <0.001 |

CBA, cryoballoon ablation; vHPSD, very high-power short-duration.

## Energy specifics

Lesion metrics obtained by vHPSD with enhanced tip irrigation catheters are broader, shallower and more homogenic compared to standard settings leading to a smaller number of PV gaps.[12]

In a trial performed by Kurose *et al.*,[31] the number of visual gaps shown in late gadolinium enhancement magnetic resonance imaging after CBA was even more frequent than after conventional RFA, which might indicate possible advantages in outcome parameters of vHPSD compared to other thermal ablations. This broad and shallow lesion formation created by vHPSD may partly explain favourable outcome. Also, catheter stability is more likely to be achieved over 7 s than over 60 or more seconds.

The higher number of observed thrombo-embolic events in the Fast Power III trial[28] might be explicable by a different catheter design and irrigation as compared to the used catheter in this trial and in the trial by Kottmaier *et al.*[16] Further studies with dedicated HPSD ablation catheters did show a favourable safety profile.[29] In the HIPAF trial, a catheter with an enhanced irrigated tip (20 mL/min) was used (Flexability Curve, Abbott, St. Paul, MN, USA). For this specific catheter design, differences in heating abilities, energy current, tissue conductivity, and lesion formation have been shown as compared to other catheters.[12] Thus, the number of reported steam pops, charring and potentially thrombo-embolic events differ as compared to other catheters.[32]

The lack of CF might have influenced the outcome of this trial. However, CF enabled enhanced irrigated catheters suitable for vHPSD ablation was introduced only after the trial did start. To obtain comparable data, the use of the newer CF version of this catheter was omitted during the trial. To offset the lack of CF for vHPSD, pacing along the PVI line was applied until non-excitability of latter.

## Cryoballoon ablation outcome

After CBA, we observed an 81.4% 1-year event-free survival, exceeding the 71% reported in the meta-analysis by Murray *et al.*[7] which served as the basis for our statistical calculations. While the meta-analysis included studies only using 1st and 2nd generation CB catheters, we exclusively used the more advanced 4th generation CB catheters which is superior to previous CB generations.[33] This might explain the higher event-free survival observed after CBA in our trial.

## Possible advantages of very high-power short-duration

Cryoballoon ablation had a significantly shorter overall procedure time compared to vHPSD, due to the necessity of 3D mapping. Of note, the mere PVI duration showed no significant difference between both groups with the potential benefit of substrate information from the obtained 3D mapping as compared to CBA. Furthermore, 3D mapping potentially reduces fluoroscopy time and the use of contrast medium, which is beneficial in the setting of chronic kidney disease.

## Safety and complications

Our findings align with previous data, confirming a favourable safety profile for vHPSD comparable to CBA, with few procedural complications.[16,17] Comparable hospitalization rates were mainly due to electrical cardioversion. Of these, 42% were performed during the blanking period. One observed PV stenosis might have been due to inaccuracy of the 3D map which has been resolved with newer mapping systems. Despite pacing the phrenic nerve, the hazard of palsy remains, although being only transient in the vast majority.

**Table 5** Safety endpoints

| | vHPSD ($n = 84$) | CBA ($n = 86$) | *P*-value |
|---|---|---|---|
| Rehospitalizations, *n* (%) | 10 (11.9) | 5 (5.8) | 0.185 |
| Electrical cardioversions, *n* (%) | 9 (10.7) | 3 (3.5) | 0.078 |
| Total events, *n* (%) | 14 (16.7) | 12 (14.0) | 0.674 |
| Periprocedural complications | | | |
| Mild | | | |
| Urinary retention, *n* | 1 | 0 | 0.494 |
| Decrease in CMAP, *n* | 0 | 1 | 1.000 |
| Phlebitis, *n* | 0 | 1 | 1.000 |
| VES, *n* | 1 | 0 | 0.494 |
| Temporary scotoma, *n* | 0 | 1 | 1.000 |
| Groin haematoma, *n* | 3 | 2 | 0.680 |
| Severe | | | |
| Transient phrenic nerve palsy, *n* | 0 | 1 | 1.000 |
| Pericardial effusion, *n* | 0 | 2 | 0.497 |
| Pneumonia, Pericarditis, *n* | 1 | 0 | 0.494 |
| Contrast medium reaction, *n* | 0 | 1 | 1.000 |
| Pulmonary vein stenosis, *n* | 1 | 0 | 0.494 |
| Gastrointestinal bleeding, *n* | 1 | 0 | 0.494 |
| TIA, *n* | 0 | 1 | 1.000 |
| Sinus node arrest, *n* | 1 | 0 | 0.494 |
| Complications during follow-up | | | |
| Mild | | | |
| Groin haematoma, *n* | 2 | 0 | 0.243 |
| Sinus bradycardia, *n* | 1 | 0 | 0.494 |
| Irritant cough, *n* | 1 | 0 | 0.494 |
| Haemoptysis, *n* | 1 | 0 | 0.494 |
| Severe | | | |
| Pericardial effusion, *n* | 0 | 1 | 1.000 |
| TIA, *n* | 0 | 1 | 1.000 |

CBA, cryoballoon ablation; CMAP, compound motor action potential; TIA, transient ischaemic attack; VES, ventricular extrasystoles; vHPSD, very high-power short-duration.

## Limitations

Some potential limitations of this clinical trial must be acknowledged.

(1) Our CBA results regarding freedom from AF were 10% higher than the estimated success rates we used for power and sample size calculations. Therefore, a larger sample size would have been necessary to achieve narrower CIs for greater statistical precision. Hence, with this sample size non-inferiority for vHPSD RFA compared to CBA could not be demonstrated.

(2) Participants were not routinely provided with an (implantable) loop recorder. Therefore, detection of arrhythmia recurrences is potentially underreported.

(3) Unlike single-shot ablation techniques such as CBA, point-by-point techniques like the vHPSD ablation are much more dependent on operator skills. This could create possible inter-operator variability, making it difficult to exclude the influence of operator skill on study outcomes especially in the present single-centre design.[8] Therefore, the study results may not be imposed on every centre since only experienced operators participated in this study. The lack of CF at the time of the study potentially influenced the outcome in the vHPSD group.

(4) Procedure times before and after including patients into this study protocol did not significantly vary in neither procedure type. Therefore, we do not anticipate that a relevant learning bias did alter these parameters. This is also supported by the notion that this parameter did not show any relevant change during the course of the study.

(5) Lastly, our centre does not routinely perform cerebral imaging for silent cerebral ischaemia, resulting in a lack of data on this complication.

# Conclusion

This randomized non-inferiority trial compared vHPSD RFA to CBA for PVI in patients with PAF. Non-inferiority for vHPSD RFA compared to CBA could not be demonstrated. For vHPSD similar safety outcome compared to CBA PVI was seen. Pulmonary vein isolation using vHPSD resulted in a longer procedure duration, while mere PVI time did not differ between the two techniques.

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## Data availability

The data underlying this article are available in the article and in its online supplementary material.

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