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Cryoballoon pulmonary vein isolation for atrial fibrillation in obese patients: A non-inferiority analysis

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ABSTRACT

Background: Patients with obesity are at higher risk of developing atrial fibrillation (AF) and benefit from radiofrequency ablation. Potentially, cryoballoon ablation (CBA) may be equally effective and safe in such patients.

Methods: We conducted a prospective, single-center study to investigate whether CBA for pulmonary vein isolation is as effective and safe in obese patients as it is in non-obese controls. Primary efficacy endpoint was recurrence of AF, atrial flutter or atrial tachycardia after a 90-day blanking period. Safety endpoints were death, stroke or procedure-associated complications. Conduction of a subgroup analysis regarding the impact of additional diabetes was predefined in case the primary efficacy endpoint was met. The study was event driven and powered for noninferiority.

Results: A total of 949 patients underwent CBA (251 obese with mean body-mass-index 33.5 ± 3 kg/m^2 and 698 non-obese with mean body-mass-index 25.3 ± 3 kg/m^2) during a 5-year recruitment period. Median follow-up was 15 months. The primary efficacy endpoint occurred in 78/251 obese and 247/698 non-obese patients (12-months Kaplan-Meier event-rate estimates, hazard ratio 0.79; 95% confidence interval [CI], 0.58 to 1.07; log-rank $P = 0.0002$ for noninferiority). No differences were observed in safety end point occurrence ($P = 0.78$). The occurrence of primary efficacy end point was found to be unaffected by the presence of diabetes in the prespecified subgroup analysis (log-rank $P = 0.57$).

Conclusion: CBA is effective and safe in obese and DM patients. Weighing the high cardiovascular risk of obese patients against a reduction of cardiovascular events by early rhythm control, CBA should be offered to this patient population.

1. Introduction

There is a global increase in obesity, cardiometabolic disease (CMD) and diabetes mellitus (DM) [1]. Obesity, CMD and DM are associated with greater risk of cardiovascular diseases such as coronary artery disease, heart failure, atrial fibrillation (AF) as well as cardiovascular mortality. [2–4].

In the context of AF, on one hand side increasing body mass index (BMI) increases the risk of AF occurrence [5] and on the other hand possibly diminishes efficacy and safety of pulmonary vein isolation (PVI) for AF management. [6–12] Nevertheless, data are equivocal as some authors have recently reported equivalent efficacy and safety of CBA for PVI in obese patients [13–15], and there is evidence suggesting adequate rates of sinus rhythm maintenance after PVI in obese patients only with effective weight reduction. [16,17] Moreover, patients with diabetes as main CMD have an approximately 35% increased risk of developing AF (particularly with poor glycemic control) [18] and a higher recurrence rate correlating with elevated glycosylated hemoglobin after AF ablation. [19–21] The concomitant presence of AF and diabetes is associated with increased rates of rehospitalization and increased cardiovascular and all-cause mortality. [22].

Recent data suggest that early rhythm control therapy, especially by PVI, significantly reduces AF recurrences [23] and cardiovascular adverse events (including cardiovascular death) in patients with AF and cardiovascular conditions [24], making CBA seem particularly useful especially in obese and CMD patients. Against the background of the

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ongoing scientific discussion, European Society of Cardiology (ESC) guidelines defined obese and cardiometabolically ill patients as a subgroup of AF patients in whom the benefits of catheter ablation have not been sufficiently studied and await further evaluation. [5].

Accordingly, this study sought to contribute to solving the question if CBA was effective and safe in patients with obesity (or DM) and AF.

2. Methods

2.1. Study design

The present trial was a prospective observational, single-center, noninferiority study with predefined primary efficacy and safety endpoints conducted at St. Josefs-Hospital (Wiesbaden, Germany) between January 2018 and March 2023). We enrolled consecutive patients undergoing CBA for PVI as a first ablation for AF. All patients provided written informed consent for the procedure and for study participation. The study was approved by the responsible regional ethics committee (Landesaerztekammer Hessen, ethics vote 2019–1474-evBO). In order to study clinically relevant patient groups, patients were divided into either non-obese (BMI < 30 kg/m^2) or obese (BMI ≥ 30 kg/m^2) groups based on their BMI measured on the day of the procedure. The use of this cutoff was based on the observation that the absolute difference in 12-month AF recurrence rate after PVI between patients with a BMI of 20–25 kg/m^2 compared with 25–30 kg/m^2 was only 0.5%, but increased substantially by 7.9% in patients with BMI ≥ 30 kg/m^2. [9] Because isometric models that correct and index left atrial (LA) dimension using body weight significantly underestimate LA size in obese patients [25–27], and allometric models scaling LA dimension to body height are not widely used, LA diameter was used to assess atrial dimension.

The concomitant presence of DM type 1 or 2 (diagnosed before CBA) was selected for subgroup analysis in the event of achieving noninferiority in the primary analysis.

2.2. Endpoints

Primary efficacy endpoint was defined as first recurrence of clinical AF (diagnosed by standard 12-lead ECG or single-lead ECG tracing of $\geq$ 30 s), atrial flutter or atrial tachycardia after a 90-day blanking period post CBA. [5] The primary safety endpoint consisted of death from any cause or stroke / transient ischemic attack within 30 days after the procedure and procedure-associated complications (procedure-related death, major groin site complications requiring treatment and prolonging hospitalization, pericardial effusion, cerebrovascular or systemic embolism, phrenic nerve palsy).

In addition, procedural parameters of CBA were collected (total procedure time, left-atrial dwell time, fluoroscopy time, contrast dye use and radiation dose).

2.3. Procedure

CBA procedure was performed in a standardized manner by experienced physicians (>500 CBAs). In brief, after double anatomically-guided puncture of the femoral vein, a steerable 15-F sheath (FlexCath Advance, MedtronicTM) was inserted into the left atrium (LA) after fluoroscopic-guided transseptal puncture (TSP) with 5000 units unfractionated heparin administered prior to TSP. An activated clotting time of 300–350 s (sec) was chosen as the target range. Non-vitamine K oral antagonists were given "minimally" interrupted (pause on the morning of CBA).

Then the second-generation "Arctic Front" (Medtronic^{TM}) balloon was introduced, inflated in LA and advanced to the ostium of each pulmonary vein. The 28-mm balloon was used in all cases. Pulmonary vein signals were recorded with an octapolar, circular mapping catheter ("Achieve", Medtronic^{TM}). Occlusion of each vein was assessed with venous angiography. Right-sided veins were ablated during phrenic nerve stimulation with a decapolar catheter ("Dynamic", Boston Scientific^{TM}). CBA was performed with freeze duration of 180 s per pulmonary vein. When visualized online, time to isolation + 120 sec was used as dosing protocol. In veins without reliable signals one 180 sec freeze was applied. All veins were re-checked at the end of the procedure. Procedures were performed under propofol sedation as standard. Propofol infusion was terminated before isolation of the last pulmonary vein to allow the shortest possible sedation times. Class I and III AAD were discontinued at the end of the 90-day blanking period and oral anticoagulation was performed according to the CHA_2DS_2-VASc score as per guidelines.

2.4. Follow-Up

Follow-up aimed to detect (clinical) recurrences of atrial arrhythmias and was based on prespecified telephone interviews at 3, 6, 12, 18, 24, 36 and 48 months. Patients were instructed to have ambulatory ECG recordings with their primary care physicians at 6-month intervals. If there was evidence of recurrence of atrial arrhythmias, ECGs were requested and reevaluated by study physicians. In patients with symptoms suggestive of recurrence of atrial arrhythmias, symptom-guided ECGs were performed in the study office.

2.5. Statistical analysis

The study was designed to demonstrate noninferiority of CBA in obese patients compared to non-obese patients. Assuming a 1-year recurrence rate of 30% in both groups with a noninferiority margin of 10% (corresponding to a hazard ratio [HR] of 1.43) and an enrollment ratio of approximately 3:1 (non-obese to obese) we calculated that 319 endpoints would be necessary to meet a power of 80% and an alpha of 5%. If noninferiority was met, a prespecified subgroup analysis could be performed testing the effect of additionally present DM in non-obese and obese patients on CBA efficacy. The Kaplan–Meier method was used to calculate event-rate estimates. Patient characteristics and procedure parameters were tested for normal distribution. Normally distributed variables were compared using two-sample *t*-test and are presented as mean and standard deviation. Dichotomous variables were compared using Chi-square test. Cox-regression analysis was performed to analyze the influence of patient characteristics on primary efficacy outcome. Significance level was set at 0.05. Statistical analyses were performed using PRISM software version 9 (GraphPad^{TM}, San Diego, CA, USA) and SPSS version 28 (IBM^{TM}, Armonk, NY, USA).

3. Results

3.1. Patient population

A total of 949 consecutive patients with symptomatic AF were enrolled and underwent CBA. Of these, 251 (26.4%) were obese and 698 (73.6%) were non-obese. Median follow-up time was 15 months (range: 3–48 months). Baseline characteristics differed with regard to younger age ($P < 0.001$), higher proportion of hypertension ($P < 0.001$) and DM ($P < 0.001$) and a slightly larger LA diameter ($P = 0.04$) in obese patients (Table 1).

The BMI distribution of the patients included in this study is shown in Table 2. Mean BMI was 33.5 ± 3 kg/m^2 in the obese group and 25.3 ± 3 kg/m^2 in the non-obese group. It is important to note that the proportion of patients with BMI > 35 kg/m^2 was 22.7% of all obese patients. The 95% percentile includes patients with a BMI between 20.8 kg/m^2 and 35.4 kg/m^2, suggesting that BMI values < 20 kg/m^2 and > 35 kg/m^2 account for a minority of study patients.

3.2. Occurrence of efficacy and safety endpoints

The number of primary efficacy endpoints required to test

Table 1
Baseline characteristics according to BMI.

Characteristic	BMI < 30 kg/m^2 (n = 698)	BMI ≥ 30 kg/m^2 (n = 251)	*P*
Age (years)	70.1 ± 10.6	66.7 ± 9.9	<0.001
Male sex	401 (57%)	139 (55%)	0.57
BMI (kg/m^2)	25.3 ± 3	33.5 ± 3	<0.001
Paroxysmal atrial fibrillation	423 (61%)	143 (57%)	0.31
Antiarrhythmic drugs (during / after blanking period)	239 (34%) / 43 (6%)	92 (37%) – 14 (6%)	0.49 / 0.74
Flecainide	107 (15%) / 20 (3%)	50 (20%) – 8 (3%)	0.09 / 0.80
Amiodarone	129 (18%) / 23 (3%)	42 (17%) – 6 (2%)	0.54 / 0.48
Dronedarone	3 (0%) / 0 (0%)	0 (0%) – 0 (0%)	0.30 / 0.99
CHA_2DS_2-VASc score	2.8 ± 1.6	2.8 ± 1.4	0.64
LA-Diameter (mm)	42 ± 9	44 ± 8	0.04
LVEF (%)	54 ± 9	55 ± 10	0.94
Heart failure (LVEF ≤ 40%)	87 (13%)	32 (13%)	0.91
Coronary artery disease	141 (20%)	54 (22%)	0.66
Hypertension	442 (63%)	194 (77%)	<0.001
Hyperlipidemia	104 (15%)	45(18%)	0.26
Diabetes	56 (8%)	56 (22%)	<0.001
Impaired renal function (GFR < 60 ml/min)	161 (23%)	67 (27%)	0.24
Previous stroke	48 (7%)	17 (7%)	0.96

Continuous data are presented as mean value ± standard deviation, numbers and percentage (in brackets) are given for absolute values. 90-day blanking period, LVEF – left ventricular ejection fraction, LA-Diameter – left atrial diameter, GFR – glomerular filtration rate.

Table 2
Characteristics of BMI for the overall cohort stratified by BMI group.

	BMI in kg/m^2						
	<20	20–25	25–30	30–35	35–40	>40	overall
Number of patients	27	285	386	194	46	11	949
Minimum	15.2	20.1	25.0	30.0	35	41.5	15.2
25% percentile	18.0	22.0	26.1	30.8	35.5	41.7	24.2
Median	19.0	23.3	27.4	32.0	36.4	42.4	26.9
75% percentile	19.7	24.2	28.4	33.4	37.3	44.3	30.2
Maximum	19.9	25.0	25.0	35.0	39.9	46.7	46.7
Interquartile range	1.7	2.2	2.1	2.6	1.8	2.6	6.0
Mean	18.8	23.1	27.4	32.3	36.6	43.1	27.5
Standard deviation	1.1	1.4	1.4	1.5	1.3	1.8	4.6

noninferiority for CBA in obese patients was achieved in March 2023. The primary efficacy endpoint occurred in 18.7% (47/251) of obese and in 22.6% (158/698) of non-obese patients at 1 year (1-year Kaplan–Meier event rate estimates, HR 0.79; 95% confidence interval [CI], 0.57–1.09; $P = 0.0002$ for noninferiority, Fig. 1). After maximum follow-up primary efficacy endpoint occurred in 30.2% (76/251) of obese and 34.8% (243/698) of non-obese patients (maximum follow-up Kaplan–Meier event rate estimates, HR 0.81; 95% CI, 0.63–1.03; $P < 0.0001$ for noninferiority).

Safety endpoints were rare. A total of 16 endpoints occurred (1.7% of all procedures). Of these, 11 (1.6%) occurred in non-obese patients (four pericardial effusions, two of which required pericardiocentesis, two transient phrenic nerve palsies, and five major groin site complications) while 5 (2%) occurred in obese patients (one pericardial effusion that did not require pericardiocentesis, two transient phrenic nerve palsies and two air embolisms into right coronary artery). There was no difference in overall safety endpoint occurrence ($P = 0.78$).

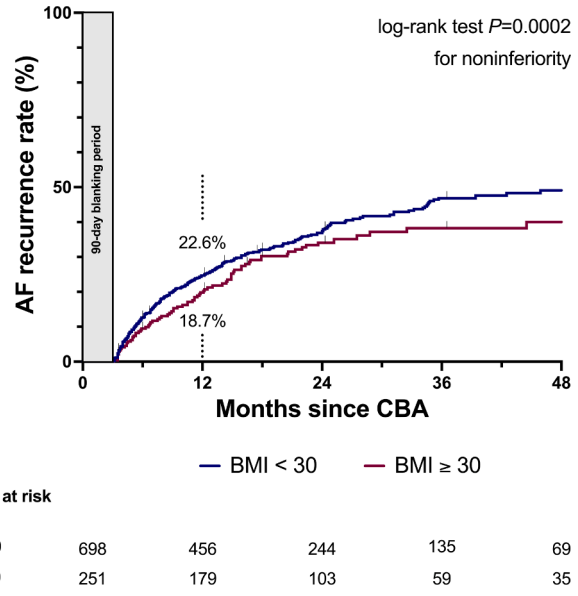

Fig. 1. Kaplan-Maier estimates for non-obese (blue) and obese (purple) patients AF – atrial fibrillation, CBA – cryoballoon ablation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.3. Influence of the additional presence of diabetes mellitus on primary efficacy endpoint

Since the primary hypothesis of the study could be confirmed, pre-specified subgroup analysis was performed to evaluate a possible influence of additional DM on ablation success.

Among 251 obese patients, 56 patients (22.3%) were affected with DM. Among non-obese patients (n = 698), there were 56 patients (8%) with DM. There was no difference with respect to mean HbA1c in obese 6.9 ± 1.1% and in non-obese patients 6.6 ± 0.9% ($P = 0.36$).

After one year the primary efficacy endpoint occurred in 24.3% (156/642) non-obese, 23.2% (13/56) non-obese patients with DM, 21.5% (42/195) obese and 19.6% (11/56) obese patients with DM (1-year Kaplan-Meier event-rate estimates, $P = 0.57$, Fig. 2). After

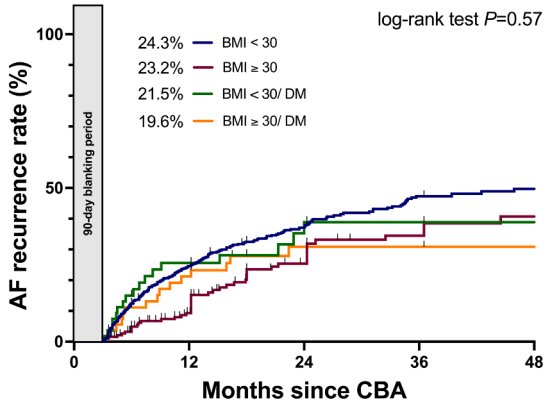

Fig. 2. Kaplan-Maier estimates for non-obese (blue), non-obese with DM (green), obese (purple) and obese patients with CM (orange) Abbreviations: DM – diabetes mellitus. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

maximum follow up primary efficacy endpoint occurred in 35.2% (226/642) non-obese, 30.8% (17/56) non-obese patients with DM, 30.4% (60/195) obese and 26.8% (15/56) obese patients with DM (Kaplan-Meier event-rate estimates, $P = 0.32$).

3.4. Association of clinical characteristics and AF entity with primary efficacy endpoint

Table 3 presents the outcome of univariate and multivariate cox-regression analysis. Multivariate analysis was performed by forced-entry using the characteristics that were statistically significant in univariate analysis.

In univariate regression analysis older age, female sex, lower BMI (continuous variable), persistent AF and larger LA diameter were associated with higher recurrence rate after CBA. After adjustment for age, sex, type of AF, and LA diameter, neither BMI as a continuous variable nor sex showed an effect on ablation outcome. Older age and persistent AF were associated with an increased recurrence rate.

No difference was found between non-obese and obese patients for primary efficacy endpoint occurrence stratified by atrial fibrillation entity (paroxysmal AF: 30.4% vs 29%, HR 1.17; 95% CI, 0.84–1.64; $P = 0.28$; persistent AF: 41.3% vs. 31.2%, HR 1.31; 95% CI, 0.92–1.81; $P = 0.28$).

3.5. Procedural parameters

Total procedure time (52 ± 15 min vs. 55 ± 16 min, $P = 0.007$), left-atrial dwell time (34 ± 13 min vs. 37 min ± 13 min, $P = 0.001$), fluoroscopy time (6.8 ± 3.4 min vs. 7.5 ± 3.9 min, $P = 0.01$), contrast dye use (42 ± 33 ml vs. 50 ± 39 ml, $P < 0.001$) and radiation dose (246 ± 245 cGy*cm^2 vs. 497 ± 596 cGy*cm^2, $P < 0.001$) were significantly higher in obese patients (Fig. 3).

4. Discussion

The present study was a prospective observational comparison of efficacy and safety of CBA between non-obese and obese patients with an additional focus on patients with DM. The key finding was that CBA was non-inferior for either the primary efficacy endpoint or the safety endpoints in obese patients and recurrence rate after CBA was unaffected by the presence of DM.

Pericardial effusion (0.5%), transient phrenic nerve palsy (0.4%) and groin complications (0.5%) were the most common safety events in the overall cohort albeit rare. The occurrence of primary safety end points was slightly lower than in large multicenter trials using CBA to treat AF. [23,28,29] This is most likely due to the extensive specialization of the performing high-volume center in CBA. [30] However, periprocedural parameters demonstrated significantly higher procedure duration, left-atrial dwell-time, fluoroscopy time, radiation dose and contrast dye use in obese patients.

Table 3
Influence of clinical characteristics on primary efficacy endpoint (cox-regression model).

Characteristic	univariate cox-regression			multivariate cox-regression		
	P	Exp (B)	95% CI	P	Exp (B)	95% CI
Age	<0.001	1.03	1.02–1.04	< 0.001	1.02	1.01–1.04
Male sex	0.02	0.77	0.77–0.96	0.25	0.87	0.69–1.1
BMI (kg/m^2)	0.04	0.98	0.95–1.0	0.12	0.98	0.95–1.0
Persistent AF	0.001	1.44	1.15–1.79	0.003	1.42	1.13–1.79
LA-Diameter	0.04	1.01	1.0–1.03	0.56	1.00	0.99–1.02
LVEF (%)	0.83	1.00	0.99–1.01			
Heart failure (LVEF ≤ 40%)	0.62	0.91	0.64–1.3			
Coronary artery disease	0.88	1.02	0.78–1.34			
Hypertension	0.91	1.01	0.8–1.28			
Hyperlipidemia	0.75	0.95	0.7–1.29			
Diabetes	0.39	0.85	0.59–1.23			
Impaired renal function (GFR < 60 ml/min)	0.29	1.45	1.15–1.48			
Previous stroke	0.11	0.66	0.39–1.1			

CI – confidence interval, LVEF – left ventricular ejection fraction, LA-Diameter – left atrial diameter, GFR – glomerular filtration rate.

4.1. Pathophysiological role of obesity in atrial fibrillation

There is 50% increased overall risk of developing AF in the presence of obesity. [31] In addition, obesity with BMI > 30 kg/m^2 appears to be sufficient to trigger the development of AF [32] and the disease progress from paroxysmal to persistent AF. [33] While the exact mechanistic basis between AF and obesity is a very complex topic of current basic research, involving endocrine, paracrine, neurohumoral, and autonomic aspects, there are some clinically relevant findings. [34] For example, obese patients with AF have shorter effective refractory periods in left atrium and around the pulmonary veins and higher left atrial pressure compared with non-obese AF patients. [35] In particular, the increased systemic blood volume increases cardiac output and ventricular wall stress and leads to myocardial hypertrophy, which in turn impairs cardiac function and may promote left atrial dilatation. [36] There may be a role of visceral/subcutaneous adipose tissue in influencing the development of AF. [34] Increasing epicardial fat tissue volume has been associated with severity of AF and recurrence rate of AF after ablation. [37] Accumulation of epicardial fat within the pericardium correlates anatomically with low-voltage-areas and decreased conduction velocity. [38] Furthermore, there is evidence for an increased adrenergic and cholinergic influence of autonomic innervation with areas of epicardial fat tissue possibly contributing to AF development. [39] The interrelationships of diabetes-related AF are similarly complex and involve structural (primarily atrial fibrosis and dilatation), electrical (increased conduction times, effective refractory period dispersion and action potential duration), electromechanical and autonomic (cardiac autonomic neuropathy by parasympathetic denervation) remodeling. [4].

4.2. PVI in obese and diabetic patients

A limited number of previous studies aimed at investigating the influence of obesity on atrial fibrillation ablation have been published so far [6,8–15] and data focusing on PVI efficacy in CMD patients are limited [18–21,40].

Consistent with our findings a large proportion of studies report younger age [6,8,9,11,13] and higher incidence of concomitant cardiovascular diseases in obese patients [6,8–13,15] at the time of catheter ablation. Younger age is most likely attributable to the increased risk of AF occurrence in obese patients [31,32] and the high burden of cardiovascular comorbidities in this patient population. Nevertheless, age correlates with the incidence of AF [41] and is independently associated with an increased recurrence rate after pulmonary vein isolation in persistent AF. [42] Whereas in univariate analysis BMI as a continuous variable showed a trend toward an inverse correlation with recurrence of AF after CBA, after adjustment for age, sex, and type of AF, BMI showed no relevant effect on treatment outcome, underscoring the findings of this noninferiority trial.

In our predefined subgroup analysis, we found that the presence of DM does not seem to influence the efficacy of catheter ablation. This contrasts to some extent with some studies that reported higher recurrence rates after catheter ablation in patients with DM. [19–21,40].

In this context, it is important to point out that increased recurrence rates in diabetic patients in both the meta-analysis by Anselmino et al.

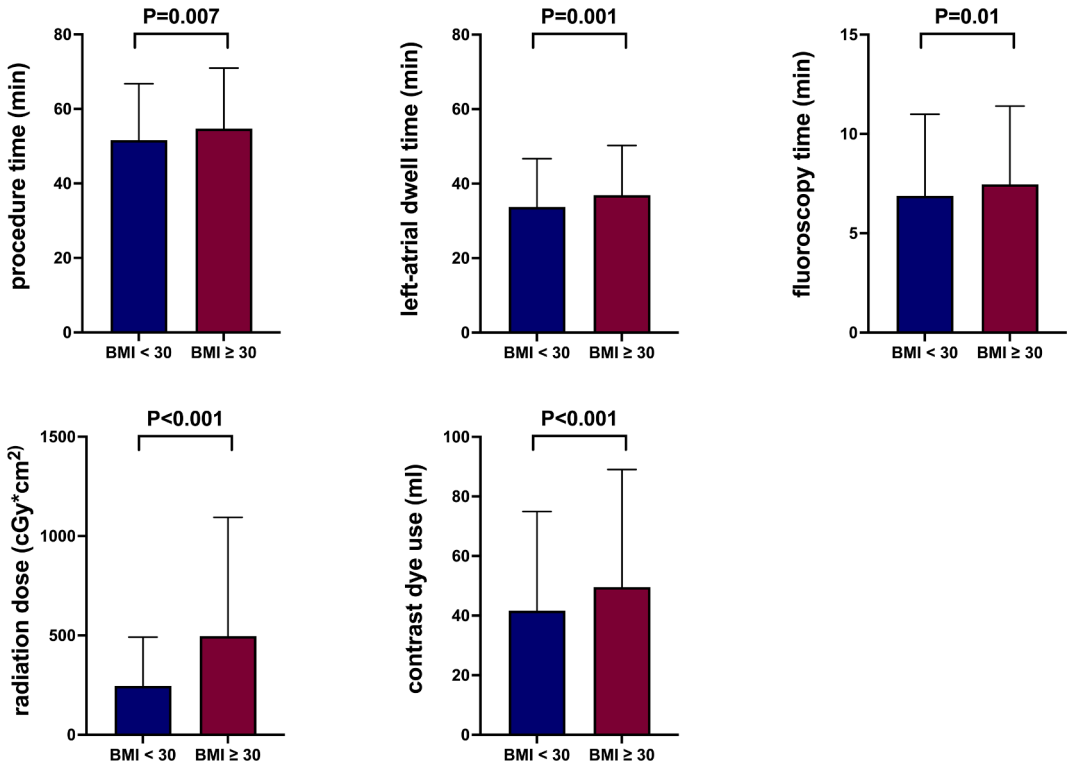

Fig. 3. Comparison of periprocedural parameters between non-obese and obese patients.

[21] and a retrospective analysis by Donnelan et al. [19] were related to elevated HbA1c levels as a result of impaired glycemic control. The latter study showed the lowest recurrence rate especially in diabetics with HbA1c below 7%. While Wang et al. [20] found a statistical trend regarding a relevant influence of long-term glycemic control in another retrospective work, the prospective multi-center study by Creta et al. [40] lacks information on baseline HbA1c values.

An HbA1c of $\leq$ 7% was also reported as a target for diabetics in the ARREST-AF (Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of Ablation) study, which achieved almost a fivefold increase in ablation success through aggressive risk management. [17] Another retrospective study by Wang et al. showed an increased risk of recurrence in diabetics independent of the HbA1c value, but there was a statistical trend towards a relevant influence of long-term glycemic control.

Overall, it can be assumed that well-controlled diabetic patients with HbA1c values below 7% have a similar recurrence rate following PVI as non-diabetic patients. This is consistent with our results, as both obese diabetic (6.9%) and non-obese diabetic (6.6%) patients had good diabetic control and a similar recurrence rate to non-diabetics.

The difference in patient characteristics complicates direct comparisons regarding the influence of obesity on treatment efficacy, because a comparison of obese and non-obese collectives under real-world conditions is always an analysis of differently ill and comorbid patients.

Regarding efficacy, different outcomes have been reported. While some studies, including single-center, multi-center and registry studies, reported higher recurrence rate after PVI in obese patients [6,8–10,12,] one multi-center and two single-center studies reported equal efficacy in this specific patient cohort. [13–15] In this context all studies using exclusively or mainly RF as energy source showed a worse outcome in obese patients [6,9,10,12], whereas studies using CBA [13,14] or different techniques but predominantly single-shot devices (CBA and multielectrode ablation balloon) [15] showed a comparable efficacy between obese and non-obese patients. While there is no simple explanation to this observation and randomized comparisons are lacking, technical issues of respective procedures might account for this observation.

With regard to safety, data are not available for all studies. While some studies reported higher procedure-associated complication rates in obese and particularly morbidly obese patients [6,11], most studies did not show increased complication rates in the presence of obesity. [9,13–15,43].

Only a very small number of the available studies report regarding periprocedural parameters. While pure procedure time is described as both unchanged and prolonged in obese patients [10,15], all papers report equally prolonged fluoroscopy times/radiation doses as does our report. [10,13,15].

4.3. *Weight reduction following catheter ablation*

In light of the impact of obesity on the incidence of AF, there have been studies on the efficacy of sustained weight loss on rhythm control. Pathak *et al.* demonstrated that weight reduction $\geq$ 10% was associated with significantly lower AF burden independent of rhythm-stabilizing therapy. [16] In contrast Gessler *et al.* did not find any effect of weight reduction on sinus rhythm maintenance. [43] The explanation may lie in the significant weight reduction in the intervention group compared with the non-intervention group, but only by 1.5 BMI points. Given the pathophysiological role of obesity in AF, the efficacy of significant weight reduction, particularly a potential reduction in visceral cardiac adipose tissue [34], on ablation success seems clinically consistent. Nevertheless, in light of our results and recent data on significant reduction of cardiovascular events (including cardiovascular deaths) by early rhythm control [24], it seems unreasonable to postpone ablation until a weight reduction $\geq$ 10% is achieved but to define sustained weight reduction as an adjunctive therapeutic goal in the post-ablation period.

5. Limitations

In this study, a standardized treatment procedure was performed by two experienced electrophysiologists in a large study sample and the

primary endpoints for safety and efficacy were predefined. Nevertheless, despite the noninferiority approach, this study is of observational character, so no causal conclusions can be drawn and differing baseline characteristic such as age, prevalence of coronary artery disease, hypertension or DM may represent confounders in the absence of randomization. Furthermore, data on the presence of obstructive sleep apnea syndrome are unavailable for our cohort.

The proportion of patients with BMI $>$ 35 kg/m^2 among obese patients was only 22.7%. The applicability of the results in patients with a BMI $>$ 35 kg/ m^2 is probably not affected, but a reliable statistically validated statement is not sufficiently possible. The study included a mixed population of patients with paroxysmal and persistent AF. The study was not designed or powered for a detection of differences between obese and non-obese patients according to the entity of AF. Nevertheless, after adjustment for age, sex, and type of atrial fibrillation, BMI showed no influence on ablation success.

Given that LA diameter was used to estimate atrial dimensions the influence of atrial size should be viewed with caution. An approach using an allometric model correcting LA dimension for height would have been more accurate.

Furthermore, clinical follow-up was based on telephone interviews, ECGs performed by primary care physicians or symptom-triggered ECGs suggestive of AF, atrial flutter, or atrial tachycardia. Since no continuous ECG-monitoring was installed and outpatient ECG was based on patient compliance and correct outpatient interpretation the overall rhythmological success rate may be overestimated. However, this is true for both non-obese and obese patients and therefore should not lead to a systematic bias in the comparison of the groups.

6. Conclusion

Whereas point-by-point ablation appears to provide poorer results for PVI in obese patients, our powered and large-scale prospective study including both patients with paroxysmal and persistent AF demonstrates that PVI with CBA is noninferior in reducing AF recurrences in obese as compared to non-obese patients, with no increase in safety endpoints. In obese patients, achievement of PVI is associated with longer procedure times, higher radiation exposure and contrast dye use. Since in our study the subgroup of patients with BMI $>$ 35 kg/m^2 represents only about 23% of all obese patients, the results must be applied with caution in these patients.

Lastly, our data provide evidence that CBA is effective for AF therapy even in of the presence of DM. Given the high cardiovascular risk of obese patients and the reduction of cardiovascular events by early rhythm control, early CBA should be offered to this patient population.

CRediT authorship contribution statement

Andreas A. Boehmer: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Moritz Rothe:** Conceptualization, Investigation. **Elena Nussbaum:** Investigation. **Christian Ruckes:** . **Bianca C. Dobre:** Investigation. **Bernhard M. Kaess:** Supervision. **Joachim R. Ehrlich:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors' department is international training center for cryoballoon ablation. JRE has served as speaker for and advisor to Medtronic.

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