Title

A Comparison of Long Term Outcomes of Index Cryo-ablation Versus Radiofrequency Ablation in Patients With Atrial Fibrillation And Systolic Heart Failure

Brief Title

Cryoablation versus RF ablation in Heart Failure

Word Count: 4465

Authors

Sandeep Prabhu[1,2]*, Nikhil Ahluwalia[1]*, Sara M Tyebally[1], Adam SC Dennis[1], Samuel O Malomo[1], Aderonke T Abiodun[1], Angelos Tyrlis[1], Dhillon G[1], Adam G[1], Honarbakhsh S[1], Sawhney V[1], Sohaib A[1], Finlay M[1], Earley MJ[1], Lambiase P[1], Schilling RJ[1], Hunter RJ[1].

*Co-first authors

Affiliations

[1]Department of Cardiology, St Bartholomew's Hospital, London, UK

[2]Baker Heart and Diabetes Research Institute, Melbourne, Australia.

Address for Correspondence

Dr Ross J Hunter

Director of Electrophysiology Research, Bart's Heart Centre

W Smithfield, London EC1A 7BE, UK

Phone: +44 20 7377 7000

Email: Ross.Hunter@nhs.net.uk

Abstract

Background:

Recent randomised studies have shown catheter ablation (CA) is an effective treatment for patients with AF and LV systolic dysfunction (LVSD), however the efficacy of an initial cryo-ablation strategy is unknown. We compared the long term outcomes of patients with an initial cryo-ablation (CRYO) versus radio-frequency ablation (RFA) strategy.

Methods:

Outcomes of patients undergoing index CA for AF from January 2008 until March 2018, with documented pre-ablation LVEF≤45% were evaluated. Patients were divided into 2 groups: those with index RF (Group 1) or CRYO (Group 2) and compared regarding procedural success and improvement in LVEF.

Results:

206 patients met inclusion criteria, 130 in RFA group and 76 in the CRYO group. There was no difference between groups in baseline LVEF, LVSD aetiology, AF phenotype and follow up duration After 30±15 months, single procedure freedom from AF/AT (>30s) was similar between the groups (38% vs 43%, p=0.48) as was multi-procedural freedom (53% vs 59%, p=0.39). There were a greater number of procedures (1.5±0.8 vs 1.2±0.4, p<0.001) in the RFA group. Both groups showed significant improvements in LVEF from baseline (RF group: 35 ± 8.0% to 46 ± 13, p<0.001; CRYO group: 33 ± 9.3% to 46 ± 16%, p<0.001), with no difference in the average Δ LVEF between the RF and CRYO groups (+11 ± 13% vs +12 ± 16%, p=0.85).

Conclusion:

An initial strategy of cryoablation in patients with comorbid AF and LVSD has comparable efficacy to RFA with respect to rhythm control and anti-heart failure therapy. Larger, randomised prospective studies are required to confirm these findings.

Introduction

Atrial fibrillation (AF) and heart failure are both emerging epidemics and frequently occur together[1, 2]. Whist previously considered a passive bystander in the setting of heart failure, AF is now recognised as an active determinant of clinical outcome[3, 4] and not infrequently, the primary driver of the heart failure itself[5, 6]. Recently, catheter ablation of AF has established itself as an effective approach to the restoration of sinus rhythm in patients with heart failure without reliance upon long term anti-arrhythmic therapy, with several randomised studies showing improvements in ventricular function[5, 7, 8], symptoms[9], reduced hospitalisations and mortality[7].

Although cryoablation has rapidly evolved as a mainstream treatment for AF in the paroxysmal phenotype, its role in the setting of persistent AF and particularly in those with structural heart disease remains largely unexplored. Given that there is limited evidence for a lesion set beyond pulmonary vein isolation at the index procedure, cryoablation may be a feasible first line therapy in this cohort. We report a large single centre comparison of long-term outcomes in patients with heart failure undergoing index ablation with either cryoablation (CRYO) or radiofrequency (RF) ablation.

Methods

Study population

This was a retrospective, single centre analysis of consecutive patients with systolic heart failure undergoing catheter ablation for AF at the Barts Heart Centre from 1st January 2008 to 30th March 2018. Patients were included if they: (1) had documented pre-procedural LVEF ≤45% as determined by either echocardiography or cardiac MR within 6 months of the index procedure; (2) underwent index catheter ablation for AF incorporating de-novo pulmonary vein isolation with either cyroballoon (CRYO) or radiofrequency (RF) ablation. Patients were excluded if (1) they had <12 months of follow up; (2) had previous left atrial ablation for AF; (3) if clinical data was incomplete.

RF Ablation Procedure

Anticoagulation was continued uninterrupted for all patients. Procedures were performed under conscious sedation or general anaesthesia. Pre-procedural TOE was performed. CARTO (Biosense Webster, CA) or Nav X / Precision (Abbott, CA) mapping systems were utilised. Following dual transeptal access, left atrial geometry was formed using a multi-polar. Wide antral circumferential ablation was performed with irrigated ablation catheters with PV isolation confirmed by the multi-polar catheter. Further substrate ablation was at the discretion of the operator, and could include further linear or CFAE based ablation strategies. Induced or spontaneous organised atrial tachycardias were mapped and ablated if possible. Patients remaining in AF at procedure end were electrically cardioverted to sinus rhythm. Anti-arrhythmics were generally continued for at least 3 months and then continued long term based on CHADS VASc score.

Cryoablation procedure

Single transeptal puncture was performed. Ablation was performed using 28mm Arctic Front Advance Cryoballoon System (Medtronic) via a 14F FlexCath Cryosheath (Medtronic, Ireland). Each PV was engaged with a multi-polar catheter (Achieve wire, Medtronic) and with demonstration of PV electrograms where possible. After inflation, pulmonary venous occlusion was confirmed with venography, and freezes between 180-240 seconds applied to each vein, aiming for abolition of PV signals and freeze temperatures between -40°C to -55°C. Freezes for the right PVs were performed with simultaneous phrenic nerve stimulation from high output pacing via a Quad catheter positioned in the right subclavian. A single good freeze was considered sufficient if it isolated a pulmonary vein, but further freezes were deployed if a vein failed to isolate, or at operator discretion if the freeze was deemed poor. In the case of documented CTI dependant atrial flutter, CTI ablation was also performed using an irrigated RF catheter (without a 3D mapping system or contact force sensing technology).

Follow up

Antiarrhythmic medications were continued for a minimum of 3 months post ablation and then weaned or ceased at the discretion of the treating physician. Follow-up included clinical assessment and 12 lead ECG, at 3 months, 6 and 12 months and then ongoing follow-up as dictated by symptoms. Patients with implantable cardiac devices capable of AF detection (dual chamber device or implantable loop recorders) had device interrogation performed at 3 months then yearly as a minimum. Patients without an intracardiac device underwent 48 hours of ambulatory monitoring at either 3 or 6 months with further monitoring dictated by symptoms. Recurrence was defined as documented AF/AT >30 seconds, or clinical symptoms suggestive or recurrence requiring pharmacological or interventional treatment, beyond a 3 month post procedural blanking period. The ongoing use of antiarrhythmic drug therapy was not counted as failure (since this was not part of a trial with a protocol to stop them necessarily) but the success rate is reported on and off antiarrhythmic drugs. Information was obtained from the hospital data-registry, and verified by assessment of medical record. Repeat ablation was offered to patients with symptomatic recurrence as clinically indicated and was performed exclusively with RF ablation, irrespective of the initial approach. The strategy involved PV re-isolation followed by mapping of induced or spontaneous atrial tachycardias and further substrate based ablation at the operator discretion.

Statistical analysis

Data are expressed as mean ± standard deviation (SD) unless otherwise indicated. After assessment of normal distribution with the Kolmogorov–Smirnov test, two-group comparisons were made using Student's t test for continuous variables, or the Chi-squared test for categorical variables. The independent samples Mann-Whitney U test was used for non-normally distributed variables. Cox regression analysis was utilised to assess the association of continuous and categorical variables with multi-procedural freedom from AF in univariate and multivariate models. A two-tailed p value of <0.05 was considered significant. Analyses were conducted using SPSS software (version 26, IBM, Chicago, Illinois).

Results

Study population

353 patient records were assessed for inclusion (147 were excluded: 58 (40%) for LVEF >45%, 42 (27%) follow data unavailable for ≥ 1 yr, 47 (33)% previous LA ablation for AF). Two hundred and six patients were included for analysis, and stratified according to ablation strategy at index procedure (RFA: n=130, CRYO: n=76). Baseline characteristics are shown in Table 1. Patients in the CRYO group were slightly older than those in the RF group (63 vs 59 years, p=0.03), and had a higher average $CHADS_2VASC$ score (2.7 vs 2.2, p=0.01). Significantly higher proportion of patients in the RF group had long-standing persistent AF (45% vs 26%, p<0.001). Beta-blockade

usage was higher in the CRYO group (78% vs 62%, p=0.01). The groups were otherwise well matched for major co-morbidities, other anti-heart failure medication usage, baseline LVEF, heart failure aetiology, NYHA functional class and LA dimensions. The average pre-procedure LVEF across the cohort was $34 \pm 8.3\%$ and the average follow up time was 30 ± 15 months, with no difference between the groups (p=0.16).

Procedural characteristics (Table 2)

Pulmonary vein isolation was achieved in 99% of patients in both groups (p=0.70). In the RF group, additional substrate modification was performed in 64% or patients, most commonly a roof line, or ablation of complex fractionated atrial electrograms (CFAE). Atrial flutter (cavo-tricuspid isthmus ablation) ablation was additionally performed more frequently in the RF group (33% vs 15%, p=0.02). Patients in the RF group had notably longer procedure times (233 ± 92 vs 90 ± 42 minutes, p<0.001) and a higher average number of procedures (1.52 ± 0.75 vs 1.15 ± 0.37, p<0.001), but a were less likely overall to be on AAD therapy at final follow up (52% vs 75%, p=0.001).

Procedural success

As shown Table 3, there was no difference between the groups with respect to single or multi-procedure freedom from arrhythmia (p=0.38 and p=0.48 respectively). Figure 1 demonstrates a Kaplan Meyer curve of freedom from AF/AT over the average follow up duration of 30 months. There was no significant difference between the curves for single or multi-procedural success. There was no difference in single or multi-procedural success between the groups when stratified by AF type (Table 3)

Significantly more patients in the RF group with multi-procedure freedom from AF were off anti-arrhythmic medications at time of last follow up (45% vs 27%, $p=0.05$). However, the average number of procedures were significantly higher in the RF group (1.52 ± 0.75), compared to the CRYO group (1.15 ± 0.37, $p<0.001$). PV re-isolation alone was the ablation strategy in significantly more patients in the CRYO group (71%), compared to the RF group (25%, $p=0.015$).

Univariate predictors of single procedure success (Table 5) included AF phenotype (paroxysmal: $p=0.015$, persistent: $p=0.025$ and long-standing persistent AF: $p=0.001$) and baseline NHYA class ($p=0.022$). Each variable maintained significance after multivariate analysis. Univariate predictors of multiprocedural success included the presence of long-standing persistent AF ($p=0.01$) and hypertension ($p=0.03$) of which only long-standing persistent AF maintained multivariate significance ($p=0.004$). Index procedure ablation strategy was not a predictor of single ($p=0.69$) or multi-procedural success ($p=0.32$).

Left ventricular ejection fraction

Average left ventricular ejection fraction improved significantly from pre ablation to post ablation (after an average of 18 ± 16 months) in both the RF group ($35 \pm 8.0\%$ to 46 ± 13, $p<0.001$) and the CRYO group ($33 \pm 9.3\%$ to $46 \pm 16\%$, $p<0.001$), with no difference in the average Δ LVEF between the RF and CRYO groups ($+11 \pm 13\%$ vs $+12 \pm 16\%$, $p=0.85$).

Complications

There were no procedure related deaths in either group. All-cause mortality over the long term follow up was 8 (6.2%) in the RF group and 2 (2.6%) in the CRYO group with no significant difference (p=0.19). Procedure related complications are shown in Table 3. There were no phrenic or oesophageal related complications in this cohort.

Discussion

This is the first study to compare the long-term post ablation outcomes between index RF ablation and CRYO ablation in in patients with AF and concurrent left ventricular systolic dysfunction, with respect to both procedural success *and* impact upon left ventricular ejection fraction. The primary findings were:

1. In patients with systolic heart failure, an index strategy of either RF ablation or CRYO ablation resulted in comparable single and multi-procedural success.
2. Both approaches resulted in comparable improvements in left ventricular function over long term follow up.
3. Index CRYO approach was associated with significantly shorter procedure time.
4. CRYO was associated with fewer repeat procedures, although more patients in the CRYO group were taking anti-arrhythmic medication at long term follow up.

Catheter ablation in heart failure

In recent years, a rapid succession of randomised clinical trials have established the role of catheter ablation as an effective anti-failure treatment in patients with concurrent AF and systolic dysfunction[5, 7-11]. Benefits have included improved quality of life, functional capacity[9], ejection fraction[5], reverse remodelling (both atrial[12] and ventricular[13]), reduced hospitalisations[7] and reduced mortality[7, 11]. However, these trials have exclusively utilised RF as the ablation strategy of choice. Whilst there is an increasing evidence base for the efficacy of cryoballoon ablation compared to RF ablation, in patients with paroxysmal AF and the absence of structural heart disease[14], there is a notable paucity of data regarding the use of cryoablation in the setting of AF and concurrent heart failure, and no studies comparing its efficacy with radiofrequency ablation. Pruszkowska et al demonstrated the feasibility of cryoballoon ablation in 30 consecutive patients with LVEF ≤ 40% and continuous monitoring with CIEDs, and demonstrated improvements in NYHA class, EHRA class, AF burden and LVEF, compared to controls undergoing cryoablation without LV dysfunction[15]. The present study is the first to demonstrate the comparable efficacy in controlling AF and improving ventricular function between index cryoablation and RF ablation. We await the outcome of a large multicentre study (CONTRA-AF) which will compare cryoablation to medical therapy in patients with heart failure. To our knowledge there are no prospective studies comparing cryoablation to RF ablation specifically in patients with LV dysfunction.

Beyond PVI in the setting of heart failure

The vast majority of AF in patients with concurrent LV dysfunction is persistent AF, and the proportion seen in this study (75%) mirrors that in other large studies. Given its nature, cryoablation invariably entails a PVI only approach to AF ablation. The parity of outcomes between cryoablation and RF ablation seen in this study suggests that a PVI-alone based approach is an effective ablation strategy in this setting, and that additional index substrate-based ablation had little bearing upon long term outcome. This finding is consistent with those published by Voskoboinik et al which showed that an index PVI only based approach (with either RF based or cryoablation) in patients with persistent AF (albeit in the absence of structural heart disease) was associated with a 12-month arrhythmia free survival rate of 66.7%[16]. This is similar to those seen in other studies[17, 18].

In the present study, not only were repeat procedures less common in the CRYO group ($p<0.001$), but significantly more patients had PV re-isolation alone ablation strategy at repeat ablation (71% vs 25%, p=0.015), suggesting additional substrate ablation performed subsequently to index procedure was not an explanation for the long-term similarity in outcome between RF and CRYO. In fact, substrate ablation has been associated with higher rates of repeat procedure, likely required to treat stable tachyarrhythmias arising from incomplete or recovered linear ablation lines[19, 20]. To date, the only large multi-centre randomised study comparing substrate ablation to PVI alone in persistent AF found no benefit to substrate modification[20]. There is some evidence that posterior wall isolation in setting of heart failure may be superior to PVI alone[5, 11] however this is yet to be tested in a prospective and randomised fashion.

AF burden vs AF recurrence

Despite the parity of efficacy between RF and cryoablation reported in this study, the overall pooled single and multi-procedural success (40% and 55% respectively) are modest, although the average follow-up of 30 months was notably longer than other studies. Despite this, the effect of ablation upon LVEF (overall +11%) was still dramatic and comparable with the magnitude seen in other studies[5, 7, 11]. This illustrates the lack of utility of the standard definition of recurrence as any AF/AT >30seconds. Recent work by Steinberg et al has demonstrated that this definition has little relationship to clinically meaningful burdens of AF, with 38% of such patients having no further AF [21]. Similarly, a reanalysis of AF burden data from the STAR-AF 2 study highlights how altering the definition of recurrence from >30s to >24 hours of AF/AT improved the success from 48% to 75% at 18 months[22]. Contemporary randomised trials of catheter ablation in patients with heart failure have all measured overall AF burden using continuous monitoring and have all shown dramatic reductions in AF burden[5, 7, 11]. The largest of these, the CASTLE-AF study, demonstrated that the median AF burden in the catheter ablation group fell to 0% following ablation and was maintained for 5 years of follow up[7]. This study again highlights that the conventional definition of AF recurrence likely has little bearing on the utility of AF ablation as an effective anti-heart failure treatment in this patient population.

Procedural considerations

Whilst RF and CRYO were equally effective in both AF control and as an anti-heart failure treatment, the index CRYO approach highlighted several potential advantages. Procedure times were markedly shorter compared to RF ablation, by an average of 140 minutes (62% shorter). This is a substantially greater difference than those demonstrated in other studies in paroxysmal AF[14], likely reflecting the additional time in two thirds of index RF cases devoted to, arguably fruitless, substrate modification. Perhaps more impressive is the fact that the groups showed parity of outcome despite the fact that patients in the CRYO group were older and had a higher average $CHADS_2VASC$ score, both features associated with worsened outcomes[7, 23, 24]. This may reflect a selection bias of the use of cryoablation in ostensibly sicker patients given its relative speed and simplicity. The later may also account for the higher usage of anti-arrhythmic medications in the CRYO group. Nonetheless, these results suggest that cryoablation may be a reasonable approach in patients considered to have a perceived high intra-procedural risk.

Limitations

There are several important limitations to note. This is a retrospective analysis and is therefore necessarily subject to selection bias which may have impacted the results. In addition, the effect of interventions such as revascularisation or up-titration of anti-failure medical therapy could not be controlled for. The findings of this non-randomised study should be regarded as hypothesis generating. The efficacy of cryoablation compared to RF ablation in heart failure should ideally be the focus of prospective randomised studies. It is hoped that these data might inform the design of such trials and provide a limited evidence base for those considering utilizing this approach clinically.

Conclusion

Cryoablation is an effective index AF ablation approach in patients with LV systolic dysfunction with comparable results to an index RF ablation with respect to single and multi-procedural freedom from AF and improvement in LV function. Cryo was associated with markedly shorter index procedure time and lower need for repeat procedures. Cryoablation is a valid and viable alternative to RF for index ablation ablation in patients with concurrent AF and systolic dysfunction.

Table 1: Baseline Characteristics

N=206	RFA (n=130)	CRYO (n=76)	P value
Demographics			
Age (years)	59 ± 12	63 ± 11	**0.03**
Gender (% female)	16%	20%	0.50
Hypertension (%)	21%	21%	0.94
Diabetes (%)	8.4%	10.5%	0.61
Ischaemic HD (%)	26%	37%	0.09
Average $CHADS_2VASC$ score	2.17 ± 1.21	2.66 ± 1.40	**0.01**
Average follow-up (months)	31.2 ± 16.4	28.1 ± 12.9	0.16
Continuous monitoring (%)	24%	34%	0.10
PPM (%)	1.5%	1.3%	0.90
ICD (%)	12%	14%	0.64
BiV (%)	9.2%	17%	0.10
Implanted loop recorder	0.7%	1.3%	0.70
Pre ablation LVEF	35 ± 8.1%	34 ± 8.7%	0.43
DCM (%)	54%	47%	0.34
Ischaemic CM (%)	26%	37%	0.10
Valvular (%)	6.9%	5.2%	0.65
Hypertrophic (%)	1.5%	0%	0.28
Other CM (%)	8.4%	17%	0.06
LA diameter	46 ± 7.0	46 ± 6.5	0.64
Paroxysmal AF (%)	21%	29%	0.17
Persistent AF (%)	80%	71%	0.13
Long-standing persistent AF (%)	45%	26%	**<0.001**
Average NYHA Class	2.37 ± 0.71	2.37 ± 0.72	0.98
Medications			
Beta-blocker (%)	62%	78%	**0.01**
ACE Inhibitor or ARB (%)	92%	91%	0.84
Spirinolactone (%)	7.9%	10%	0.60
AAD therapy (%)	47%	54%	0.38
AAD therapy + Beta blocker (%)	83%	89%	0.22
Amiodarone (%)	36%	41%	0.48
Sotalol (%)	7.6%	7.9%	0.95
Flecanide (%)	4.5%	3.9%	0.83
Vitamin K antagonist (%)	33%	32%	0.85
NOAC (%)	64%	68%	0.53

Table 2: Procedural Characteristics

N=206	RF (n=130)	CRYO (n=76)	P Value
PVI isolation achieved	99%	99%	0.70
Roof line	52%		
Mitral isthmus line	24%		
Posterior wall isolation	22%		
CFAE ablation	47%		
Any substrate modification	64%		
Cavo-tricuspid Isthmus ablation	33%	18%	**0.02**
Contact sensing catheter	87%		
RF time / Freeze time (mins)	52 ± 23	19.6 ± 8.0	
Procedure time	233 ± 92	90 ± 42	**<0.001**
DAP (mGy/cm^3)	1208 ± 3585	470 ± 715	0.09
Repeat ablation	37%	30%	0.30
Average number of procedures	1.52 ± 0.75	1.15 ± 0.37	**<0.001**
AAD therapy at final follow up	52%	75%	**0.001**

Table 3: Complications

N=206	RF (n=130)	CRYO (n=76)	P value
Cardiac tamponade	2.8%	0%	0.25
Stroke / TIA*	0%	0%	1.0
Vascular complication*	0%	2.2%	0.24
Phrenic nerve injury	0%	0%	1.0
Oesophageal injury	0%	0%	1.0

*Intra-procedural or within 30 days post procedure

**Requiring intervention or blood transfusion.

Table 4: Overall procedural success and stratified by AF type.

N=206	RF (n=130)	CRYO (n=76)	P value
Single procedure success			
Overall	38%	43%	0.48
Off AAD (%)	32%	30%	0.87
Paroxysmal AF	59%	50%	0.52
Persistent AF	33%	41%	0.34
Long-standing persistent AF	21%	21%	0.99
Multi-procedural success			
Overall	53%	59%	0.39
Off AAD (%)	45%	27%	**0.049**
Paroxysmal AF	70%	64%	0.62
Persistent AF	49%	57%	0.29
Long-standing persistent AF	41%	50%	0.55

Table 5. – Univarite and multivariable predictors of procedural success

Variable	Single procedure success			
	Univariate			Multivariate
	SPS yes (n=83)	SPS no (n=123)	P value	P value
Age (years)	62 ± 13	60 ± 11	0.42	
Gender (% male)	87%	80%	0.19	
Paroxysmal AF	32%	18%	**0.015**	**0.007**
Persistent AF	68%	82%	**0.025**	**0.012**
LS Persistent AF	18%	45%	**<0.001**	**0.001**
Index RF procedure	64%	61%	0.69	
Baseline LVEF	36 ±%	33 ± 8.7%	0.11	
LA area (mm^2)	27 ± 5.0	32 ± 5.8	0.09	
Hypertension	19%	22%	0.64	
Baseline NYHA Class	2.2 ± 0.8	2.5 ± 0.7	**0.022**	**0.015**
Variable	**Multi procedure success**			
	Univariate			**Multivariate**
	MPS yes (n=114)	**MPS no (n=92)**	**P value**	**P value**
Age (years)	61 ± 12	61 ± 12	0.86	
Gender (% male)	82%	83%	0.92	
Paroxysmal AF	29%	17%	**0.05**	0.053
Persistent AF	72%	83%	0.07	
LS Persistent AF	26%	43%	**0.010**	**0.004**
Index RF procedure	60%	66%	0.32	
Baseline LVEF	34 ± 8.6%	34 ± 8.5%	0.86	
LA area (mm^2)	28 ± 7.6	32 ± 6.6	0.10	
Hypertension	11%	23%	**0.028**	0.87
Baseline NYHA Class	2.3 ± 0.7	2.5 ± 0.7	0.73	

Figure 1 – Kaplan Meyer analyses of single and multi-procedure success

Figure 1 shows single and multi-procedural success post index AF ablation.

References

1. Lund LH, Savarese G. Global Public Health Burden of Heart Failure. Cardiac Failure Review 2017;**03**(01).
2. Chugh SS, Roth GA, Gillum RF, Mensah GA. Global burden of atrial fibrillation in developed and developing nations. Glob Heart 2014;**9**(1):113-9.
3. Turagam MK, Garg J, Whang W, Sartori S, Koruth JS, Miller MA, Langan N, Sofi A, Gomes A, Choudry S, Dukkipati SR, Reddy VY. Catheter Ablation of Atrial Fibrillation in Patients With Heart Failure: A Meta-analysis of Randomized Controlled Trials. Ann Intern Med 2018.
4. Anselmino M, Matta M, D'Ascenzo F, Bunch TJ, Schilling RJ, Hunter RJ, Pappone C, Neumann T, Noelker G, Fiala M, Bertaglia E, Frontera A, Duncan E, Nalliah C, Jais P, Weerasooriya R, Kalman JM, Gaita F. Catheter ablation of atrial fibrillation in patients with left ventricular systolic dysfunction: a systematic review and meta-analysis. Circ Arrhythm Electrophysiol 2014;**7**(1941-3084 (Electronic)):1011-1018.
5. Prabhu S, Taylor AJ, Costello BT, Kaye DM, McLellan AJA, Voskoboinik A, Sugumar H, Lockwood SM, Stokes MB, Pathik B, Nalliah CJ, Wong GR, Azzopardi SM, Gutman SJ, Lee G, Layland J, Mariani JA, Ling LH, Kalman JM, Kistler PM. Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction: The CAMERA-MRI Study. J Am Coll Cardiol 2017;**70**(16):1949-1961.
6. Prabhu S, Ling LH, Ullah W, Hunter RJ, Schilling RJ, McLellan AJ, Earley MJ, Sporton SC, Voskoboinik A, Blusztein D, Mariani JA, Lee G, Taylor AJ, Kalman JM, Kistler PM. The Impact of Known Heart Disease on Long-Term Outcomes of Catheter Ablation in Patients with Atrial Fibrillation and Left Ventricular Systolic Dysfunction: A Multicenter International Study. J Cardiovasc Electrophysiol 2016;**27**(3):281-9.
7. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, Schunkert H, Christ H, Vogt J, Bansch D, Investigators C-A. Catheter Ablation for Atrial Fibrillation with Heart Failure. N Engl J Med 2018;**378**(5):417-427.
8. Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, Goromonzi F, Sawhney V, Duncan E, Page SP, Ullah W, Unsworth B, Mayet J, Dhinoja M, Earley MJ, Sporton S, Schilling RJ. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). Circ Arrhythm Electrophysiol 2014;**7**(1):31-8.
9. Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP, Rahman-Haley SL, McDonagh TA, Underwood SR, Markides V, Wong T. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. J Am Coll Cardiol 2013;**61**(18):1894-903.
10. Khan MN, Jais P, Cummings J, Di Biase L, Sanders P, Martin DO, Kautzner J, Hao S, Themistoclakis S, Fanelli R, Potenza D, Massaro R, Wazni O, Schweikert R, Saliba W, Wang P, Al-Ahmad A, Beheiry S, Santarelli P, Starling RC, Dello Russo A, Pelargonio G, Brachmann J,

Schibgilla V, Bonso A, Casella M, Raviele A, Haissaguerre M, Natale A. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. N Engl J Med 2008;**359**(17):1778-85.
11. Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C, Lakkireddy D, Reddy M, Jais P, Themistoclakis S, Dello Russo A, Casella M, Pelargonio G, Narducci ML, Schweikert R, Neuzil P, Sanchez J, Horton R, Beheiry S, Hongo R, Hao S, Rossillo A, Forleo G, Tondo C, Burkhardt JD, Haissaguerre M, Natale A. Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device: Results From the AATAC Multicenter Randomized Trial. Circulation 2016;**133**(17):1637-44.
12. Sugumar H, Prabhu S, Voskoboinik A, Young S, Gutman SJ, Wong GR, Parameswaran R, Nalliah CJ, Lee G, McLellan AJ, Taylor AJ, Ling LH, Kalman JM, Kistler PM. Atrial Remodeling Following Catheter Ablation for Atrial Fibrillation-Mediated Cardiomyopathy: Long-Term Follow-Up of CAMERA-MRI Study. JACC Clin Electrophysiol 2019;**5**(6):681-688.
13. Prabhu S, Costello BT, Taylor AJ, Gutman SJ, Voskoboinik A, McLellan AJA, Peck KY, Sugamar H, Iles L, Pathik B, Nalliah CJ, Wong GR, Azzopardi SM, Lee G, Mariani J, Kaye DM, Ling L-H, Kalman JM, Kistler PM. Regression of Diffuse Ventricular Fibrosis Following Restoration of Sinus Rhythm With Catheter Ablation in Patients With Atrial Fibrillation and Systolic Dysfunction. JACC: Clinical Electrophysiology 2018:682.
14. Kuck K-H, Brugada J, Fürnkranz A, Metzner A, Ouyang F, Chun KRJ, Elvan A, Arentz T, Bestehorn K, Pocock SJ, Albenque J-P, Tondo C. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. New England Journal of Medicine 2016;**374**(23):2235-2245.
15. Pruszkowska P, Lenarczyk R, Gumprecht J, Jedrzejczyk-Patej E, Mazurek M, Kowalski O, Sokal A, Podolecki T, Morawski S, Streb W, Mitrega K, Kalarus Z. Cryoballoon ablation of atrial fibrillation in patients with advanced systolic heart failure and cardiac implantable electronic devices. Kardiol Pol 2018;**76**(7):1081-1088.
16. Voskoboinik A, Moskovitch JT, Harel N, Sanders P, Kistler PM, Kalman JM. Revisiting pulmonary vein isolation alone for persistent atrial fibrillation: A systematic review and meta-analysis. Heart Rhythm 2017;**14**(5):661-667.
17. Shao M, Shang L, Shi J, Zhao Y, Zhang W, Zhang L, Li Y, Tang B, Zhou X. The safety and efficacy of second-generation cryoballoon ablation plus catheter ablation for persistent atrial fibrillation: A systematic review and meta-analysis. PLoS One 2018;**13**(10):e0206362.
18. Straube F, Hartl S, Dorwarth U, Wankerl M, Bunz B, Ebersberger U, Hoffmann E. Cryoballoon ablation for persistent atrial fibrillation - Large single-center experience. J Cardiol 2016;**68**(6):492-497.
19. Baldinger SH, Chinitz JS, Kapur S, Kumar S, Barbhaiya CR, Fujii A, Romero J, Epstein LM, John R, Tedrow UB, Stevenson WG, Michaud GF. Recurrence of Atrial Arrhythmias Despite Persistent Pulmonary Vein Isolation After Catheter Ablation for Atrial Fibrillation: A Case Series. JACC Clin Electrophysiol 2016;**2**(6):723-731.
20. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, Macle L, Morillo CA, Haverkamp W, Weerasooriya R, Albenque JP, Nardi S, Menardi E, Novak P, Sanders P, Investigators SAI. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med 2015;**372**(19):1812-22.
21. Steinberg JS, O'Connell H, Li S, Ziegler PD. Thirty-Second Gold Standard Definition of Atrial Fibrillation and Its Relationship With Subsequent Arrhythmia Patterns: Analysis of a Large Prospective Device Database. Circ Arrhythm Electrophysiol 2018;**11**(7):e006274.

22. Conti S, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, Macle L, Morillo CA, Haverkamp W, Weerasooriya R, Albenque JP, Nardi S, Menardi E, Novak P, Sanders P, Verma A. Effect of Different Cutpoints for Defining Success Post-Catheter Ablation for Persistent Atrial Fibrillation: A Substudy of the STAR AF II Trial. JACC Clin Electrophysiol 2017;**3**(5):522-523.
23. Letsas KP, Efremidis M, Giannopoulos G, Deftereos S, Lioni L, Korantzopoulos P, Vlachos K, Xydonas S, Kossyvakis C, Sideris A. CHADS2 and CHA2DS2-VASc scores as predictors of left atrial ablation outcomes for paroxysmal atrial fibrillation. Europace 2014;**16**(2):202-7.
24. Yang E, Ipek EG, Balouch M, Mints Y, Chrispin J, Marine JE, Berger RD, Ashikaga H, Rickard J, Calkins H, Nazarian S, Spragg DD. Factors impacting complication rates for catheter ablation of atrial fibrillation from 2003 to 2015. Europace 2017;**19**(2):241-249.