JAFIB
Original Research
Journal of Atrial Fibrillation

www. jafib.com

A Meta-Regression Analysis of Atrial Fibrillation Ablation in Patients with Systolic Heart Failure

Mohammed Ruzieh[1], Morgan K. Moroi[2], Nader M. Aboujamous[3], Mehrdad Ghahramani[1], Gerald V. Naccarelli[1], Matthew Nudy[3], Khalil Kanjwal[4], Andrew J Foy[1].

[1]*Penn State Heart and Vascular Institute. Hershey, PA.*
[2]*Penn State College of Medicine. Hershey, PA.*
[3]*Penn State Department of Internal Medicine. Hershey, PA.*
[4]*Michigan State University. McLaren Greater Lansing, MI.*

Abstract

Background: Meta-analyses of randomized controlled trials comparing atrial fibrillation (AF) ablation to medical therapy in patients with heart failure (HF) reported improvement in left ventricular ejection fraction (LVEF), quality of life using the Minnesota Living with HF Questionnaire (MLWHFQ), and 6-minute walk test (6MWT). Nonetheless, there was significant heterogeneity not accounted for suggesting that not all HF patients derive the same effect from AF ablation.

Objectives: To evaluate if baseline LVEF or the etiology of the cardiomyopathy would moderate the efficacy of AF ablation.

Methods: We performed random effects meta-regression using the mean baseline LVEF and total percentage of patients with non-ischemic cardiomyopathy (NICMP) in the placebo arms as moderator variables.

Results: Six trials with a total of 687 patients were included. The baseline LVEF in the control arm of trials ranged from 25% - 42.9%, and the percentage of patients with NICMP within each trial varied from 35% to 100%. When baseline LVEF was used as the moderator variable, no significant change in heterogeneity was observed for any of the outcomes of interest (R2 0.00 – 0.02). However, when controlling for NICMP, heterogeneity dropped substantially for the outcomes of LVEF (I2 44.7%, R2 0.91), and MLWHFQ (I2 0.00%, R2 1.00) but not 6MWT (I2 67.4%, R2 0.00). This indicates that improvement in LVEF and MLWHFQ was greater in the AF ablation group when more patients with NICMP were included in the trials.

Conclusions: In patients with systolic HF, AF ablation may be more beneficial in patients with NICMP.

Introduction

Atrial fibrillation (AF) and heart failure (HF) are two common conditions that often coexist and can predispose each to one another.[1-3] Guidelines do not provide a clear consensus regarding the best approach for management of AF in patients with HF. Multiple randomized controlled trials (RCTs) examined the role of catheter ablation in AF patients with HF and demonstrated improvement in left ventricular function (LVEF) and quality of life.[2-8] Recently, several meta-analyses[9-11] have analyzed these trials and reported improvement in the pooled outcome of LVEF, 6-minute walk distance and quality of life. However, wide variation for the difference in each of these outcome measures was noted between trials suggesting that not all HF patients with AF derive the same effect from ablation and there is a need to better understand which patients with HF are most likely to benefit from AF ablation.

Key Words

Atrial fibrillation, Heart failure, Non-ischemic, Cardiomyopathy.

Corresponding Author
Mohammed Ruzieh
Penn State Heart and Vascular Institute
500 University Drive PO Box 850, MC H047
Hershey, PA 17033

When conducting meta-analyses, some variation in treatment effect between trials is expected due to differences in study quality (e.g. potential bias in design, acquisition and adjudication of specific data elements) which may become evident when performing bias assessment with validated instruments such as the Cochrane Bias Assessment tool. In other cases, variation may be related to differences in patient sampling, the application of the intervention and management strategies in the control groups. This may be intentional on the part of investigators and meant to address gaps or areas of uncertainty. In each of the cases above, differences in trial-level effects may be expected and intuitively understood and contribute to the overall understanding of an interventions effect. However, in other cases, variation may not be easily explained by these factors and, when this is the case, confidence in the generalizability of a summary effect measure should decrease and the evidence-based community should seek to understand the source of variability in efforts to better target the intervention to those most likely to benefit or not.

A method to understand the source of variability in clinical trials is to perform meta-regression analyses where the treatment effect of the trial is measured against one or more moderator variables. Intuitively, this approach is not that different from performing

regression analyses of single datasets to determine how the presence of baseline covariates contributes to the outcome of interest. Similarly, meta-regression of clinical trials seeks to understand how differences in covariates among the study groups of individual clinical trials contribute to the observed treatment effects.

We hypothesized that the wide variation in the treatment effects of AF ablation for HF patients observed in the published clinical trials is due to differences in the patient populations of the individual trials and that understanding this may contribute to better application of AF ablation in HF patients. Specifically, we hypothesized that baseline LVEF and the etiology of the cardiomyopathy (i.e. ischemic versus non-ischemic) would moderate the efficacy of ablation on outcomes of LVEF improvement, 6-minute walk distance and quality of life. To test this hypothesis, we conducted a meta-regression analysis of several covariates, which we felt could contribute to the heterogeneity of effects observed between trials.

Methods

Data collection and extraction

We searched Medline, Google Scholar, the Cochrane Central Register for RCTs, and ClinicalTrials.gov for studies that examined AF catheter ablation in patients with HF (latest search date: Dec 1, 2018). Three authors (M.R., M.M. and A.F.) drafted the study protocol which was then revised by all coauthors. Two authors (M.R. and M.M.) independently reviewed all articles and abstracts for inclusion, and independently extracted information on patient's characteristics, study design, intervention, follow-up, and outcomes in a standardized manner. Discrepancies were discussed and resolved by consensus.

Trials that randomized patients with AF and systolic HF to catheter ablation versus medical therapy were included.

Outcome and quality assessment

The primary outcomes of interest were LVEF, Minnesota Living with Heart Failure Questionnaire (MLWHFQ) scores, and 6-minute walk distance. We used the Cochrane Risk of Bias table and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system, to report risk of bias and quality of study outcomes in each study, respectively.

Statistical analysis

The primary analyses were performed using RevMan version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration; Copenhagen, Denmark). We used the inverse variance random effects model to calculate the pooled mean difference in the outcomes of interest. Sensitivity analysis was performed as following: (i) comparing trials that randomized patients to AF catheter ablation vs. rate control, (ii) comparing AF catheter ablation to medical therapy in patients with persistent AF only, and (iii) individually eliminating studies to detect if any is the cause of heterogeneity.

To examine whether baseline LVEF or etiology of cardiomyopathy contributed to the heterogeneity in the outcomes, we performed random effects meta-regression using comprehensive Meta-Analysis Version 3, Borenstein, M., Hedges, L., Higgins, J., & Rothstein, H. Biostat, Englewood, NJ 2013. For these regression analyses, the mean baseline LVEF and total percentage of patients with non-ischemic cardiomyopathy in the placebo arms of trials were used as moderator variables.

We created meta-regression linear prediction graphs by plotting the moderator variable on the x-axis and treatment effect measure on the y-axis. The bubbles were plotted in proportion to the contribution of each study to the regression model.

The following parameters were used to test the model of heterogeneity: (i) Tau^2 which is the estimate of the true variance among studies, (ii) I^2 which represents the percentage of variability in the effect risk estimate among studies due to heterogeneity rather than chance (with I^2 <25% considered as low, I^2 >75% considered as high, and in between [25% to 75%] as intermediate), and (iii) R^2 which represents the proportion of between-study variance explained by the moderator.

A two-sided p-value of <0.05 was considered to be statistically significant.

Results

Qualitative Synthesis

We included six trials in our analysis, [Figure 1]. A total of 687 patients were included (342 patients randomized to catheter ablation and 345 patients randomized to medical therapy alone). The mean age in the trials ranged from 55 to 64 years, and the mean follow-up time ranged from six months to 38 months. The average baseline LVEF was 33.2% in the ablation arm and 34.0% in the control arm. Non-ischemic cardiomyopathy was present in 199 (58.2%) patients in the ablation arm and 170 (49.3%) patients in the control arm. 297 (86.8%) patients in the ablation arm and 286 (83.0%) in the control arm, had persistent AF. Further patients' characteristics are shown in [Table 1].

Risks of bias and quality assessment

Study limitations and biases (per Cochrane and GRADE criteria) are summarized in [Table 2]. Randomization was performed using random number generation in all trials. None of the trials tested AF ablation against a sham procedure and thus patients and their treating physicians were not blinded. This creates performance and outcomes assessment bias. Therefore, our confidence in the outcome assessment is moderate. Assessment of LVEF was blinded in four trials.[2, 3, 5, 6]

All studies appropriately described crossovers and dropouts. Crossover occurred in two patients in the study by Jones et. al.[3] and in 46 patients in the CASTLE AF trial.[8] Loss to follow-up was most prevalent in the CASTLE AF trial (33 [9.1%] patients). Further details on interventions and follow up are provided in [Table 3].

Evaluation of the funnel plots revealed no evidence of publication bias.

Table 1: Characteristics of patients included in the studies

	MacDonald		Jones		Hunter		Di Biase		Prabhu		Marrouche	
	Ablation arm	Rate control	Ablation arm	Rate control	Ablation arm	Rate control	Ablation arm	Amiod-arone	Ablation arm	rate control	Ablation arm	Medical therapy
Mean age (yrs)	62.3 ± 6.7	64.4 ± 8.3	64 ± 10	62 ± 9	55 ± 12	60 ± 10	62 ± 10	60 ± 11	59 ± 11	62 ± 9.4	64	64
Female gender	23%	21%	19%	8%	4%	4%	25%	27%	6%	12%	13%	16%
No. of patients	22	19	26	26	26	24	102	101	33	33	179	184
Follow up (months)	9.7	6.9	12	12	12	6	24	24	6	6	37.6 ± 20.4	37.4 ± 17.7
Persistent AF	100%	100%	100%	100%	96%	88%	100%	100%	100%	100%	70%	65%
NYHA class	II & III	II & III	II & III	II & III	II & III	II & III	II & III	II & III	≥II	≥II	I-IV	I-IV
ICMP	50%	47%	38%	27%	23%	29%	62%	65%	0%	0%	40%	52%
NICMP	50%	53%	62%	73%	77%	71%	38%	35%	100%	100%	60%	48%
LVEF %	36.1 ± 11.9	42.9 ± 9.6	22 ± 8	25 ± 7	31.8 ± 7.7	33.7 ± 12.1	29 ± 5	30 ± 8	32 ± 9.4	34 ± 7.8	32.5	31.5
LA diameter (mm)	N/A	N/A	50 ± 6	47 ± 7	52 ± 11	50 ± 10	47 ± 4	48 ± 5	48 ± 6	47 ± 8	48	49.5
6 min walk distance (meters)	317.5 ± 125.8	351.8 ± 117.1	416 ± 78	411 ± 109	N/A	N/A	348 ± 111	350 ± 130	491 ± 147	489 ± 132	N/A	N/A
Quality of life	55.8 ± 19.8	59.2 ± 22.4	42 ± 23	49 ± 21	N/A	N/A	52 ± 24	50 ± 27	N/A	N/A	N/A	N/A
Diabetes Mellitus	32%	21%	N/A	N/A	N/A	N/A	22%	24%	4%	5%	24%	36%
HTN	64%	58%	N/A	N/A	30%	33%	45%	48%	13%	12%	72%	74%
CAD	50%	53%	42%	50%	N/A	N/A	62%	65%	N/A	N/A	27%*	36%*

AF: Atrial fibrillation, CAD: Coronary artery disease, HTN: Hypertension, ICMP: Ischemic cardiomyopathy, NICMP: Non-ischemic cardiomyopathy, N/A: Not available.
*History of myocardial infarction.

Outcomes

LVEF: Data for difference in change in LVEF was available from all six trials. Compared to medical therapy alone, AF catheter ablation was associated with a significant increase in LVEF (mean difference 6.4%; 95% CI: 2.8 – 10.0; P< 0.001), [Figure 2]. In a sensitivity analysis when including only trials that had a blinded assessment of LVEF, AF catheter ablation was not associated with a statistically significant increase in LVEF (mean difference 5.3%; 95% CI: -0.6 – 11.2; P= 0.08). The heterogeneity test was significant (Tau^2= 16.2; df= 5; P< 0.001, I^2= 91%), and it did not improve on sensitivity analysis.

When baseline LVEF of the placebo group was used as the moderator variable, we observed no significant change in heterogeneity (Tau^2= 15.9; df= 4; P< 0.001, I^2= 91.1%, R^2= 0.02). However, when percentage of patients with non-ischemic cardiomyopathy in the placebo group was used as the moderator variable, heterogeneity dropped significantly and a strong linear relationship was observed such that as the percentage of patients with non-ischemic cardiomyopathy increased in the trials, the difference in change in LVEF was greater with ablation (Tau^2= 1.5; df= 4, I^2= 44.7%; P= 0.12, R^2: 0.91), [Figure 2]. This means that most of the variation observed in the treatment effect of the difference in change in LVEF between the ablation and control groups from the original meta-analysis could be explained by the percentage of patients in the trials who had non-ischemic cardiomyopathy.

Quality of life based on MLWHFQ scores: Four trials reported data on MLWHFQ. There was a significant improvement in the MLWHFQ scores in the AF catheter ablation group when compared to the medical therapy group (mean difference -8.0; 95% CI: -14.3 – -1.7; P= 0.01), [Figure 3]. There was moderate heterogeneity (Tau^2= 14.1, df= 3; P= 0.22, I^2 = 33%).

Baseline LVEF was not related to the observed treatment effects (Tau^2= 35.6; df= 2; P= 0.11, I^2= 54.4%, R2= 0.00). On the other hand, when the percentage of patients with non-ischemic cardiomyopathy was used as the moderator variable, heterogeneity dropped to zero and a strong linear relationship was observed such that as the percentage of patients with non-ischemic cardiomyopathy increased in the trials, improvement in MLWHFQ scores was greater with ablation (Tau^2= 0.0; df= 2; P= 0.41, I^2= 0.0%, R^2= 1.00), [Figure 3]. This means that nearly all of the variation observed in the treatment effect of mean difference in change in MLWHFQ scores between the ablation and control groups from the original meta-analysis could be explained by the percentage of patients in the trials who had non-ischemic cardiomyopathy.

6-minute walk distance in meters: Data on 6-minute walk distance were reported in five trials. The mean increase in 6-minute walk distance was higher in the AF catheter ablation group compared to the medical therapy group (mean difference 24.2; 95% CI: 5.7 – 42.7; P= 0.01), [Figure 4]. Heterogeneity was significant (Tau^2=

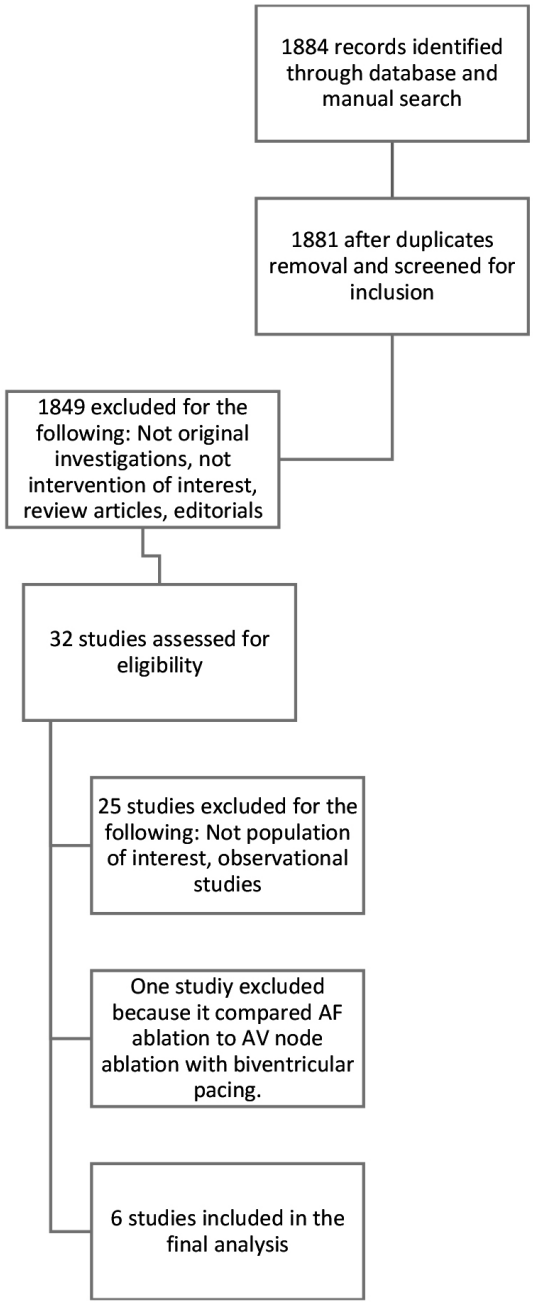

Figure 1: PRISMA diagram showing search strategy results.

235.9; df= 4, P= 0.01, I^2= 70%). On sensitivity analysis, most of the heterogeneity was driven by the AATAC and CASTLE AF trials[6,8], and when excluded from the analysis, the heterogeneity became low (I2: 0.0%) without significant change in the point estimate, P< 0.05).

Controlling for baseline LVEF didn't result in significant change in heterogeneity (Tau^2= 289.0; df= 3; P= 0.005, I^2= 77.0%, R^2= 0.00). Similarly, we didn't observe significant change in heterogeneity when the percentage of patients with non-ischemic cardiomyopathy was used as the moderator variable (Tau^2= 228.2; df= 3; P = 0.03, I^2= 67.4%, R^2 = 0.00), [Figure 4]. This means that the variation observed in the treatment effect of mean difference in change in 6-minute walk distances between the ablation and control groups from the original meta-analysis could not be explained by the percentage of patients in the trials who had non-ischemic cardiomyopathy.

Cardiovascular mortality, heart failure hospitalizations, and stroke: With the exception of the AATAC[6] and CASTLE AF trials,[8] the

Table 2: Risk of bias assessment

Bias	Study	Judgement	Support for judgement
Random sequence generation (selection bias)			
	MacDonald 2011	Low risk	Computer generated
	Jones 2013	Low risk	Computer generated
	Hunter 2014	Low risk	Random number generator
	Di Biase 2016	Low risk	Computer generated
	Prabhu 2017	Low risk	Computer generated
	Marrouche 2018	Low risk	Computer generated
Allocation concealment (selection bias)			
	MacDonald 2011	Low risk	Computer generated randomization
	Jones 2013	Low risk	Computer generated randomization
	Hunter 2014	Low risk	Random number generator
	Di Biase 2016	Low risk	Computer generated randomization
	Prabhu 2017	Low risk	Computer generated randomization
	Marrouche 2018	Low risk	Computer generated randomization
Blinding of participants and personnel (performance bias)			
	MacDonald 2011	High risk	No blinding
	Jones 2013	High risk	No blinding
	Hunter 2014	High risk	No blinding
	Di Biase 2016	High risk	No blinding
	Prabhu 2017	High risk	No blinding
	Marrouche 2018	High risk	No blinding
Blinding of outcome assessment (detection bias)			
	MacDonald 2011	Moderate risk	Only scans analysis was blinded
	Jones 2013	Low risk	People conducting cardiopulmonary exercise test and imaging analysis were blinded
	Hunter 2014	Moderate risk	Only echocardiogram analysis was blinded
	Di Biase 2016	Moderate risk	Only echocardiogram analysis was blinded
	Prabhu 2017	High risk	No blinding
	Marrouche 2018	High risk	No blinding
Incomplete outcome data addressed (attrition bias)			
	MacDonald 2011	Low risk	No significant attrition
	Jones 2013	Low risk	No significant attrition
	Hunter 2014	Low risk	No significant attrition
	Di Biase 2016	Low risk	No significant attrition
	Prabhu 2017	Low risk	No significant attrition
	Marrouche 2018	Low risk	No significant attrition
Selective reporting (reporting bias)			
	MacDonald 2011	Low risk	
	Jones 2013	Low risk	
	Hunter 2014	Low risk	
	Di Biase 2016	Low risk	
	Prabhu 2017	Low risk	
	Marrouche 2018	Low risk	

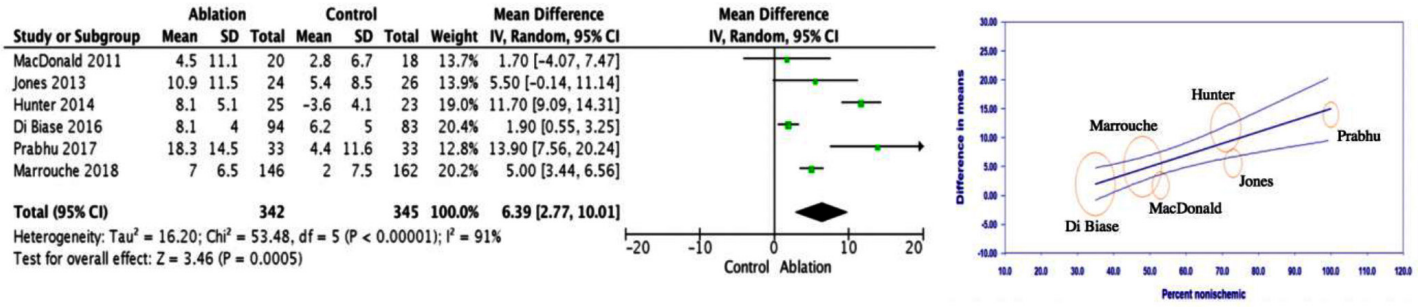

Figure 2: Change in LVEF, meta-analysis (left) and meta-regression (right) results.

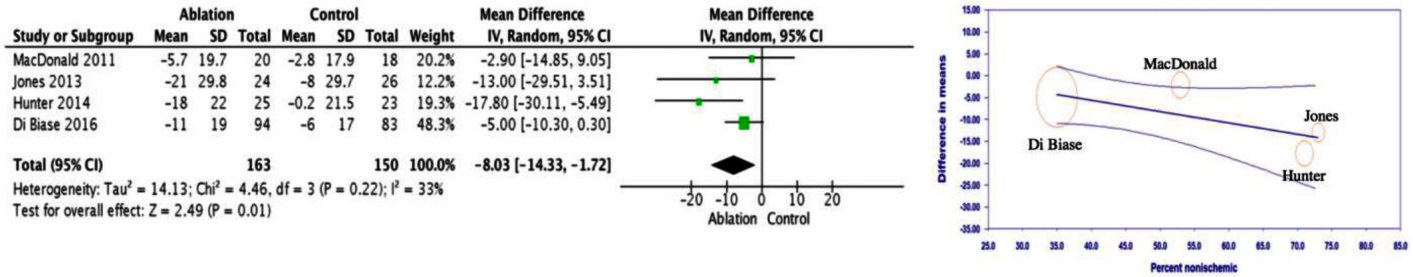

Figure 3: Change in MLWHFQ, meta-analysis (left) and meta-regression (right) results.

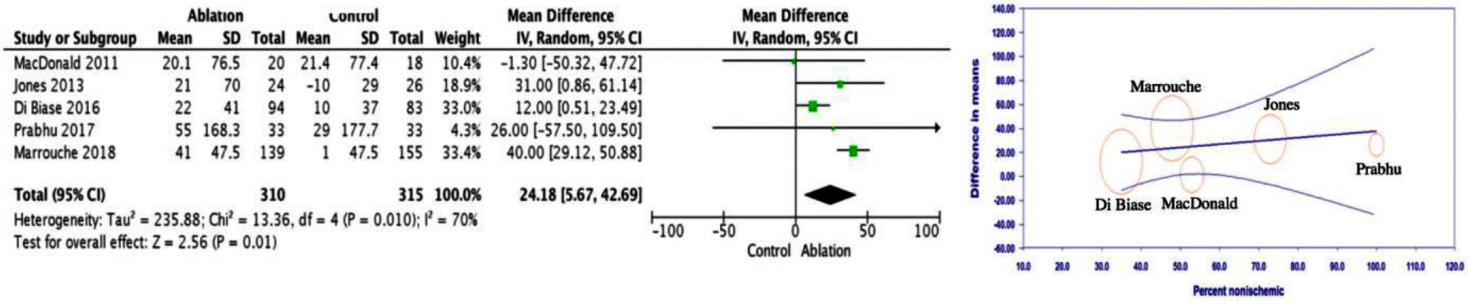

Figure 4: Change in 6MWT, meta-analysis (left) and meta-regression (right) results.

Table 3: Intervention and follow-up

	MacDonald	Jones	Hunter	Di Biase	Prabhu	Marrouche
Ablation strategy	PVI ± Linear lesions and sources of complex fractionated electrograms ± Cardioversion ± cavotricuspid isthmus ablation	PVI ± Linear lesions ± left atrial complex fractionated electrograms ± Cardioversion ± cavotricuspid isthmus ablation.	PVI with ablation of complex or fractionated electrograms ± Linear lesions ± Cavotricuspid isthmus ablation	PVI, and left atrial posterior wall isolation ± SVC isolation ± Linear lesions ± left atrial complex fractionated electrograms ± cardioversion	PVI, left posterior wall isolation ± cardioversion	PVI, Additional ablation lesions were made at the discretion of the operators
Frequency of monitoring (months)	3 & 6	3,6 & 12	1, 3 & 6	3, 6, 12 & 24	3 & 6	3, 6, 12, 24, 36, 48 & 60
Method of assessing rhythm on follow up	24h Holter monitor	48h Holter monitor ± existing implantable devices	48h Holter monitor	ECG, and existing implantable devices	24h Holter monitor and ILR	Existing implantable devices
Repeat ablation	6 (28.6%)	5 (19.2%)	14 (53.8%)	1.4 ± 0.6 per person	Repeat procedure was allowed (frequency not given)	37 (24.5%)
Crossover	None	2	None	None	None	46
Loss to follow up	3	None	1	None	1	33
AAD on follow up	Oral amiodarone for 3 months in all patients post ablation.	AAD stopped post ablation unless indicated by other reasons	AAD stopped post ablation unless indicated by other reasons	AAD allowed for 3 months after the first ablation	12 patients post ablation	48 patients in the ablation arm and 64 in the control arm.

remaining trials were not designed nor powered to detect a difference in cardiovascular mortality or HF hospitalizations.

Unplanned hospitalizations and death were significantly higher in the amiodarone arm in the AATAC trial[6] (58 [57%] vs. 32 [31%]; P < 0.001) and (18 [18%] vs. 8 [8%]; P= 0.037), respectively.

In the CASTLE AF trial,[8] cardiovascular mortality and HF hospitalizations were significantly higher in the medical treatment arm (41 [22.3%] vs. 20 [11.2%]; P= 0.008) and (66 [37.9%] vs. 37 [23.7%] P= 0.004), respectively. Stroke occurred at higher rates in the medical treatment arm, however, this didn't reach statistical significance (11 [6.0%] vs. 5 [2.8%]; P= 0.14).

Discussion

In this meta-regression analysis of randomized controlled trials, it appears that patients with non-ischemic cardiomyopathy benefit more from AF catheter ablation compared to those with ischemic cardiomyopathy. This can be inferred from the regression analyses showing that the difference in change in LVEF and MLWHFQ scores was greater and in favor of the AF ablation group when more patients with non-ischemic cardiomyopathy were included in the trials. Each of these outcomes was found to have a strong linear relationship with the regression line, R^2 values ranging from 0.91 – 1.0 when the percentage of patients with non-ischemic cardiomyopathy was plotted on the x-axis and treatment effect was plotted on the y-axis, [Figures 2-3]. On the contrary, the regression line for 6MWT was flat, indicating that the improvement in 6MWT was not affected by the percentage of patients with non-ischemic cardiomyopathy included in the trials. This is not surprising as the heterogeneity for 6MWT was driven by the AATAC and CASTLE AF trials,[6, 8] and when excluded from the analysis, the heterogeneity dropped significantly (I^2: 0.0%). On the other hand, it does not appear that baseline LVEF was related to the efficacy of ablation in these trials for any of the outcomes assessed.

Multiple meta-analysis of RCTs[9, 10, 12] and observational studies[13] reported improvement in LVEF, 6-minute walk distance and quality of life when catheter ablation is used as a treatment strategy in patients with AF and systolic HF. Nonetheless, there was significant heterogeneity in the outcome measures that was unaccounted for. While the results of the pooled outcomes of this analysis are similar to previously published reports, this is the first meta-regression of RCTs to examine the source of heterogeneity among studies that we are aware of.

The greater benefit of AF catheter ablation seen in patients with non-ischemic cardiomyopathy may not be surprising if many of these patients have tachycardia induced cardiomyopathy that would be expected to improve with restoration of sinus rhythm. Conversely, restoration of sinus rhythm may be less likely to improve cardiac function and related outcomes when cardiomyopathy is due to ischemia. The results of this analysis support previous report by Ling et al[14] who performed AF ablation in 16 patients with cardiomyopathy and no late-gadolinium enhancement on cardiac magnetic resonance imaging. At six months follow-up, LVEF improved from 40% ± 10% to 60% ± 6% in the 15 patients who maintained sinus rhythm post ablation.

These results are novel and interesting and should be viewed as hypothesis generating. There are important limitations to this meta-regression analysis. First, each of the associations derived from the separate regressions are limited by the small number of trials. Second, the overall quality of the individual trials was assessed as moderate only due to the potential for performance and ascertainment bias. Third, the meta-regression was performed based on the mean percentage of non-ischemic cardiomyopathy in each study. An individual level meta-analysis would more accurately address our questions. Nonetheless, these data are not available for the authors. Despite this limitation, we still find bio-plausibility in the regression results. For the regression analysis of difference in change in LVEF, where significant heterogeneity in this outcome was not reduced by sensitivity testing, the percentage of patients with non-ischemic cardiomyopathy in each trial varied from a low of 35% to a high of 100%. This is a significant spread of cardiomyopathy percentage over the trials, which could plausibly affect outcomes of the intervention. Also, the difference in change in mean LVEF between trials ranged from nearly 0% to 15%. This spread is outside the range of typical inter-reader variability using echocardiography and enough to be considered clinically meaningful. Furthermore, when visually examining the regression plot there is no single trial that significantly deviates from the regression line intercept and its 95% confidence interval bounds. If on the other hand, the spread in non-ischemic cardiomyopathy percentage across trials ranged from 40-50% and mean LVEF difference from 0-5% it would be less credible to assert that a true relationship existed and even more so if one or more trials deviated significantly from the regression line.

Conflicts of interest

None.

Funding

None.

Disclosure

None.

Conclusion

In patients with systolic HF, AF catheter ablation appears to be more beneficial in patients with non-ischemic cardiomyopathy. More studies are needed to specifically examine this group of patients and test this hypothesis.

References

1. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, Ellinor PT, Cheng S, Vasan RS, Lee DS, Wang TJ, Levy D, Benjamin EJ and Ho JE. Atrial Fibrillation Begets Heart Failure and Vice Versa: Temporal Associations and Differences in Preserved vs. Reduced Ejection Fraction. Circulation. 2016;133:484-492.
2. MacDonald MR, Connelly DT, Hawkins NM, Steedman T, Payne J, Shaw M, Denvir M, Bhagra S, Small S, Martin W, McMurray JJV and Petrie MC.

Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. Heart. 2011;97:740-747.

3. Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP, Rahman-Haley SL, McDonagh TA, Underwood SR, Markides V and Wong T. A Randomized Trial to Assess Catheter Ablation Versus Rate Control in the Management of Persistent Atrial Fibrillation in Heart Failure. Journal of the American College of Cardiology. 2013;61:1894-1903.
4. Khan MN, Jaïs 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, Russo AD, Pelargonio G, Brachmann J, Schibgilla V, Bonso A, Casella M, Raviele A, Haïssaguerre M and Natale A. Pulmonary-Vein Isolation for Atrial Fibrillation in Patients with Heart Failure. New England Journal of Medicine. 2008;359:1778-1785.
5. 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 and 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;7:31-8.
6. 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 and 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;133:1637-44.
7. 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 L-h, Kalman JM and Kistler PM. Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction: The CAMERA-MRI Study. Journal of the American College of Cardiology. 2017;70:1949-1961.
8. 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 and Bänsch D. Catheter Ablation for Atrial Fibrillation with Heart Failure. New England Journal of Medicine. 2018;378:417-427.
9. Kheiri B, Osman M, Abdalla A, Haykal T, Ahmed S, Bachuwa G, Hassan M and Bhatt DL. Catheter ablation of atrial fibrillation with heart failure: An updated meta-analysis of randomized trials. International Journal of Cardiology. 2018;269:170-173.
10. Briceño DF, Markman TM, Lupercio F, Romero J, Liang JJ, Villablanca PA, Birati EY, Garcia FC, Di Biase L, Natale A, Marchlinski FE and Santangeli P. Catheter ablation versus conventional treatment of atrial fibrillation in patients with heart failure with reduced ejection fraction: a systematic review and meta-analysis of randomized controlled trials. Journal of Interventional Cardiac Electrophysiology. 2018;53:19-29.
11. Ruzieh M, Foy AJ, Aboujamous NM, Moroi MK, Naccarelli GV, Ghahramani M, Kanjwal S, Marine JE and Kanjwal K. Meta-Analysis of Atrial Fibrillation Ablation in Patients with Systolic Heart Failure. Cardiovascular Therapeutics. 2019;36:1-10.
12. Al Halabi S, Qintar M, Hussein A, Alraies MC, Jones DG, Wong T, MacDonald MR, Petrie MC, Cantillon D, Tarakji KG, Kanj M, Bhargava M, Varma N, Baranowski B, Wilkoff BL, Wazni O, Callahan T, Saliba W and Chung MK. Catheter Ablation for Atrial Fibrillation in Heart Failure Patients: A Meta-Analysis of Randomized Controlled Trials. JACC Clinical electrophysiology. 2015;1:200-209.
13. Wilton SB, Fundytus A, Ghali WA, Veenhuyzen GD, Quinn FR, Mitchell LB, Hill MD, Faris P and Exner DV. Meta-Analysis of the Effectiveness and Safety of Catheter Ablation of Atrial Fibrillation in Patients With Versus Without Left Ventricular Systolic Dysfunction. American Journal of Cardiology. 2010;106:1284-1291.
14. Ling L-H, Taylor AJ, Ellims AH, Iles LM, McLellan AJA, Lee G, Kumar S, Lee G, Teh A, Medi C, Kaye DM, Kalman JM and Kistler PM. Sinus rhythm restores ventricular function in patients with cardiomyopathy and no late gadolinium enhancement on cardiac magnetic resonance imaging who undergo catheter ablation for atrial fibrillation. Heart Rhythm. 2013;10:1334-1339.