Improved Survival in Patients with Atrial Fibrillation and Heart Failure Undergoing Catheter Ablation Compared to Medical Treatment: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Jorge Romero[1], Mohamed Gabr[1], Isabella Alviz[1], David Briceno[1], Juan Carlos Diaz[1], Daniel Rodriguez[1], Kavisha Patel[1], Dalvert Polanco[1], Chintan Trivedi[2], Sanghamitra Mohanty[2], Domenico Della Rocca[2], Dhanunjaya Lakkireddy[3], Andrea Natale[2], and Luigi Di Biase[1]

[1]Montefiore Medical Center
[2]Saint David's Healthcare
[3]HCA Midwest Health System

June 6, 2022

Abstract

Introduction: Increasing evidence has suggested improved outcomes in atrial fibrillation (AF) patients with heart failure (HF) undergoing catheter ablation (CA) as compared to medical therapy. We sought to investigate the benefit of CA on outcomes of patients with AF and HF as compared to medical therapy. **Methods and Results**: A systematic review of PubMed, Embase, and Cochrane Central Register of Clinical Trials was performed for clinical studies evaluating the benefit of CA for patients with AF and HF. Primary endpoint was all-cause mortality. Secondary endpoints included atrial-arrhythmia recurrence and improvement in left ventricular ejection fraction (LVEF). Eight randomized controlled trials were included with a total of 2121 patients (mean age: 65 ± 5 years; 72% male). Mean follow-up duration was 32.9 ± 14.5 months. All-cause mortality in patients who underwent CA was significantly lower than in the medical treatment group (8.8% vs. 13.5%, RR 0.65, 95% CI 0.51-0.83, P=0.0005). A 35% relative risk reduction and 4.7% absolute risk reduction in all-cause mortality was observed with CA. Rates of atrial-arrhythmia recurrence were significantly lower in the CA group (39.9% vs 69.6%, RR 0.55, 95% CI 0.40-0.76, P=0.0003). Improvement in LVEF was significantly higher in patients undergoing CA (+9.4 ±7.6%) as compared to conventional treatment (+3.3±8%) (Mean difference 6.2, 95% CI 3.6-8.8, P<0.00001). **Conclusion:** CA for AF in patients with HF decreases all-cause mortality, improves atrial-arrhythmia recurrence rate and LVEF when compared to medical management. CA should be considered the treatment of choice to improve survival in this select group of patients.

Improved Survival in Patients with Atrial Fibrillation and Heart Failure Undergoing Catheter Ablation Compared to Medical Treatment: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

(Short title: Catheter Ablation for Atrial Fibrillation in Patients with Heart Failure)

Jorge Romero, MD, FHRS;[a*] Mohamed Gabr, MD;[a*] Isabella Alviz, MD;[a] David Briceno, MD;[a] Juan Carlos Diaz, MD;[a]Daniel Rodriguez, MD;[a] Kavisha Patel, MD;[a] Dalvert Polanco, MD;[a] Chintan Trivedi, MD, FHRS;[b] Sanghamitra Mohanty, MD, FHRS;[b] Domenico Della Rocca, MD;[b]Dhanunjaya Lakkireddy, MD, FHRS;[c] Andrea Natale, MD, FHRS;[b] Luigi Di Biase, MD, PhD, FHRS[a]

[a] Cardiac Arrhythmia Center, Division of Cardiology, Department of Medicine. Montefiore-Einstein Center for Heart and Vascular Care, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY.

[b] Texas Cardiac Arrhythmia Institute, St. David's Medical Center, Austin, TX.

[c] Kansas City Heart Rhythm Institute, HCA Midwest Health, Kansas City, MO.

[*] *Both authors have equally contributed to this manuscript.*

Corresponding author:

Luigi Di Biase, MD, PhD, FACC, FHRS

Section Head Electrophysiology

Director of Arrhythmia Services

Professor of Medicine

Montefiore Medical Center, Albert Einstein College of Medicine

111 East 210th Street

Bronx, NY 10467

Tel: 718-920-6746 Fax: 718-920-6798

Email: dibbia@gmail.com

Word count: 4787

DECLARATIONS

Funding: No funding was received for conducting this study.

Conflicts of interest:

Dr. Di Biase is a consultant for Stereotaxis, Biosense Webster, Boston Scientific, Abbott; has received speaker honoraria/travel support from Medtronic, Atricure, Bristol Meyers Squibb, Pfizer and Biotronik. Dr. Natale is a consultant for Biosense Webster, Stereotaxis, Abbott; has received speaker honoraria/travel support from Medtronic, Atricure, Biotronik and Janssen. Remaining authors report no conflict of interest.

Availability of data and material:

All data generated or analyzed during this study are included in this published article.

Ethics approval:

Study was performed in accordance with ethical standards of the institution. No ethical approval is required.

Acknowledgments: none

ABSTRACT

Introduction: Increasing evidence has suggested improved outcomes in atrial fibrillation (AF) patients with heart failure (HF) undergoing catheter ablation (CA) as compared to medical therapy. We sought to investigate the benefit of CA on outcomes of patients with AF and HF as compared to medical therapy.

Methods and Results : A systematic review of PubMed, Embase, and Cochrane Central Register of Clinical Trials was performed for clinical studies evaluating the benefit of CA for patients with AF and HF. Primary endpoint was all-cause mortality. Secondary endpoints included atrial-arrhythmia recurrence and improvement in left ventricular ejection fraction (LVEF).

Eight randomized controlled trials were included with a total of 2121 patients (mean age: 65 ± 5 years; 72% male). Mean follow-up duration was 32.9 ± 14.5 months. All-cause mortality in patients who underwent CA

was significantly lower than in the medical treatment group (8.8% vs. 13.5%, RR 0.65, 95% CI 0.51-0.83, P=0.0005). A 35% relative risk reduction and 4.7% absolute risk reduction in all-cause mortality was observed with CA. Rates of atrial-arrhythmia recurrence were significantly lower in the CA group (39.9% vs 69.6%, RR 0.55, 95% CI 0.40-0.76, P=0.0003). Improvement in LVEF was significantly higher in patients undergoing CA (+9.4 ±7.6%) as compared to conventional treatment (+3.3±8%) (Mean difference 6.2, 95% CI 3.6-8.8, P<0.00001).

Conclusion: CA for AF in patients with HF decreases all-cause mortality, improves atrial-arrhythmia recurrence rate and LVEF when compared to medical management. CA should be considered the treatment of choice to improve survival in this select group of patients.

KEYWORDS: heart failure, catheter ablation, atrial fibrillation, all-cause mortality, left ventricular ejection fraction, arrhythmia recurrence

INTRODUCTION

Atrial fibrillation (AF) and heart failure (HF) often occur concomitantly in patients. While their interrelationship is not completely understood, it has been evident that they share risk factors and each of these conditions can worsen the progression of the other. AF has been linked with a five-fold rise in incident HF;[1]it may also cause a reduction in left ventricular ejection fraction (LVEF) by tachycardia-induced cardiomyopathy.[2] On the contrary, HF can escalate the risk of developing AF, propelled by high left ventricular filling pressures and atrial stretch. Moreover, the mortality associated with the coexistence of these conditions is higher than in patients with either condition alone. Presence of AF in patients with HF has been linked with a 40% increase in mortality.[3]

HF is estimated to affect 6.5 million adults in the US, and accounts for nearly 1 million emergency department visits and hospitalizations, 80 000 deaths, and $30 billion in healthcare costs annually. Similarly, AF is the most commonly encountered cardiac arrhythmia in clinical practice, and its prevalence is projected to increase from 5.2 million in 2010 to 12.1 million cases in the US by 2030. Prevalence of AF in patients with HF has been described to range from 6% to 35% in various studies, with a higher prevalence being observed in patients with symptomatic HF. With an aging population, the prevalence of these two conditions is only expected to increase over time.

Restoring sinus rhythm in patients with AF and HF has shown to improve survival and LVEF.[4-6] In this meta-analysis, we sought to evaluate the impact of catheter ablation (CA) on all-cause mortality in patients with AF and HF as compared to medical therapy.

METHODS

The present meta-analysis was performed in accordance with the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.

Search strategy

We searched PubMed, Embase, and Cochrane Central Register of Clinical Trials (Cochrane Library, Issue 02, 2017) databases from January 1st, 1996 through April 2022 to identify trials evaluating the outcomes of AF ablation vs. medical therapy in patients with CHF. We used the terms ("Atrial Fibrillation" OR "AF") AND ("Ablation" OR "Catheter Ablation" OR "CA" OR "Radiofrequency Ablation" OR "RFA") AND ("CHF" OR "Heart Failure" OR "Congestive Heart Failure"). The language of the articles was restricted to English only. The reference lists of identified articles were also reviewed.

Eligibility criteria

Studies with the following characteristics were considered eligible: 1. Study design was a prospective, randomized controlled trial (RCT); 2. Included HF patients with documented AF undergoing CA therapy; 3. Compared the all-cause mortality between the ablation group and the standard / medical therapy groups;

4. Compared improvement in LVEF; 5. Compared other outcomes such as quality of life using Minnesota Living with Heart Failure Questionnaire (MLWHFQ), change in 6-minute walk distance (6-MWD), and atrial-arrhythmia recurrence. Abstracts, case reports, conference presentations, editorials, reviews, and expert opinions were excluded from our analysis.

Primary and secondary endpoints

The primary endpoint of our analysis was all-cause mortality during follow-up after CA. The secondary endpoints included improvement in LVEF, atrial-arrhythmia recurrence, change in MLWHFQ and 6-MWD.

Data extraction and quality appraisal

Three investigators (J.R., M.G. and L.D.B) independently screened all titles, abstracts and manually searched the full text versions of all relevant studies that fulfilled the inclusion criteria. References of the retrieved articles were independently reviewed for further identification of potentially relevant studies. Disagreements were resolved arbitrarily (J.R. and L.D.B), and consensus was reached after discussion. We extracted characteristics of each study including methodology and baseline patient characteristics, all-cause mortality, change in LVEF, atrial-arrhythmia recurrence rates, change in MLWHFQ and 6-MWD, ablation strategy, and duration of follow-up for our analysis. If the above-mentioned information was not readily available in the written article, the principal investigator of the study was contacted to obtain pertinent information. Studies not including the aforementioned outcomes in their analysis were not included in the analysis for that particular outcome.

Quality assessment

The quality and reporting of the included RCTs were assessed using the Cochrane Risk of Bias Tool. Quality of the included RCTs was summarized visually.

Statistical analysis

Descriptive statistics are presented as number of cases (n) for dichotomous and categorical variables. Statistical analysis was performed in line with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, using Review Manager (RevMan version 5.3, the Cochrane Collaboration, 2014). Heterogeneity was assessed using the I^2 statistics, which is the proportion of total variation observed among the studies attributable to differences between studies rather than sampling error (chance). Data were summarized across groups using the Mantel-Haenszel Risk Ratio (RR) Fixed-Effect model if I^2 <25. We considered I^2 less than 25% as low andI^2 greater than 25% as high. The Random-Effects Model was used if I^2 [?]25%. Publication bias was estimated visually by funnel plots.

RESULTS

Baseline characteristics

A total of 2929 studies were identified using the pre-specified search criteria **(Figure 1)** . After a detailed evaluation of these studies, 8 studies that comprised a total of 2121 participants were included.[4-10] Baseline characteristics of included studies are summarized in **Table 1** . Ablation strategy utilized and details of follow-up have been summarized in **Table 2** . The largest study included 778 patients and the smallest included 50 patients. Mean follow-up duration was 32.9 +- 14.5 months. Mean age of the study population was 65 +- 5 years; the majority of patients were male (72%). Mean LVEF in the included studies was 41.6 +- 7.8% in the ablation group and 42 +- 8.4 % in the medical therapy group.

Characteristics of included studies

All eight of the included studies were prospective, RCTs that compared outcomes of patients with AF and HF undergoing CA as compared to medical therapy.[4-11] Of the 2121 patients included, 1056 patients underwent CA, while 1065 patients received medical therapy. Five of the included studies only had patients with persistent AF;[4,7-10] in the three remaining studies, patients with paroxysmal AF were also included.[5,6,11]

Quality assessment and publication bias

Funnel plots did not suggest publication bias in all studied outcomes**(Figure 2)** . All the studies included in this meta-analysis had good methodological quality indicating "low risk of bias". All 8 studies were classified as high-quality based on the Cochrane Risk of Bias Tool **(Figure 3).**

Impact on all-cause mortality

All-cause mortality in patients with HF who underwent CA for AF was significantly lower compared to patients who received medical treatment alone (8.8% vs. 13.5 %, respectively, risk ratio (RR) 0.65, 95% confidence interval (CI) 0.51-0.83, P=0.0005). A 34.8% relative risk reduction and 4.7% absolute risk reduction in all-cause mortality was observed with CA **(Figure 4A, Figure 5A)** .

Impact on LVEF

Improvement in the LVEF was significantly higher in patients undergoing CA (+9.4+-7.6%) compared to conventional treatment (+3.3+-8%) (mean difference 6.2, 95% CI 3.6-8.8, P<0.00001)**(Figure 4B, Figure 5B)** .

Atrial-arrhythmia recurrence

At a mean follow-up duration of 34.3 +- 14.7 months for this outcome in studies that reported it, atrial-arrhythmia recurrence was significantly lower in patients who underwent CA compared to medical therapy (39.9% vs 69.6%, RR 0.55, 95% CI 0.40-0.76, P=0.0003) **(Figure 4C, Figure 5C)** .

Change in quality of life assessment and functional capacity

Improvement in quality of life, as evaluated by decrease in MLWHFQ, was significantly better in CA group (mean decrease -15.1+-12 vs -10.6+-12, Mean difference -4.8, 95% CI -8.6 to -1, P=0.01) **(Figure 6A)** .

Change in functional capacity, as assessed by 6-MWD, showed a significant improvement in the CA group compared to medical therapy group (39 +- 43 meters vs. 22 +- 41 meters, Mean difference 19.3, 95% CI 5.8 - 32.8, P=0.005) **(Figure 6B)** .

DISCUSSION

To the best of our knowledge, this is the largest meta-analysis of randomized controlled trials evaluating the outcomes of patients with AF and HF undergoing CA as compared to medical therapy to date. The principal findings are as follows:

1. At a mean follow-up of 32.9 +- 14.5 months, a 35% relative risk reduction and 4.7% absolute reduction in all-cause mortality was observed with CA of AF compared to medical therapy in patients with HF.
2. CA for AF in HF was associated with a significantly higher improvement in LVEF compared to medical therapy (+9+-8% compared to +3+-8, respectively).
3. CA for AF in HF was associated with a significant reduction in atrial-arrhythmia recurrence as compared to medical therapy.
4. CA for AF in HF was associated with a significant improvement in quality of life as opposed to medical therapy.

Multiple RCTs have demonstrated an improvement in the outcomes of patients with AF and HF, with CA when compared to medical therapy.[4-8] According to the 2019 AHA/ACC/HRS guidelines for the management of patients with AF, CA is considered reasonable in select patients with heart failure with a reduced ejection fraction (HFrEF) for its potential benefit in decreasing mortality and hospitalization rates (Class IIb recommendation).[12]More recently, the European society of cardiology guidelines assigned catheter ablation a class I recommendation in patients with paroxysmal AF and HF with reduced ejection fraction.[13] However, CA has not yet been adopted as the standard of care for rhythm control in HF.

Over a decade ago, AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) subanalysis noted that maintenance of sinus rhythm was an important determinant of survival.[14]Anti-arrhythmic

drugs (AADs) are not linked with improved survival indicating that any beneficial effect of these drugs is offset by their adverse effects. In patients with AF and HF, the available AADs recommended by current guidelines are amiodarone and dofetilide. Long-term utilization of amiodarone is linked with hepatic, pulmonary and thyroid toxicity. Dofetilide requires hospitalization due to risk of severe QTc prolongation and torsades de pointes in up to 3% of patients. In addition, its utilization is restricted in patients with renal dysfunction, a common condition that preexists with HF. The AF-CHF (Atrial Fibrillation and Congestive Heart Failure)[15]and DIAMOND-CHF (Danish Investigators of Arrhythmia and Mortality on Dofetilide in Congestive Heart Failure) trials[16] with predominant and exclusive utilization of amiodarone and dofetilide, respectively, noted that use of neither of these AADs was associated with a reduction in mortality despite reduction in AF burden.

CA offers an appealing alternative therapy to restore sinus rhythm while avoiding the adverse effects associated with the use of AADs. In PABA-CHF (Pulmonary Vein Isolation for Atrial Fibrillation in Patients with Heart Failure) trial, a prospective, multicenter RCT published by our group, CA for AF and HF (EF [?] 40%) was demonstrated to be superior to atrioventricular-node ablation with biventricular pacing for the composite endpoint of improvement in LVEF (35% vs 28%, P<0.001), 6-MWD (340m vs 297m, P<0.001) and MLWHF score (60 vs 82, P<0.001).[17] CAMTAF (A Randomized Controlled Trial of Catheter Ablation Versus Medical Treatment of Atrial Fibrillation in Heart Failure), demonstrated significant improvement in LVEF in patients with persistent AF and HF (EF <50%), at 6-month follow-up (40+-12% vs 31+-13%, P=0.015).[8] Subsequently, AATAC (Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device),[4] a multicenter, RCT published by our group noted superiority of CA for persistent AF and HF over amiodarone in improving freedom from atrial-arrhythmia recurrence (70% vs 34%, P< 0.001), at 2-year follow-up. A significant reduction in the unplanned hospitalization rate (31% vs 57%, P<0.001) and mortality rate (8% vs 18%, P=0.037) was also noted.[4]In CAMERA-MRI (Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction), a RCT of patients with persistent AF and HF (EF [?]45%), significant improvement in LVEF (18+-13% vs 4.4+-13%, P<0.0001) was noted in the ablation arm, with the absence of late gadolinium enhancement predicting greater improvement in LVEF (10.7%, P=0.0069).[10] CASTLE-AF (Catheter Ablation for Atrial Fibrillation with Heart Failure) trial, a RCT, which enrolled patients with paroxysmal or persistent AF and HF (EF [?] 35%) demonstrated a significant improvement in the primary composite endpoint of all-cause mortality or HF hospitalization rate (28.5% vs. 44.6%, p=0.007), at a mean follow-up of 37.8 months.[6]

In CABANA (Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation) trial, the largest RCT to date comparing CA for AF to medical therapy in 2204 patients, CA did not significantly improve the primary composite outcome of death, serious bleeding, cardiac arrest, or disabling stroke per intention-to-treat analysis (8% vs. 9.2%, p=0.30).[18] However, in the sub-group analysis of 778 patients with HF, the results were favorable for CA, with a 36% relative reduction in the primary composite outcome (HR: 0.64, 95% CI: 0.41-0.99) and 43% relative reduction in all-cause mortality (HR: 0.57, 95% CI: 0.33-0.96), at a median follow-up of 48.5 months.[5] In addition, more recently, RAFT-AF (Randomized Ablation-based Rhythm-control Versus Rate-control Trial in Patients with Heart Failure and Atrial Fibrillation), reported results from a RCT of 411 patients.[11] In the study's analysis, the primary composite outcome of all-cause mortality and heart failure events was not significantly different between the catheter ablation and medical therapy groups (23.4% vs 32.5% events, respectively, p=0.066), despite a trend for improved outcomes. On the other hand, CA compared to medical therapy was associated with statistically significant improvement in LVEF (10.1+-1.2% vs 3.8+-1.2%, p=0.017), six minute walk distance (44.9+-9.1 meters 27.5+-9.7 meters, p=0.025), MLWHFQ (LSMD of -5.4, 95%CI (-10.5, -0.3), p=0.0036), and NT-proBNP (mean change -77.1% vs -39.2%, p<0.0001). Results from AMICA (Catheter Ablation Versus Best Medical Therapy in Patients With Persistent Atrial Fibrillation and Congestive Heart Failure) trial,[9] and a study by MacDonald et al,[19] contrasted the largely positive results seen in other studies. AMICA trial, a RCT comparing CA to medical therapy in patients with persistent or longstanding persistent AF with HF, described no significant improvement in LVEF between the

ablation group and medical therapy group at 12-month follow-up.[9] MacDonald et al, in a RCT of patients with persistent AF and advanced HF (EF <35%) also did not demonstrate a significant improvement in LVEF on cardiac magnetic resonance imaging, at 6-month follow-up.[19] Both of these trials enrolled majority of patients with advanced HF which may have led to a lower benefit from CA.[9,19] This was also noted in CASTLE-AF sub-analysis, where CA in patients with NYHA classes I and II was associated with a stronger improvement in outcomes as compared to NYHA classes III and IV.[20] As such, early CA to achieve rhythm control in HF patients could be crucial in achieving significant benefits, similar to what has been recently been described in non-HF populations. Moreover, the short duration of follow-up could have been insufficient to detect the beneficial outcomes of CA. This was evident, for instance, in the CASTLE-AF study, where the beneficial effect of CA on all-cause mortality, and HF hospitalization rates were seen at a significantly longer follow-up duration (median: ˜37 months).[6] Finally, significant cost reductions could result from AF CA in HF patients. Lima et al recently described a significant reduction in 30-day readmissions (16.8% vs 18.8%, P = 0.02) in patients with HF undergoing CA for AF compared with a propensity score matched group receiving medical therapy.[21] Importantly, although the costs of the index hospitalization were significantly higher for the CA group, after readmission, overall costs were similar between the two groups. Field et al found significant reductions in AF-related hospitalizations (64%), emergency department [22] visits (51%), and HF related hospitalizations (22%), all of which translated into a reduction in AF related costs and ED related costs. As such, increasing the use of CA for AF in HF is expected to be highly cost effective, with an incremental cost of $38,496-74,403 per QALY gained compared to medical therapy.[23]

In a meta-analysis of 856 patients with AF and HFrEF, CA demonstrated significant improvement in all-cause mortality (10% vs. 19%, OR: 0.46, 95% CI: 0.29-0.72) and freedom from AF (70% vs. 18%, OR: 0.03, 95% CI: 0.01-0.11).[24] The results of the present meta-analysis are also consistent with other meta-analyses published on this subject.

Limitations

Several limitations must be taken into consideration while interpreting the results of our meta-analysis. The sample size for some of the included studies along with the number of studies assessing some of the reported outcomes was relatively small. In addition, there was considerable variability amongst studies in terms of inclusion of patients with different NYHA classification subtypes, HF types (preserved versus reduced), etiology of cardiomyopathy, and type of AF included, making it difficult to stipulate which population derives the greatest benefit from CA. Moreover, although pulmonary vein isolation was the main approach in all the studies, there was significant variation in additional ablation strategies utilized. Additionally, there was variability in the intervention used in the control groups, with some studies adopting amiodarone alone for rhythm control, a rate control strategy, or a combination of rate and rhythm control. There was also variation in the duration of AAD utilization after CA for AF.

CONCLUSION

CA for AF in patients with HF significantly decreases all-cause mortality, improves LVEF, reduces atrial-arrhythmia recurrence and improves quality of life in comparison to medical management. CA should be considered the treatment of choice for rhythm control to in this select group of patients with AF and HF.

REFERENCES

1. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. *BMJ.* 2016;354:i4482.

2. Gopinathannair R, Etheridge SP, Marchlinski FE, Spinale FG, Lakkireddy D, Olshansky B. Arrhythmia-Induced Cardiomyopathies: Mechanisms, Recognition, and Management. *J Am Coll Cardiol.*2015;66(15):1714-1728.

3. Mamas MA, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyses L. A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. *Eur J Heart Fail.* 2009;11(7):676-683.

4. Di Biase L, Mohanty P, Mohanty S, et al. 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):1637-1644.

5. Packer DL, Piccini JP, Monahan KH, et al. Ablation Versus Drug Therapy for Atrial Fibrillation in Heart Failure: Results from the CABANA Trial. *Circulation.* 2021.

6. Marrouche NF, Brachmann J, Andresen D, et al. Catheter Ablation for Atrial Fibrillation with Heart Failure. *N Engl J Med.*2018;378(5):417-427.

7. Jones DG, Haldar SK, Hussain W, et al. 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):1894-1903.

8. Hunter RJ, Berriman TJ, Diab I, et al. 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):31-38.

9. Kuck KH, Merkely B, Zahn R, et al. Catheter Ablation Versus Best Medical Therapy in Patients With Persistent Atrial Fibrillation and Congestive Heart Failure: The Randomized AMICA Trial. *Circ Arrhythm Electrophysiol.* 2019;12(12):e007731.

10. Prabhu S, Taylor AJ, Costello BT, et al. 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.

11. Parkash R, Wells GA, Rouleau J, et al. Randomized Ablation-Based Rhythm-Control Versus Rate-Control Trial in Patients with Heart Failure and Atrial Fibrillation: Results from the RAFT-AF trial.*Circulation.* 2022.

12. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.*2019;74(1):104-132.

13. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *European heart journal.* 2021;42(5):373-498.

14. Corley SD, Epstein AE, DiMarco JP, et al. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study.*Circulation.* 2004;109(12):1509-1513.

15. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med.*2008;358(25):2667-2677.

16. Torp-Pedersen C, Moller M, Bloch-Thomsen PE, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. *N Engl J Med.* 1999;341(12):857-865.

17. Khan MN, Jais P, Cummings J, et al. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. *N Engl J Med.*2008;359(17):1778-1785.

18. Packer DL, Mark DB, Robb RA, et al. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA.* 2019;321(13):1261-1274.

19. MacDonald MR, Connelly DT, Hawkins NM, et al. 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(9):740-747.

20. Sohns C, Zintl K, Zhao Y, et al. Impact of Left Ventricular Function and Heart Failure Symptoms on Outcomes Post Ablation of Atrial Fibrillation in Heart Failure: CASTLE-AF Trial. *Circ Arrhythm Electrophysiol.* 2020;13(10):e008461.

21. Lima FV, Kennedy KF, Sheikh W, et al. Thirty-day readmissions after atrial fibrillation catheter ablation in patients with heart failure.*Pacing and clinical electrophysiology : PACE.* 2020;43(9):930-940.

22. Peigh G, Wasserlauf J, Kaplan RM, et al. Repeat pulmonary vein isolation with or without FIRM-guided ablation for recurrent atrial fibrillation with pulmonary vein reconnection. *J Cardiovasc Electrophysiol.* 2020;31(5):1031-1037.

23. Chew DS, Loring Z, Anand J, et al. Economic Evaluation of Catheter Ablation of Atrial Fibrillation in Patients with Heart Failure With Reduced Ejection Fraction. *Circulation Cardiovascular quality and outcomes.* 2020;13(12):e007094.

24. Briceno DF, Markman TM, Lupercio F, et al. 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. *J Interv Card Electrophysiol.* 2018;53(1):19-29.

Fig. 1: Process of study selection

Hosted file

`image1.emf` available at https://authorea.com/users/477530/articles/571911-improved-survival-in-patients-with-atrial-fibrillation-and-heart-failure-undergoing-catheter-ablation-compared-to-medical-treatment-a-systematic-review-and-meta-analysis-of-randomized-controlled-trials

Hosted file

`image2.emf` available at https://authorea.com/users/477530/articles/571911-improved-survival-in-patients-with-atrial-fibrillation-and-heart-failure-undergoing-catheter-ablation-compared-to-medical-treatment-a-systematic-review-and-meta-analysis-of-randomized-controlled-trials

Fig. 2: Funnel plots: A) All-cause mortality; B) Change in left ventricular ejection fraction; C) Atrial-arrhythmia recurrence

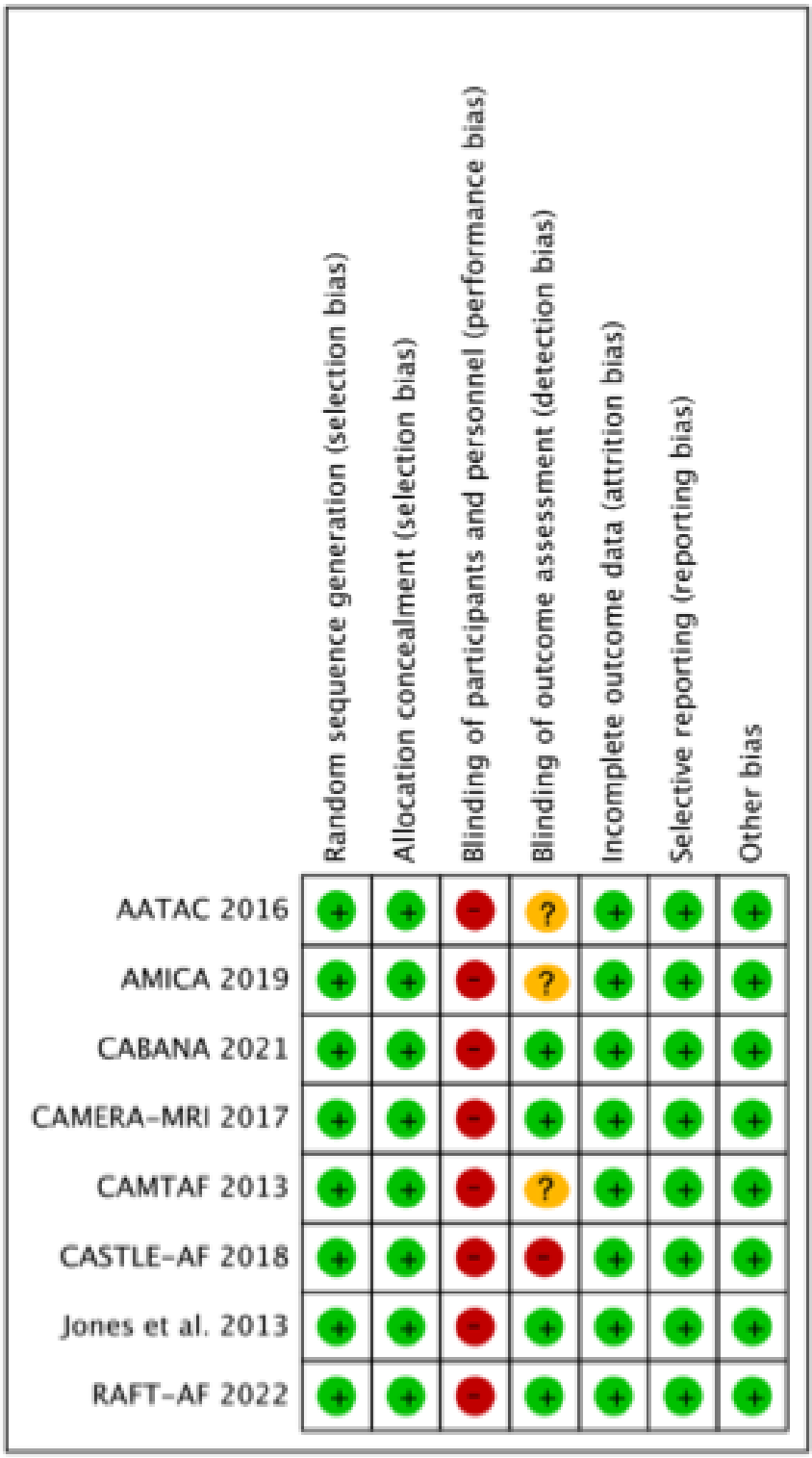


Fig. 3: Quality assessment of randomized controlled trials using Cochrane Risk of Bias Tool.

Hosted file

image4.emf available at https://authorea.com/users/477530/articles/571911-improved-survival-in-patients-with-atrial-fibrillation-and-heart-failure-undergoing-catheter-ablation-compared-to-medical-treatment-a-systematic-review-and-meta-analysis-of-randomized-controlled-trials

Fig. 4: Central Illustration. A) All-cause mortality; B) Change in left ventricular ejection fraction; C) Atrial-arrhythmia recurrence

Fig. 5 : A) All-cause mortality; B) Change in left ventricular ejection fraction; C) Atrial-arrhythmia recurrence

Hosted file

image5.emf available at https://authorea.com/users/477530/articles/571911-improved-survival-in-patients-with-atrial-fibrillation-and-heart-failure-undergoing-catheter-ablation-compared-to-medical-treatment-a-systematic-review-and-meta-analysis-of-randomized-controlled-trials

Diamond indicates overall summary estimates for the analysis: width of the diamond represents 95% CI; width of the shaded square represents the size of the population. CI: confidence interval; M-H: Mantel–Haenszel.

Fig. 6: A) Change in MLWHFQ; B) Change in 6-MWD

Hosted file

image6.emf available at https://authorea.com/users/477530/articles/571911-improved-survival-in-patients-with-atrial-fibrillation-and-heart-failure-undergoing-catheter-ablation-compared-to-medical-treatment-a-systematic-review-and-meta-analysis-of-randomized-controlled-trials

Diamond indicates overall summary estimates for the analysis: width of the diamond represents 95% CI; width of the shaded square represents the size of the population. CI: confidence interval; M-H: Mantel–Haenszel; MLWHFQ: Minnesota Living with Heart Failure Questionnaire; 6-MWD: 6-minute walk distance.

Table 1: Baseline characteristics.

Mean age (years)
Female gender
No. of patients
Follow up (months)
Persistent AF
NYHA class
ICM
NICM
LVEF %
LA diameter (mm)
6 min walk distance (meters)
Quality of life
Diabetes Mellitus
HTN
CAD

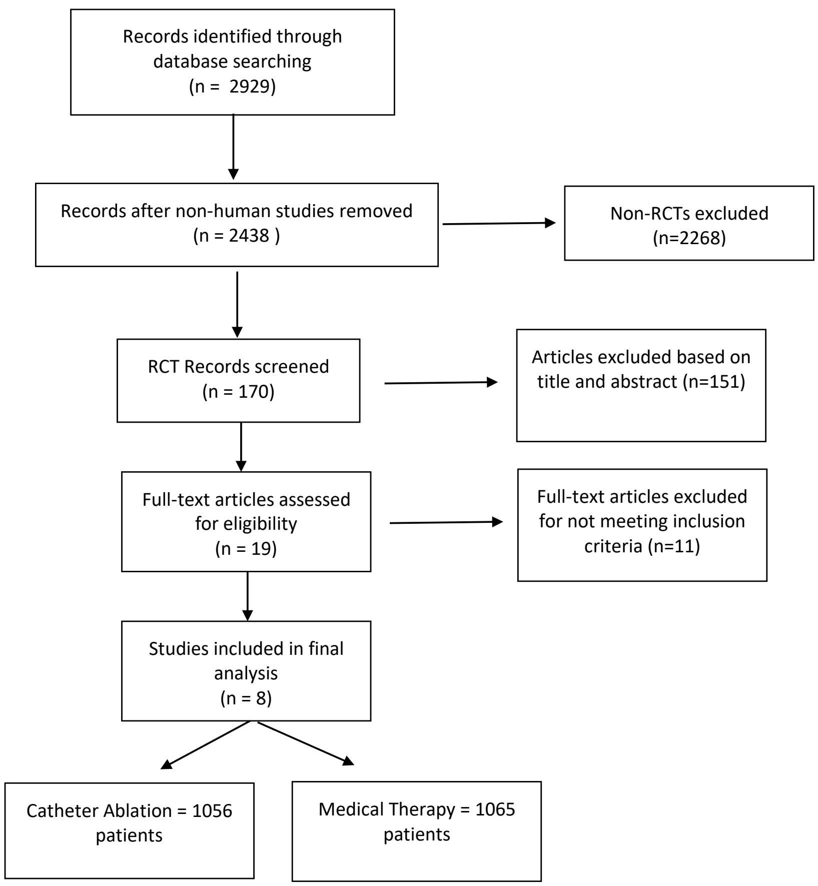
AF: Atrial fibrillation, **CAD:** Coronary artery disease, **NYHA: New York Heart Association, LVEF: left ventricula**

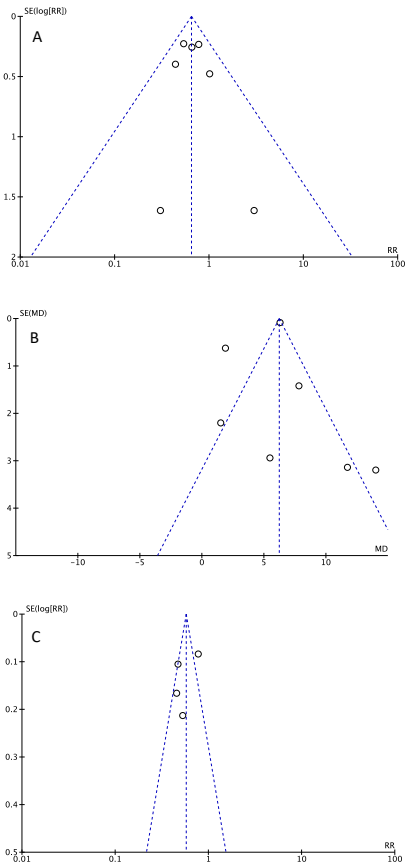
Table 2: Ablation strategy and follow-up.

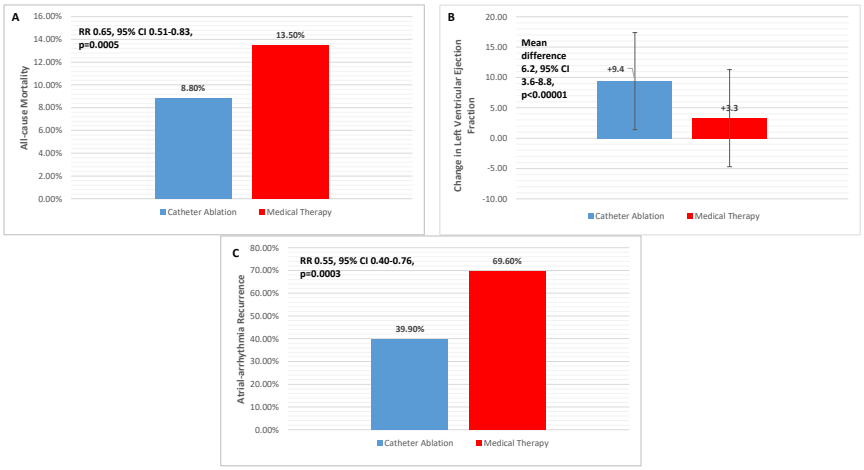
	AMICA 2019	CAMERA-MRI 2017	Jones et al. 2013	CAMTAF 2013	AATAC 2016	CABANA 2021	CASTLE-AF 2018	RAFT-AF 2022
Ablation strategy	PVI ± linear lesions, ablation of complex fractionated electrograms, or combination ± Cardioversion	PVI + posterior wall isolation ± Cardioversion	PVI + linear lesions + left atrial complex fractionated electrograms ± Cardioversion and cavotricuspid isthmus ablation	PVI with ablation of complex or fractionated electrograms ± linear lesions ± Cavotricuspid isthmus ablation	PVI + posterior wall isolation ± SVC isolation ± linear lesions ± left atrial complex fractionated electrograms ± Cardioversion	PVI ± Linear lesions ± ganglion plexus ± electrogram-based approaches	PVI ± additional ablation lesions at the discretion of the operators	PVI ± complex atrial fr tionated electro-grams roof lin mitral isthmus line ± l atrial posteri wall isolatio
Frequency of monitoring (months)	1, 3, 6, & 12	1.5, 3 & 6	3,6 & 12	1, 3 & 6	3, 6, 12 & 24	3, 6, & 12 months, then every 6 months	3, 6, 12, 24, 36, 48 & 60	2, 4, & months then every 6 months
Method of assessing rhythm on follow up	12-lead ECG at follow-up, patient-performed surface devices, & implantable devices	Holter monitor at 3 and 6 months	ECG at follow-up + 48h Holter monitor at 6 and 12 months ± existing implantable devices	12-lead ECG, 48h Holter monitor	ECG at 3 and 24 months, and existing implantable device interrogation at 3, 6, 12, and 24 months	CABANA monitoring system: ECG event recorder, with 24-hour autodetect and 96-hour Holter monitoring every 6 months	Existing implantable device interrogation	12-lead ECG at each follow-up for all patients + 14-day ambulatory monitoring (CardioSTAT) at 12- and 24-months in 7 centers

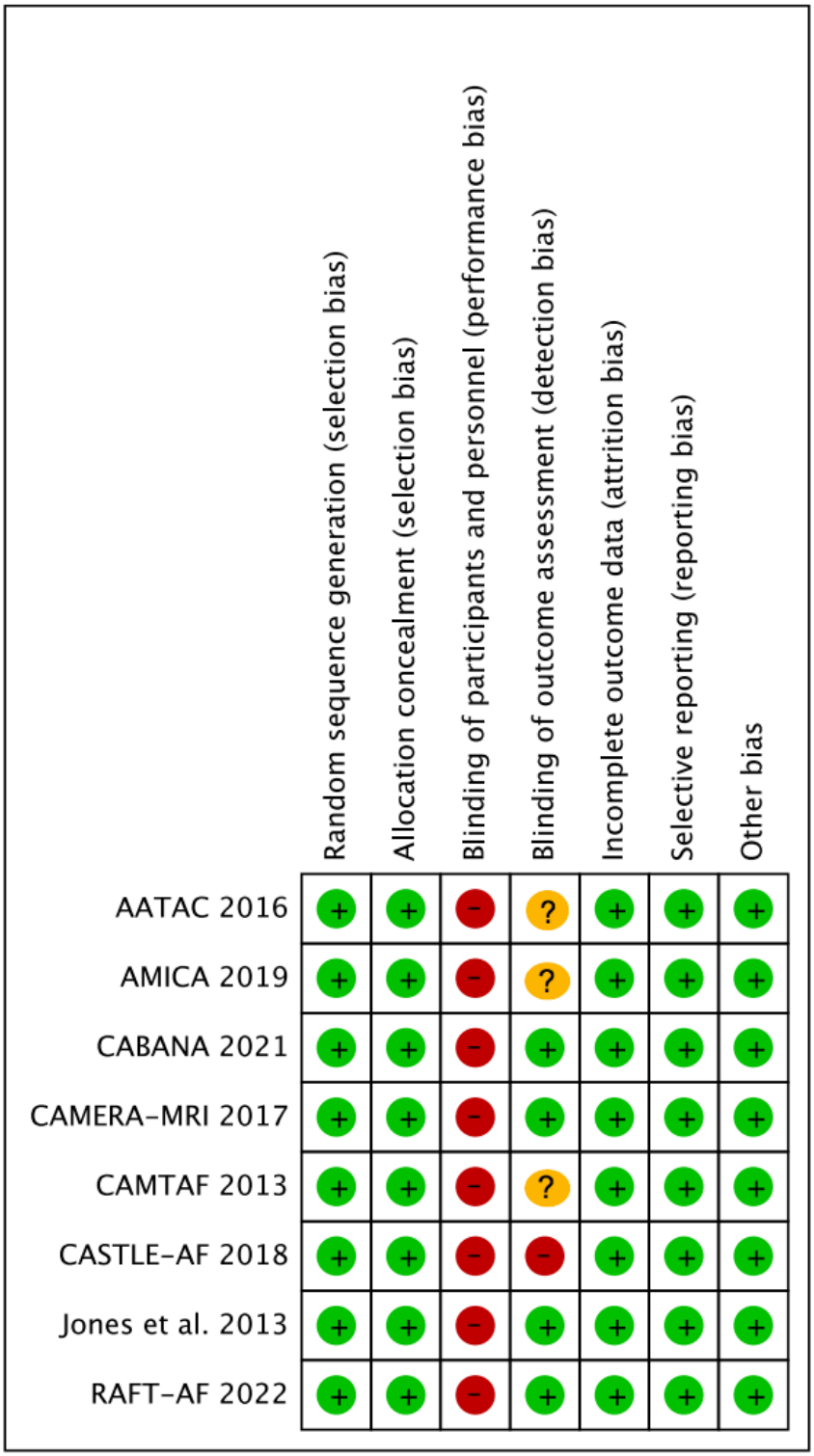
	AMICA 2019	CAMERA-MRI 2017	Jones et al. 2013	CAMTAF 2013	AATAC 2016	CABANA 2021	CASTLE-AF 2018	RAFT-AF 2022
Repeat ablation	10 (15%)	Allowed if symptomatic recurrence >3 months after procedure	5 (19.2%)	14 (53.8%)	1.4 ± 0.6 procedures per person	Repeat procedure was allowed	37 (24.5%)	77 (37.6%)
Crossover	3	3	2	None	None	None	46 (28 to medical therapy, 18 to ablation)	None
Loss to follow-up	17 ablation, 13 medical therapy	None	None	1 ablation, 1 medical therapy	None	N/A	23 ablation, 10 medical therapy	3 ablation, 4 medical therapy
AAD on follow-up	Amiodarone in 23 patients (34%) in the ablation arm and 39 (54%) in the control arm at 12 month follow-up	AAD resumed if present or started after early recurrence	AAD stopped post ablation unless indicated by other reasons	AAD stopped post ablation unless indicated by other reasons	AAD allowed during the blanking period (3 months)	AAD allowed during the blanking period (3 months)	48 patients (25%) in the ablation arm and 64 (35%) in the control arm	AAD allowed weeks p ablation and as adjunct therapy after [?] ablation procedu 48 patie (22.8%) the ablation group a 12 patie (6.2%) AAD at last follow-u

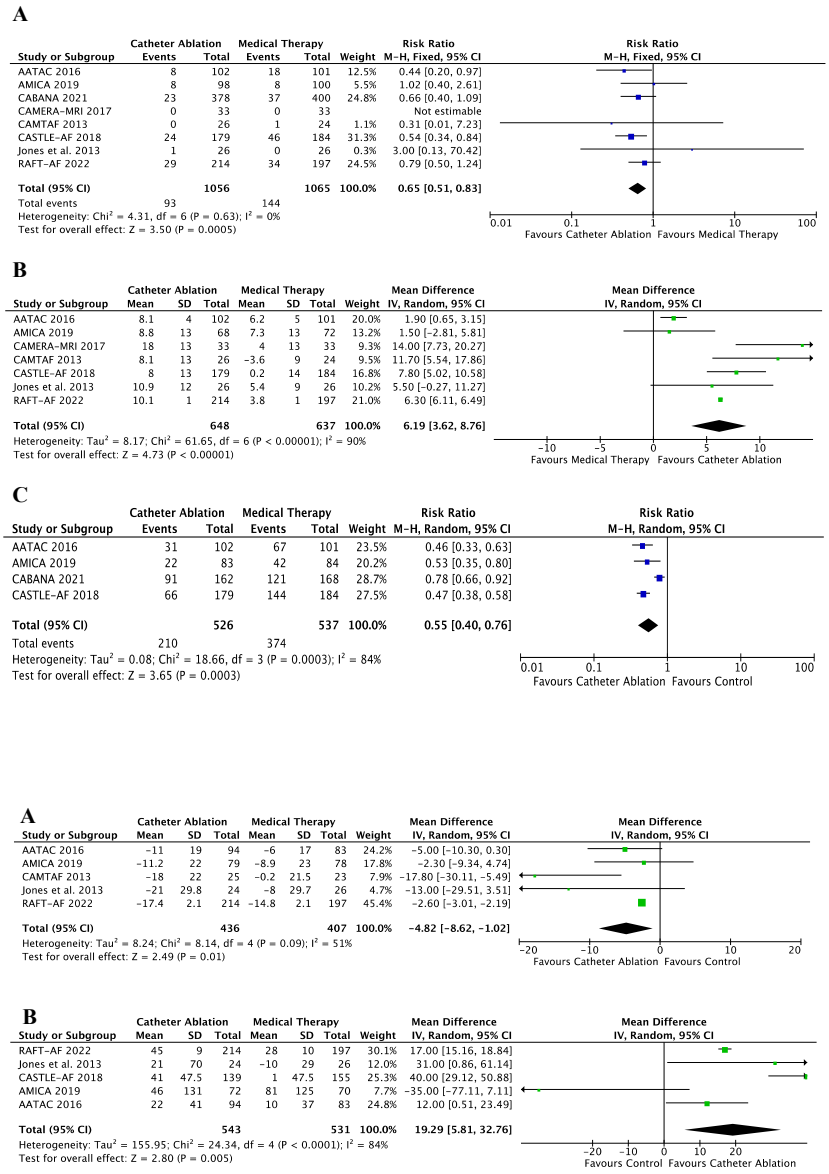
	AMICA 2019	CAMERA-MRI 2017	Jones et al. 2013	CAMTAF 2013	AATAC 2016	CABANA 2021	CASTLE-AF 2018	RAFT-AF 2022
PVI: Pulmonary vein isolation, **AAD:** Antiarrhythmic drug, **N/A:** Not available	**PVI:** Pulmonary vein isolation, **AAD:** Antiarrhythmic drug, **N/A:** Not available	**PVI:** Pulmonary vein isolation, **AAD:** Antiarrhythmic drug, **N/A:** Not available	**PVI:** Pulmonary vein isolation, **AAD:** Antiarrhythmic drug, **N/A:** Not available	**PVI:** Pulmonary vein isolation, **AAD:** Antiarrhythmic drug, **N/A:** Not available	**PVI:** Pulmonary vein isolation, **AAD:** Antiarrhythmic drug, **N/A:** Not available	**PVI:** Pulmonary vein isolation, **AAD:** Antiarrhythmic drug, **N/A:** Not available	**PVI:** Pulmonary vein isolation, **AAD:** Antiarrhythmic drug, **N/A:** Not available	











Hosted file

Tables Updated 6:2022.docx available at https://authorea.com/users/477530/articles/571911-improved-survival-in-patients-with-atrial-fibrillation-and-heart-failure-undergoing-catheter-ablation-compared-to-medical-treatment-a-systematic-review-and-meta-analysis-of-randomized-controlled-trials