Comprehensive Evaluation of Catheter Ablation versus Medical Therapy in Atrial Fibrillation and Heart Failure: An Umbrella Review

Muhammad Uzair Siddique[1], Muhammad Hazma Ilyas[1], Ahmed Arham Niaz[1], Daniya Waqas[1], Usama Afraz Younas[1], safwan safdar[1], Danish Zahir[1], Usman Saeed[1], Ali Shehram[1], Fatima Tanveer[1], Ali Ahmad[1], and Taha Nadeem[1]

[1]Affiliation not available

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Abstract

Background: The precise relationship between atrial fibrillation (AF), which affects a significant number of individuals, and heart failure (HF) remains poorly understood. With over 12 million projected cases of AF and 8 million of HF in the United States by 2030, the need for clarity led us to conduct the first-ever umbrella review, aiming to understand the inconsistent findings regarding the efficacy of catheter ablation (CA) versus medical therapy (MT) in this population.

Methods: A comprehensive search was conducted across PubMed, Cochrane Library, and Google Scholar to identify relevant studies for inclusion in this umbrella review. The GRADE method was utilized to assess the overall certainty of the evidence thoroughly. Furthermore, the quality of the included reviews was carefully evaluated using the AMSTAR 2 and Cochrane Collaboration risk of bias tool.

Results: After careful review, six systematic reviews and meta-analyses were selected for analysis. Notably, Catheter ablation (CA) was associated with a significant reduction in all-cause mortality (RR [95% CI]: 0.55 [0.44, 0.68], I2: 60%, p-value: $<$0.00001), and Heart failure (HF) hospitalization risk (RR [95% CI]: 0.61 [0.54, 0.70], I2: 0%, p-value: $<$0.00001), as well as a decrease in atrial fibrillation (AF) recurrence rates (RR [95% CI]: 0.36 [0.27, 0.47], I2: 0%, p-value: $<$0.00001). Secondary efficacy outcomes, including changes in cardiac function parameters, favored CA over MT, with significant improvements observed in Left ventricular ejection fraction (LVEF) and 6-minute walk test (6MWT).

Conclusion: AF and HF patients who received CA instead of MT had better functional outcomes and safety. The CA group has significantly lower all-cause mortality, HF hospitalization, AF recurrence, and LVEF, 6MWT, and VO2 max improvements than the MT group. Future research should include all participants with HF and AF to obtain a complete analysis.

Highlights

- Catheter ablation (CA) treatment significantly reduced the risk of all-cause mortality compared to medical therapy (MT).
- CA was associated with a significant decrease in HF hospitalization risk compared to MT.
- CA demonstrated a significant decrease in AF recurrence risk compared to MT.
- CA led to significant improvements in left ventricular ejection fraction (LVEF) and exercise capacity (6MWT).
- There was a non-significant decrease in brain natriuretic peptide (BNP) levels with CA compared to MT

Introduction

Atrial fibrillation (AF) and heart failure (HF) frequently coexist in patients, with a complicated yet incompletely understood link [1]. Specifically, despite their common roots, both illnesses appear to promote and

exacerbate one another. According to recent projections, more than 12 million people in the United States will have AF, while approximately 8 million will have HF by 2030. It is essential to highlight that the occurrence of AF increases with the severity of heart failure, with prevalence ranging from 5% in functional class I patients to nearly 50% in functional class IV [2]. Both are common among our aging population, and the death rate associated with their co-occurrence is significantly higher than for either disease alone [3]. Furthermore, they share common risk factors, such as aging, hypertension, diabetes, obesity, sleep apnea, and coronary disease [4]. Moreover, it has been proposed that AF might cause severe HF by tachycardia-induced cardiomyopathy [5]. In contrast, HF can be caused by high filling pressures and atrial stretch associated with AF [3].

Rate and rhythm control drugs as medical therapy (MT) have traditionally been the foundation of therapy for attaining rate and rhythm control in individuals with AF. Nevertheless, the principal limitations of this approach are the poor selection of MT options for patients with HF, their moderate efficacy in preserving sinus rhythm, and the incidence of serious adverse events [6]. The guidelines also support a limited number of pharmacologic alternatives for rhythm control in HF patients, including dofetilide and amiodarone, both of which have recognized concerns such as arrhythmia and multi-organ toxicity. However, many randomized controlled trials (RCTs) have shown that catheter ablation (CA) of AF is not only safe but also more effective than MT in maintaining sinus rhythm and preventing AF recurrence [7]. Similarly, several RCTs consistently show that CA improves left ventricular ejection fraction and quality of life and reduces cardiovascular hospitalizations compared to medical therapy [8].

Due to inconsistent findings in earlier meta-analyses on the effects of MT against CA in patients with AF and HF, we conducted the first umbrella review of the systematic reviews and meta-analyses accessible. To guarantee consistency in our findings when utilizing this evidence-based approach, we included studies that covered all patients with AF and HF while omitting those with a small number of cases.

Methodology

This comprehensive review followed the guidelines outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and the Cochrane Collaboration Handbook [9, 10].

Search Approach

The search was conducted across multiple databases, including PubMed, Cochrane Library, and Google Scholar, to ensure a comprehensive exploration of the scientific literature. A wide range of keywords and Medical Subject Headings (MeSH) were thoughtfully selected to ensure inclusivity. These keywords covered aspects such as "catheter ablation," "CA," "medical therapy," "MT," "atrial fibrillation," "heart failure," "patients," "comparison," "treatment outcomes," "intervention," "cardiovascular," and "meta-analysis." A detailed summary of the search strategy, including specific combinations of keywords and operators, can be found in Supplementary Table S1.

To maintain the integrity of the process and minimize potential selection bias, two independent researchers searched, resolving any discrepancies through consensus. In cases of persistent discrepancies, a third researcher was involved to ensure resolution and reliability.

Study Inclusion and Exclusion Criteria

Inclusion Criteria:

The umbrella review on "Catheter Ablation versus Medical Therapy of Atrial Fibrillation in Patients with Heart Failure" incorporated studies that met rigorous inclusion criteria. These criteria comprised meta-analyses that synthesized data from primary studies comparing catheter ablation (CA) and medical therapy (MT) specifically for atrial fibrillation (AF) in patients diagnosed with heart failure (HF). Only meta-analyses directly addressing this comparative intervention within the context of concurrent atrial fibrillation and heart failure were considered eligible. Studies involving human participants across all age groups and demographic

backgrounds were included. The review focused on meta-analyses reporting relevant clinical outcomes such as mortality rates, arrhythmia recurrence, quality of life enhancements, and adverse events. Furthermore, only peer-reviewed meta-analyses published in reputable scientific journals were deemed suitable for inclusion. To ensure broad accessibility, studies published in English or with available translations were considered.

Exclusion Criteria:

Meta-analyses that did not directly compare CA with MT in patients diagnosed winth both AF and HF were excluded. Additionally, studies comparing interventions other than CA and MT for atrial fibrillation in HF patients were not considered. Meta-analyses based solely on animal models or laboratory experiments were also excluded from the review. Furthermore, abstracts presented at conferences without subsequent full-text publication were omitted due to limited data availability and lack of peer review. Systematic reviews without meta-analysis or quantitative synthesis of data were excluded to ensure the inclusion of only studies offering comprehensive data analysis.

Data Extraction

Relevant information encompassing publication details, study attributes, participant features, and clinical outcomes was extracted. The outcomes were divided into efficacy and safety outcomes. The efficacy outcomes were further divided into primary and secondary outcomes. Primary efficacy outcomes included all-cause mortality, HF hospitalization, and AF recurrence. Secondary efficacy outcomes included a change in Left ventricular ejection fraction (LVEF), change in the 6-minute walk test (6MWT), change in maximal oxygen consumption (VO2 max), change in Minnesota Living with Heart Failure Questionnaire (MLHFQ), and change in Brain natriuretic peptide (BNP).

The safety endpoints included were pericardial effusion/tamponade and major adverse cardiovascular events (MACEs).

Assessment of Risk of Bias

The methodological robustness of the included reviews and meta-analyses underwent a thorough examination by two independent researchers utilizing the AMSTAR 2 tool. This tool offers a comprehensive evaluation across 16 critical methodological domains, providing a detailed assessment. The overall quality of the studies was then categorized as high, moderate, low, or critically low, guided by established criteria [11].

To gauge the inherent risk of bias in randomized controlled trials (RCTs) included in individual meta-analyses, we employed the Cochrane Collaboration risk of bias tool [12]. This tool systematically evaluates eight potential sources of bias, including random sequence generation, allocation concealment, blinding of participants and assessors, outcome assessments, and management of incomplete outcome data.

The certainty of evidence and the strength of recommendations drawn from meta-analyses underwent rigorous scrutiny using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method [13]. This method categorizes evidence into four tiers: 'high,' 'moderate,' 'low,' and 'very low.' Initially set at the 'high' level, the GRADE assessment was adjusted based on identified risks of bias, inconsistencies in results, indirect evidence, imprecision, or publication bias. Two researchers independently conducted the GRADE assessment for each study's primary efficacy outcomes, engaging in discussions and reaching agreements to resolve any discrepancies.

Statistical Analysis

All statistical analyses were conducted utilizing STATA 16 and Review Manager version 5.4. Categorical outcomes were evaluated by computing Risk Ratios (RR) along with 95% Confidence Intervals (CIs), employing the random-effects model. Mean differences were calculated for continuous data, with statistical significance determined by $P < 0.05$. The I2 statistic was employed to assess heterogeneity among study associations [14]. Sensitivity analyses were performed to assess the robustness of summary estimates and identify any individual studies significantly contributing to heterogeneity, notably when it exceeded 75%.

Egger's regression asymmetry test was utilized to examine evidence of small-study effects for primary efficacy outcomes [15], with a p-value below 0.05 indicating such effects. 'P-hacking' [16] and assessment of publication bias were conducted through funnel plots of primary outcomes.

In terms of ethical considerations and conflicts of interest, this umbrella review relies solely on previously published systematic reviews and meta-analyses, eliminating the necessity to gather or analyze primary data from human participants. Consequently, ethical review board approval and patient consent are not applicable to this study. The authors affirm that there are no conflicts of interest, whether financial or non-financial, that could influence the impartiality or interpretation of the findings in this umbrella review. The entire research process and outcomes remain independent of external affiliations or funding sources, ensuring a commitment to unbiased reporting.

Results

Study Selection

Initially, a total of 25 systematic reviews and meta-analyses were identified, and subsequent removal of duplicate entries was carried out. Upon thorough examination of the full texts, a final selection of 6 systematic reviews and meta-analyses [17-22] was made. These chosen studies collectively compiled data from 10 randomized controlled trials (RCTs). Among the 6 meta-analyses, 4 focused solely on pulmonary vein isolation (PVI) [18, 19, 21, 22] as the ablation strategy, while the remaining 2 [17, 20] examined PVI in combination with additional ablation strategies. Only one study [22] assessed rate control drugs as medical therapy, whereas the remaining 5 studies evaluated both rate and rhythm control drugs. Patients with both paroxysmal and persistent atrial fibrillation (AF) were investigated, with the exception of one study by Zhu et al. [22], which exclusively included patients with persistent AF. Table 1 provides a brief overview of the characteristics of the included meta-analyses.

Risk of Bias of Included Studies

The methodological quality evaluations of the six systematic reviews and meta-analyses were assessed using the AMSTAR 2 tool, as outlined in Supplementary Table S2. Each of these six studies received a moderate quality rating. The GRADE assessment, provided in Supplementary Table S3, demonstrated high levels of certainty in the reviews included in our study. Individual randomized controlled trials (RCTs) underwent a thorough quality assessment using the Cochrane risk of bias tool, revealing trials with a moderate to low risk of bias, as depicted in Supplementary Figure S1.

Primary Efficacy Outcomes

The primary efficacy outcomes included all-cause mortality, HF hospitalization, and AF recurrence.

- All-cause mortality:

Data on all-cause mortality was provided by 5 out of 6 studies. The pooled analysis indicated that CA treatment was associated with a significantly reduced risk of all-cause mortality compared to MT (RR [95% CI]: 0.55 [0.44, 0.68], I2: 60%, p-value: <0.00001), as illustrated in Figure 1.

- HF Hospitalization:

Information on HF hospitalization was available from 4 out of 6 studies. The pooled analysis showed that CA treatment was associated with a significant decrease in the risk of HF hospitalization compared to MT (RR [95% CI]: 0.61 [0.54, 0.70], I2: 0%, p-value: <0.00001), as depicted in Figure 2.

- AF recurrence rate:

Data on AF recurrence was reported by 2 out of 6 studies. The pooled analysis revealed a significant reduction in the risk of AF recurrence with CA treatment compared to MT (RR [95% CI]: 0.36 [0.27, 0.47], I2: 0%, p-value: <0.00001),as shown in Figure 3.

Secondary Efficacy Outcomes

The secondary efficacy outcomes included changes in LVEF, 6MWT, VO2 max, MLFHQ, and BNP. All six studies provided data on LVEF, 6MWT, and MLFHQ. The pooled analysis indicated that CA treatment was linked to a significant increase in LVEF and 6MWT and a significant decrease in MLFHQ compared to MT. However, due to significant in-study heterogeneity in 6MWT and MLFHQ, a sensitivity analysis was conducted. Excluding the study by Elgendy et al. [18] reduced the high in-study heterogeneity in both 6MWT and MLFHQ from 85% to 0%.

Three out of six studies reported data on VO2 max, showing a significant increase with CA treatment compared to MT. Two out of six studies reported BNP data, indicating a non-significant decrease with CA treatment compared to MT. Despite the high heterogeneity, a sensitivity analysis could not be performed as fewer than three studies reported the outcome.

Safety Outcomes

The safety outcomes included pericardial effusion/tamponade and MACEs. Only one meta-analysis by Magnocavallo et al. [17] reported data on safety outcomes. It indicated that CA was linked to a non-significant decrease in the risk of pericardial effusion/tamponade compared to MT. However, the same study revealed a non-significant increase in the risk of MACEs with CA compared to MT.

P-hacking, Publication Bias and small study effect

The absence of evidence suggesting P-hacking in our research indicates that the outcomes were not manipulated to fit a preconceived conclusion. Our analysis of primary efficacy outcomes was thorough, involving an ample number of studies, which allowed for a detailed examination through funnel plot analysis. The symmetry observed in the funnel plots for each primary outcome suggests the absence of publication bias, as illustrated in Supplementary Figure S2. Additionally, Egger's regression asymmetry test was employed to evaluate small study effects, with all values exceeding 0.05, indicating a lack of significant evidence supporting such effects. Details of Egger's regression asymmetry test results can be found in Table 3.

Discussion

Although MT is widely utilized in the management of AF, its efficacy has been limited in controlled trials. It is essential to note that significant adverse effects are also a possibility [22]. Considerable research efforts have demonstrated that the implementation of a rhythm control strategy for the management of atrial fibrillation may offer few benefits in comparison to rate control [23]. However, comprehensive subgroup analyses conducted during these trials have revealed that patients who attain sinus rhythm have higher survival rates, highlighting the inadequate effectiveness of MT in maintaining sinus rhythm [24]. CA with pulmonary vein isolation (PVI) is an innovative and increasingly popular approach for treating AF, providing an alternative to maintaining sinus rhythm. Some researchers have advocated for catheter ablation as the primary treatment option for AF [25]. However, the argument around this proposition still needs to be solved. Given the lack of solid data and the fact that catheter ablation is associated with a complication rate as high as 6%, according to a global survey, caution is exercised when prescribing it as the first treatment option [26].

Our umbrella review of 6 different meta-analysis aimed to compare and produce firm evidence on the safety and efficacy profile of CA with MT in patients with AF. Considering safety outcomes, CA has shown to decrease the risk of all-cause mortality, HF hospitalization and AF recurrence clinically significant over MT. Shantha et al. [27] conducted a study which revealed that the utilization of MT subsequent to catheter

ablation (CA) was associated with a reduced likelihood of all-cause mortality (hazard ratio [HR] = 0.62, p = 0.02) in an unadjusted propensity-matched analysis. After implementing comprehensive adjustment, while the statistical significance of the mortality difference between the two groups decreased, a noticeable pattern emerged that indicated a possible benefit in mortality from MT (HR: 0.66, p = 0.05). In 2019, Guo et al. [28] conducted a thorough investigation, which revealed a significant decline of approximately 38% ($p < 0.001$) in all-cause hospitalizations subsequent to AF ablation. The reduction in hospitalizations was characterized by a substantial decline in arrhythmic hospitalizations, with a notable 56% decrease in hospitalizations associated with atrial fibrillation and AF ($p < 0.001$). Furthermore, the effectiveness of AF ablation in reducing nonarrhythmic cardiovascular hospitalizations was predominantly demonstrated by a significant 43% reduction in HF hospitalizations (p = 0.019). AF ablation had no noticeable impact on hospitalizations relating to non-cardiovascular disease. Additionally, a significant reduction in the use of Class I and III AADs was observed in the year following ablation, falling from 64% to 40% ($p < 0.001$).

Considering other functional improvement, MT was shown to have more improvement in LVEF, 6MWT and VO2 max than CA group. Improvement in these parameters depend on severity and duration of the condition of patient as per observations. As an illustration, MacDonald et al. [29] observed reduced rates of success in conjunction with no improvements in exercise tolerance or LVEF. However, it is crucial to acknowledge that the individuals who were enrolled in this study had more advanced chronic heart failure (CHF), had a longer duration of AF, and had a lower functional status [approximately 90% of subjects were categorized as NYHA Functional Class III]. Moreover, the research carried out by Chang et al. [30] demonstrated that the CA group exhibited no observable improvement in comparison to the MT group. Prior meta-analyses hypothesized that CA could increase the 6MWT distance and VO2 max, two parameters that are considered independent predictors of survival in patients with heart failure (HF). Nevertheless, the inclusion of data obtained from the AMICA trial included by Chang et al. [30] in the analysis failed to reveal any noticeable discrepancy in the 6MWT distance.

Our study had some strengths as well as some limitations. In terms of strengths, our study exhibited minimal publication bias and heterogeneity due to the fact that all the studies incorporated in this umbrella review encompassed the entire patient population with AF and HF, thereby minimizing variations in patient baseline demographics. Secondly, this review produces new evidence-based results which vary from previous meta-analysis hence eliminating all discrepancies in previously published meta-analysis. Firstly, as with all comprehensive review articles, despite careful efforts to reduce confounding variables, there is the possibility of unmeasured covariates influencing treatment outcomes among AF patients with HF, such as socioeconomic status, healthcare accessibility, treatment adherence, and lifestyle factors. Second, the heterogeneity in the quality of evidence obtained from constituent studies may jeopardize the overall reliability of the umbrella review's conclusions. Disparities in research quality might result from differences in sample numbers, study durations, outcome assessments, and confounding variable control.

Conclusion

Patients with AF and HF who receive CA as opposed to MT experience improved functional outcomes and safety. Improvement in change in LVEF, 6MWT, and VO2 max, all-cause mortality, hospitalization for HF, and AF recurrence rates are substantially reduced in the CA group compared to the MT group. In order to ensure a comprehensive analysis, future research endeavors should encompass all participants who experience HF and AF simultaneously.

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Table 1: Characteristics of the included studies

Study authors	**Magnocavallo et al. [17]**
No. of studies included	9
Year of Publication	2022
Type of studies included	RCTs
Total No. of patients	2155
No. of patients in CA group	1077
No. of patients in MT group	1078
Type of ablation strategy	Pulmonary vein isolation (PVI), CFAE Ablation, Posterior Wall Isolation, SVC Isolati
Type of Medical therapy	Medical rhythm and rate control drugs (Amiodarone, class IA, IC, or III)
Follow-up duration (months)	12
Type of AF	Paroxysmal/Persistent
Primary outcomes	All-cause mortality and HF hospitalization
Secondary outcomes	CV death, AF recurrence rate, [?]LVEF, [?]MLHFQ, [?]VO2 max, [?]6MWT, and [?]BI

CA: Catheter ablation, MT: Medical therapy, RCTs: Randomized controlled trial, AF: Atrial fibrillation, NM: Not mentioned, CFAE: Complex fractionated atrial electrograms. SVC: Superior Vena Cava Isolation, HF: Heart failure, CV: Cardiovascular, [?]LVEF: Change in left ventricular ejection fraction, QOL: Quality of life, [?]MLHFQ: Change in Minnesota living with heart failure questionnaire, 6MWT: Change in Six-minute walk test, [?]VO2 max: Maximum rate of oxygen consumption, [?]BNP: Change in Brain natriuretic peptide.

Table 2: Secondary Efficacy Outcomes

Outcomes	**Effect measure (RR or MD)**	**95% CI**	**P value**	**I2**

Change in LVEF	MD: 4.35	3.11, 5.58	< 0.00001	17%
Change in 6MWT	MD: 15.88	2.86, 28.91	0.02	85%
Change in VO2 max	MD: 3.02	1.81, 4.20	< 0.00001	0%
Change in MLFHQ	MD: -6.73	-11.45, -2.01	0.005	85%
Change in BNP	MD: -3.48	-24.50, 17.53	0.75	88%

RR- Relative risk, MD- Mean difference, I2- Heterogeneity, LVEF: Left ventricular ejection fraction, MLHFQ: Minnesota living with heart failure questionnaire, 6MWT: Six-minute walk test,

VO2 max: Maximum rate of oxygen consumption, Brain natriuretic peptide.

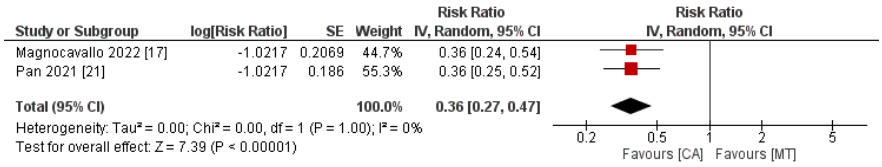


Figure 1: This is a caption

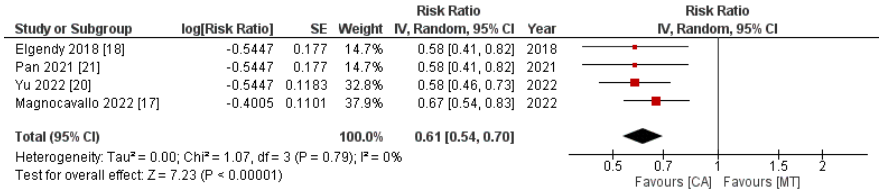


Figure 2: This is a caption

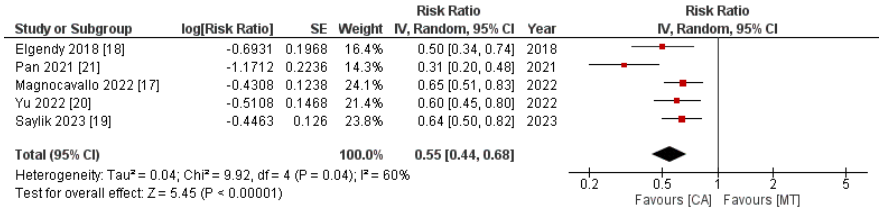


Figure 3: This is a caption

Supplementary Table S1: Search Strategy

Database	Search Strategy	Number of articles found
PubMed	("catheter ablation"[MeSH Terms] OR ("catheter"[All Fields] AND "ablation"[All Fields]) OR "catheter ablation"[All Fields] OR ("crit arts"[Journal] OR "ca cancer j clin"[Journal] OR "ca"[All Fields])) AND ((("medic"[All Fields] OR "medical"[All Fields] OR "medicalization"[MeSH Terms] OR "medicalization"[All Fields] OR "medicalizations"[All Fields] OR "medicalize"[All Fields] OR "medicalized"[All Fields] OR "medicalizes"[All Fields] OR "medicalizing"[All Fields] OR "medically"[All Fields] OR "medicals"[All Fields] OR "medicated"[All Fields] OR "medication s"[All Fields] OR "medics"[All Fields] OR "pharmaceutical preparations"[MeSH Terms] OR ("pharmaceutical"[All Fields] AND "preparations"[All Fields]) OR "pharmaceutical preparations"[All Fields] OR "medication"[All Fields] OR "medications"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapies"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "therapy s"[All Fields] OR "therapys"[All Fields])) OR ("methods"[MeSH Subheading] OR "methods"[All Fields] OR "mt"[All Fields]) OR (("j rehabil assist technol eng"[Journal] OR "rate"[All Fields]) AND ("controlling"[All Fields] OR "controllability"[All Fields] OR "controllable"[All Fields] OR "controllably"[All Fields] OR "controller"[All Fields] OR "controller s"[All Fields] OR "controllers"[All Fields] OR "controlling"[All Fields] OR "controls"[All Fields] OR "prevention and control"[MeSH Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "control"[All Fields] OR "control groups"[MeSH Terms] OR ("control"[All Fields] AND "groups"[All Fields]) OR "control groups"[All Fields]) AND ("agent"[All Fields] OR "agents"[All Fields])) OR ("rhythm"[All Fields] AND ("controlling"[All Fields] OR "controllability"[All Fields] OR "controllable"[All Fields] OR "controllably"[All Fields] OR "controller"[All Fields] OR "controller s"[All Fields] OR "controllers"[All Fields] OR "controlling"[All Fields] OR "controls"[All Fields] OR "prevention and control"[MeSH Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "control"[All Fields] OR "control groups"[MeSH Terms] OR ("control"[All Fields] AND "groups"[All Fields]) OR "control groups"[All Fields]) AND ("agent"[All Fields] OR "agents"[All Fields])) OR (("anti-arrhythmia agents"[Pharmacological Action] OR "anti-arrhythmia agents"[MeSH Terms] OR ("anti-arrhythmia"[All Fields] AND "agents"[All Fields]) OR "anti-arrhythmia agents"[All Fields] OR ("anti"[All Fields] AND "arrhythmic"[All Fields]) OR "anti-arrhythmic"[All Fields]) AND ("drug s"[All Fields] OR "pharmaceutical preparations"[MeSH Terms] OR ("pharmaceutical"[All Fields] AND "preparations"[All Fields]) OR "pharmaceutical preparations"[All Fields] OR "drugs"[All Fields]))) AND ("atrial fibrillation"[MeSH Terms] OR ("atrial"[All Fields] AND "fibrillation"[All Fields]) OR "atrial fibrillation"[All Fields] OR ("atrial fibrillation"[MeSH Terms] OR ("atrial"[All Fields] AND "fibrillation"[All Fields]) OR "atrial fibrillation"[All Fields] OR "AFib"[All Fields]) OR "AF"[All Fields]) AND ("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields] OR ("hepatol forum"[Journal] OR "hf"[All Fields]))	12
Cochrane library	(Catheter ablation OR CA) AND (Medical therapy OR MT OR rate control agents OR rhythm control agents OR anti-arrhythmic drugs) AND (atrial fibrillation OR AFib OR AF) AND (Heart failure OR HF)	10
Google scholar	(Catheter ablation OR CA) AND (Medical therapy OR MT OR rate control agents OR rhythm control agents OR anti-arrhythmic drugs) AND (atrial fibrillation OR AFib OR AF) AND (Heart failure OR HF)	2

Supplementary Table S2 - Assessing the Methodological Quality of Systematic Reviews – AMSTAR2

References	AMSTAR2 Items*																Overall Rating †
	1	2	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	
Magnocavallo, et al. (2022) [17]	No	Yes	Yes	PY	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	No	Yes	Moderate
Elgendy, et al. (2018) [18]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Moderate
Saylık, et al. (2023) [19]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	Moderate
Yu, et al. (2022) [20]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	Moderate
Pan, et al. (2021) [21]	No	Yes	Yes	PY	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	No	Yes	Moderate
Zhu, et al. (2016) [22]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	Moderate
Total Amount of Yes	4	6	3	4	6	6	4	6	6	1	6	0	4	6	3	3	

PY: Partial Yes.

*AMSTAR items:

1. Did the research questions and inclusion criteria for the review include the components of PICO/PECO?
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
3. Did the review authors explain their selection of the study designs for inclusion in the review?
4. Did the review authors use a comprehensive literature search strategy?
5. Did the review authors perform study selection in duplicate?
6. Did the review authors perform data extraction in duplicate?
7. Did the review authors provide a list of excluded studies and justify the exclusions?
8. Did the review authors describe the included studies in adequate detail?
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
10. Did the review authors report on the sources of funding for the studies included in the review?
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

†Rating overall confidence in the results of the review:

• High: No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.

• Moderate: More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.

• Low: One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.

• Critically low: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

*Multiple non-critical weaknesses may diminish confidence in the review, and it may be appropriate to move the overall appraisal down from moderate to low confidence.

Shea et al. 2017. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomized or non-randomized studies of healthcare interventions, or both

Supplementary Table S3: Grade Assessment of the Meta-analyses and Systematic Reviews Included

Author(s): Magnocavallo et al (2022) [17]

Question: CA compared to MT for AFib

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CA**	**MT**	**Relative (95% CI)**	**Absolute (95% CI)**		
All-cause mortality (follow-up: mean 12 months)												
9	randomized trials	not serious	not serious	not serious	not serious	none	1077	1078	**RR 0.65** (0.51 to 0.82)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ High	CRITICAL
Heart Failure Hospitalization (follow-up: mean 12 months)												
9	randomized trials	not serious	not serious	not serious	not serious	none	1077	1078	**RR 0.67** (0.54 to 0.82)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ High	CRITICAL
AFib recurrence (follow-up: mean 12 months)												
9	randomized trials	not serious	not serious	not serious	not serious	none	1077	1078	**RR 0.36** (0.24 to 0.54)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ High	CRITICAL

CI: confidence interval; **RR:** risk ratio

Author(s): Elgendy et al (2018) [18]

Question: CA compared to MT for AFib

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CA	MT	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow-up: mean 26 months)												
6	randomized trials	not serious	not serious	not serious	not serious	none	388	387	**RR 0.50** (0.34 to 0.74)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ High	CRITICAL
Heart Failure Hospitalization (follow-up: mean 26 months)												
6	randomized trials	not serious	not serious	not serious	not serious	none	388	387	**RR 0.58** (0.41 to 0.81)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ High	CRITICAL

CI: confidence interval; **RR:** risk ratio

Author(s): Saylık et al (2023) [19]

Question: CA compared to MT for AFib

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CA	MT	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow-up: mean 12 months)												
10	randomized trials	not serious	not serious	not serious	not serious	none			**RR 0.64** (0.50 to 0.82)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁⨁ High	CRITICAL

CI: confidence interval; **RR:** risk ratio

Author(s): Yu et al (2022) [20]

Question: CA compared to MT for AFib

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CA	MT	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow-up: mean 12 months)												
8	randomized trials	not serious	not serious	not serious	not serious	none	834	859	**RR 0.60** (0.45 to 0.80)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁⨁⨁ High	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CA	MT	Relative (95% CI)	Absolute (95% CI)		
Heart Failure Hospitalization (follow-up: mean 12 months)												
8	randomized trials	not serious	not serious	not serious	not serious	none	834	859	**RR 0.58** (0.46 to 0.73)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁⨁⨁ High	CRITICAL

CI: confidence interval; **RR:** risk ratio

Author(s): Pan et al (2021) [21]

Question: CA compared to MT for AFib

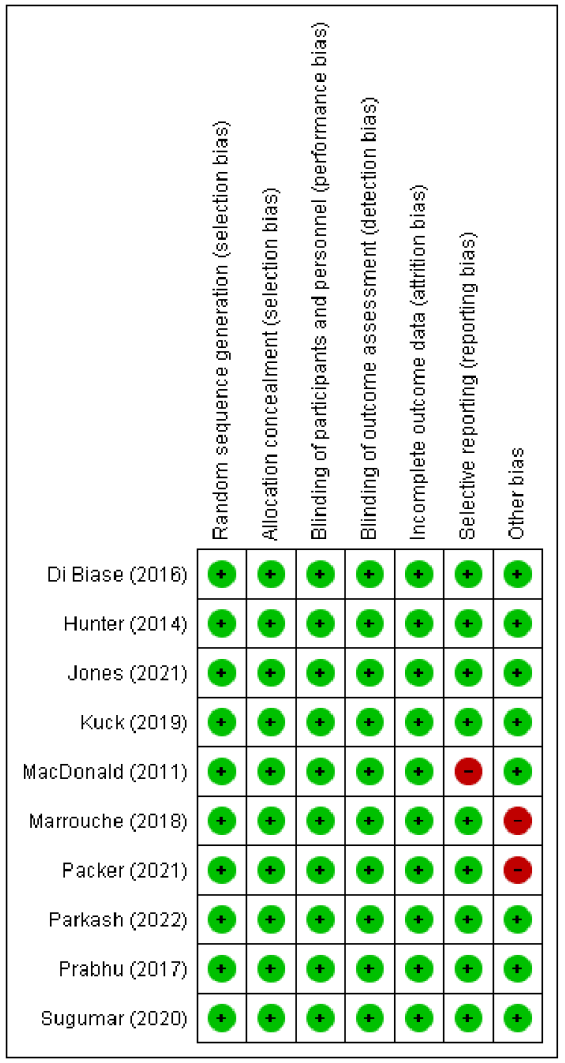
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CA	MT	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow-up: mean 16 months)												
6	randomized trials	not serious	not serious	not serious	not serious	none	388	387	**RR 0.31** (0.20 to 0.47)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁⨁⨁ High	CRITICAL

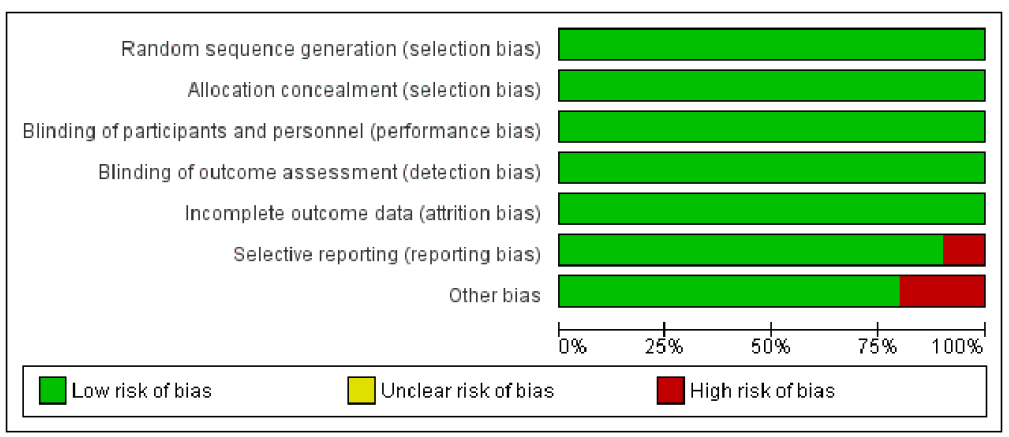
Heart Failure Hospitalizations (follow-up: mean 16 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CA	MT	Relative (95% CI)	Absolute (95% CI)		
6	randomized trials	not serious	not serious	not serious	not serious	none	388	387	**RR 0.56** (0.44 to 0.71)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁⨁⨁ High	CRITICAL
AFib recurrence (follow-up: mean 16 months)												
6	randomized trials	not serious	not serious	not serious	not serious	none	-/388	-/387	**RR 0.36** (0.25 to 0.53)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁⨁⨁ High	CRITICAL

CI: confidence interval; **RR:** risk ratio

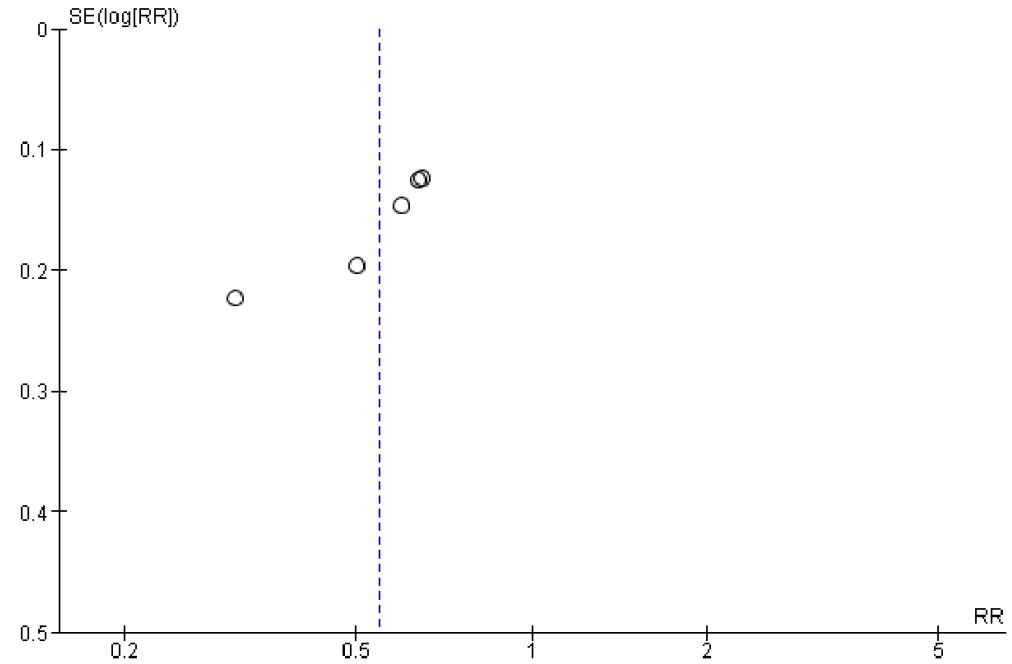
Supplementary Figure 1: Cochrane risk of bias assessment for individual Randomized controlled trials (RCTs)



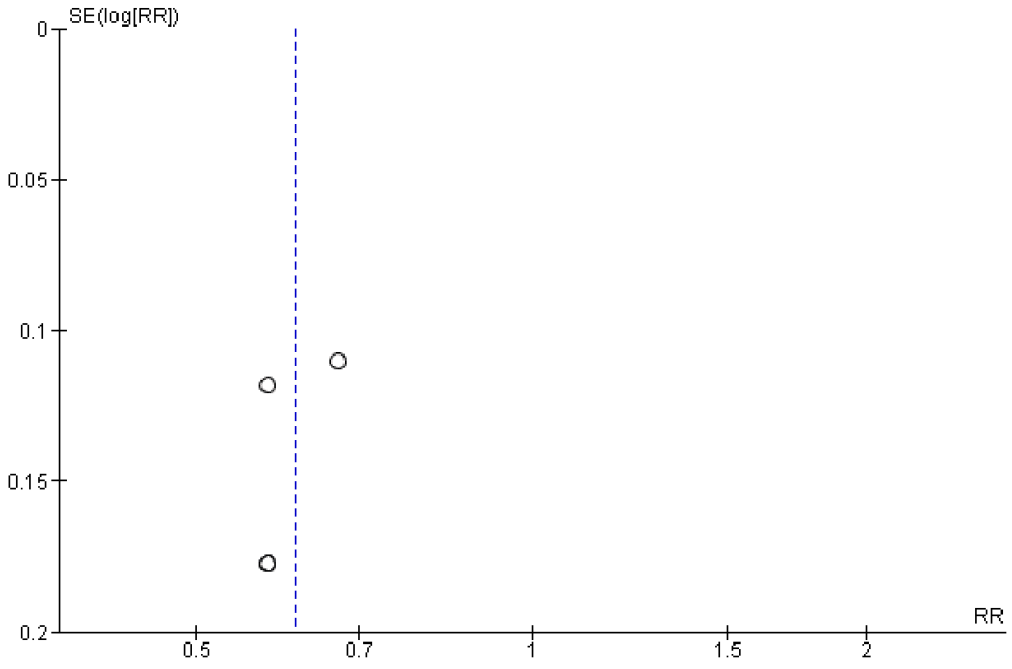


Supplementary Figure S2: Funnel plots of primary efficacy outcomes

A



B



A) All-cause mortality, B) Heart failure hospitalization. The funnel plots showed no risk of publication bias; Std Error: Standard Error