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# Catheter ablation versus medical therapy in atrial fibrillation: an umbrella review of meta-analyses of randomized clinical trials

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## Abstract

This umbrella review synthesizes data from 17 meta-analyses investigating the comparative outcomes of catheter ablation (CA) and medical treatment (MT) for atrial fibrillation (AF). Outcomes assessed were mortality, risk of hospitalization, AF recurrence, cardiovascular events, pulmonary vein stenosis, major bleeding, and changes in left ventricular ejection fraction (LVEF) and MLHFQ score. The findings indicate that CA significantly reduces overall mortality and cardiovascular hospitalization with high strength of evidence. The risk of AF recurrence was notably lower with CA, with moderate strength of evidence. Two associations reported an increased risk of pulmonary vein stenosis and major bleeding with CA, supported by high strength of evidence. Improved LVEF and a positive change in MLHFQ were also associated with CA. Among patients with AF and heart failure, CA appears superior to MT for reducing mortality, improving LVEF, and reducing cardiovascular rehospitalizations. In nonspecific populations, CA reduced mortality and improved LVEF but had higher complication rates. Our findings suggest that CA might offer significant benefits in managing AF, particularly in patients with heart failure. However, the risk of complications, including pulmonary vein stenosis and major bleeding, is notable. Further research in understudied populations may help refine these conclusions.

**Keywords** Atrial fibrillation, Catheter ablation, Medical treatment, Meta-analysis, Mortality, Cardiovascular hospitalization, Heart failure, Pulmonary vein stenosis, Left ventricular ejection fraction, Major bleeding

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## Introduction

Atrial fibrillation (AF) is a chronic and progressive medical condition associated with substantial morbidity, functional and quality of life (QoL) impairment, and increased mortality risk [1, 2]. ... When symptomatic, AF negatively impacts the quality of life (QoL) due to accompanying cardiac or noncardiac symptoms such as palpitations, shortness of breath, and extreme fatigue [3]. Furthermore, as the population ages, AF becomes more prevalent and poses increased risks of morbidity and mortality from AF-related complications, primarily stroke and congestive heart failure [4].

Since its introduction in 1998, catheter ablation (CA) has been an effective rhythm-control strategy for symptomatic AF patients [5, 6]. CA has made continuous progress, resulting in improved procedural success and complication rates [7]. However, AF management still relies heavily on medical treatment (MT) [8]. Medical treatment is limited in certain conditions due to lack of efficacy, proarrhythmic effects, limited use in patients with kidney or liver disease, and drug–drug interactions [8]. The effect of ablation on patients with heart failure has reduced cardiovascular rehospitalization and AF recurrence.

Several studies have compared the outcomes of CA vs. MT for AF. For example, the CABANA (Catheter Ablation vs. Antiarrhythmic Drug Therapy for Atrial Fibrillation) trial reported that CA did not significantly reduce the primary end point of death, disabling stroke, severe bleeding, or cardiac arrest compared with MT [9]. Several meta-analyses comparing CA vs. MT reported outcomes such as a reduction in all-cause mortality and hospitalizations, improvement in left ventricular ejection fraction (LVEF), and greater freedom from atrial arrhythmia and AF [10]. However, contrasting evidence on the effectiveness of CAs for these outcomes is available from meta-analyses, and the determination of the credibility of these findings remains to be assessed. Umbrella reviews provide a structured and critical summary of the evidence from several meta-analyses and enable the grading of evidence by evaluating the strength and precision of the associations and the presence of bias [11, 12].

In this umbrella review, we aimed to systematically identify relevant meta-analyses of RCTs, summarize their findings, and assess the evidence to provide a comprehensive picture of the outcomes of CAs vs. MT.

## Methods

The protocol for this study was registered with the Open Science Framework (OSF) (<https://osf.io/v436d>). This umbrella review was reported following the 2020 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines [13].

## Search strategy and eligibility criteria

We searched PubMed, EMBASE, Epistemonikos, and the Cochrane Database of Systematic Reviews (CDSR) from database inception to Feb 28, 2023. No language restriction was applied. Search results were imported to EndNote20, and duplicate references were removed. The library was then exported to Rayyan.ai for title and abstract screening. Each article was screened by the title and abstract by two randomly selected authors (P. G, A. S, W. M, P. K, M. D, M. A, M. K, Ai. T, J. G, A. R, N. N) to check for eligibility for the study. Randomization of authors and blinding was performed with Rayyan.ai. Any discrepancies were resolved by discussion with the third reviewer (S.S.).

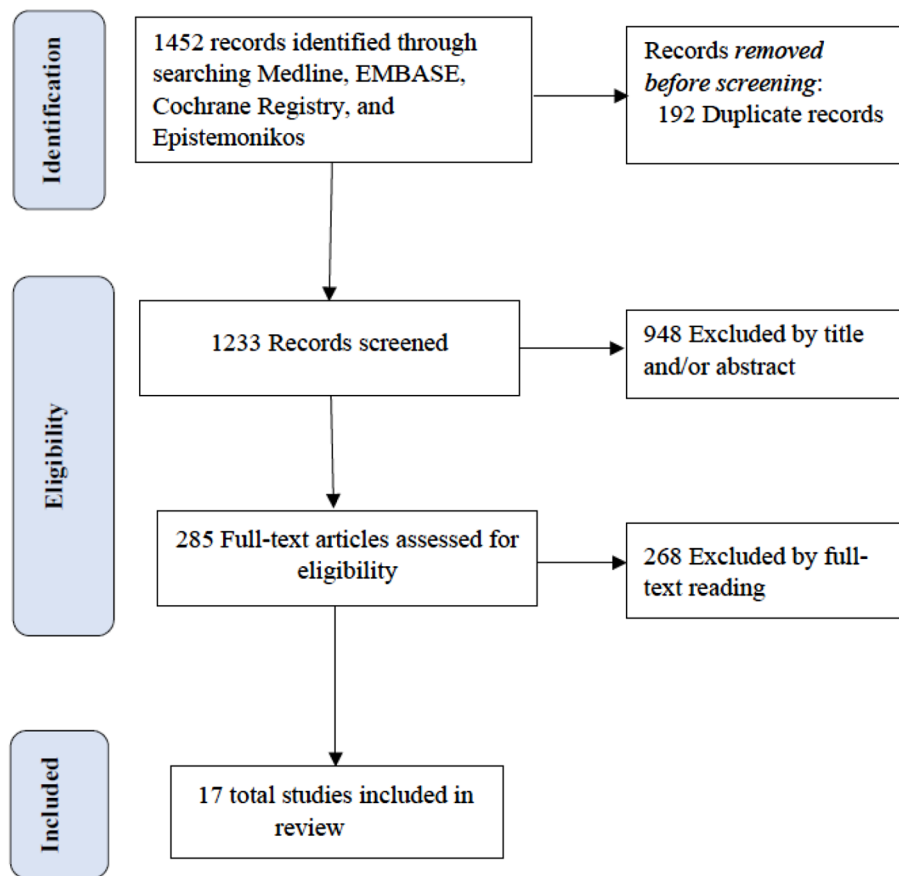
We included meta-analyses of RCTs investigating the outcomes of AF, comparing CA with MT. When more than one meta-analysis study was available for the same research question, we selected the meta-analysis with the most extensive data set, as previously described [14–16]. We excluded (i) meta-analyses of studies with other study designs (e.g., cohort, case–control studies); (ii) pooled analyses of a nonsystematic selection of observational studies and nonsystematic reviews; and (iii) meta-analyses that provided insufficient or inadequate data for quantitative synthesis. Subgroup categories of studies included (a) patients with heart failure (HF), (b) patients without HF, (c) patients with and without HF, and (d) patients with unspecified HF. The detailed PRISMA flow diagram is as shown in Fig. 1.

## Data extraction and quality assessment

Two reviewers (MS, AB) independently performed data extraction and quality assessment, which was checked by another two reviewers (SS, AT). Any existing discrepancies were resolved by consensus. The quality of meta-analyses was assessed using the AMSTAR-2-A Measurement Tool to Assess Systematic Reviews and graded as high, moderate, low, or critically low [17]. Sheets of the extracted data are available online on the Mendeley Data repository.

## Statistical analysis

We extracted effect sizes from individual studies that were categorized based on the population, intervention, comparator, and outcomes to generate the unique association in AF patients receiving CA vs. MT. For each association, effect sizes (mean difference [MD], standardized mean difference [SMD], and risk ratio [RR]) of individual studies were extracted. Then, the meta-analyses were reperformed to calculate the pooled effect sizes and 95% CIs using a random-effects model under the DerSimonian and Laird method [21]. The  $I^2$  statistic was utilized to assess heterogeneity [18]. Egger regression asymmetry was used to determine the evidence of small-study effects



**Fig. 1** PRISMA flow diagram

[19]. A P value of  $<0.10$  was taken as statistical evidence for the presence of small-study effects. An  $I^2$  value  $\geq 70\%$  was considered significant heterogeneity. Statistical analyses were conducted using Stata version 17.0 (StataCorp, College Station, TX, USA).

#### Assessment of the credibility of the evidence

We evaluated the quality of evidence per association provided in a meta-analysis of RCTs using the GRADE criteria (Grading of Recommendations, Assessment, Development, and Evaluations) framework to classify the evidence as high, moderate, low, and very low [20]. Five domains, including (1) risk of bias in the individual studies, (2) inconsistency, (3) indirectness, (4) imprecision, and (5) publication bias, were assessed using GRADEpro version 3.6.1 (McMaster University) to generate the credibility of the evidence.

## Results

### Cohort characteristics

We identified 1,452 studies, scrutinized 252 full-text articles, and ultimately included 17 meta-analyses in this umbrella review. Seventeen eligible studies [21–36] described 33 potential associations/meta-analyses,

including 33 individual meta-analyses of outcomes associated with CA. The descriptive characteristics of the included studies are provided in Supplementary Table 1. The median number of RCTs per meta-analysis was 8.5 (interquartile interval [IQI]: 6.75–11), with a median sample size of 2,496 (IQI: 1,038–3,714).

### Study associations and strength of evidence

A summary of all 33 associations is presented in Supplementary Table 1. Twenty-one of the 33 examined associations (63.6%) were statistically significant at  $p < 0.05$ . Seventeen associations (51.2%) had considerable heterogeneity.

The strength of evidence assessed using GRADE found that 30 had equivalent levels of support from high, moderate, and low strength of evidence (10 associations each, [30.3%]). In the rest of the comparison, three associations were supported by deficient levels of evidence (0.1%).

### Study outcomes

#### Mortality

Among the 21 statistically significant associations (Supplementary Table 1), two reported a decreased overall

mortality risk (RR, 0.55 to 0.72) with CA compared to MT. They were supported by a high strength of evidence.

#### **Risk of hospitalization**

Of the three associations that reported a significantly lowered risk of cardiovascular hospitalization, one association [30] was supported by high strength of evidence (RR, 0.37).

#### **Risk of AF recurrence**

One significant association reported a reduced risk of AF recurrence (RR, 0.46) with CA, backed by moderate strength of evidence.

#### **Risk of cardiovascular events and arrhythmias**

Two other associations of reduced risk of a cardiovascular event and recurring atrial arrhythmia were reported with moderate and low strength of evidence, respectively.

#### **Risk of pulmonary vein stenosis**

One significant associations reported an increased risk of pulmonary vein stenosis (RR, 2.34) with high strength of evidence with CA.

#### **Major bleeding**

One significant associations reported an increased risk of major bleeding (RR, 3.88) with high strength of evidence with CA.

#### **Change in LVEF and MLHFQ**

Two associations at moderate and low strength of evidence reported an improved LVEF (MD, 5.65–6.45), and one at high strength of evidence reported a positive change in the ‘Minnesota Living with heart failure questionnaire,’ (MLHFQ) (MD, 12.14) from CA. The summary of the outcomes is as shown in Fig. 2.

## **Discussion**

In this umbrella review, we summarize 33 studies with clinical outcomes in four broad atrial fibrillation (AF) patient categories: (a) patients with heart failure (HF), (b) patients without HF, (c) patients with and without HF, and (d) patients with unspecified HF. Our analysis helps broaden our understanding of the patient population with AF that would benefit the most from a CA.

The main findings of this study are as follows:

- 1) CA is superior to MT in reducing mortality in a patient population with HF (high certainty) and a population with and without HF (moderate certainty).
- 2) The improvement in LVEF was greater in the CA group than in the MT group in patients with HF

(very low certainty) and patients with unspecified HF (low certainty).

- 3) CA is better than MT in cardiovascular hospitalization rates in most groups, except for patients with unspecified HF. However, the supported evidence certainty is high only in the HF group.
- 4) The AF recurrence rate was better in all groups treated with CA with low certainty of evidence.

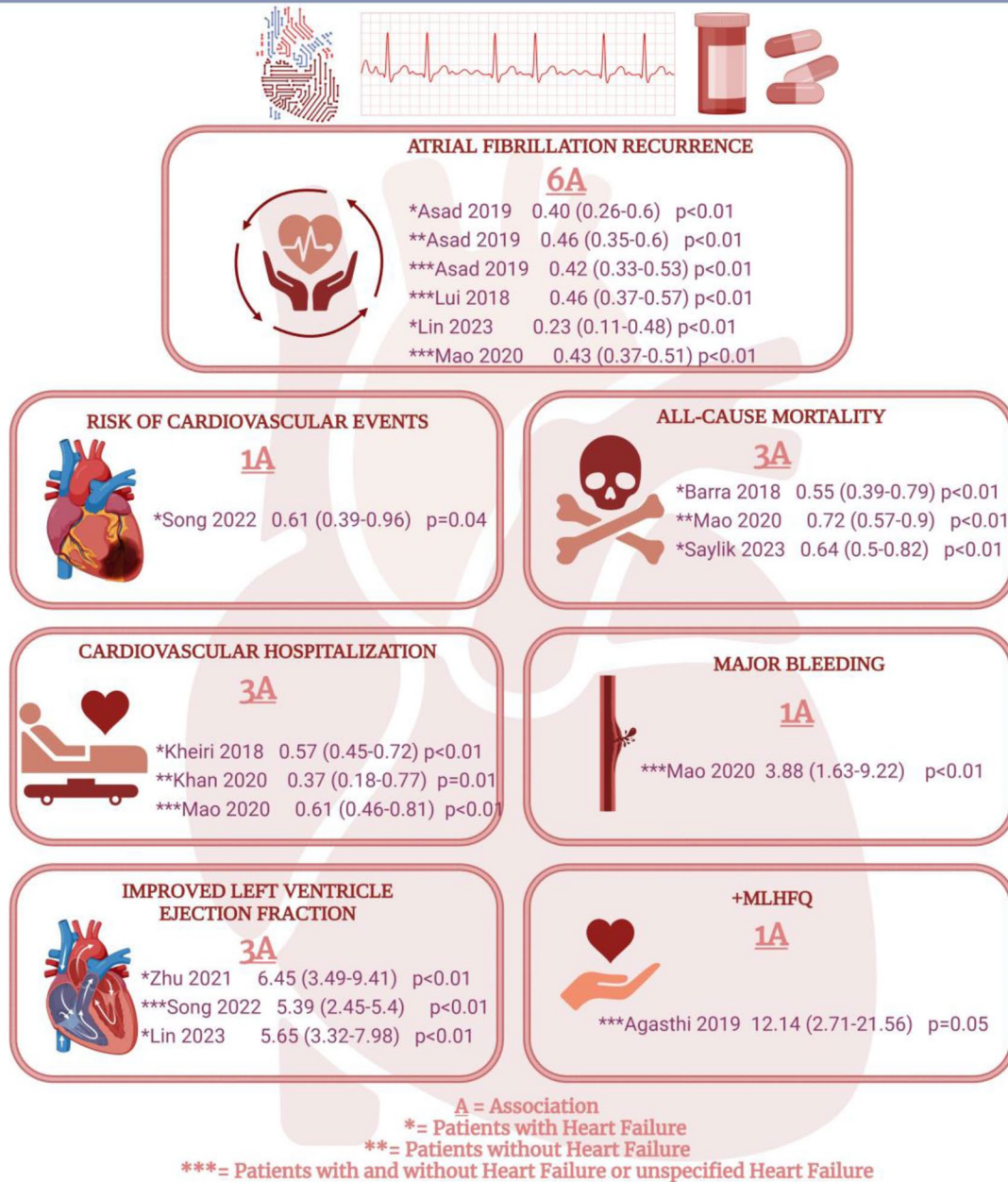
Complications, including major bleeding and pulmonary vein stenosis, are high in the CA arm in patients with and without HF supported with high certainty. The overall incidence of peri-ablation complications is low.

#### **All-cause mortality**

Our analysis shows that CA was superior to MT in mortality outcomes in two AF groups: (a) patients with HF, as studied by Barra et al. [30] and (b) patients with and without HF, as studied by Mao et al. [29]. The associated certainty of the evidence is high to moderate, and the quality of meta-analyses reporting these results is high. There was no heterogeneity found in the results from both meta-analyses. AF per se is associated with the risk of morbidity and mortality, but when it occurs in conjunction with HF, it is associated with increased mortality [37, 38].

Patients with heart failure with reduced ejection fraction (HFrEF) depend on atrial contraction to maintain sound cardiac output, and treating AF also reduces the incidence of tachycardia-mediated cardiomyopathy [39]. Multiple studies have demonstrated that ablation is superior to antiarrhythmics in maintaining sinus rhythm [40, 41]. This effect on improved left ventricular function is probably associated with the mortality benefit in the CA arm [42, 43]. Barra et al. reported on the AATAC and CASTLE AF trials [30]. One explanation for why Mao et al. failed to demonstrate mortality benefits in the CA group in patients without HF is due to low event rates [29]. It is estimated that more than 6000 patients need to be recruited in the non-HF arm [44]. The authors reported that the CA arm had mortality benefits in the group, including patients with and without HF. This finding was linked to the HF studies included in the analysis. A study by Zheng et al. showed improved all-cause mortality in the CA arm in patients with unspecified HF [28]. However, the results were not statistically significant ( $p=0.745$ ), and the quality of the meta-analysis on AMSTAR 2 was critically low. Multiple small studies with a shorter follow-up duration (<1 year) are a significant drawback of the Zheng et al. analysis. Data on mortality outcomes in patients with heart failure with preserved ejection fraction are limited to a few observational studies [45–51]. In a retrospective study by Hayrioglu MI et

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**Fig. 2** Central illustration visual representation of findings from the umbrella review

al. on octogenarians implanted with dual chamber permanent pacemakers, the presence of AF was found to be an independent risk factor for long-term mortality [52]. Our current analysis shows that CA is a successful strategy for improving hard endpoints such as mortality.

### Improvement in LVEF

Atrial fibrillation can lead to worsening of HF by the following mechanisms: a) AF-induced loss of atrial'systole' impairs the filling of the left ventricle (LV) during ventricular diastole, which causes the cardiac output to drop by up to 25%, and b) irregular and rapid ventricular conduction can cause tachycardia-induced cardiomyopathy. Restoration of sinus rhythm improves cardiac

function by increasing stroke volume and LV emptying even before the improvement of LV contractility [53]. The CAMERA-MRI study demonstrated that restoration of sinus rhythm in the CA arm causes improvement in left ventricular function, especially in the absence of ventricular fibrosis on cardiac MRI [54]. This highlights the importance of restoring sinus rhythm in improving LVEF. Zhu et al. reported improvement in LVEF in the CA arm compared to MT in patients with HF with very low certainty of evidence [27]. In a different meta-analysis, Song et al. reported similar findings in patients with unspecified HF with low certainty [26]. They also performed a trial sequel analysis of the LVEF outcome, improving precision. However, both studies reported that their outcomes have high heterogeneity. This difference could be explained by the different cardiac imaging modalities used in various studies and the observer-dependent variation associated with measuring LVEF [55].

#### All cardiovascular events and stroke

In the current umbrella review, Song et al. is the only study that shows a lower rate of cardiovascular events in the CA arm, seen in patients with HF. The strength of evidence is moderate and low quality on AMSTAR2 evaluation. This study included 11 studies analyzing stroke outcomes, which is a notable strength of this study. The CAPA trial is the only trial that has shown statistically significant stroke reduction [56]. The population included in this trial was younger, with a lower CHA<sub>2</sub>DS<sub>2</sub>-VASc score than that seen in the CABANA trial. Other meta-analyses failed to demonstrate statistically significant results regarding stroke events, as they needed more power [25, 29]. The CABANA trial, even though being the largest of the studies, failed to show positive outcomes for the following reasons: a) reduced 'true' estimate effect due to high rate of crossovers and withdrawals, affecting the results of intention to treat analysis and b) background anticoagulation causing a lesser number of strokes in both arms [9]. This UA demonstrates that CA is safe for preventing CV events; however, more robust evidence is warranted. Current guidelines recommend anticoagulation after ablation beyond two months based on the individual patient's risk profile, which is the CHA<sub>2</sub>-DS<sub>2</sub>-VASc score (Class IC-EO) [57]. The OCEAN trial is an ongoing study evaluating optimal antithrombotic treatment strategies for patients with stroke risk factors after successful ablation [58].

#### Change in MLHFQ and cardiovascular hospitalization

Our analysis shows that CA, compared to MT, showed the most significant improvement in the MLHFQ; however, there was high heterogeneity [23]. This effect is seen in patients with unspecified HF, and the quality of evidence, according to the GRADE system, is low.

Other studies by Zhu et al. (low certainty on GRADE) in patients with HF and Shi et al. (very low certainty on GRADE) in patients with and without HF, respectively, also showed improvement in MLHFQ, both studies with heterogeneity [24, 27]. Except for the ATTAC trial, all other studies included in the analyses were small and had a short follow-up duration.

Previous studies have shown that the time spent in sinus rhythm is associated with improved quality of life [59]. The results from the ATTAC trial also show that CA is superior to amiodarone in maintaining sinus rhythm and increased exercise tolerance in patients with AF and HFrEF [43]. Health care costs significantly influence quality of life (QOL). Multiple studies show that CA is cost-effective in the long term, even though it has a high upfront cost [60, 61]. However, there are some challenges with studying the actual effect of CA on QOL that are worth mentioning. Blinding quality assessment is very difficult, and additionally, there is a risk of bias due to the subjective nature of QOL assessment.

#### Cardiovascular hospitalization

The rate of cardiovascular (CV) hospitalization was lower in the CA arm than in the MT arm in three patient groups: (a) patients with HF, (b) patients without HF, and (c) patients with and without HF. All three results are statistically significant, with only Kheiri et al. showing no heterogeneity in their analysis. The certainty of the evidence is high in the HF group (Kheiri et al.) and low in the non-HF group as well as with and without the HF group (Khan et al., Mao et al.). Mao et al. is the only high-quality analysis on AMSTAR 2 grading. A retrospective cohort study of the nationwide readmissions database (NRD) by Arora et al. showed that at one year, CA reduced readmissions due to AF but did not reduce readmissions due to heart failure, irrespective of the type of HF [62]. However, given the study's observational nature and NRD being an administrative database, one should be cautious when interpreting these results.

#### Periprocedural complications

##### Major bleeding

In this analysis, major bleeding complications due to CA were reported to be high in the study by Mao et al. [29]. Zheng et al. noted a high rate of cardiac tamponade in CA vs. AADs, but the absolute incidence was 0.55%. A large meta-analysis by Gupta et al. that included >80,000 patients undergoing CA showed a low incidence of periprocedural complications. The complication rate has declined over the years, reflecting improved ablation technology and experience worldwide [63]. Real-world data from an extensive United States hospital database also show low complication rates [64]. These complications may be affected by the patient's comorbidities,

ablation strategy, experience of the operator, and adequacy of periprocedural anticoagulation. Our analysis showed that CA is a relatively safe procedure with a small risk of periprocedural complications.

#### **Pulmonary vein stenosis**

Mao et al. [29] reported higher rates of pulmonary vein stenosis associated with CA. Early ablative techniques, which targeted focal ablation directly within the venous ostia have demonstrated an increased incidence of pulmonary vein stenosis. Improved understanding of risk factors for pulmonary vein stenosis and adoption of newer ablation techniques like circumferential ablation and antral isolation have led to substantial reduction in pulmonary vein stenosis [65].

#### **AF recurrence**

Overall, studies on AF recurrence resulted in CA's superiority over MT. Asad et al. reported positive results in patients with HF, patients without HF, and patients with/without HF, all three outcomes with high heterogeneity [22]. The strength of evidence is low, and the quality of the meta-analysis is moderate. Lui et al. reported similar results in patients with unspecified HF, with low certainty of evidence [21]. Asad et al. showed that CA was superior to MT in paroxysmal and persistent AF.

Similarly, Lui et al. showed it as an effective first-line and second-line therapy strategy. Most clinical trials focused on AF recurrence as an outcome in a binary fashion. However, a more relevant parameter would be the assessment of the overall AF burden measured as percent time in AF, number of episodes, and duration of the most extended episode [66]. The ARREST-AF study is a trial that should show that aggressive risk factor reduction improves the long-term success of AF ablation [67]. This strategy could positively impact other AF outcomes and needs to be validated in larger RCTs. Pulmonary vein isolation (PVI) continues to remain the cornerstone of CA for AF treatment. Most of the times PVI is carried out empirically based on the hypothesis that the pulmonary veins are the source of ectopic trigger. However, AF can be triggered by many non-PV related sources, causing recurrence of AF after a successful PVI. Several ablation strategies in addition to pulmonary vein isolation (PVI) including left atrial posterior wall isolation, superior vena cava isolation, ligament of Marshall and coronary sinus ablation, ganglion plexus ablation and renal denervation have been tried in managing AF recurrence. The results from these strategies have been very heterogeneous and future studies are needed to determine the appropriate strategy to manage AF recurrence [68].

#### **Clinical implication and future direction**

Numerous prediction risk score models help determine an intervention's outcomes. For example, the ATLAS score is a clinical tool used to estimate the rate of AF recurrence after a CA procedure. Our umbrella review can help build a similar model that would help predict the patient population that would greatly benefit from CA. Future trials should focus on a patient population that is not well studied, for example, patients with HFpEF, females, and the elderly population. In the last decade, artificial intelligence (AI) has shown its effectiveness in AF management in various ways. AI-enabled electrocardiogram (ECG) algorithm was found to be effective in predicting the recurrence of paroxysmal AF following CA. The future of AI-guided AF management is promising, however currently the high-quality data required to develop AI systems is still limited [52].

#### **Strengths and limitations**

This umbrella analysis is the largest of its kind, studying 28 outcomes simultaneously associated with CA for atrial fibrillation. For each outcome, the meta-analysis that included the most significant number of studies was included in the review, thus providing adequate statistical power. Each association was qualitatively assessed on the GRADE scale for strength of evidence, and all the meta-analyses included in the current review were analyzed using AMSTAR2 to evaluate their quality.

Despite these advantages, there were some limitations in our present study. We did not appraise the quality of primary studies included in the meta-analyses. Some primary studies included in the meta-analyses were smaller with short follow-ups, and some were open-labeled, which can potentiate bias. Some notable methodological heterogeneity relates to the preliminary study's different ablation techniques, AF recurrence detection methods, single vs. multiple ablations, and anticoagulation protocols. A few patient-level factors, including the type of AF (paroxysmal vs. persistent AF), degree of HF, and patients' CHA<sub>2</sub>DS<sub>2</sub>-VASc, could affect clinical estimates but were not studied in this current UA.

#### **Conclusion**

This umbrella review suggests that in patients with AF and heart failure, CA is superior to MT for reducing mortality (with high certainty), improving LVEF (very low certainty), and reducing cardiovascular rehospitalizations (high certainty). In a nonspecific population study comprising patients known to be with and without heart failure, CA is seen to be superior to MT for reducing mortality (with moderate certainty), improving LVEF (low certainty), and increasing complication rates such as pulmonary vein stenosis and major bleeding events (high certainty). In studies with populations with an unknown

history of heart failure, overall, CA was a safe procedure with a small risk of periprocedural complications.

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12872-023-03670-5>.

**Supplementary Material 1:** Summary of studies

**Supplementary Material 2:** AMSTAR 2: Critical appraisal tool for systematic reviews that includes randomized or non-randomized studies of healthcare interventions, or both

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None.

## Author contributions

A.T and S.S: Conceptualization, Methodology, Project administration, Writing - Review & Editing, Data curation, Resources, Formal Analysis, Validation, Investigation; A.B: Methodology, Data Curation, Project administration, Validation; K.B: Investigation, Data Curation, Validation; P.G: Data Curation, Validation; M.S: Data Curation, Validation, Resources, A.M.S: Data Curation, Validation, Writing - Review & Editing; W.A.M: Data Curation, Validation; P.A.K: Visualization, Data Curation; M.D: Writing - Original Draft, Data Curation, Validation; M.A.A: Data Curation, Validation; M.O.K: Data Curation, Validation; Ai.T: Writing - Review & Editing, Data Curation, Validation; J.G: Writing - Original Draft, Data Curation, Validation; D.A: Data Curation, Validation; A.R: Data Curation, Validation, Writing - Review & Editing; N.N: Data Curation, Validation; A.H: Data Curation, Validation, Resources; Y.S: Validation, Supervision; B.N: Writing - Review & Editing; N.M: Writing - Review & Editing; C.V.D: Writing - Review & Editing; A.D: Writing - Review & Editing; S.G: Writing - Review & Editing, Validation; K.N: Writing - Review & Editing, Validation; S.D: Writing - Review & Editing, Validation. All authors reviewed the manuscript.

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## Data availability

The datasets used/analysed during the current study are available from the corresponding author on reasonable request.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

### Disclosure

None.

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