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Catheter Ablation Versus Medical Therapy in Persistent Atrial Fibrillation Across the Spectrum from Pre–Heart Failure to Symptomatic Heart Failure: A Systematic Review and Meta-Analysis

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Abstract

Background

Catheter ablation is increasingly used for rhythm control in atrial fibrillation (AF) with heart failure (HF), but its effects on ventricular function, functional status, and clinical outcomes remain incompletely defined for non-paroxysmal AF specifically. We aimed to quantify the effects of catheter ablation versus medical therapy in patients with persistent or long-standing persistent AF and concomitant HF. We searched PubMed, Scopus, ScienceDirect, EBSCO, and the Cochrane Library through May 2026 for randomised controlled trials and peer-reviewed subgroup analyses enrolling adults with non-paroxysmal AF and HF at least Stage B ACC/AHA. Outcomes were pooled as mean differences (MDs) or risk ratios (RRs) using random-effects meta-analysis. Risk of bias was assessed with RoB 2 and certainty of evidence with GRADE.

Results

Ten randomised controlled trials and two extended follow-up studies, comprising 2853 participants, were included. Catheter ablation improved left ventricular ejection fraction (MD 6.28%, 95% CI 2.45 to 10.11), disease-specific quality of life (MD -6.97), and New York Heart Association functional class (MD -0.70), increased freedom from AF (RR 1.84), and reduced unplanned rehospitalisation (RR 0.54). All-cause mortality did not differ significantly in the primary analysis (RR 0.72; P = 0.13) but showed a directional reduction approaching significance on long-term follow-up (P = 0.05). Six-minute walk distance and stroke or transient ischaemic attack did not differ between groups. An exploratory subgroup analysis suggested that the magnitude of structural benefit may vary by medical comparator strategy.

Conclusions

In persistent and long-standing persistent AF spanning pre-heart failure to symptomatic HF, catheter ablation improves ventricular function, quality of life, functional class, and arrhythmia-free survival, and reduces rehospitalisation, with a directional but not definitive reduction in long-term mortality. These findings support catheter ablation as a disease-modifying rather than purely symptomatic strategy in this population.

Background

Persistent atrial fibrillation (AF) is a progressive arrhythmia associated with adverse atrial and ventricular remodeling, impaired cardiac performance, and reduced functional capacity.[1, 2] Although conventional medical therapy—including rate and rhythm control drugs—has long been the cornerstone of AF management, randomized trials have demonstrated that pharmacological strategies often fail to achieve durable rhythm control and provide limited improvement in structural and functional outcomes.[1, 3] Moreover, antiarrhythmic drugs are frequently associated with proarrhythmic risks, extracardiac toxicities, and negative inotropic effects, further limiting their long-term clinical utility. [4]

Catheter ablation has emerged as a superior rhythm-control strategy.[5, 6] It has been demonstrated that ablation is associated with significant improvements in left ventricular ejection fraction (LVEF), exercise capacity as measured by the 6-minute walk distance (6MWD), and patient-reported QoL outcomes, particularly in AF patients with heart failure.[7, 8] However, most existing trial and meta-analysis combine heterogeneous AF populations, frequently mixing paroxysmal and persistent AF, despite their distinct pathophysiology, remodeling burden, and response to therapy.[2] Many studies prioritize arrhythmia recurrence as the primary endpoint, while underrepresenting patient-centered and functional outcomes such as LVEF recovery, 6MWD, New York Heart Association (NYHA) functional classification, and QoL—measures that are directly relevant to daily functioning and long-term prognosis. Although multiple meta-analyses have evaluated catheter ablation in AF with HF—indeed, the volume of such analyses has prompted formal concern regarding redundancy in this field—no synthesis to date has restricted inclusion exclusively to randomized evidence enrolling non-paroxysmal (persistent and long-standing persistent) AF with concomitant HF, nor incorporated the most recent trials employing contemporary ablation technologies.[9]

Therefore, this meta-analysis is needed to provide a focused and updated synthesis of the evidence comparing catheter ablation versus medical therapy (rate and/or rhythm control drugs) in patients with persistent AF and across HF spectrum with an emphasis on clinically meaningful outcomes including LVEF, 6MWD, NYHA and QoL. By integrating contemporary trials and addressing these critical gaps, this study aims to clarify the true functional and structural benefits of ablation in persistent AF, thereby informing clinical decision-making and guideline development.

The persistence of this uncertainty is reflected in contemporary guidance. The 2026 ESC Guidelines for the management of heart failure explicitly identify the selection of patients with reduced and preserved ejection fraction who may benefit from AF ablation as an outstanding gap in evidence, alongside the need for adequately powered randomised trials defining the best strategy for AF management in HF, better characterisation of patients with arrhythmia-associated HF, and randomised trials of management options for patients with AF-associated HF. [10] The present systematic review and meta-analysis addresses this gap directly by restricting inclusion to a phenotypically defined population, non-paroxysmal AF with concomitant HF, and by quantifying the structural, functional, and clinical consequences of catheter ablation relative to medical therapy across the spectrum from pre-heart failure to symptomatic heart failure.

Methods

Protocol and Registration

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD420251134536). Several refinements to the analysis plan were made post-registration: (i) a subgroup analysis by medical comparator strategy was conducted to explore the substantial heterogeneity observed in the primary outcome analysis; (ii) sensitivity analyses, including leave-one-out analysis for the primary outcome, were conducted to assess robustness of pooled estimates; (iii) a separate pooled analysis of extended observational follow-up data (Sugumar et al. 2020 for CAMERA-MRI[11]; Zakeri et al. 2023 for CAMTAF and ARC-HF[12]), conducted to assess the durability of LVEF improvement on longer-term follow-up. This long-term analysis was conducted separately from, rather than added to, the primary analysis; (iv) a subgroup analysis of unplanned rehospitalization by baseline heart failure phenotype (HFrEF versus non-HFrEF baseline) was added to explore effect modification across the heart failure spectrum represented in the included trials.

Eligibility Criteria

We included randomized controlled trials and peer-reviewed standalone subgroup analyses derived from such trials that enrolled adults (≥ 18 years) with non-paroxysmal atrial fibrillation (persistent or long-standing persistent AF) and concomitant heart failure (defined as at least classified as Stage B according ACC/AHA Guidelines)[13], as an enrolment criterion, comparing catheter ablation (pulmonary vein isolation with or without additional substrate modification) with medical therapy (rate control, pharmacological rhythm control, or both). Stage B ACC/AHA was adopted as the inclusion threshold to capture the continuum of AF-associated structural and functional remodeling, recognizing that ventricular dysfunction in non-paroxysmal AF frequently precedes overt HF symptoms and that symptom attribution is unreliable when AF and HF coexist. The implications of this inclusive definition for the pooled estimates are addressed in the Discussion. Trials enrolling mixed paroxysmal and non-paroxysmal AF as a single cohort were excluded; however, dedicated peer-reviewed subgroup analyses isolating non-paroxysmal AF cohorts were eligible, on which basis the CABANA[14] persistent and long-standing persistent subgroup analyses were included. CASTLE-AF[24] was excluded because it enrolled both paroxysmal and non-paroxysmal AF as a single cohort, with no peer-reviewed standalone non-paroxysmal subgroup analysis available. Studies reporting only acute procedural outcomes, lacking extractable data, or available only as conference abstracts were excluded.

Search Strategy and Study Selection

We systematically searched PubMed (MEDLINE), Scopus, ScienceDirect, EBSCO, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to May 2026. Search terms combined controlled vocabulary (MeSH and Emtree) and free-text terms for atrial fibrillation, catheter ablation, pulmonary vein isolation, heart failure, randomized controlled trial, and related synonyms, combined using Boolean operators. The full search strategy for each database is provided in Additional file 1: Table S1. Reference lists of included articles, prior systematic reviews, and relevant guideline documents were hand-searched for additional eligible studies. ClinicalTrials.gov and the EU Clinical Trials Register were searched for completed but unpublished trials in the persistent AF population. No language restrictions were applied.

Records identified through database searching were imported into Mendeley reference manager (Mendeley Ltd., London, UK) for de-duplication, and subsequently transferred to Rayyan (Rayyan Systems Inc., Cambridge, MA, USA) for screening. Two reviewers (DPA and MFA) independently screened titles and abstracts against eligibility criteria. Full texts of potentially eligible studies were retrieved and independently assessed by the same reviewers. Disagreements were resolved by discussion or by adjudication from a third reviewer (MRF).

Data Extraction

Two reviewers (DPA and MRF) independently extracted data using a pre-piloted standardized extraction form, with MFA serving as adjudicator for disagreements. Extracted variables included: study identifiers (first author, year, trial name, country, registration number); design characteristics (randomization method, blinding, follow-up duration); participant characteristics (sample size per arm, age, sex, baseline LVEF, NYHA class, AF duration, AF type); intervention details (ablation technique, energy source, additional lesion sets); comparator definition (rate control, pharmacological rhythm control, or both); and outcome data (means, standard deviations, event counts, or hazard ratios as reported). Where standard deviations were not reported, they were derived from confidence intervals or standard errors using methods described in the Cochrane Handbook for Systematic Reviews of Interventions, version 6.4. For Song et al.[14], standard deviations for change in LVEF were back-calculated from reported confidence intervals using the Cochrane Review Manager calculator. For trials reporting outcomes at multiple timepoints or providing data only in Kaplan-Meier curves, time-specific event counts were extracted to maintain methodological consistency across the included trials. CAPA and CABANA non paroxsymal AF subgroup reported atrial fibrillation recurrence and primary endpoint events in Kaplan-Meier survival curves spanning 60 months of follow-up.[15, 16] To align with the typical reporting timeframe of comparator trials (12–24 months), event counts at the 24-month timepoint were extracted using WebPlotDigitizer (version 5) by two reviewers independently, with subsequent consensus verification. For outcomes without intermediate timepoint analysis available, end-of-follow-up data were used.

Statistical Analysis

Continuous outcomes were pooled as mean differences (MDs) and dichotomous outcomes as risk ratios (RRs), each with 95% confidence intervals, using a DerSimonian–Laird random-effects model with inverse-variance weighting; statistical heterogeneity was quantified using the I^2 statistic. NYHA functional class was analyzed as a continuous variable using mean differences, consistent with prior heart failure meta-analyses, while acknowledging the ordinal nature of the scale. Given the substantial heterogeneity (I^2=88%) observed in the primary LVEF analysis, a subgroup analysis was conducted to investigate effect modification by medical comparator strategy (rate control alone vs. comparators including pharmacological rhythm control), with subgroup interaction

assessed using the chi-square test for subgroup differences. Sensitivity analyses included leave-one-out analysis for the primary outcome to assess robustness of pooled estimates. Formal quantitative assessment of publication bias by funnel plot or Egger's test was not performed because fewer than ten studies contributed to each outcome, in line with Cochrane Handbook recommendations; we instead verified prospective registration for all included randomized trials and reviewed major trial registries for completed but unpublished trials. All analyses were conducted in Review Manager (RevMan, version 5.4; The Cochrane Collaboration, Copenhagen, Denmark), with two-sided $P < 0.05$ considered statistically significant.

Clinical Outcomes

The primary outcome was the change in LVEF from baseline to study end. Secondary outcomes were: 6MWD; disease-specific quality of life as measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ); NYHA functional class; freedom from atrial fibrillation (defined per each trial's protocol, generally as freedom from any sustained atrial arrhythmia exceeding 30 seconds beyond the post-procedural blanking period); unplanned rehospitalization (defined per each trial's protocol, generally defined as unscheduled admission for heart failure worsening or arrhythmia recurrence, as reported in the source trials); and stroke or transient ischemic attack. We acknowledge that the unplanned rehospitalization outcome incorporated heterogeneous event definitions across trials: some trials reported composite heart failure or arrhythmia events (notably AATAC[17]), while others reported new-onset heart failure (CAPA[15], AVANT GUARD[18]). This conceptual heterogeneity is addressed in the Discussion. All-cause mortality was analyzed using two complementary approaches stratified by observation period to capture both primary and durable mortality effects. The primary all-cause mortality analysis included mortality events from six randomized trials with primary follow-up of two years or less (with the CABANA non-paroxysmal subgroup[16] presented as two strata reflecting the original publication's reporting), excluding CAPA[15] whose 54-month follow-up was analyzed within the long-term analysis given its extended observation period **(Additional file 2: Figure S9).** The long-term all-cause mortality analysis incorporated data from trials and follow-up studies with observation periods exceeding two years post-randomization (Sugumar 2020 CAMERA-MRI[11], Zakeri 2023 CAMTAF and ARC-HF[12], CABANA non-paroxysmal subgroup[16], and CAPA study[15] **(Additional File 2: Figure S10).**

Risk of Bias and Certainty of Evidence

Risk of bias was assessed independently by two reviewers (CP and AJ) using the Cochrane Risk of Bias 2.0 (RoB 2) tool across the five pre-specified domains, with disagreements resolved by adjudication from a third reviewer (RF). Per-trial judgments across each domain are presented in **Additional file 2: Figure S5** (traffic light plot). All randomized trials carried at least some concerns for risk of bias attributable to the open-label design that is inherent to procedural intervention trials, in which blinding of patients and operators is not feasible. Across the randomization domain, all but Wu et al. CAPA were judged at low risk, reflecting adequately described random sequence generation and allocation concealment in the published protocols. For deviations from intended interventions, five trials (Prabhu CAMERA-MRI[19], AMICA[20], Sugumar 2020[11], CAPA[15], and CABANA non-paroxysmal subgroup[16]) were judged at high risk, reflecting documented or substantial protocol deviations including crossover from medical therapy to ablation and per-protocol analyses that may have introduced post-randomization bias. The remaining trials carried some concerns on this domain, consistent with the open-label design and varying degrees of intervention adherence. Missing outcome data and measurement of outcome were generally judged at low risk across most trials, with some concerns identified in Zakeri et al,[12] and Song et al,[14] due to the observational follow-up nature and reporting characteristics. Selection of the reported result was judged at low risk for all trials, as primary outcomes and analysis plans were prospectively registered.

Overall, AATAC[17] was judged at low risk of bias, while five trials (Prabhu 2017 CAMERA-MRI[19], AMICA[20], Sugumar 2020 CAMERA-MRI[11], CAPA[15], and CABANA non paroxsymal subgroup[16] were judged at high risk primarily driven by deviations from intended interventions; the remainder were judged with some concerns. This open-label design and the variable risk of bias contributed to the systematic downgrading of GRADE certainty by one level for all outcomes. Summary of findings tables were generated using GRADEpro GDT (McMaster University, Ontario, Canada).

Results

Study Characteristics

Through a systematic search of PubMed, Scopus, ScienceDirect, Cochrane, and EBSCO, a total of 4416 records were identified. After duplicate removal, the titles and abstracts of 1055 studies were screened based on inclusion and exclusion criteria. Sixty-six studies are eligible for full-text assessment. Ten original RCTs and two follow-up studies met the inclusion criteria and were included in this review (Fig. 1)

A total of 2853 participants from 10 original studies were randomized into the CA group and the MT group, with 1492 and 1361 participants, respectively. The study population was characterized by a mean age of 65.4 years and a significant male predominance of 71.6%. Baseline clinical metrics across the trials showed a mean left atrial diameter (LaD) of 46.6 mm, a mean LVEF of 44%, and a mean 6MWD of 423.9 meters. While the primary follow-up duration for the trials ranged from 6 to 24 months, long-term observational data extended to a median of up to 3.2 years. Outcome reporting was extensive: Primary all-cause mortality data were extracted from 6 trial studies (with CABANA non-paroxysmal subgroup presented as two strata), and long-term mortality from 4 trial studies ; 8 studies reported on LVEF improvement, stroke or TIA, and heart failure rehospitalization; 6 studies reported on freedom from atrial fibrillation; 4 studies on 6-minute walk distance changes; and 5 studies specifically utilized the Minnesota Living with Heart Failure Questionnaire to assess quality of life. The trials included participants with both ischemic and non-ischemic etiologies, with one trial including only patients with ischemic etiology. Only 1 trial conducted pulsed field ablation (AVANT GUARD)[18], other studies conducted radiofrequency ablation (RFA) with pulmonary vein isolation (PVI) as the main ablation procedure (Table 1).[11, 12, 14–23]

Table 1
Baseline Characteristic

Study Name/ID	Intervention group	Control group	Type of AF	Total participant (CA/MT)	Male, *n* (%)	Age, y (CA/MT)	Total follow-up (mo)	Baseline LVEF (CA/MT)	Baseline LAD (CA/MT)	Baseline 6MWD (CA/MT)	Baselin MLHFQ (CA/MT
CAMERA-MRI Late Study	Catheter ablation	Rate control	Persistent	33/33	60 (90.9)	60.5 ± 10.7/ 58.8 ± 11.8	12	36.1 ± 9.7/ 34.6 ± 9.1	48 ± 5.5/ 47 ± 8.2	NR	NR
ARC-HF and CAMTAF	Catheter ablation	Rate control	Persistent & Long-standing persistent	52/50	93 (91.2)	60 ± 51.71/ 63 ± 55.67	N/A	29.9[23.5–33.5]/ 31.9[24.0-43.1]	51[44–54]/ 47[42–53]	NR	35[22–58]/ 49[32–64]
CABANA Secondary Analysis	Catheter ablation	Rate or rhythm control	Persistent & Long-standing persistent	638/619	845 (67.2)	68[62–72]/ 67 [62–72]	60	NR	NR	NR	NR
NCT05827172	Radio-frequency catheter ablation	Rate control	Persistent	45/44	60 (67.4)	69.5 ± 3.8/ 69.5 ± 4.1	12	36.1 ± 2.7/ 36.5 ± 2.1	47.1 ± 4.8/ 46.6 ± 4.6	482.5 ± 84.9/ 493.5 ± 94.4	NR
CAPA	Catheter ablation	Rhythm control and/or rate control	Persistent & Long-standing persistent	327/321	421 (64.9)	64.8 ± 12.6/ 64.4 ± 13.6	60	53.3 ± 9.3/ 51.9 ± 9.4	45 ± 8.5/ 46 ± 7.8	443 ± 109/ 431 ± 97	NR
NCT00292162	Radio-frequency catheter ablation	Rate control	Persistent	20/18	32 (84.2)	62.7 ± 6.7/ 64.4 ± 8.3	6	36.1 ± 11.9/ 42.9 ± 9.6	NR	317.5 ± 125.8/ 351.8 ± 117.1	55.8 ± 19.8/ 59.2 ± 22.4
ARC-HF	Catheter ablation	Rate control	Persistent	26/26	45 (86.5)	64 ± 10/ 62 ± 9	12	22 ± 8 / 25 ± 7	46 ± 7 / 50 ± 6	416 ± 78/ 411 ± 109	42 ± 23, 49 ± 21
CAMTAF	Catheter ablation	Rate control	Persistent & Long-standing persistent	26/24	48 (96)	55 ± 12/ 60 ± 10	12	31.8 ± 7.7/ 33.7 ± 12.1	52 ± 11/ 50 ± 10	NR	NR
AATAC	Catheter ablation	Amiodarone	Persistent	102/101	151 (74.3)	62 ± 10/ 60 ± 11	24	NR	47 ± 4.2/ 48 ± 4.9	NR	NR
CAMERA-MRI	Catheter ablation	Rate control	Persistent & Long-standing persistent	33/33	60 (90.9)	59 ± 11/ 62 ± 9.4	6	32 ± 9.4 / 34 ± 7.8	48 ± 5.5/ 47 ± 8.2	491 ± 147/ 489 ± 132	*Invalid-using SF-36*
AMICA	Catheter ablation	Rate or rhythm control	Persistent & Long-standing persistent	68/72	126 (90)	65 ± 8/ 65 ± 8	12	27.8 ± 9.5/ 24.8 ± 8.8	50 ± 6 / 51 ± 5	NR	NR
AVANT-GUARD	Pulse Field Catheter Ablation	Rhythm Control	Persistent	207/102	142 (69)	68.1 ± 8.5 / 67.4 ± 8.7	12	56.3 ± 7.4 / 56.3 ± 7.4	43 ± 6 / 43 ± 6	NR	NR

Primary Outcome: Left Ventricular Ejection Fraction

Catheter ablation produced a significant improvement in LVEF compared with medical therapy. Pooling seven randomized trials (n = 636), the mean difference was 6.28% (95% CI 2.45–10.11; P = 0.001) in favor of ablation, with substantial between-study heterogeneity (I^2=88%, Tau^2=21.60; Chi^2=48.50, P < 0.00001) (Fig. 2).

Sensitivity Analyses for the Primary Outcome

Leave-one-out analysis confirmed that no single trial drove the pooled LVEF effect: sequential exclusion of each contributing trial yielded mean differences ranging from 4.95% to 7.20%, with all P-values < 0.01 and the pooled estimate remaining statistically significant in every iteration (**Additional file 1: Table S2**).A separate pooled analysis of extended observational follow-up data from Sugumar CAMERA-MRI[11] and Zakeri et al. (CAMTAF and ARC-HF)[12] yielded a long-term pooled estimate of 8.38% (95% CI 3.61–13.15; P = 0.0006; I^2=0%), consistent with persistence of the LVEF improvement over longer observation periods, although these extended cohorts are no longer randomized and are therefore susceptible to treatment crossover, uncontrolled subsequent management, and confounding. This long-term estimate closely concords with the rate-control comparator subgroup of the primary analysis (MD 8.40%, **Additional file 2: Figure S6**).

Subgroup Analysis: Effect Modification by Comparator Strategy

A subgroup analysis stratified by medical comparator strategy was conducted to explore the substantial heterogeneity observed in the primary LVEF analysis, demonstrating significant effect modification (test for subgroup differences, P = 0.007) (Fig. 3). In trials comparing ablation with rate control alone (five trials, n = 293), the LVEF improvement was large (MD 8.40%, 95% CI 3.81–13.00; I^2=69%). In trials comparing ablation with comparators that included pharmacological rhythm control (two trials, n = 343; AATAC[17] and AMICA[20]), the incremental benefit was smaller though still statistically significant (MD 1.87%, 95% CI 0.67–3.06; I^2=0%).

Secondary Outcome

Six-minute walk distance. Pooled across four trials (n = 429), it did not differ significantly between groups (MD 2.63 m, 95% CI − 22.37 to 27.63; P = 0.84; I^2=54%) (**Additional file 2: Figure S7**).

Quality of life. Disease-specific quality of life measured by the MLHFQ improved with ablation compared with medical therapy across five trials (n = 481; MD − 6.97, 95% CI − 12.11 to − 1.83; P = 0.008; I^2=48%) (Fig. 4), exceeding the commonly accepted minimal clinically important difference of five points.

NYHA functional class. Across three trials (n = 203), ablation reduced NYHA class compared with medical therapy (MD − 0.70, 95% CI − 0.85 to − 0.56; P < 0.00001; I^2=0%) (Fig. 5).

Freedom from atrial fibrillation. Across six trials (n = 2124) ; ablation was associated with substantially higher freedom from AF (RR 1.84, 95% CI 1.55–2.19; P < 0.00001; I^2=60%) (Fig. 6). Although moderate heterogeneity was observed, the direction of effect favored ablation in all contributing trials, with point estimates ranging from 1.47 to 2.50 and confidence intervals uniformly excluding the null.

Stroke or transient ischemic attack. Across five trials (n = 1143; 22/658 vs 25/485 events), the difference between groups did not reach statistical significance (RR 0.69, 95% CI 0.38–1.24; P = 0.22; I^2=0%) (**Additional file 2: Figure S8**).

Unplanned rehospitalization. Across seven trials (n = 1516; 68/804 vs 126/712 events), Catheter ablation significantly reduced the risk of unplanned rehospitalization compared with medical therapy (RR 0.54; 95% CI 0.42–0.69; p < 0.00001). The effect was consistent across subgroups, with no significant heterogeneity (I^2 = 0%, p = 0.73) Five studies of HFrEF demonstrated a 43% relative risk reduction (RR 0.57; 95% CI 0.43–0.74; p < 0.0001). Heterogeneity was negligible (I^2 = 0%), indicating consistent findings across trials. The AATAC trial[17] contributed the largest statistical weight in the HFrEF subgroup (55.5%), reflecting its substantial sample size and event count. Two studies with non-HFrEF baseline showed a numerically larger risk reduction (RR 0.38; 95% CI 0.19–0.76; p = 0.006), also without heterogeneity (I^2 = 0%). However, the subgroup difference was not statistically significant (p for interaction = 0.29, I^2 = 9.6%), suggesting that the treatment effect does not differ significantly by HF phenotype. (Fig. 7).

All-cause mortality. All-cause mortality was assessed across two complementary analyses. The primary all-cause mortality analysis **(Additional file 2: Figure S9)** included six randomized trials (with the CABANA non-paroxysmal subgroup analysis[16] presented as two strata reflecting the original publication's reporting) enrolling 2109 participants (1149 in catheter ablation arms; 960 in medical therapy arms), with 39 events in the ablation arm and 48 in the medication arm. The pooled risk ratio was 0.72 (95% CI 0.47–1.10; P = 0.13; I^2=0%), indicating a 28% relative risk reduction with catheter ablation that did not reach statistical significance. The secondary long-term follow-up analysis **(Additional file 2: Figure S10)** included four trial studies (with the CABANA non-paroxysmal subgroup[16] presented as two strata) with follow-up periods more than 2 years post-randomization, enrolling 2073 participants (1095 in ablation arms; 978 in medication arms), with 66 events in the ablation arm and 58 in the medication arm. The pooled risk ratio was 0.72 (95% CI 0.52–1.00; P = 0.05; I^2=0%), approaching statistical significance with the upper confidence bound at the null effect boundary.

Certainty of Evidence

GRADE assessment yielded moderate-certainty evidence for the primary LVEF outcome, and for most secondary outcomes (6MWD, MLHFQ, NYHA, freedom from AF, Unplanned rehospitalization), each downgraded by one level for risk of bias due to open-label design. Two outcomes were rated as low certainty: stroke or TIA, downgraded for risk of bias and imprecision (95% CI crossing the null with limited event accrual). A complete summary of the findings table is provided in **Additional file 1: Table S3**.

Procedural Safety

Safety data were available across nine of the included randomized trials enrolling 934 patients in the catheter ablation arms **(Additional file 1: Table S4)**. The pooled major complication rate was approximately 4.9%, broadly consistent with the pooled rate of 4.51% (95% CI 3.76–5.32%) reported by Benali and colleagues in a meta-analysis of 89 randomized trials of radiofrequency and cryoballoon catheter ablation across general atrial fibrillation populations.[24] This finding suggested that catheter ablation can be performed with acceptable safety profile in patients with established heart failure and structural cardiac remodeling when conducted at experienced centers.

Notable specific safety considerations include a periprocedural stroke incidence of 1.0% (9 of 934 procedures), with 6 of these 9 strokes occurring in the AVANT GUARD[18] trial prior to a protocol-mandated pause that instituted mandatory left atrial thrombus screening, uninterrupted anticoagulation, and minimum activated clotting time thresholds; no further strokes occurred after protocol modification. The atrioesophageal fistula rate was 0.1% (1 of 934 patients), with the single event occurring in a radiofrequency cohort and none in pulsed field ablation, consistent with the recognized safety advantage of pulsed field technology for this rare but catastrophic complication. The procedure-related mortality rate (0.1%, 1 of 934) is consistent with established safety estimates in general atrial fibrillation populations. A detailed breakdown of complications per trial is provided in **Additional file 1: Table S4**.

Discussion

In this systematic review and meta-analysis restricted to patients with persistent AF and concomitant HF at least stage B ACC/AHA, catheter ablation was associated with a clinically meaningful improvement in LVEF (MD 6.28%, 95% CI 2.45–10.11), alongside a directional reduction in long-term all-cause mortality (borderline significance), fewer unplanned rehospitalization, higher freedom from AF, and a patient-perceptible improvement in disease-specific quality of life. Six-minute walk distance and stroke/TIA did not differ significantly between groups. The magnitude of LVEF benefit was strongly modified by the medical comparator used and by baseline LV systolic function, with direct implications for patient selection and trial interpretation.

LVEF and Sources of Heterogeneity

The pooled 6.28-percentage-point LVEF gain is both statistically robust and clinically relevant, as reverse remodeling of this magnitude has been consistently associated with improved survival and reduced HF events in HF cohorts.[25] Substantial between-study heterogeneity (I^2=88%), however, precludes uncritical generalization of a single summary estimate. Leave-one-out sensitivity analyses confirmed that no single trial drove the pooled effect (MD range 4.95–7.20%; all $P < 0.01$), and a separate pooled analysis of extended observational follow-up data from Sugumar et al.[11] and Zakeri et al.[12] yielded a concordant estimate (MD 8.38%, I^2=0%), closely matching the rate-control comparator subgroup of the primary analysis (MD 8.40%) and consistent with persistence of structural recovery over longer observation periods, an inference that remains hypothesis-generating given the non-randomized nature of these extended cohorts.

Effect Modification by Comparator Strategy

A subgroup analysis exploring the substantial between-study heterogeneity in the primary LVEF analysis identified a significant interaction by medical comparator strategy (Chi^2 P = 0.007). Although this analysis is exploratory, the credibility of the finding is supported by directional consistency across both subgroups, biological plausibility, and a single pre-defined subgroup contrast tested. Against rate control alone, the LVEF benefit was large (MD 8.40%, 95% CI 3.81–13.00); against pharmacological rhythm control (amiodarone in AATAC[17]; combined rate and rhythm in AMICA[20]), the incremental benefit was smaller but still significant (MD 1.87%, 95% CI 0.67–3.06). Only two trials (AATAC and AMICA) contributed to the rhythm-control comparator subgroup, and these differed from the rate-control trials in baseline LV systolic function, patient selection, and treatment protocols. As a between-trial (ecological) comparison, this interaction is susceptible to confounding by these factors and cannot isolate the comparator strategy from correlated population differences. The gradient may therefore suggest—but cannot establish—that a substantial fraction of ventricular recovery after ablation reflects restoration and maintenance of sinus rhythm itself rather than ablation-specific effects. This finding should be regarded as exploratory and hypothesis-generating. Consistent with this interpretation, the EAST-AFNET 4 trial[2] demonstrated that early rhythm control—whether pharmacological or ablative—improves cardiovascular outcomes over rate control alone, and the hemodynamic cost of AF in HF (loss of atrial contribution, irregular RR intervals, rate-related myocardial inefficiency) is well characterized in tachycardia-mediated cardiomyopathy.[25, 26]

Functional Capacity, Quality of Life, NYHA and Arrhythmia Recurrence

The MLHFQ improvement (MD − 6.97) exceeds the commonly cited five-point minimal clinically important difference and is therefore likely patient-perceptible.[27, 28] Catheter ablation produced a substantial and clinically meaningful improvement in NYHA functional class (MD − 0.70), corresponding to nearly a full NYHA class reduction. The consistency of effect across all three included trials, absence of statistical heterogeneity (I^2=0%), and narrow confidence interval support the robustness of this finding. The magnitude aligns with concurrent improvements in LVEF and QoL observed in our analyses, consistent with the hypothesised mechanism of sinus rhythm restoration ameliorating tachycardia-mediated cardiomyopathy and improving overall cardiac function. In contrast, 6MWD did not differ between groups (MD 2.63 m), likely reflecting the multifactorial determinants of exercise limitation in AF with HF, modest sample sizes, and limited discriminatory capacity in populations with preserved ambulation. Freedom from AF was substantially higher with ablation (RR 1.84, 95% CI 1.55–2.19); four trials with zero sustained sinus rhythm in the rate-control arm were reported narratively.

Mortality, Hospitalization, and Stroke /TIA

In this meta-analysis, catheter ablation was not associated with a statistically significant reduction in stroke or TIA compared with medical therapy. Many trials mandated oral anticoagulation regardless of treatment assignment, which is the primary stroke prevention strategy in AF. Therefore, any incremental benefit of ablation on stroke risk would be expected to be modest when background anticoagulation is optimized.

The pooled all-cause mortality analyses demonstrated a remarkably consistent point estimate of risk reduction (RR 0.72) across both the primary analysis and the long-term follow-up analysis, with statistical significance approached only in the latter analysis, where greater event accumulation enabled adequate statistical power. The convergence of point estimates across analytical horizons is consistent with a modest mortality benefit; however, because the long-term analysis incorporates non-randomized extended follow-up data alongside randomized trials, the borderline statistical significance observed in that analysis should be interpreted with corresponding caution and not as confirmatory evidence of a survival benefit.

Catheter ablation produced a substantial reduction in unplanned hospitalization for heart failure or arrhythmia compared with medical therapy, representing approximately a 46% relative risk reduction across seven randomized trials. The magnitude is consistent with the landmark CASTLE-AF trial[29], which demonstrated that catheter ablation in symptomatic HFrEF reduced the composite of mortality and heart failure hospitalization, and extends this observation to a broader spectrum of patients with persistent atrial fibrillation and structural cardiac disease, including those without baseline clinical heart failure but with evidence of structural remodeling (Stage B ACC/ AHA Heart Failure)[13].

The biological coherence of this finding is supported by parallel improvements in functional outcomes observed in our analyses, including left ventricular ejection fraction, NYHA functional class, quality of life, and exercise capacity, supporting a unifying mechanism whereby restoration of sinus rhythm reduces tachycardia-mediated cardiomyopathy and prevents progressive atrial structural remodeling. While statistical heterogeneity remained absent (I^2=0%) supporting consistent effect direction across populations, this conceptual heterogeneity in outcome definitions should temper inference about the specific clinical mechanism — heart failure prevention versus heart failure worsening prevention versus arrhythmia recurrence reduction — underlying the pooled

benefit. Clinically, this finding nevertheless supports catheter ablation as a meaningful intervention to reduce healthcare utilization and associated morbidity in patients with atrial fibrillation across the heart failure phenotype spectrum.

Comparison with Previous Studies and Meta-Analyses

Our findings align directionally with Virk et al.[30] and Simader et al.[31], each reporting LVEF and mortality benefits of ablation in AF with HF, and with the broader body of meta-analyses in this field whose proliferation has itself been the subject of a dedicated redundancy assessment.[9] We distinguish this work in three respects. First, we restricted inclusion to trials requiring non-paroxysmal AF and HF at least Stage B ACC/AHA at enrolment, reducing the phenotypic heterogeneity of prior analyses that incorporated paroxysmal AF. Second, whereas a recent Bayesian network meta-analysis compared rate-control, rhythm-control, and ablation strategies in AF with HF using indirect evidence, we provide a complementary, within-population pairwise contrast by formally testing medical comparator strategy as an effect modifier.[32] Third, we incorporated the most recent randomized evidence, including the first pulsed-field ablation trial in this setting (AVANT-GUARD[18]). The slightly lower LVEF effect size relative to some earlier analyses likely reflects these more restrictive inclusion criteria.

Clinical Implication

These data support catheter ablation as an effective rhythm-control strategy in carefully selected patients with persistent AF and across spectrum of HF, particularly those currently managed with rate control alone, where the incremental benefit appears greatest. The attenuated effect against pharmacological rhythm control suggests the clinically relevant question is less “ablation versus no rhythm control” than “which rhythm-control strategy, and for whom?” Patients with limited ventricular fibrosis appear most likely to experience substantive LV recovery, consistent with the 2024 ESC AF guidelines[33] and the 2023 ACC/AHA/ACCP/HRS recommendations[34], both of which endorse early rhythm control in AF with LV dysfunction. The accelerating refinement of ablation technologies, including pulsed field ablation, nevertheless underscores the need for dedicated trials evaluating these contemporary modalities specifically in heart failure populations.

Strengths and Limitations

Strengths include prospective registration (PROSPERO CRD420251134536), restriction to a clinically coherent population, a priori-specified comparator strategy subgroup with additional post-registration refinements transparently disclosed, sensitivity analyses, and incorporation of extended follow-up. Several limitations warrant acknowledgement. Primary-outcome heterogeneity was high (I^2=88%), although largely explained by the comparator-strategy subgroup. Several trials were small and open-label by necessity. Formal quantitative publication-bias assessment (funnel plot, Egger’s test) was not performed because fewer than ten studies contributed to each outcome, in line with Cochrane recommendations[35]; prospective trial registration was verified qualitatively instead. In addition, the long-term mortality and LVEF analyses combined randomized trial data with extended observational follow-up cohorts in which randomization no longer held; these analyses are therefore best regarded as supportive and hypothesis-generating rather than confirmatory.

Our eligibility criterion permitted inclusion of patients with structural heart disease at the Stage B threshold, which is broader than the symptomatic HF populations of conventional HF trials. Notably, however, this inclusive definition affected only the event-based dichotomous outcomes (all-cause mortality, stroke/TIA, unplanned rehospitalization, and freedom from AF), to which the larger AF-population trials enrolling patients without mandatory symptomatic HF (CABANA non-paroxysmal subgroup, CAPA, and AVANT-GUARD) contributed. By contrast, every trial contributing to the structural and functional outcomes—LVEF, MLHFQ, NYHA class, and 6MWD—enrolled symptomatic HF populations with reduced ejection fraction. The core structural and functional estimates of this meta-analysis are therefore derived from a symptomatic HF population and are not driven by the inclusion of asymptomatic Stage B patients.

Conclusions

This systematic review and meta-analysis demonstrates that, in patients with persistent and long-standing persistent atrial fibrillation and heart failure at least Stage B ACC/AHA, catheter ablation improves left ventricular systolic function (mean improvement of 6.28 percentage points in ejection fraction), disease-specific quality of life, New York Heart Association functional class, and freedom from atrial fibrillation, while reducing unplanned rehospitalization. All-cause mortality showed a directional reduction (RR 0.72) consistent across the primary and long-term follow-up analyses, with statistical significance approached only in the long-term analysis (P = 0.05) due to greater event capture; six-minute walk distance and stroke or transient ischemic attack did not differ significantly between groups.

A subgroup analysis exploring the substantial between-study heterogeneity in the primary outcome identified medical comparator strategy as a potential effect modifier, with a larger structural benefit observed when ablation was compared with rate control alone than with pharmacological rhythm control. Although exploratory and limited by few contributing trials and between-trial confounding, this finding raises the hypothesis that much of the ventricular recovery attributable to ablation may reflect sinus rhythm restoration itself rather than ablation-specific effects, and warrants direct testing in future trials.

Future randomized trials should directly compare catheter ablation with contemporary pharmacological rhythm control strategies, incorporate pre-procedural cardiac imaging to phenotype atrial and ventricular substrate, and employ patient-centered endpoints to clarify which patients with non-paroxysmal AF and HF derive the greatest benefit from invasive rhythm control.

Abbreviations

AF
Atrial fibrillation
ACC

American College of Cardiology
AHA
American Heart Association
CI
Confidence interval
GRADE
Grading of Recommendations, Assessment, Development and Evaluations
HF
Heart failure
HFrEF
Heart failure with reduced ejection fraction
LVEF
Left ventricular ejection fraction
MD
Mean difference
MLHFQ
Minnesota Living with Heart Failure Questionnaire
NYHA
New York Heart Association
PFA
Pulsed-field ablation
PRISMA
Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO
International Prospective Register of Systematic Reviews
RCT
Randomised controlled trial
RoB 2
Cochrane Risk of Bias tool version 2
RR
Risk ratio
TIA
Transient ischaemic attack
6MWD
Six-minute walk distance.

Declarations

Author Contribution

DPA conceived and designed the study. DPA, MRF, CP and RF performed the literature search, study selection, and data extraction, with MFA serving as adjudicator for disagreements. DPA, CP, RF, and AJ conducted the statistical analysis. DPA and CP assessed risk of bias and certainty of evidence. DDH and KF drafted the manuscript. DPA, MFA and MRF reviewed and edited the manuscript. All authors critically revised the manuscript and read and approved the final version.

Acknowledgement

Not applicable.

Data Availability

All data generated or analysed during this study are included in this published article and its additional files. The review protocol was prospectively registered in PROSPERO (CRD420251134536).

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Figures

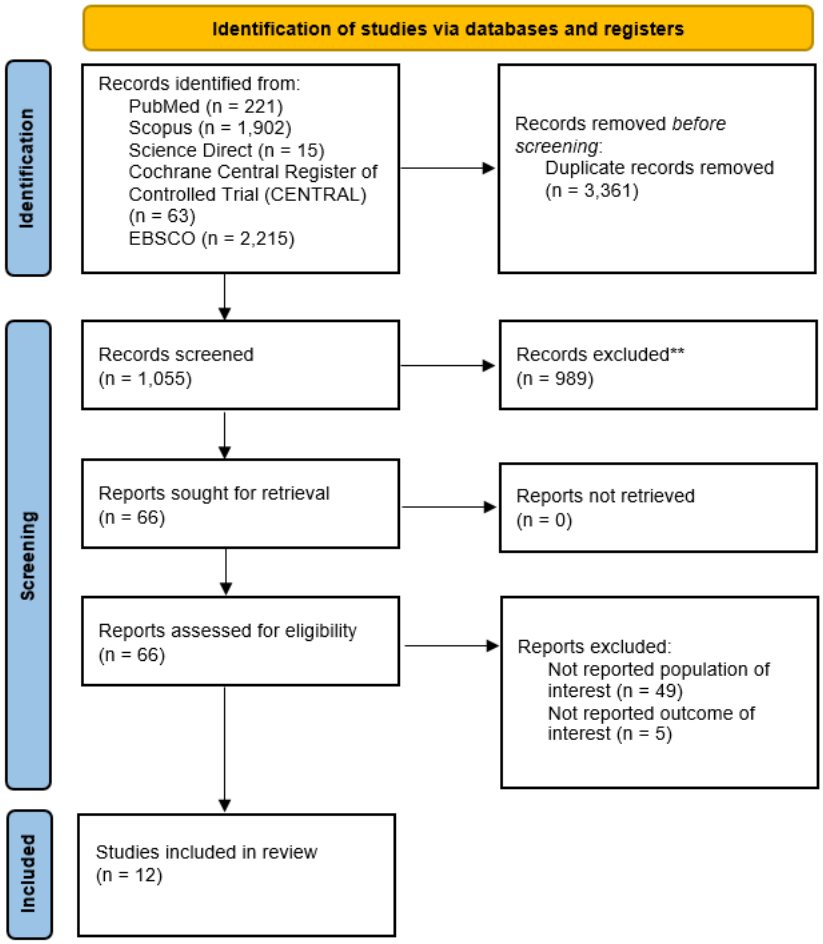

Figure 1

PRISMA flow diagram

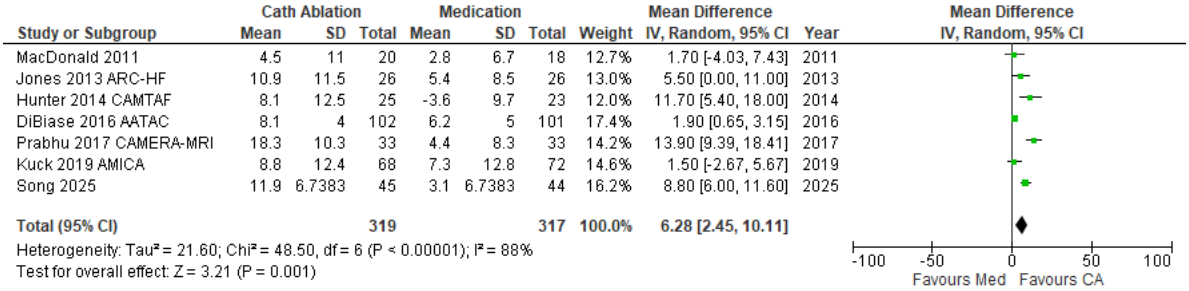

Figure 2

LVEF changes

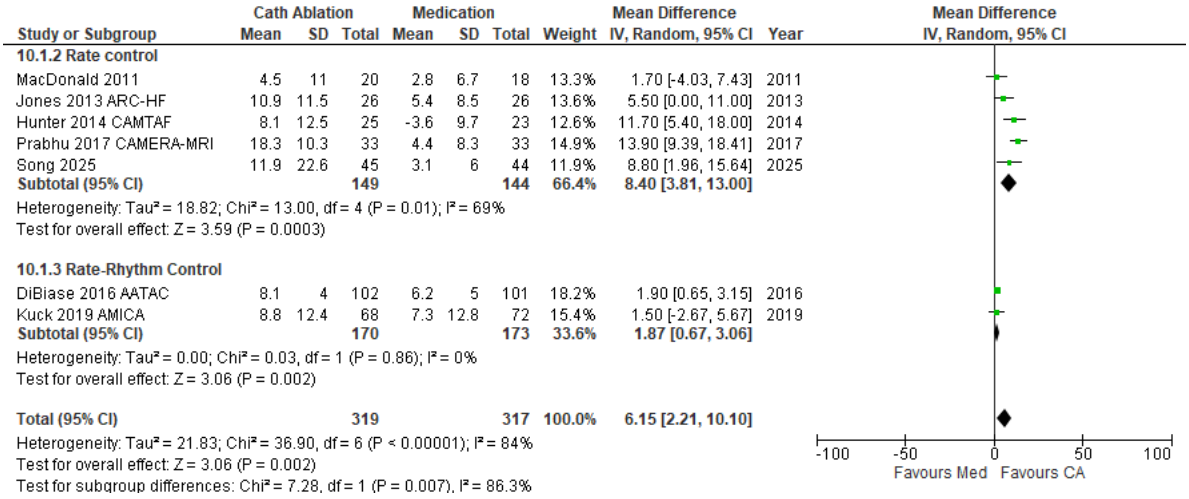

Figure 3

LVEF changes (Rate control only & Rate-rhythm control)

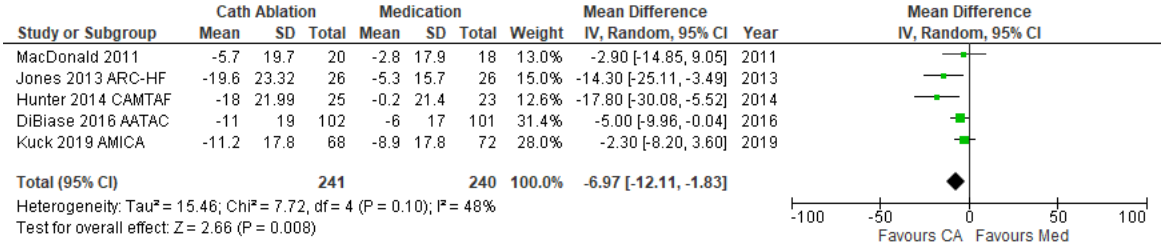

Figure 4

Improvement of Quality of Life (QoL) by MLHFQ score

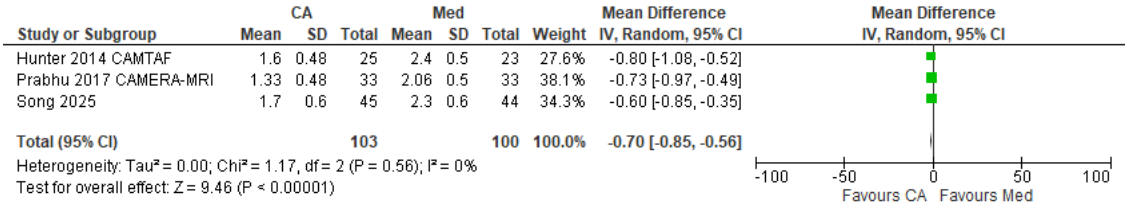

Figure 5

NYHA Classification Improvement

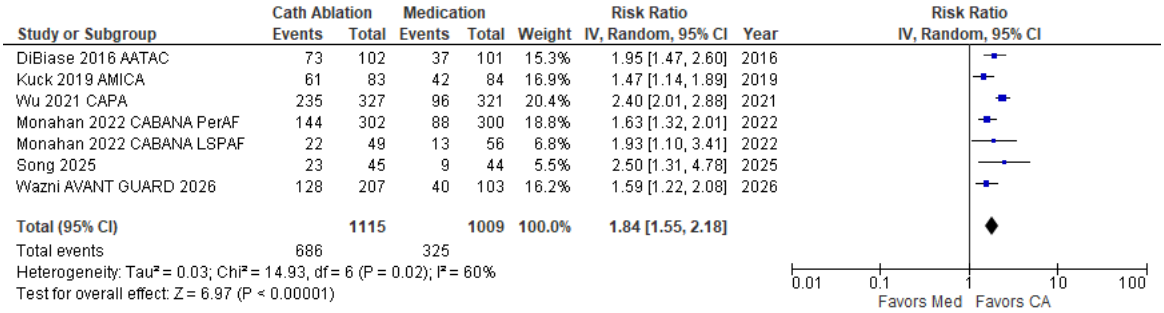

Figure 6

Freedom of AF

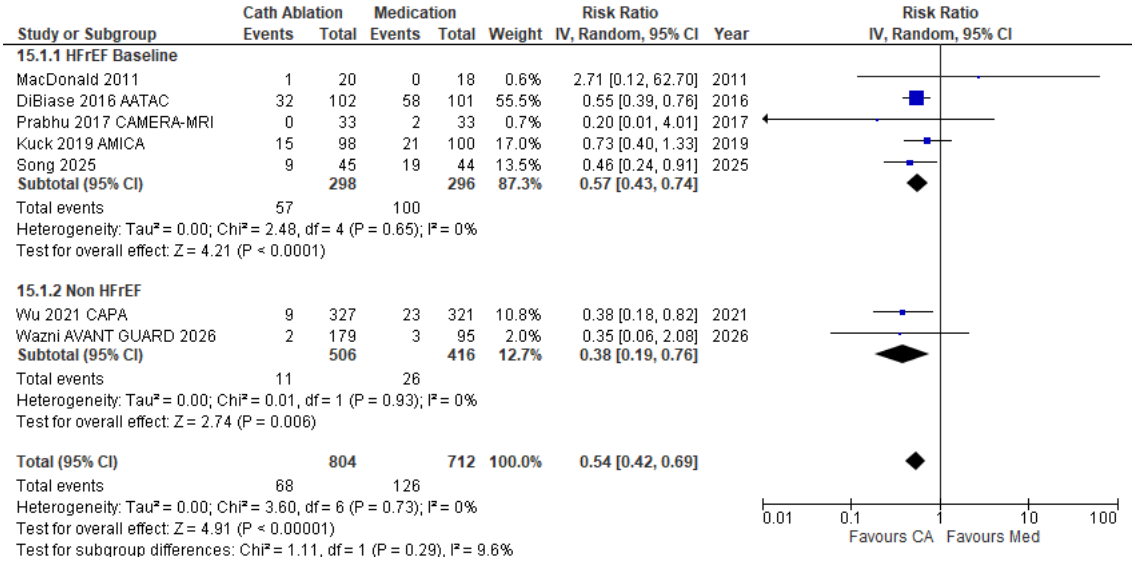

Figure 7

Unplanned Rehospitalization

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