Supplemental Online Content

Turagam MK, Musikantow D, Whang W, et al. Assessment of catheter ablation or antiarrhythmic drugs for first-line therapy of atrial fibrillation: a meta-analysis of randomized clinical trials. *JAMA Cardiol*. Published online April 28, 2021. doi:10.1001/jamacardio.2021.0852

eFigure 4. Forest Plot Demonstrating Additional Ablation After Ablation vs AAD

This supplemental material has been provided by the authors to give readers additional information about their work.

eStudy Protocol

Catheter Ablation or Antiarrhythmic Drugs for First-Line Therapy of Atrial Fibrillation: A Meta-analysis of Randomized Controlled Trials

A. Background & Significance

Current guidelines recommend maintenance of sinus rhythm with antiarrhythmic drugs (AADs) in patients with symptomatic paroxysmal AF. (1,2) However, paroxysmal AF seldom responds to AADs and is associated with significant toxicity. (3,4) On the other hand, catheter ablation for paroxysmal atrial fibrillation is superior to drug therapy in maintaining freedom from AF and improving quality of life in patients who failed AADs (5,6) Previous randomized controlled trials (RCTs) evaluating ablation as compared with AADs as first-line therapy have used point-by-point radiofrequency (RF) ablation. (7-9) However, those studies failed to demonstrate any difference cardiovascular outcomes and were limited by high rates of AF recurrence, serious adverse events, repeat procedures and cross-over rates.

Recently, AF ablation using single shot using Cryoballoon showed superior efficacy and comparable safety when compared with AADs in patients with paroxysmal AF. (10-12) In addition, the Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4) showed that early rhythm control resulted in better cardiovascular outcomes including stroke than rate control perhaps suggesting that rhythm control with catheter ablation if performed safely may be superior as a first-line treatment for patients with AF. (13) Although, controversy exists there are several findings that justify use of catheter ablation as first-line therapy in patients with paroxysmal AF. To understand this further, we propose this study which is a pooled analysis of all the randomized studies comparing the safety and efficacy of catheter ablation (both RF and cryo) versus AADs as first-line therapy in patients with paroxysmal AF.

B. Objectives and Specific Aims

The objective of this study is to perform a metaanalysis of randomized clinical trials (RCTs) comparing catheter ablation (CA) to antiarrhythmic drugs (AAD) as first-line therapy in patients with symptomatic paroxysmal atrial fibrillation (AF).

Specific Aim 1: To estimate the effectiveness of catheter ablation *vs*. AADs as first-line therapy for freedom from recurrent symptomatic or asymptomatic atrial arrhythmias.

Specific Aim 2: To estimate (i) hospitalization rates, (ii) the proportion of cross-over to the alternative therapy, (iii) additional ablation after the initial therapy with either catheter ablation or AADs had failed and (iv) major adverse events including mortality between catheter ablation *vs*. AADs in patients with paroxysmal AF.

C. Research Design and Methods

(i) Search Strategy

An extensive search will be conducted in PubMed, Scopus, Google Scholar, and various major scientific conference sessions including abstracts published at the American College of Cardiology, American heart association, European Society of Cardiology Congress, European Heart Rhythm Association Scientific Session and Heart Rhythm Society to identify clinical trials of interest. The search will be conducted by two investigators and will not have date or language restrictions. Two investigators (MT and DM) independently performed searches which included the following keywords: 'atrial fibrillation', 'ablation', 'antiarrhythmic', and 'random*'. Information on unpublished studies were obtained from clinicaltrials.gov and Google.

(ii) Study Selection & Outcomes

Study eligibility criteria will include the following:

1. Prospective randomized controlled trials (RCTs) with at least 12 months of follow up.
2. Studies comparing AF ablation versus AADs as initial therapy in patients with symptomatic AF.
3. Studies that included human subject aged ≥ 18 years
4. Studies that examined clinical outcomes including – (i) Freedom from atrial arrhythmias, (ii) AF recurrence, (iii) Major adverse events and (iv) Mortality.
5. Published in English language.

Clinical Outcomes

1. The primary outcome of this analysis was recurrence of any atrial arrhythmia (both symptomatic and asymptomatic) including AF, atrial flutter, or atrial tachycardia.
2. Secondary outcome of interest was the following: (i) Symptomatic atrial arrhythmias, (ii) Hospitalizations, (iii) Additional ablation after failed initial treatment with either catheter ablation or AADs, (iv) trial cross-over to alternate therapy, (v) composite of serious adverse events and (vi) mortality.
3. Serious adverse events included a composite of vascular complications (femoral bleeding, hematoma, pseudoaneurysm and groin infection), pericardial effusion (with and without tamponade), pulmonary vein stenosis, phrenic palsy, systemic thromboembolism, symptomatic bradycardia, syncope, and atrial flutter with 1:1 conduction.

(iii) Data Extraction

Two investigators will independently perform the literature search and screen relevant studies & published abstracts that meet study inclusion/exclusion criteria. All the studies that meet study criteria based on the title/abstract will be reviewed in detail and final selection will be made. The data will be extracted using a standardized data collection form. Any discrepancies between the two investigators will be resolved with consultation with the senior investigator.

D. Data Synthesis

Risk ratios will be used to pool differences in binary events, and mean differences to pool differences in continuous outcomes. Summary estimates and 95% confidence intervals (CI) will be reported. Mantel-Haenszel risk ratio (RR) random effects model (DerSimonian and Laird method), Freedman-Tukey double arcsine transformation or random-effects model with the Paule-Mandel method will be used to pool data as appropriate. The Hartung-Knapp small-sample adjustment was used as the number of studies is less than 10. (14) Sensitivity analyses will be performed when appropriate to assess the contribution of each study to the pooled estimate. Heterogeneity of effects among the included studies will be assessed by Higgins I-squared (*I2*)

statistic. All analyses will be were conducted using StataCorp and RevMan 5.3. All p values were 2-sided, and p value of <0.05 was considered significant.

E. References

1. Hindricks G, Potpara T, Dagres N et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). European heart journal 2020.
2. January CT, Wann LS, Calkins H et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. Circulation 2019;140:e125-e151.
3. Roy D, Talajic M, Dorian P et al. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. The New England journal of medicine 2000;342:913-20.
4. Doyle JF, Ho KM. Benefits and risks of long-term amiodarone therapy for persistent atrial fibrillation: a meta-analysis. Mayo Clinic proceedings 2009;84:234-42.
5. Khan AR, Khan S, Sheikh MA, Khuder S, Grubb B, Moukarbel GV. Catheter ablation and antiarrhythmic drug therapy as first- or second-line therapy in the management of atrial fibrillation: systematic review and meta-analysis. Circulation Arrhythmia and electrophysiology 2014;7:853-60.
6. Packer DL, Mark DB, Robb RA et al. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. Jama 2019;321:1261-1274.
7. Wazni OM, Marrouche NF, Martin DO et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. Jama 2005;293:2634-40.
8. Cosedis Nielsen J, Johannessen A, Raatikainen P et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. The New England journal of medicine 2012;367:1587-95.
9. Morillo CA, Verma A, Connolly SJ et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. Jama 2014;311:692-700.
10. Wazni OM, Dandamudi G, Sood N et al. Cryoballoon Ablation as Initial Therapy for Atrial Fibrillation. The New England journal of medicine 2020.
11. Andrade JG, Wells GA, Deyell MW et al. Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation. The New England journal of medicine 2020.
12. Velagic V, Pavlovic N, Chierchia G-B et al. Abstract 13915: Cryoballoon Catheter Ablation versus Antiarrhythmic Drug as a First-Line Therapy for Patients With Paroxysmal Atrial Fibrillation: Results of the Cryo-FIRST Study. Circulation 2020;142:A13915-A13915.

13. Kirchhof P, Camm AJ, Goette A et al. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. The New England journal of medicine 2020;383:1305-1316.
14. Hartung J KG SB. Statistical Meta-Analysis with Applications. Wiley & Blackwell 2008.

eData Collection Form

Name of the Extractor:

Date:

1. **Name of the Study:**
2. **First Author's Name:**
3. **Title of the study:**
4. **Study Country:**
5. **Publication Year:**
6. **Journal:**
7. **Is it a Randomized Controlled Trial:** Yes No
8. **What type of Randomized Controlled Trial (explain):**
9. **Type of Ablation performed:**
10. **Additional ablation details:**
11. **Type of drug therapy:**
    - **Class I** Yes No
    - **Class III** Yes No
12. **Reported Outcomes (circle):**
    - **Atrial Arrhythmia recurrence**
    - **Symptomatic atrial arrhythmia recurrence**
    - **Additional ablation**
    - **Crossover**
    - **Complications**
    - **Other Outcomes**

12. How was randomization conducted? Yes No

13. Was allocation concealed: Yes No

14. Was there blinding during randomization: Yes No

15. Was there blinding during outcome assessment: Yes No

16. Was there a study run-in period: Yes No

17. Was there an intention to treat analysis: Yes No

18. Were there any major study methodological issues:

Please specify:

Patient demographics, procedure characteristics and outcomes of the included trials

	Catheter Ablation	Drug therapy
Year of publication		
Funding source		
Age (years)		
Patients Screened		
Patients enrolled		
Randomization		
Period of pharmacological optimization		
Blinding adjudication		
Primary Endpoint		
Cross over to ablation (%)		
Cross over to drug therapy (%)		
Total Follow up (Months)		
Type of medications (catheter ablation/ medical therapy) (%) Class I AADs Class III AADs Oral anticoagulants		
Paroxysmal AF (%)		
Time since AF diagnosis (years)		
NYHA class I II III IV		
Baseline LA diameter (mean±SD)		

Baseline LVEF (%) (mean±SD)		
Frequency of monitoring (months)		
Monitoring modality		
Ablation strategy		
Ablation success with one procedure (%)		
Freedom from atrial arrhythmias in catheter ablation group on follow up (%)		
Freedom from atrial arrhythmias in the drug therapy group on follow up (%)		
Freedom from symptomatic atrial arrhythmias in the catheter ablation group on follow up (%)		
Freedom from symptomatic atrial arrhythmias in the AAD group on follow up (%)		
Complications (%)		
Mortality (%)		

eTable 1. Inclusion and Exclusion Criteria of The Included Studies

Study	Inclusion Criteria	Exclusion criteria
RAAFT-1	• Monthly symptomatic paroxysmal AF ≥3 months	• <18 years and >75 years • Prior AF/AFL ablation • Prior cardiac surgery • Prior treatment with AADs • Contraindication to long-term OAC
MANTRA-PAF	• ≥2 episodes of symptomatic paroxysmal AF within 6 months	• AF lasting >7 days • Age > 70 years • Prior treatment with class IC or III AADs • Prior AF ablation • LA diameter > 5cm • LVEF<40% • Contraindication to long-term OAC • Moderate-severe mitral valve disease • NYHA class ≥ III • Secondary cause for AF
RAAFT-2	• Symptomatic paroxysmal AF lasting >30s but ≤4 episodes in prior 6 months • Age>18 and <75 years • No prior AADs	• LA diameter > 5.5 cm • LVEF<40% • Moderate to severe LVH (>1.5 cm) • Valvular disease, coronary disease, or post-cardiac surgery within 6 months • Prior AF ablation • Contraindications to oral anticoagulation • Severe pulmonary disease • Prior pacemaker/ICD

		• Expected survival <1 year
STOP AF	• Symptomatic paroxysmal AF • Age ≥18 and <80 years • EKG documentation of AF 6 months prior to enrollment	• Prior class I or III AADs for ≥7 days • LA diameter > 5 cm • Previous AF ablation • Previous LA surgical procedure • Prior persistent AF • NYHA class >III and/or LVEF<45% • Prior stroke/TIA within 6 months • Hypertrophic cardiomyopathy • Any cardiac surgery, MI, PCI within 3 months • Moderate-severe mitral stenosis/regurgitation
EARY AF	• Non-permanent symptomatic AF within the last 24 months (episodes of AF must be >30) • Age ≥18 years	• Daily use of class I or III AADs at sufficient doses (flecainide >50 mg BID, sotalol >80 mg BID, propafenone >150 mg BID, or dronedarone 40 mg BID) • Prior LA ablation • LA diameter >5.5 cm • LVEF<35% • Prosthetic valves • MI, PCI or cardiac surgery within 3 months • NYHA class ≥III • Severe LVH >1.8 cm
CRYO-FIRST	• Symptomatic paroxysmal atrial fibrillation (<7 days) including ≥ 2 symptomatic episodes (past 6 month) and ≥ 1 documented AF episode (past 1 year) • Age 18-75 years	• Persistent AF/AFL • Prior Class I or III AAD treatment • Left atrial ablation • Permanent pacemaker • Prior cardiac surgery

	• Structurally normal heart (LVEF ≥ 50%; IV septum ≤12mm; LVD < 46mm) • Normal ECG (QRS width ≤ 120mm; QTc < 440ms; PQ ≤ 210ms)	• Prior TIA or stroke • NYHA class ≥II

eTable 2. Detailed Risk Bias Assessment Of All The Included Trials For Reporting Atrial Arrhythmia Recurrence Using The Cochran Risk Of Bias Tools

Bias Type	*RAAFT-1*	*MANTRA-PAF*	*RAAFT-2*	*STOPAF*	*EARLY AF*	*CRYO-FIRST*
Selection Bias						
Random sequence generation	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Allocation concealment	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Performance Bias						
Blinding of participants and personnel	High risk	High risk	High risk	High risk	High risk	High risk
Detection Bias						
Blinding of outcome assessment	High risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Attrition Bias						
Incomplete outcome data	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Reporting Bias						
Selective reporting	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

eTable 3. Detailed Risk Bias Assessment of All The Included Trials For Reporting Symptomatic Atrial Arrhythmias Using The Cochran Risk Of Bias Tools

Bias Type	RAAFT-1	MANTRA-PAF	RAAFT-2	EARLY AF
Selection Bias				
Random sequence generation	Low risk	Low risk	Low risk	Low risk
Allocation concealment	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Performance Bias				
Blinding of participants and personnel	High risk	High risk	High risk	High risk
Detection Bias				
Blinding of outcome assessment	High risk	Unclear risk	Unclear risk	Unclear risk
Attrition Bias				
Incomplete outcome data	Low risk	Low risk	Low risk	Low risk
Reporting Bias				
Selective reporting	Unclear risk	Unclear risk	Unclear risk	Unclear risk

eTable 4. Detailed Risk Bias Assessment of All the Included Trials For Reporting Hospitalization Using The Cochran Risk Of Bias Tools

Bias Type	RAAFT-1	MANTRA-PAF	STOPAF
Selection Bias			
Random sequence generation	Low risk	Low risk	Low risk
Allocation concealment	Unclear risk	Unclear risk	Unclear risk
Performance Bias			
Blinding of participants and personnel	High risk	High risk	High risk
Detection Bias			
Blinding of outcome assessment	High risk	Unclear risk	Unclear risk
Attrition Bias			
Incomplete outcome data	Low risk	Low risk	Low risk
Reporting Bias			
Selective reporting	Low risk	Low risk	Low risk

eTable 5. Detailed Risk Bias Assessment of All The Included Trials For Reporting Mortality Using The Cochran Risk Of Bias Tools

Bias Type	MANTRA-PAF	RAAFT-2	STOPAF	EARLY AF	CRYO-FIRST
Selection Bias					
Random sequence generation	Low risk	Low risk	Low risk	Low risk	Low risk
Allocation concealment	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Performance Bias					
Blinding of participants and personnel	High risk	High risk	High risk	High risk	High risk
Detection Bias					
Blinding of outcome assessment	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Attrition Bias					
Incomplete outcome data	Low risk	Low risk	Low risk	Low risk	Low risk
Reporting Bias					
Selective reporting	Low risk	Low risk	Low risk	Low risk	Low risk

eTable 6. Detailed Risk Bias Assessment of All the Included Trials For Reporting Composite Of Major Adverse Events Using The Cochran Risk Of Bias Tools

Bias Type	RAAFT-1	MANTRA-PAF	RAAFT-2	STOPAF	EARLY AF	CRYO-FIRST
Selection Bias						
Random sequence generation	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Allocation concealment	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Performance Bias						
Blinding of participants and personnel	High risk	High risk	High risk	High risk	High risk	High risk
Detection Bias						
Blinding of outcome assessment	High risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Attrition Bias						
Incomplete outcome data	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Reporting Bias						
Selective reporting	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

eTable 7. Detailed Risk Bias Assessment of All the Included Trials For Reporting Outcomes Of Additional Ablation Using The Cochran Risk Of Bias Tools

Bias Type	RAAFT-1	MANTRA-PAF	RAAFT-2	STOPAF	EARLY AF	CRYO-FIRST
Selection Bias						
Random sequence generation	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Allocation concealment	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Performance Bias						
Blinding of participants and personnel	High risk	High risk	High risk	High risk	High risk	High risk
Detection Bias						
Blinding of outcome assessment	High risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Attrition Bias						
Incomplete outcome data	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Reporting Bias						
Selective reporting	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

eTable 8. Detailed Risk Bias Assessment of All the Included Trials For Reporting Outcomes Of Study Cross-Over Using The Cochran Risk Of Bias Tools

Bias Type	*RAAFT-1*	*MANTRA-PAF*	*RAAFT-2*	*STOPAF*	*EARLY AF*	*CRYO-FIRST*
Selection Bias						
Random sequence generation	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Allocation concealment	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Performance Bias						
Blinding of participants and personnel	High risk	High risk	High risk	High risk	High risk	High risk
Detection Bias						
Blinding of outcome assessment	High risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Attrition Bias						
Incomplete outcome data	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Reporting Bias						
Selective reporting	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

eTable 9. Procedure Details Across the Included Trials

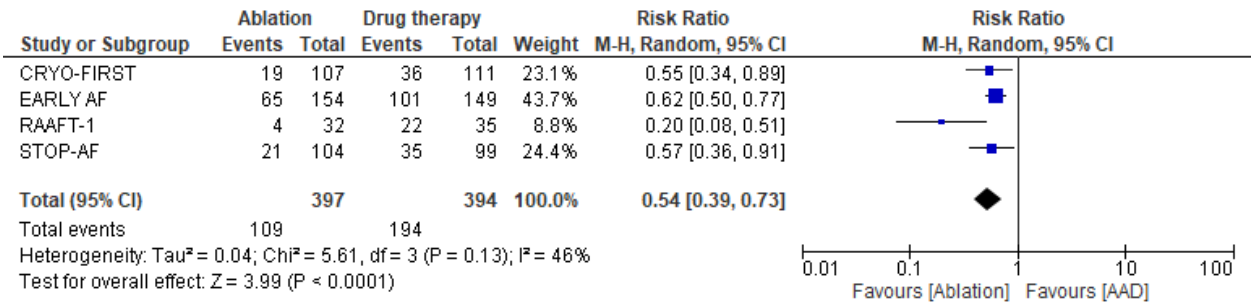
Study	Ablation Energy	Ablation catheter	Type of ablation	Anticoagulation after ablation	Class I/III AADs post-ablation	Blanking period
RAAFT-1	RF	8 mm (Biosense Webster)	PVI	Warfarin for at least 3 months	None	2 months
RAAFT-2	RF	N/R	PVI, Additional ablation*	Warfarin for at least 3 months	Allowed for 3 months	3 months
MANTRA PAF	RF	8 mm (Navistar DS) or 3.5 mm irrigated (Thermocool)	PVI, Additional ablationν	Warfarin for whole study period	Allowed for 3 months	3 months
STOP AF	Cryo	Cryoballoon (Arctic front)	PVI	Warfarin/NOAC for at least 2 months	Allowed+ for 80 days	3 months
EARLY AF	Cryo	Cryoballoon (Arctic front), Cryocatheter (Freezor Max)	PVI±CTI^	Warfarin/NOAC	None	3 months
CRYO-FIRST	Cryo	Cryoballoon (Arctic front)	PVI	N/R	N/R	3 months

^ In the event of documented right atrial flutter with a RF or Cryoablation**;** *******linear ablation lesions, ablation targeting common fractionated atrial electrograms, superior vena cava isolation, ganglion plexi ablation and Cavotricuspid isthmus ablation; ν linear ablation lesions along the roof, mitral and CTI ablation. ; +excluding amiodarone; N/R: Not reported

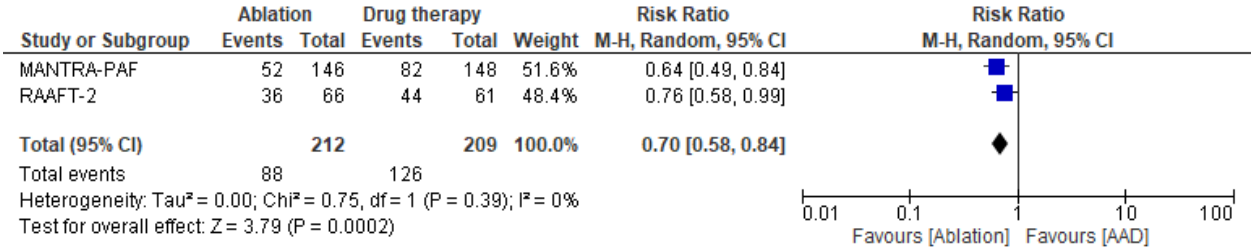
eTable 10. Results of The Sensitivity Analysis

Study Excluded	Risk Ratios	95% Confidence Intervals	p-value	I^2
Recurrence of Atrial Arrhythmias				
RAAFT-1	0.65	0.57 to 0.74	<0.00001	0%
RAAFT-2	0.58	0.48 to 0.71	<0.00001	33%
MANTRA PAF	0.59	0.46 to 0.76	<0.00001	53%
STOP AF	0.62	0.50 to 0.76	<0.00001	51%
EARLY AF	0.60	0.46 to 0.78	0.0001	53%
CRYO-FIRST	0.62	0.50 to 0.77	<0.00001	50%
Symptomatic atrial arrhythmias				
RAAFT-1	0.52	0.35 to 0.79	0.002	32%
RAAFT-2	0.37	0.25 to 0.55	<0.00001	1%
MANTRA PAF	0.44	0.22 to 0.86	0.02	69%
EARLY AF	0.43	0.21 to 0.92	0.03	69%
Hospitalization				
RAAFT-1	0.38	0.21 to 0.67	0.0009	0%
MANTRA PAF	0.30	0.14 to 0.63	0.001	38%
STOP AF	0.18	0.06 to 0.50	0.001	0%
Additional Ablation				
RAAFT-1	0.54	0.18 to 1.6	0.28	91%
RAAFT-2	0.69	0.17 to 2.75	0.60	89%
MANTRA PAF	0.32	0.19 to 0.55	<0.0001	0%
STOP AF	0.54	0.18 to 1.65	0.28	91%
EARLY AF	0.54	0.18 to 1.65	0.28	91%
CRYO-FIRST	0.67	0.17 to 2.6	0.57	93%
Cross-over				
RAAFT-1	0.21	0.13 to 0.35	<0.00001	6%
RAAFT-2	0.15	0.04 to 0.63	0.009	54%
MANTRA PAF	0.14	0.04 to 0.52	0.003	42%
STOP AF	0.21	0.13 to 0.35	<0.00001	6%
EARLY AF	0.21	0.13 to 0.35	<0.00001	6%
CRYO-FIRST	0.23	0.15 to 0.37	<0.00001	0%
Major Adverse Events				
RAAFT-1	1.70	0.86 to 3.34	0.12	0%
RAAFT-2	1.38	0.63 to 3.05	0.42	15%
MANTRA PAF	1.40	0.60 to 3.30	0.44	17%
STOP AF	1.73	0.90 to 3.34	0.10	0%
EARLY AF	1.24	0.60 to 2.55	0.56	0%
CRYO-FIRST	1.52	0.81 to 2.85	0.19	0%

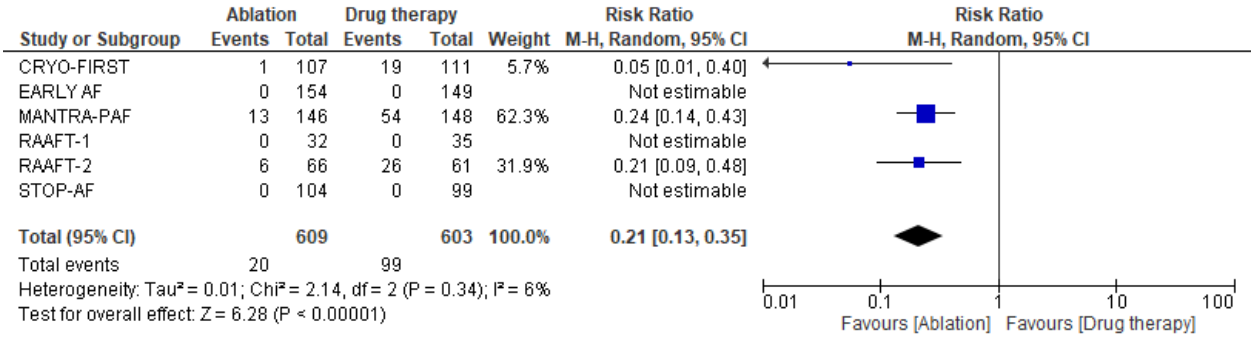
eFigure 1. Forest Plot Demonstrating Atrial Arrhythmia Recurrence After Ablation *vs* AAD at <u>1-Year</u> Follow Up



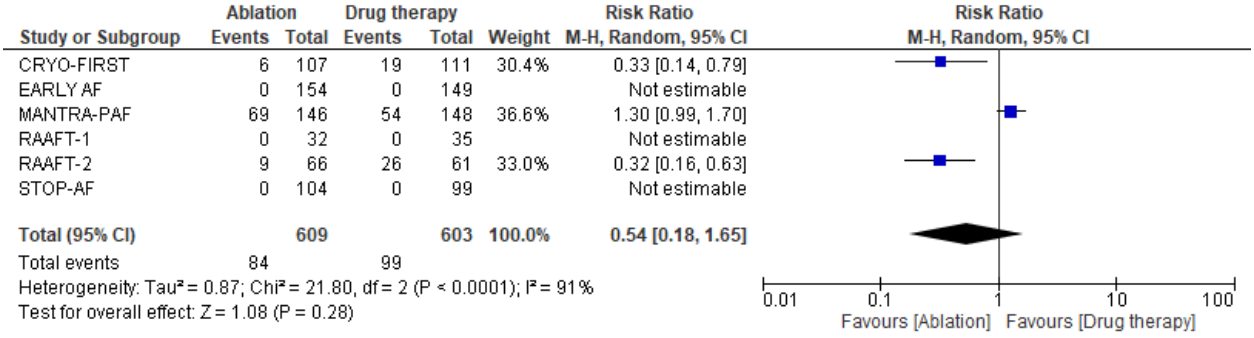
eFigure 2. Forest Plot Demonstrating Atrial Arrhythmia Recurrence After Ablation *vs* AAD at <u>2-Year</u> Follow Up



eFigure 3. Forest Plot Demonstrating Study Cross-Over After Ablation *vs* AAD



eFigure 4. Forest Plot Demonstrating Additional Ablation After Ablation *vs* AAD



CRYO-FIRST: 4 ablations during blanking period and 2 ablations after blanking period; RAAFT-2: 1 ablation during blanking period and 8 after blanking period.