Catheter Ablation as a First-Line Treatment for Atrial Fibrillation and Atrial Flutter: Focused Updated

Final Appendix

May 11, 2026

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Catheter Ablation as a First-Line Treatment for Atrial Fibrillation and Atrial Flutter: Focused Update – Draft Appendix

Provided by:

Aggregate Analytics, Inc.

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Appendix A. Search Strategies

Appendix Table A-1. Pubmed search strategy

#	Search code	Hits
1	“atrial fibrillation” OR “Atrial Fibrillation”[MeSH] OR “afib”	123,720
2	“atrial flutter” OR “Atrial Flutter”[MeSH] OR “macroreentrant atrial tachycardia*” OR “typical flutter” OR “atypical flutter” OR (isthmus AND flutter)	10,533
3	#1 OR #2	128,020
4	ablation OR “pulmonary vein*” OR “Pulmonary Veins”[MeSH] OR "Pulmonary vein isolation" OR "Pulmonary vein antrum isolation" OR “Radiofrequency Ablation”[MeSH] OR Cryoablation OR “cryoballoon ablation” OR (“Cryosurgery”[MeSH] AND ablat*) OR (microwave AND ablat*) OR "laser ablation" OR "pulsed field ablation" OR ((“atrioventricular node” OR “AV node” OR “AV nodal” OR “atrioventricular junction” OR “AV junction”) AND ablat*)	190,035
5	#1 AND #4	26,578
6	#2 AND #4	3,801
7	#3 AND #4	28,248
8	"Anti-Arrhythmia Agents"[Mesh] OR “antiarrhythmic drugs” OR “anti-arrhythmic drugs” OR “AAD” OR “medical therapy” OR “drug therapy” OR “pharmacologic*” OR “conservative” OR Amiodarone OR Cordarone OR Nexterone OR Pacerone OR Dronedarone OR Multaq OR Dofetilide OR Tikosyn OR Sotalol OR Betapace OR Sorine OR Flecainide OR Tambocor OR Propafenone OR Rythmol OR “Beta-blocker” OR “Beta blocker” OR Metoprolol OR Lopressor OR Atenolol OR Tenormin OR Propranolol OR Inderal OR Bisoprolol OR Zebeta OR Bisotab OR Concor OR Carvedilol OR Coreg OR “Calcium Channel Blocker” OR Diltiazem OR Cardizem OR Verapamil OR Calan OR Nadolol OR Corgard OR Timolol OR Blocadren OR Digox* OR Lanoxin OR Digitek	3,585,789
9	"Electric Countershock"[Mesh] OR “Cardioversion” OR "Maze Procedure”[Mesh] OR Maze OR "Left Atrial Appendage Closure"[Mesh] OR “Left Atrial Appendage” OR “LAA” OR “LAAO” OR "Pacemaker, Artificial"[Mesh] OR “pacemaker” OR "Defibrillators, Implantable"[Mesh] OR “implantable cardioverter defibrillator” OR “ICD”	203,166
10	#8 OR #9	3,755,226
11	#7 AND #10	9,201

#	Search code	Hits
12	"Randomized Controlled Trial"[pt] OR "Controlled Clinical Trial"[pt] OR "Pragmatic Clinical Trial"[pt] OR "Equivalence Trial"[pt] OR "Clinical Trial, Phase III"[pt] OR "Randomized Controlled Trials as Topic"[mh] OR "Controlled Clinical Trials as Topic"[mh] OR "Random Allocation"[mh] OR "Double-Blind Method"[mh] OR "Single-Blind Method"[mh] OR Placebos[Mesh:NoExp] OR "Control Groups"[mh] OR (random*[tiab] OR sham[tiab] OR placebo*[tiab]) OR ((singl*[tiab] OR doubl*[tiab]) AND (blind*[tiab] OR dumm*[tiab] OR mask*[tiab])) OR ((tripl*[tiab] OR trebl*[tiab]) AND (blind*[tiab] OR dumm*[tiab] OR mask*[tiab])) OR (control*[tiab] AND (study[tiab] OR studies[tiab] OR trial*[tiab] OR group*[tiab])) OR (Nonrandom*[tiab] OR "non random*"[tiab] OR "non-random*"[tiab] OR "quasi-random*"[tiab] OR quasirandom*[tiab]) OR allocated[tiab] OR (("open label"[tiab] OR "open-label"[tiab]) AND (study[tiab] OR studies[tiab] OR trial*[tiab])) OR ((equivalence[tiab] OR superiority[tiab] OR "non-inferiority"[tiab] OR noninferiority[tiab]) AND (study[tiab] OR studies[tiab] OR trial*[tiab])) OR ("pragmatic study"[tiab] OR "pragmatic studies"[tiab]) OR ((pragmatic[tiab] OR practical[tiab]) AND trial*[tiab]) OR ((quasiexperimental[tiab] OR "quasi-experimental"[tiab]) AND (study[tiab] OR studies[tiab] OR trial*[tiab])) OR (phase[ti] AND (III[ti] OR 3[ti]) AND (study[ti] OR studies[ti] OR trial*[ti])) OR (phase[ot] AND (III[ot] OR 3[ot]) AND (study[ot] OR studies[ot] OR trial*[ot]))	4,964,246

#	Search code	Hits
13	"systematic"[filter] OR "meta-analysis"[pt] OR "meta-analysis as topic"[mh] OR "meta analy*"[tw] OR metanaly*[tw] OR metaanaly*[tw] OR "met analy*"[tw] OR "integrative research"[tiab] OR "integrative review*"[tiab] OR "integrative overview*"[tiab] OR "research integration*"[tiab] OR "research overview*"[tiab] OR "collaborative review*"[tiab] OR "collaborative overview*"[tiab] OR "systematic review"[pt] OR "systematic reviews as topic"[mh] OR "systematic review*"[tiab] OR "technology assessment*"[tiab] OR "technology overview*"[tiab] OR "technology appraisal*"[tiab] OR "Technology Assessment, Biomedical"[mh] OR HTA[tiab] OR HTAs[tiab] OR "comparative efficacy"[tiab] OR "comparative effectiveness"[tiab] OR "outcomes research"[tiab] OR "indirect comparison*"[tiab] OR "Bayesian comparison"[tiab] OR (("indirect treatment"[tiab] OR "mixed-treatment"[tiab]) AND comparison*[tiab]) OR Embase*[tiab] OR Cinahl*[tiab] OR "systematic overview*"[tiab] OR "methodological overview*"[tiab] OR "methodologic overview*"[tiab] OR "methodological review*"[tiab] OR "methodologic review*"[tiab] OR "quantitative review*"[tiab] OR "quantitative overview*"[tiab] OR "quantitative synthes*"[tiab] OR "pooled analy*"[tiab] OR Cochrane[tiab] OR Medline[tiab] OR Pubmed[tiab] OR Medlars[tiab] OR handsearch*[tiab] OR "hand search*"[tiab] OR "meta-regression*"[tiab] OR metaregression*[tiab] OR "data synthes*"[tiab] OR "data extraction"[tiab] OR "data abstraction*"[tiab] OR "mantel haenszel"[tiab] OR peto[tiab] OR "der-simonian"[tiab] OR dersimonian[tiab] OR "fixed effect*"[tiab] OR "multiple treatment comparison"[tiab] OR "mixed treatment meta-analys*"[tiab] OR "umbrella review*"[tiab] OR (("multiple paramet*"[tiab]) AND ("evidence synthesis"[tiab])) OR (("multi-paramet*"[tiab]) AND ("evidence synthesis"[tiab])) OR ((multiparameter*[tiab]) AND ("evidence synthesis"[tiab])) OR "Cochrane Database Syst Rev"[Journal] OR "health technology assessment winchester, england"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal] OR "Int J Technol Assess Health Care"[Journal] OR "GMS Health Technol Assess"[Journal] OR "Health Technol Assess (Rockv)"[Journal] OR "Health Technol Assess Rep"[Journal]	821,340
14	(cohort studies[MeSH Terms] OR (cohort[Text Word] OR controlled clinical trial[Publication Type]) OR (case-control studies[MeSH Terms])) OR ((case[Text Word] AND control*[Text Word]))	4,362,156
15	#12 OR #13 OR #14 [all study designs]	8,102,143
16	#12 OR #13 [RCTs, SRs only]	5,430,683
17	#11 AND #15 [all study designs]	4,607
18	#11 AND #16 [RCTs, SRs only]	2,595
19	Cadaver*[tw] OR cadaver[mh] OR Infant[mh] OR Child*[mh] OR Adolescent[mh]	4,359,368
20	#17 NOT #19 [all study designs]	4,419
21	#18 NOT #19 [RCTs, SRs only]	2,520

#	Search code	Hits
22	#20 AND LIMITS: From 2000/1/1 to 2025/10/5, Abstract, English, Humans [all study designs]	1,496
23	#21 AND LIMITS: From 2000/1/1 to 2025/10/5, Abstract, English, Humans [RCTs, SRs only]	1,829

Appendix Table A-2. Cochrane Search Strategy

#	Search code
1	"atrial fibrillation"
2	MeSH descriptor: [Atrial Fibrillation] explode all trees
3	("atrial fibrillation"):ti,ab,kw OR ("Afib"):ti,ab,kw (Word variations have been searched)
4	("atrial flutter"):ti,ab,kw OR ("macroreentrant atrial tachycardia*"):ti,ab,kw OR ("typical flutter"):ti,ab,kw OR ("isthmus" AND "flutter"):ti,ab,kw (Word variations have been searched)
5	(#1 OR #2 OR #3) OR #4
6	"ablation" OR "pulmonary vein" OR "pulmonary vein isolation" OR "pulmonary vein antrum isolation" OR cryoablation OR "cryoballoon ablation" OR (microwave AND ablat*) OR "laser ablation" OR "pulsed field ablation" OR ("atriventricular node" AND ablat*) OR ("AV node" AND ablat*) OR ("AV nodal" AND ablat*) OR ("atrioventricular junction" AND ablat*) OR ("AV junction" and ablat*)
7	MeSH descriptor: [Pulmonary Veins] explode all trees
8	MeSH descriptor: [Radiofrequency Ablation] explode all trees
9	MeSH descriptor: [Cryosurgery] explode all trees
10	ablat*
11	#6 OR #7 OR #8 OR (#9 AND #10)
12	#5 AND #11
13	“antiarrhythmic drugs” OR “anti-arrhythmic drugs” OR “AAD” OR “medical therapy” OR “drug therapy” OR “pharmacologic*” OR “conservative” OR "Amiodarone" OR "Cordarone" OR "Nexterone" OR "Pacerone" OR "Dronedarone" OR "Multaq" OR "Dofetilide" OR "Tikosyn" OR "Sotalol" OR "Betapace" OR "Sorine" OR "Flecainide" OR "Tambocor" OR "Propafenone" OR "Rythmol" OR “Beta-blocker” OR “Beta blocker” OR "Metoprolol" OR "Lopressor" OR "Atenolol" OR "Tenormin" OR "Propranolol" OR "Inderal" OR "Bisoprolol" OR "Zebeta" OR "Bisotab" OR "Concor" OR "Carvedilol" OR "Coreg" OR “Calcium Channel Blocker” OR "Diltiazem" OR "Cardizem" OR "Verapamil" OR "Calan" OR "Nadolol" OR "Corgard" OR "Timolol" OR "Blocadren" OR "Digox*" OR "Lanoxin" OR "Digitek"
14	MeSH descriptor: [Anti-Arrhythmia Agents] explode all trees
15	MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees
16	#13 OR #14 OR #15
17	#14 OR #15
18	“Cardioversion” OR Maze OR “Left Atrial Appendage” OR “LAA” OR “LAAO” OR “pacemaker” OR “implantable cardioverter defibrillator” OR “ICD”
19	MeSH descriptor: [Electric Countershock] explode all trees
20	MeSH descriptor: [Maze Procedure] explode all trees
21	MeSH descriptor: [Left Atrial Appendage Closure] explode all trees
22	MeSH descriptor: [Pacemaker, Artificial] explode all trees
23	MeSH descriptor: [Defibrillators, Implantable] explode all trees
24	#18 OR #19 OR #20 OR #21 OR #22 OR #23
25	#17 OR #24
26	#12 AND #25

Appendix B. Excluded Articles

Appendix Table B-1. Studies excluded at full-text review

Citation	Reason for Exclusion
Adiyaman A, Buist TJ, Beukema RJ, et al. Randomized Controlled Trial of Surgical Versus Catheter Ablation for Paroxysmal and Early Persistent Atrial Fibrillation. Circulation Arrhythmia and electrophysiology 2018;11:e006182.	Ineligible Comparator
Al-Kaisey AM, Parameswaran R, Bryant C, et al. Atrial Fibrillation Catheter Ablation vs Medical Therapy and Psychological Distress: A Randomized Clinical Trial. Jama 2023;330:925-33.	Ineligible Population
Andrade JG, Khairy P, Macle L, et al. Incidence and significance of early recurrences of atrial fibrillation after cryoballoon ablation: insights from the multicenter Sustained Treatment of Paroxysmal Atrial Fibrillation (STOP AF) Trial. Circulation Arrhythmia and electrophysiology 2014;7:69-75.	Ineligible Study Design
Arbelo E, De Ponti R, Cohen L, et al. Clinical and economic impact of first-line or drug-naïve catheter ablation and delayed second-line catheter ablation for atrial fibrillation using a patient-level simulation model. Journal of medical economics 2024;27:1168-79.	Ineligible Study Design
S. W. E. Baalman, N. W. E. van den Berg, J. Neefs, W. R. Berger, E. R. Meulendijks, R. de Bruin-Bon, B. J. Bouma, W. J. P. van Boven, A. H. G. Driessen and J. R. de Groot, 2022 Left atrial strain and recurrence of atrial fibrillation after thoracoscopic surgical ablation: a subanalysis of the AFACT study	Ineligible Intervention
T. D. Bahnson, A. Giczewska, D. B. Mark, A. M. Russo, K. H. Monahan, H. R. Al-Khalidi, A. P. Silverstein, J. E. Poole, K. L. Lee and D. L. Packer, 2022 Association Between Age and Outcomes of Catheter Ablation Versus Medical Therapy for Atrial Fibrillation: Results From the CABANA Trial	Ineligible Population
E. Bertaglia, G. Stabile, G. Senatore, A. Colella, M. Del Greco, H. Goessinger, F. Lamberti, M. Lowe, R. Mantovan, N. Peters, C. Pratola, P. Raatikainen, P. Turco and R. Verlato, 2007 A clinical and health-economic evaluation of pulmonary vein encircling ablation compared with antiarrhythmic drug treatment in patients with persistent atrial fibrillation (Catheter Ablation for the Cure of Atrial Fibrillation-2 study)	Ineligible Population
E. Bertaglia, G. Senatore, L. De Michieli, A. De Simone, C. Amellone, S. Ferretto, V. La Rocca, M. Giuggia, D. Corrado, F. Zoppo and G. Stabile, 2017 Twelve-year follow-up of catheter ablation for atrial fibrillation: A prospective, multicenter, randomized study	Ineligible Population
A. Blandino, E. Toso, M. Scaglione, M. Anselmino, F. Ferraris, D. Sardi, A. Battaglia and F. Gaita, 2013 Long-term efficacy and safety of two different rhythm control strategies in elderly patients with symptomatic persistent atrial fibrillation	Ineligible Population
C. Blomström-Lundqvist, S. Gizurarson, J. Schwieler, S. M. Jensen, L. Bergfeldt, G. Kennebäck, A. Rubulis, H. Malmborg, P. Raatikainen, S. Lönnerholm, N. Höglund and D. Mörtsell, 2019 Effect of Catheter Ablation vs Antiarrhythmic Medication on Quality of Life in Patients With Atrial Fibrillation: The CAPTAF Randomized Clinical Trial	Ineligible Population
V. Boyalla, S. Haldar, H. Khan, I. Kralj-Hans, W. Banya, J. Lord, A. Satishkumar, T. Bahrami, A. De Souza, J. R. Clague, D. P. Francis, W. Hussain, J. W. Jarman, D. G. Jones, Z. Chen, N. Mediratta, J. Hyde, M. Lewis, R. Mohiaddin, T. V. Salukhe, V. Markides, J. McCready, D. Gupta and T. Wong, 2024 Long-term clinical outcomes and cost-effectiveness of catheter vs thoracoscopic surgical ablation in long-standing persistent atrial fibrillation using continuous cardiac monitoring: CASA-AF randomized controlled trial	Ineligible Comparator
J. Brachmann, C. Sohns, D. Andresen, J. Siebels, S. Sehner, L. Boersma, B. Merkely, E. Pokushalov, P. Sanders, H. Schunkert, D. Bänsch, L. Dagher, Y. Zhao, C. Mahnkopf, K. Wegscheider and N. F. Marrouche, 2021 Atrial Fibrillation Burden and Clinical Outcomes in Heart Failure: The CASTLE-AF Trial	Ineligible Population
B. Brüggenjürgen, S. Kohler, N. Ezzat, T. Reinhold and S. N. Willich, 2013 Cost effectiveness of antiarrhythmic medications in patients suffering from atrial fibrillation	Ineligible Publication Type
T. J. Buist, A. Adiyaman, R. J. Beukema, J. J. J. Smit, P. Delnoy, M. E. W. Hemels, H. T. Sie, A. R. Ramdat Misier and A. Elvan, 2020 Quality of life after catheter and minimally invasive surgical ablation of paroxysmal and early persistent atrial fibrillation: results from the SCALAF trial	Ineligible Comparator

Citation	Reason for Exclusion
T. J. Bunch, J. E. Poole, A. P. Silverstein, K. L. Lee, H. R. Al-Khalidi, G. Hindricks, A. Romanov, E. Pokushalov, T. D. Bahnson, M. R. Daniels, J. P. Piccini, D. B. Mark and D. L. Packer, 2024 Prognostic Impact of Sinus Rhythm in Atrial Fibrillation Patients: Separating Rhythm Outcomes From Randomized Strategy Findings From the CABANA Trial	Ineligible Study Design
M. U. Butt, N. Okumus, A. Jabri, C. Thomas, Y. Tarabichi and S. Karim, 2022 Early Versus Late Catheter Ablation of Atrial Fibrillation and Risk of Permanent Pacemaker Implantation in Patients With Underlying Sinus Node Dysfunction	Ineligible Population
Calvert P, Farinha JM, Gupta D, et al. A comparison of medical therapy and ablation for atrial fibrillation in patients with heart failure. Expert review of cardiovascular therapy. 2022 Mar;20(3):169-83. PMID: 35255780.	Ineligible Publication Type
Camm AJ, Breithardt G, Crijns H, et al. Real-life observations of clinical outcomes with rhythm- and rate-control therapies for atrial fibrillation RECORDAF (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation). Journal of the American College of Cardiology. 2011 Jul 26;58(5):493-501. PMID: 21777747.	Ineligible Intervention
Capocci S, Tomasi L, Bolzan B, et al. Atrial fibrillation ablation versus medical therapy in arrhythmia-induced cardiomyopathy: a propensity score analysis. Journal of cardiovascular medicine (Hagerstown, Md.). 2025 Jun 1;26(6):314-9. PMID: 40472176.	Ineligible Population
Carlsson J, Miketic S, Windeler J, et al. Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. Journal of the American College of Cardiology. 2003 May 21;41(10):1690-6. PMID: 12767648.	Ineligible Intervention
Castellá M, Kotecha D, van Laar C, et al. Thoracoscopic vs. catheter ablation for atrial fibrillation: long-term follow-up of the FAST randomized trial. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2019 May 1;21(5):746-53. PMID: 30715255.	Ineligible Comparator
Chan PS, Vijan S, Morady F, et al. Cost-effectiveness of radiofrequency catheter ablation for atrial fibrillation. Journal of the American College of Cardiology. 2006 Jun 20;47(12):2513-20. PMID: 16781382.	Ineligible Population
Chao TF, Chan YH, Chiang CE, et al. Early Rhythm Control and the Risks of Ischemic Stroke, Heart Failure, Mortality, and Adverse Events When Performed Early (<3 Months): A Nationwide Cohort Study of Newly Diagnosed Patients with Atrial Fibrillation. Thrombosis and haemostasis. 2022 Nov;122(11):1899-910. PMID: 35322396.	Ineligible Intervention
Chen HS, Wen JM, Wu SN, et al. Catheter ablation for paroxysmal and persistent atrial fibrillation. The Cochrane database of systematic reviews. 2012 Apr 18;2012(4):CD007101. PMID: 22513945.	Ineligible Population
Chen YW, Bai R, Lin T, et al. Pacing or ablation: which is better for paroxysmal atrial fibrillation-related tachycardia-bradycardia syndrome? Pacing and clinical electrophysiology : PACE. 2014 Apr;37(4):403-11. PMID: 24456243.	Ineligible Population
Chen S, Pürerfellner H, Meyer C, et al. Rhythm control for patients with atrial fibrillation complicated with heart failure in the contemporary era of catheter ablation: a stratified pooled analysis of randomized data. European heart journal. 2020 Aug 7;41(30):2863-73. PMID: 31298266.	Ineligible Population
Chen S, Pürerfellner H, Ouyang F, et al. Catheter ablation vs. antiarrhythmic drugs as 'first-line' initial therapy for atrial fibrillation: a pooled analysis of randomized data. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2021 Dec 7;23(12):1950-60. PMID: 34405878.	Ineligible Study Design
Chew DS, Loring Z, Anand J, et al. Economic Evaluation of Catheter Ablation of Atrial Fibrillation in Patients with Heart Failure With Reduced Ejection Fraction. Circulation. Cardiovascular quality and outcomes. 2020 Dec;13(12):e007094. PMID: 33280436.	Ineligible Population
Chew DS, Li Y, Cowper PA, et al. Cost-Effectiveness of Catheter Ablation Versus Antiarrhythmic Drug Therapy in Atrial Fibrillation: The CABANA Randomized Clinical Trial. Circulation. 2022 Aug 16;146(7):535-47. PMID: 35726631.	Ineligible Population

Citation	Reason for Exclusion
Chiappini B, Martìn-Suàrez S, LoForte A, et al. Cox/Maze III operation versus radiofrequency ablation for the surgical treatment of atrial fibrillation: a comparative study. The Annals of thoracic surgery. 2004 Jan;77(1):87-92. PMID: 14726041.	Ineligible Population
Chieng D, Sugumar H, Segan L, et al. Atrial Fibrillation Ablation for Heart Failure With Preserved Ejection Fraction: A Randomized Controlled Trial. JACC. Heart failure. 2023 Jun;11(6):646-58. PMID: 36868916.	Ineligible Population
Cho MS, Lee JH, Nam GB, et al. Comparison between catheter ablation versus permanent pacemaker implantation as an initial treatment for tachycardia-bradycardia syndrome patients: a prospective, randomized trial. BMC cardiovascular disorders. 2024 May 10;24(1):246. PMID: 38730404.	Ineligible Population
Choi AD, Hematpour K, Kukin M, et al. Ablation vs medical therapy in the setting of symptomatic atrial fibrillation and left ventricular dysfunction. Congestive heart failure (Greenwich, Conn.). 2010 Jan-Feb;16(1):10-4. PMID: 20078622.	Ineligible Population
Chong E, Chang HY, Chen YY, et al. When Atrial Fibrillation Co-Exists with Coronary Artery Disease in Patients with Prior Coronary Intervention - Does Ablation Benefit? Heart, lung & circulation. 2016 Jun;25(6):538-50. PMID: 26839165.	Ineligible Population
De Maat GE, Van Gelder IC, Rienstra M, et al. Surgical vs. transcatheter pulmonary vein isolation as first invasive treatment in patients with atrial fibrillation: a matched group comparison. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2014 Jan;16(1):33-9. PMID: 23796618.	Ineligible Comparator
Di Biase L, Mohanty P, Mohanty S, et al. Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device: Results From the AATAC Multicenter Randomized Trial. Circulation. 2016 Apr 26;133(17):1637-44. PMID: 27029350.	Ineligible Population
Dickow J, Kany S, Roth Cardoso V, et al. Outcomes of Early Rhythm Control Therapy in Patients With Atrial Fibrillation and a High Comorbidity Burden in Large Real-World Cohorts. Circulation. Arrhythmia and electrophysiology. 2023 May;16(5):e011585. PMID: 36942567.	Ineligible Population
Dilk P, Uhe T, Forkmann M, et al. Pulmonary vein isolation versus SHAM-pulmonary vein isolation for symptomatic relief in patients with atrial fibrillation-Design and rationale of the PVI-SHAM-AF trial. American heart journal. 2025 Dec;290:93-104. PMID: 40513974.	Ineligible Publication Type
Ding WY, Williams E, Das M, et al. Cryoballoon pulmonary vein isolation as first line treatment for typical atrial flutter (CRAFT): study protocol for a randomised controlled trial. Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing. 2021 Apr;60(3):427-32. PMID: 32385774.	Ineligible Comparator
Du X, Guo L, He X, et al. A comparison of the real world effectiveness of catheter ablation and drug therapy in atrial fibrillation patients in a Chinese setting. BMC cardiovascular disorders. 2017 Jul 27;17(1):204. PMID: 28750608.	Ineligible Population
Eckardt L, Sehner S, Suling A, et al. Attaining sinus rhythm mediates improved outcome with early rhythm control therapy of atrial fibrillation: the EAST-AFNET 4 trial. European heart journal. 2022 Oct 21;43(40):4127-44. PMID: 36036648.	Ineligible Population
Eckardt L, Wolfes J, Frommeyer G. Benefits of early rhythm control of atrial fibrillation. Trends in cardiovascular medicine. 2024 Jul;34(5):288-94. PMID: 37054762.	Ineligible Publication Type
Esato M, An Y, Ogawa H, et al. Major adverse cardiovascular events and mortality after catheter ablation in Japanese patients with atrial fibrillation: The Fushimi AF Registry. Heart and vessels. 2021 Aug;36(8):1219-27. PMID: 33575844.	Ineligible Population
Eysenck W, Sulke N, Freemantle N, et al. The effect of atrial fibrillation intervention on nocturnal respiratory events in elderly patients with persistent AF. The clinical respiratory journal. 2019 May;13(5):280-8. PMID: 30793493.	Ineligible Population
Fengsrud E, Wickbom A, Almroth H, et al. Total endoscopic ablation of patients with long-standing persistent atrial fibrillation: a randomized controlled study. Interactive cardiovascular and thoracic surgery. 2016 Aug;23(2):292-8. PMID: 27068249.	Ineligible Intervention

Citation	Reason for Exclusion
Forleo GB, Mantica M, De Luca L, et al. Catheter ablation of atrial fibrillation in patients with diabetes mellitus type 2: results from a randomized study comparing pulmonary vein isolation versus antiarrhythmic drug therapy. Journal of cardiovascular electrophysiology. 2009 Jan;20(1):22-8. PMID: 18775050.	Ineligible Population
Fukui A, Tanino T, Yamaguchi T, et al. Catheter ablation of atrial fibrillation reduces heart failure rehospitalization in patients with heart failure with preserved ejection fraction. Journal of cardiovascular electrophysiology. 2020 Mar;31(3):682-8. PMID: 31985099.	Ineligible Population
Gao L, Moodie M. Modelling the lifetime cost-effectiveness of catheter ablation for atrial fibrillation with heart failure. BMJ open. 2019 Sep 5;9(9):e031033. PMID: 31492790.	Ineligible Population
Geng J, Zhang Y, Wang Y, et al. Catheter ablation versus rate control in patients with atrial fibrillation and heart failure: A multicenter study. Medicine. 2017 Dec;96(49):e9179. PMID: 29245366.	Ineligible Population
Geuzebroek GS, Ballaux PK, van Hemel NM, et al. Medium-term outcome of different surgical methods to cure atrial fibrillation: is less worse? Interactive cardiovascular and thoracic surgery. 2008 Apr;7(2):201-6. PMID: 18045831.	Ineligible Population
Gupta D, Ding WY, Calvert P, et al. Cryoballoon Pulmonary Vein Isolation as First-Line Treatment for Typical Atrial Flutter. Heart (British Cardiac Society). 2023 Feb 14;109(5):364-71. PMID: 36396438.	Ineligible Comparator
Haigney MC. Ablation should not be first-line therapy for the treatment of atrial fibrillation. Expert review of cardiovascular therapy. 2007 Jul;5(4):673-9. PMID: 17605646.	Ineligible Publication Type
Haldar S, Khan HR, Boyalla V, et al. Catheter ablation vs. thoracoscopic surgical ablation in long-standing persistent atrial fibrillation: CASA-AF randomized controlled trial. European heart journal. 2020 Dec 14;41(47):4471-80. PMID: 32860414.	Ineligible Comparator
Hermida JS, Chen J, Meyer C, et al. Cryoballoon catheter ablation versus antiarrhythmic drugs as a first-line therapy for patients with paroxysmal atrial fibrillation: Rationale and design of the international Cryo-FIRST study. American heart journal. 2020 Apr;222:64-72. PMID: 32018203.	Ineligible Publication Type
Hunter RJ, Berriman TJ, Diab I, et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). Circulation. Arrhythmia and electrophysiology. 2014 Feb;7(1):31-8. PMID: 24382410.	Ineligible Population
Ishiguchi H, Lip GYH. In symptomatic AF, catheter ablation vs. medical therapy reduced depression and anxiety symptoms at 12 mo. Annals of internal medicine. 2024 Jan;177(1):JC4. PMID: 38163378.	Ineligible Publication Type
Jenkins LS, Brodsky M, Schron E, et al. Quality of life in atrial fibrillation: the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. American heart journal 2005;149:112-20.	Ineligible Intervention
Jin MN, Kim TH, Kang KW, et al. Atrial Fibrillation Catheter Ablation Improves 1-Year Follow-Up Cognitive Function, Especially in Patients With Impaired Cognitive Function. Circulation Arrhythmia and electrophysiology 2019;12:e007197.	Ineligible Outcomes
Jons C, Hansen PS, Johannessen A, et al. The Medical ANtiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation (MANTRA-PAF) trial: clinical rationale, study design, and implementation. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2009;11:917-23.	Ineligible Publication Type
Kalman JM, Al-Kaisey AM, Parameswaran R, et al. Impact of early vs. delayed atrial fibrillation catheter ablation on atrial arrhythmia recurrences. European heart journal 2023;44:2447-54.	Ineligible Population
Kanagaratnam P, McCready J, Tayebjee M, et al. Ablation versus anti-arrhythmic therapy for reducing all hospital episodes from recurrent atrial fibrillation: a prospective, randomized, multi-centre, open label trial. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2023;25:863-72.	Ineligible Population

Citation	Reason for Exclusion
Kanthasamy V, Schilling R, Zongo O, et al. Feasibility of double-blinded, placebo-controlled interventional study for assessing catheter ablation efficacy in persistent atrial fibrillation: Insights from the ORBITA AF feasibility study. American heart journal 2024;269:56-71.	Ineligible Intervention
Kany S, Cardoso VR, Bravo L, et al. Eligibility for early rhythm control in patients with atrial fibrillation in the UK Biobank. Heart (British Cardiac Society) 2022;108:1873-80.	Ineligible Intervention
Karatela MF, Calkins H. Catheter ablation as first line therapy for atrial fibrillation. Progress in cardiovascular diseases 2025;91:33-7.	Ineligible Publication Type
Katapadi A, Garg J, Chelikam N, et al. Pilot Study of Early Catheter Ablation and Neurological Outcomes in Atrial Fibrillation-Related Stroke: RESCUE-STROKE. JACC Clinical electrophysiology 2025;11:969-76.	Ineligible Study Design
Khaykin Y. Cost-effectiveness of catheter ablation for atrial fibrillation. Current opinion in cardiology 2007;22:11-7.	Ineligible Publication Type
Khaykin Y, Wang X, Natale A, et al. Cost comparison of ablation versus antiarrhythmic drugs as first-line therapy for atrial fibrillation: an economic evaluation of the RAAFT pilot study. Journal of cardiovascular electrophysiology 2009;20:7-12.	Ineligible Outcomes
Kim D, Yang PS, You SC, et al. Comparative Effectiveness of Early Rhythm Control Versus Rate Control for Cardiovascular Outcomes in Patients With Atrial Fibrillation. Journal of the American Heart Association 2021;10:e023055.	Ineligible Intervention
Kim D, Yang PS, You SC, et al. Treatment timing and the effects of rhythm control strategy in patients with atrial fibrillation: nationwide cohort study. BMJ (Clinical research ed) 2021;373:n991.	Ineligible Intervention
Kim D, Yang PS, You SC, et al. Age and Outcomes of Early Rhythm Control in Patients With Atrial Fibrillation: Nationwide Cohort Study. JACC Clinical electrophysiology 2022;8:619-32.	Ineligible Intervention
Kim D, Yang PS, You SC, et al. Association of rhythm control with incident dementia among patients with atrial fibrillation: a nationwide population-based cohort study. Age and ageing 2022;51.	Ineligible Intervention
Kim D, Yang PS, You SC, et al. Early Rhythm Control Therapy for Atrial Fibrillation in Low-Risk Patients : A Nationwide Propensity Score-Weighted Study. Annals of internal medicine 2022;175:1356-65.	Ineligible Intervention
Kim S, Kim KA, Park S, et al. Maintenance of Sinus Rhythm Is Associated With Lower Incidence of Stroke in Patients With Drug-Refractory Atrial Fibrillation. Pacing and clinical electrophysiology : PACE 2025;48:106-13.	Ineligible Population
Kirchhof P, Breithardt G, Camm AJ, et al. Improving outcomes in patients with atrial fibrillation: rationale and design of the Early treatment of Atrial fibrillation for Stroke prevention Trial. American heart journal 2013;166:442-8.	Ineligible Publication Type
Kirchhof P, Camm AJ, Goette A, et al. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. The New England journal of medicine 2020;383:1305-16.	Ineligible Intervention
Kochhäuser S, Khaykin Y, Beardsall J, et al. Comparison of outcomes after cardioversion or atrial fibrillation ablation in patients with differing periprocedural anticoagulation regimens. The Canadian journal of cardiology 2014;30:1541-6.	Ineligible Comparator
Kuck KH, Lebedev DS, Mikhaylov EN, et al. Catheter ablation or medical therapy to delay progression of atrial fibrillation: the randomized controlled atrial fibrillation progression trial (ATTEST). Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2021;23:362-9.	Ineligible Population
Kumar S, Ling LH, Halloran K, et al. Esophageal hematoma after atrial fibrillation ablation: incidence, clinical features, and sequelae of esophageal injury of a different sort. Circulation Arrhythmia and electrophysiology 2012;5:701-5.	Ineligible Study Design
Lawin D, Stellbrink C, Chun KJ, et al. Impact of atrial fibrillation diagnosis-to-ablation time on 24-month efficacy and safety outcomes in the Cryo Global Registry. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2025;27.	Ineligible Population
Lee SR, Choi EK, Lee SW, Han KD, Oh S, Lip GYH. Early Rhythm Control in Patients With Incident Atrial Fibrillation Who Had a Prior Stroke. JACC Clinical electrophysiology 2023;9:1121-33.	Ineligible Intervention

Citation	Reason for Exclusion
Leung LWM, Imhoff RJ, Marshall HJ, et al. Cost-effectiveness of catheter ablation versus medical therapy for the treatment of atrial fibrillation in the United Kingdom. Journal of cardiovascular electrophysiology 2022;33:164-75.	Ineligible Population
Lima FV, Kennedy KF, Sheikh W, et al. Thirty-day readmissions after atrial fibrillation catheter ablation in patients with heart failure. Pacing and clinical electrophysiology : PACE 2020;43:930-40.	Ineligible Study Design
Lin YJ, Chao TF, Tsao HM, et al. Successful catheter ablation reduces the risk of cardiovascular events in atrial fibrillation patients with CHA2DS2-VASc risk score of 1 and higher. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2013;15:676-84.	Ineligible Population
Long S, Sun Y, Dai S, et al. Safety and efficacy of catheter ablation in atrial fibrillation patients with heart failure with preserved ejection fraction. BMC cardiovascular disorders 2025;25:47.	Ineligible Intervention
Loutrianakis E, Barakat T, Olshansky B. Early versus late atrial fibrillation after atrial flutter ablation. Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing 2002;6:173-80.	Ineligible Population
Luo Q, Li X, Xie Y, et al. Long-term outcomes of cryoballoon versus robotic magnetic navigation guided radiofrequency ablation in patients with persistent atrial fibrillation. Scientific reports 2025;15:6181.	Ineligible Comparator
I. Mann, T. Sasikaran, B. Sandler, D. Babalis, N. Johnson, E. Falaschetti, A. Copley, M. Tayebjee, D. Todd, E. Shepherd, J. McCready, N. F. Poulter and P. Kanagaratnam, 2019 Ablation versus Anti-Arrhythmic Therapy for Reducing All Hospital Episodes from Recurrent Atrial Fibrillation (AVATAR-AF): Design and rationale	Ineligible Publication Type
M. Manninger, J. Ebner, D. Zweiker, R. Sieghartsleitner, B. Mastnak, E. Bisping, P. Lercher, R. Riedlbauer, B. Rotman, H. Brussee and D. Scherr, 2018 Is there a difference in rhythm outcome between patients undergoing first line versus second line paroxysmal atrial fibrillation ablation?	Ineligible Study Design
M. Mansour, E. K. Heist, R. Agarwal, T. J. Bunch, E. Karst, J. N. Ruskin and S. Mahapatra, 2018 Stroke and Cardiovascular Events After Ablation or Antiarrhythmic Drugs for Treatment of Patients With Atrial Fibrillation	Ineligible Intervention
D. B. Mark, K. J. Anstrom, S. Sheng, J. P. Piccini, K. N. Baloch, K. H. Monahan, M. R. Daniels, T. D. Bahnson, J. E. Poole, Y. Rosenberg, K. L. Lee and D. L. Packer, 2019 Effect of Catheter Ablation vs Medical Therapy on Quality of Life Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial	Ineligible Population
P. Martens, S. N. Augusto, Jr., J. Erzeel, L. Pison, W. Mullens and W. H. W. Tang, 2025 Effects of Atrial Fibrillation Ablation for Heart Failure With Preserved Ejection Fraction: Insights From CABANA	Ineligible Population
L. C. B. Martins, C. F. Pisani, F. K. Dorfman, F. C. C. Darrieux, T. C. Wu, A. P. Ferraz, D. T. Hachul, C. C. Castro, R. R. D. Prado, L. V. F. Souza, L. Sacilloto, G. D. A. Pessente, C. J. Grupi, M. O. Chokr, C. H. Nomura, K. R. Oliveira, C. P. Balbo, S. L. Melo, P. Veronese and M. I. Scanavacca, 2024 Randomized Study Comparing Radiofrequency Ablation with the PVAC Gold System vs. Antiarrhythmic Drugs in Elderly Patients with Symptomatic Atrial Fibrillation	Ineligible Population
C. McKenna, S. Palmer, M. Rodgers, D. Chambers, N. Hawkins, S. Golder, S. Van Hout, C. Pepper, D. Todd and N. Woolacott, 2009 Cost-effectiveness of radiofrequency catheter ablation for the treatment of atrial fibrillation in the United Kingdom	Ineligible Population
K. Miura, N. Ikemura, T. Kimura, Y. Katsumata, I. Ueda, K. Tanimoto, T. Ohki, D. Shinmura, K. Negishi, K. Fukuda, S. Takatsuki and S. Kohsaka, 2020 Treatment strategies and subsequent changes in the patient-reported quality-of-life among elderly patients with atrial fibrillation	Ineligible Population
H. Miyama, N. Ikemura, T. Kimura, Y. Katsumata, S. Yamashita, K. Yamaoka, S. Ibe, O. Sekine, I. Ueda, I. Nakamura, K. Negishi, S. Kohsaka, S. Takatsuki and M. Ieda, 2024 Predictors and incidence of health status deterioration in patients with early atrial fibrillation	Ineligible Study Design

Citation	Reason for Exclusion
M. Moersdorf, J. G. P. Tijssen, N. F. Marrouche, H. Crijns, A. Costard-Jaeckle, L. Bergau, G. Hindricks, N. Dagres, S. Sossalla, R. Schramm, H. Fox, T. Fink, M. El Hamriti, V. Sciacca, F. Konietschke, V. Rudolph, J. Gummert, P. Sommer and C. Sohns, 2024 Prognosis of patients in end-stage heart failure with atrial fibrillation treated with ablation: Insights from CASTLE-HTx	Ineligible Population
K. H. Monahan, T. J. Bunch, D. B. Mark, J. E. Poole, T. D. Bahnson, H. R. Al-Khalidi, A. P. Silverstein, M. R. Daniels, K. L. Lee and D. L. Packer, 2022 Influence of atrial fibrillation type on outcomes of ablation vs. drug therapy: results from CABANA	Ineligible Population
L. Mont, F. Bisbal, A. Hernández-Madrid, N. Pérez-Castellano, X. Viñolas, A. Arenal, F. Arribas, I. Fernández-Lozano, A. Bodegas, A. Cobos, R. Matía, J. Pérez-Villacastín, J. M. Guerra, P. Ávila, M. López-Gil, V. Castro, J. I. Arana and J. Brugada, 2014 Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study)	Ineligible Population
Nogueira A, Felix N, Kalil F, et al. A Bayesian Interpretation of CABANA and Other Randomized Controlled Trials for Catheter Ablation in Patients With Atrial Fibrillation. Journal of cardiovascular electrophysiology 2025;36:617-24.	Ineligible Publication Type
Nyong J, Amit G, Adler AJ, et al. Efficacy and safety of ablation for people with non-paroxysmal atrial fibrillation. The Cochrane database of systematic reviews 2016;11:CD012088.	Ineligible Publication Type
Oka S, Kai T, Hoshino K, et al. Rate Versus Rhythm Control in Tachycardia-Induced Cardiomyopathy Patients with Persistent Atrial Flutter. International heart journal 2021;62:119-26.	Ineligible Intervention
Osmancik P, Havránek Š, Bulková V, et al. Catheter ablation versus antiarrhythmic drugs with risk factor modification for treatment of atrial fibrillation: a protocol of a randomised controlled trial (PRAGUE-25 trial). BMJ open 2022;12:e056522.	Ineligible Publication Type
Osmancik P, Roubicek T, Havranek S, et al. Catheter Ablation vs Lifestyle Modification With Antiarrhythmic Drugs to Treat Atrial Fibrillation: PRAGUE-25 Trial. Journal of the American College of Cardiology 2025;86:18-28.	Ineligible Population
Packer DL, Mark DB, Robb RA, et al. Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) Trial: Study Rationale and Design. American heart journal 2018;199:192-9.	Ineligible Publication Type
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;321:1261-74.	Ineligible Population
Packer DL, Piccini JP, Monahan KH, et al. Ablation Versus Drug Therapy for Atrial Fibrillation in Heart Failure: Results From the CABANA Trial. Circulation 2021;143:1377-90.	Ineligible Population
Pappone C, Rosanio S, Augello G, et al. Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation: outcomes from a controlled nonrandomized long-term study. Journal of the American College of Cardiology 2003;42:185-97.	Ineligible Population
Park J, Shim J, Lee JM, et al. Risks and Benefits of Early Rhythm Control in Patients With Acute Strokes and Atrial Fibrillation: A Multicenter, Prospective, Randomized Study (the RAFAS Trial). Journal of the American Heart Association 2022;11:e023391.	Ineligible Intervention
Park YJ, Park JW, Yu HT, et al. Sex difference in atrial fibrillation recurrence after catheter ablation and antiarrhythmic drugs. Heart (British Cardiac Society) 2023;109:519-26.	Ineligible Intervention
Parkash R, Wells G, Rouleau J, et al. A randomized ablation-based atrial fibrillation rhythm control versus rate control trial in patients with heart failure and high burden atrial fibrillation: The RAFT-AF trial rationale and design. American heart journal 2021;234:90-100.	Ineligible Publication Type
Parkash R, Wells GA, Rouleau J, et al. Randomized Ablation-Based Rhythm-Control Versus Rate-Control Trial in Patients With Heart Failure and Atrial Fibrillation: Results from the RAFT-AF trial. Circulation 2022;145:1693-704.	Ineligible Intervention
Pelargonio G, Prystowsky EN. Rate versus rhythm control in the management of patients with atrial fibrillation. Nature clinical practice Cardiovascular medicine 2005;2:514-21.	Ineligible Intervention

Citation	Reason for Exclusion
Pires LM, Leiria TL, de Lima GG, Kruse ML, Nesralla IA, Kalil RA. Comparison of surgical cut and sew versus radiofrequency pulmonary veins isolation for chronic permanent atrial fibrillation: a randomized study. Pacing and clinical electrophysiology : PACE 2010;33:1249-57.	Ineligible Intervention
Poole JE, Bahnson TD, Monahan KH, et al. Recurrence of Atrial Fibrillation After Catheter Ablation or Antiarrhythmic Drug Therapy in the CABANA Trial. Journal of the American College of Cardiology 2020;75:3105-18.	Ineligible Population
Pragliola C, Mastroroberto P, Gaudino M, Chello M, Covino E. Staged transthoracic approach to persistent atrial fibrillation (TOP-AF): study protocol for a randomized trial. Trials 2014;15:190.	Ineligible Population
Rettmann ME, Holmes DR, 3rd, Monahan KH, et al. Treatment-Related Changes in Left Atrial Structure in Atrial Fibrillation: Findings From the CABANA Imaging Substudy. Circulation Arrhythmia and electrophysiology 2021;14:e008540.	Ineligible Outcomes
Reynolds MR, Zimetbaum P, Josephson ME, Ellis E, Danilov T, Cohen DJ. Cost-effectiveness of radiofrequency catheter ablation compared with antiarrhythmic drug therapy for paroxysmal atrial fibrillation. Circulation Arrhythmia and electrophysiology 2009;2:362-9.	Ineligible Intervention
Reynolds MR, Lamotte M, Todd D, et al. Cost-effectiveness of cryoballoon ablation for the management of paroxysmal atrial fibrillation. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2014;16:652-9.	Ineligible Population
Richter B, Gwechenberger M, Kriegisch M, Albinni S, Marx M, Gössinger HD. Combined circular multielectrode catheter and point-by-point ablation is superior to point-by-point ablation alone in eliminating atrial fibrillation. International journal of cardiology 2013;168:3721-7.	Ineligible Comparator
Rillig A, Magnussen C, Ozga AK, et al. Early Rhythm Control Therapy in Patients With Atrial Fibrillation and Heart Failure. Circulation 2021;144:845-58.	Ineligible Intervention
Russo AM, Zeitler EP, Giczewska A, et al. Association Between Sex and Treatment Outcomes of Atrial Fibrillation Ablation Versus Drug Therapy: Results From the CABANA Trial. Circulation 2021;143:661-72.	Ineligible Population
S. Saksena and A. Slee, 2025 Rate Versus Rhythm Control for Atrial Fibrillation with Heart Failure	Ineligible Comparator
Saksena S, Ken-Opurum J, McKindley DS, et al. Arrhythmia Recurrence and Rhythm Control Strategies After Catheter Ablation of Newly Diagnosed Atrial Fibrillation (ARRC-AF Study). JACC Clinical electrophysiology 2025;11:763-75.	Ineligible Study Design
Sang CH, Chen K, Pang XF, et al. Depression, anxiety, and quality of life after catheter ablation in patients with paroxysmal atrial fibrillation. Clinical cardiology 2013;36:40-5.	Ineligible Population
Schneider R, Lauschke J, Tischer T, et al. Pulmonary vein triggers play an important role in the initiation of atrial flutter: Initial results from the prospective randomized Atrial Fibrillation Ablation in Atrial Flutter (Triple A) trial. Heart rhythm 2015;12:865-71.	N<20 or <10 per Group
Sciacca V, Sohns C, Crijns H, et al. Effects of atrial fibrillation ablation on arrhythmia burden and ventricular function in end-stage heart failure: Lessons from CASTLE-HTx. European journal of heart failure 2025;27:255-63.	Ineligible Comparator
Sindby JE, Vadmann H, Lundbye-Christensen S, et al. Percutaneous versus thoracoscopic ablation of symptomatic paroxysmal atrial fibrillation: a randomised controlled trial - the FAST II study. Journal of cardiothoracic surgery 2018;13:101.	Ineligible Population
Sohns C, Zintl K, Zhao Y, et al. Impact of Left Ventricular Function and Heart Failure Symptoms on Outcomes Post Ablation of Atrial Fibrillation in Heart Failure: CASTLE-AF Trial. Circulation Arrhythmia and electrophysiology 2020;13:e008461.	Ineligible Population
Sohns C, Marrouche NF, Costard-Jäckle A, et al. Catheter ablation for atrial fibrillation in patients with end-stage heart failure and eligibility for heart transplantation. ESC heart failure 2021;8:1666-74.	Ineligible Publication Type
Sohns C, Fox H, Marrouche NF, et al. Catheter Ablation in End-Stage Heart Failure with Atrial Fibrillation. The New England journal of medicine 2023;389:1380-9.	Ineligible Population

Citation	Reason for Exclusion
Song Z, Wang SY, Qidong Z, et al. Catheter ablation versus medical rate control for persistent atrial fibrillation in older heart failure patients with reduced ejection fraction. Heart (British Cardiac Society) 2025;111:811-7.	Ineligible Population
Stulak JM, Dearani JA, Sundt TM, 3rd, Daly RC, Schaff HV. Ablation of atrial fibrillation: comparison of catheter-based techniques and the Cox-Maze III operation. The Annals of thoracic surgery 2011;91:1882-8; discussion 8-9.	Ineligible Study Design
Sugihara C, Furniss S, Hyde J, Lewis M, Sulke N. Results of the first investigator-initiated randomized clinical trial of nMARQTM, PVACTM, and thoracoscopic ablation for paroxysmal atrial fibrillation. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2018;20:f384-f91.	Ineligible Comparator
Sugumar H, Prabhu S, Costello B, et al. Catheter Ablation Versus Medication in Atrial Fibrillation and Systolic Dysfunction: Late Outcomes of CAMERA-MRI Study. JACC Clinical electrophysiology 2020;6:1721-31.	Ineligible Population
Svedung Wettervik V, Schwieler J, Bergfeldt L, et al. Long-term health-related quality of life and rhythm outcomes of catheter ablation versus antiarrhythmic drugs in patients with atrial fibrillation. Heart rhythm 2025;22:944-51.	Ineligible Population
Tanner H, Makowski K, Roten L, et al. Catheter ablation of atrial fibrillation as first-line therapy--a single-centre experience. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2011;13:646-53.	Ineligible Comparator
Thomas KL, Al-Khalidi HR, Silverstein AP, et al. Ablation Versus Drug Therapy for Atrial Fibrillation in Racial and Ethnic Minorities. Journal of the American College of Cardiology 2021;78:126-38.	Ineligible Population
Tsuda T, Kato T, Usuda K, et al. Effect of Catheter Ablation for Atrial Fibrillation in Heart Failure With Mid-Range or Preserved Ejection Fraction - Pooled Analysis of the AF Frontier Ablation Registry and Hokuriku-Plus AF Registry. Circulation journal : official journal of the Japanese Circulation Society 2023;87:939-46.	Ineligible Population
Ventura M, Elvas L, Providência L. Previous therapy with amiodarone increases the recurrence rate in successfully ablated patients with isthmus-dependent atrial flutter. Revista portuguesa de cardiologia : orgao oficial da Sociedade Portuguesa de Cardiologia = Portuguese journal of cardiology : an official journal of the Portuguese Society of Cardiology 2004;23:1303-11.	Ineligible Publication Type
Verma A. Atrial-fibrillation ablation should be considered first-line therapy for some patients. Current opinion in cardiology 2008;23:1-8.	Ineligible Publication Type
Voight J, Akkaya M, Somasundaram P, et al. Risk of new-onset atrial fibrillation and stroke after radiofrequency ablation of isolated, typical atrial flutter. Heart rhythm 2014;11:1884-9.	Ineligible Study Design
Z. Wang, M. Li, C. Jiang, M. Zhao, H. Guo, Y. Lai, Y. Wang, M. Gao, S. Xia, L. He, X. Guo, S. Li, N. Liu, C. Jiang, R. Tang, N. Zhou, C. Sang, D. Long, X. Du, J. Dong and C. Ma, 2025 Non-early catheter ablation vs drug therapy in atrial fibrillation: Results from the CABANA trial	Ineligible Population
Wang Z, Wu Y, Jiang C, et al. Catheter Ablation vs Drug Therapy in Patients With Atrial Fibrillation and Nonmodifiable Recurrence Risk Factors: A Secondary Analysis of the CABANA Randomized Clinical Trial. JAMA network open 2025;8:e2528124.	Ineligible Population
Wang Z, Wu Y, Jiang C, et al. Catheter Ablation vs Drug Therapy in Patients With Atrial Fibrillation and Nonmodifiable Recurrence Risk Factors: A Secondary Analysis of the CABANA Randomized Clinical Trial. JAMA network open 2025;8:e2528124.	Ineligible Intervention
Wijffels MC, Crijns HJ. Rate versus rhythm control in atrial fibrillation. Cardiology clinics 2004;22:63-9.	Ineligible Publication Type
Wilber DJ, Pappone C, Neuzil P, et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. Jama 2010;303:333-40.	Ineligible Population
Willems S, Borof K, Brandes A, et al. Systematic, early rhythm control strategy for atrial fibrillation in patients with or without symptoms: the EAST-AFNET 4 trial. European heart journal 2022;43:1219-30.	Ineligible Comparator

Citation	Reason for Exclusion
Willems S, Wegner F, Eckardt L. Clinical Practice Guideline: Preventive Measures and Treatment Options for Atrial Fibrillation. Deutsches Arzteblatt international 2025;122:439-44.	Ineligible Study Design
Willett LR, Kim S. In paroxysmal AF, first-line catheter ablation vs. antiarrhythmic drugs reduces atrial arrhythmia recurrence. Annals of internal medicine 2021;174:JC140.	Ineligible Publication Type
Wu G, Huang H, Cai L, et al. Long-term observation of catheter ablation vs. pharmacotherapy in the management of persistent and long-standing persistent atrial fibrillation (CAPA study). Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2021;23:731-9.	Ineligible Population
Wu L, Narasimhan B, Bhatia K, et al. One year outcomes of atrial fibrillation ablation: Contemporary analysis of the United States Nationwide Readmission Database. Pacing and clinical electrophysiology : PACE 2022;45:1151-9.	Ineligible Population
Wynn GJ, Das M, Bonnett LJ, Gupta D. Quality-of-life benefits of catheter ablation of persistent atrial fibrillation: a reanalysis of data from the SARA study. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2015;17:222-4.	Ineligible Population
Younes H, Noujaim C, Mekhael M, et al. Atrial fibrillation ablation as first-line therapy for patients with heart failure with reduced ejection fraction (HFrEF): evaluating the impact on patient survival. Expert review of cardiovascular therapy 2023;21:111-21.	Ineligible Publication Type
Zakeri R, Ahluwalia N, Tindale A, et al. Long-term outcomes following catheter ablation versus medical therapy in patients with persistent atrial fibrillation and heart failure with reduced ejection fraction. European journal of heart failure 2023;25:77-86.	Ineligible Population
Zeitler EP, Li Y, Silverstein AP, et al. Effects of Ablation Versus Drug Therapy on Quality of Life by Sex in Atrial Fibrillation: Results From the CABANA Trial. Journal of the American Heart Association 2023;12:e027871.	Ineligible Population
Zhang J, Wang L, Li Y, et al. Atrial fibrillation phenotypes identified through cluster analysis in the CABANA study. International journal of cardiology 2025;438:133606.	Ineligible Population
Zheng ZH, Fan J, Ji CC, et al. Long-Term Outcomes and Improvements in Quality of Life in Patients with Atrial Fibrillation Treated with Catheter Ablation vs. Antiarrhythmic Drugs. American journal of cardiovascular drugs : drugs, devices, and other interventions 2021;21:299-320.	Ineligible Publication Type
Zucchelli G, Chun KRJ, Khelae SK, et al. Impact of first-line cryoablation for atrial fibrillation on healthcare utilization, arrhythmia disease burden and efficacy outcomes: real-world evidence from the Cryo Global Registry. Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing 2023;66:711-22.	Ineligible Comparator

Appendix C. Risk of Bias, Strength of Evidence, QHES, and AMSTAR-2

Each included comparative study is rated against pre-set criteria that resulted in a Risk of Bias (ROB) assessment and presented in a table. Assessment of RCTs followed appropriate criteria based on methods described in *the Cochrane Handbook for Systematic Reviews of Interventions*[4] and guidance from the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[1] In keeping with the AHRQ methods, each study was given a final rating of "good", "fair", or "poor" quality as described below in Table D1. Discrepancies in ratings between reviewers were resolved through discussion and consensus. Where blinding is not possible, studies will automatically be rated as "fair" given the potential for biased assessment of outcomes. The final quality assessments are provided in Appendix E.

Table D2 provides an example of the format used to assess ROB for comparative studies of testing/therapy. Additional criteria for non-randomized studies includes consideration of how patients are selected and appropriate control for confounding. Table D3 provides an example for non-randomized studies of interventions. Table D4 provides an example for evaluating administrative database studies. A "No" indicates that the criterion was not met; an "Unclear" indicates that the criterion could not be determined with the information provided or was not reported by the author. Risk of bias assessments were not conducted for case series; all were considered High risk of bias.

Appendix Table C-1. Definition of the risk of bias categories for individual studies of testing

Rating	Description and Criteria
Good	• Least risk of bias; study results generally considered valid • Employ valid methods for selection, inclusion, and allocation of patients to testing; report similar baseline characteristics in different test groups; clearly describe attrition and have low attrition; use appropriate means for preventing bias (e.g., blinding of patients, care providers, and outcomes assessors); and use appropriate analytic methods (e.g., intention-to-treat analysis)
Fair	• Study is susceptible to some bias but not enough to necessarily invalidate results • May not meet all criteria for good quality, but no flaw is likely to cause major bias; the study may be missing information making it difficult to assess limitations and potential problems • This category is broad; studies with this rating will vary in strengths and weaknesses; some fair-quality studies are likely to be valid, while others may be only possibly valid
Poor	• Significant flaws that imply biases of various kinds that may invalidate results; the study contains "fatal flaws" in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting or serious problems with intervention delivery • Study results are at least as likely to reflect flaws in the study design or execution as the true difference between the compared interventions • Considered to be less reliable than higher quality studies when synthesizing the evidence, particularly if discrepancies between studies are present

Appendix Table C-2: Assessment of ROB for Individual Randomized Control Trials

Methodological Principle	Author 1, 2023	Author 2 2024	Author 3, 2021
Study design			
Randomized controlled trial	■	■	■
Random sequence generation			
Concealed allocation			
Groups comparable at baseline*			
Outcome assessors independent or blinded			
Care providers blinded			
Patients blinded			
Reporting of attrition			
Complete follow-up of ≥80%			
<10% difference in follow-up between groups			
Intention to treat			
Outcomes prespecified			
Risk of Bias			

Unclear indicates that the study had insufficient detail to determine whether criteria were met
*Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed.

Appendix Table C-3: Assessment of ROB for Individual Non-Randomized Studies of Interventions

Methodological Principle	Author 1, 2024	Author 2, 2019	Author 3, 2020
Did the study attempt to enroll a random sample or consecutive patients meeting inclusion criteria (inception cohort) from same underlying population?			
Were the groups comparable at baseline on key prognostic factors?			
Did the article report attrition?			
Overall loss to follow up acceptable? (≤20%) Differential loss to follow up acceptable? (≤10%)			
Were the outcomes investigated prespecified and defined?			
Did the study clearly describe and use accurate methods for ascertaining outcomes, exposures, and potential confounders?			
Were outcome assessors and/or data analysts blinded to treatment?			
Did the study perform appropriate statistical analyses on potential confounders or otherwise control for confounding (e.g. restriction, stratification, matching)?			
Was the duration of follow-up reasonable for investigated events?			
Risk of Bias			

NA = not applicable (due to being a case series)
Unclear indicates that the study had insufficient detail to determine whether criteria were met

Assessment of Economic Studies

Full formal economic analyses evaluate both costs and clinical outcomes of two or more alternative interventions. The four primary types are cost minimization analysis (CMA), cost-utility analysis (CUA), cost-effectiveness analysis (CEA), and cost-benefit analyses (CBA). Each employs different methodologies, potentially complicating critical appraisal, but some common criteria can be assessed across studies.

No standard, universally accepted method of critical appraisal of economic analyses is currently in use. A number of checklists [Canadian, BMJ, AMA] are available to facilitate critique of such studies. The Quality of Health Economic Studies (QHES) instrument developed by Ofman, et al. embodies the primary components relevant for critical appraisal of economic studies.[5] It also incorporates a weighted scoring process which was used as one factor to assess included economic studies. This tool has not yet undergone extensive evaluation for broader use but provides a valuable starting point for critique. Table D4 below provides a template of the instrument.

In addition to assessment of criteria in the QHES, other factors are important in critical appraisal of studies from an epidemiologic perspective to assist in evaluation of generalizability and potential sources of study bias.

Such factors include:

- Are the interventions applied to similar populations (e.g., with respect to age, gender, medical conditions, etc.)? To what extent are the populations for each intervention comparable and are differences considered or accounted for? To what extent are population characteristics consistent with “real world” applications of the comparators?

- Are the sample sizes adequate so as to provide a reasonable representation of individuals to whom the technology would be applied?

- What types of studies form the basis for the data used in the analyses? Data (e.g., complication rates) from randomized controlled trials or well-conducted, methodologically rigorous cohort studies for data collection are generally of highest quality compared with case series or studies with historical cohorts.

- Were the interventions applied in a comparable manner (e.g., similar protocols, follow-up procedures, evaluation of outcomes, etc.)?

- How were the data and/or patients selected or sampled (e.g., a random selection of claims for the intervention from a given year/source or all claims)? What specific inclusion/exclusion criteria or processes were used?

Were the outcomes and consequences of the interventions being compared comparable for each? (e.g., were all of the relevant consequences/complications for each intervention considered or do they primarily reflect those for one intervention?

Appendix Table C-4. Assessment of Quality of Health Economic Studies Criteria

Question	Possible Points*	Criteria For Credit*
1. Was the study **objective** presented in a clear, specific, and measurable manner?	7	Authors must fully describe the objective; is it measurable?
2. Were the **perspective** of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4	Authors must state perspective, provide rationale AND have done the correct analysis corresponding to the perspective
3. Were **variable estimates** used in the analysis from the best available source (i.e., randomized controlled trial - best, expert opinion - worst)?	8	No credit if most of estimates are not from the best sources available
4. If estimates came from a **subgroup analysis**, were the groups prespecified at the beginning of the study?	1	-
5. Was **uncertainty** handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9	NO credit if they do not give details regarding type of sensitivity analysis, methods (e.g. what assumptions or factors were varied/why), AND the results (what factors are influential, what is the range of ICERs, etc.)
6. Was **incremental analysis** performed between alternatives for resources and costs?	6	-
7. Was the methodology for **data abstraction** (including the value of health states and other benefits) stated?	5	No credit if sources of model inputs and process of choosing model inputs not specified
8. Did the **analytic horizon allow time** for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7	No credit if time horizon is too short to allow for important outcomes
9. Was the **measurement of costs** appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8	No credit if sources of cost data or methods of estimating costs not clearly described
10. Were the primary **outcome measure(s**) for the economic evaluation clearly stated and did they include the major short-term, long-term and negative outcomes included?	6	NO credit if major important outcomes are not included or if time horizon did not allow for important outcomes to be measured
11. Were the health outcomes **measures/scales valid** and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7	No credit if sources of outcome data or not clearly described or if outcome data is not appropriate for the study population/outcome of interest (i.e. using utility weights from QOL measures that aren't validated or apply to a different population)
12. Were the **economic model** (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	8	Must provide explicit detail for methods and should be able to trace/identify specific components, how they were derived, etc.
13. Were the choice of economic model, main **assumptions, and limitations** of the study stated and justified?	7	NO credit if insufficient detail of model, assumptions AND limitations are provided (No credit if they do not provide justifications/rationale)
14. Did the author(s) explicitly discuss direction and magnitude of potential **biases?**	6	NO credit if no discussion of direction and magnitude of biases
15. Were the **conclusions/recommendations** of the study justified and based on the study results?	8	NO credit if conclusions/recommendations are stronger than warranted based on findings
16. Was there a statement disclosing the **source of funding** for the study?	3	-
Total	100	-

ICER = Incremental Cost-Effectiveness Ratio; QOL = quality of life.

* Study must fit criteria in order to receive full points. Partial credit is not given. If criteria is not met, then the question receives no points.

Application of AMSTAR 2 to systematic reviews

Table D6 shows our criteria for RoB assessment based on the AMSTAR-2 tool. AMSTAR-2 is the revised and updated version of AMSTAR published in 2007 used for critical appraisal of systematic reviews (Shea, 2017).[8] It is not intended to provide an overall score, as high scores may hide weaknesses in critical domains. In light of this, we used a modified AMSTAR tool as determined by Dettori et al (2020).[3] Table D7 (adapted from Dettori 2020) describes how overall scores were determined considering critical domains.[2] Bold items in table 1 were considered as critical items. The original AMSTAR-2 guidance suggests grading each item as no or yes, with items 2, 4, 7, 8, and 9 allowing for a 'partial yes'. We considered a 'yes' or 'partial yes' as yes.

Appendix Table C-5. Criteria for assessing systematic reviews based on AMSTAR-2

Item	Criteria
1: Did the research questions and inclusion criteria for the review include the components of PICO?	• **Yes** if all components of PICO are described somewhere in the report. • **No** if any components of PICO are missing.
2: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	• **Yes** if the protocol or review methods were established prior to review. • **No** if no protocol or discussion/description of methods decided prior to review.
3: Did the review authors explain their selection of the study designs for inclusion in the review?	• **Yes** if study design inclusion is justified or discussed. No penalty for restricting study designs. • **No** if no discussion of justification for inclusion.
4: Did the review authors use a comprehensive literature search strategy?	• **Yes** if 2 or more electronic databases were searched and key words are available in report or appendices. No penalty for language restrictions. • **No** if less than 2 electronic databases were searched or key words are unavailable.
5: Did the review authors perform study selection in duplicate?	• **Yes** if selection at title/abstract and full text reviews were performed by 2 authors with consensus upon disagreement or single author selecting with a second checking agreement on sample and a kappa reported of ≥0.80. • **No** if no second author involved or no kappa reported.
6: Did the review authors perform data extraction in duplicate?	• **Yes** if abstraction was performed by 2 authors with consensus upon disagreement or single author abstracting with a second checking agreement on sample and a kappa of reported of ≥0.80. • **No** if no second author involved or no kappa reported.

Item	Criteria
7: Did the review authors provide a list of excluded studies and justify the exclusions?	• **Yes** if a list of potentially relevant studies is reported in appendix or discussed in text with citations with justification for exclusion. List of references must be provided. • **No** if no list of references provided or not potentially relevant but excluded studies are discussed.
8: Did the review authors describe the included studies in adequate detail?	• **Yes** if study characteristics are reported in sufficient detail to determine whether the studies met PICO criteria and provides framework to judge heterogeneity. • **No** if study characteristics are not reported or table 1 does not include age, sex, (and #'s).
9: Did the review authors use a satisfying technique for assessing the RoB in individual studies that were included in the review?	**RCTS** • **Yes** if important domains similar to Cochrane. **Cohort studies** • **Yes** if it addresses all of the following: confounding, selection bias, measurement bias, and selective reporting of outcomes (Newcastle okay if all 8 questions included). **Case series** (study of incidence, no direct comparison) • **Yes** if selection bias, measurement bias, and selective reporting of outcomes met (Newcastle okay IF questions #1, 2, 3, 4, 6, 7, and 8 addressed). **For all studies** • **No** if there is obvious evidence that the authors misapplied an acceptable technique.
10: Did the review authors report on the sources of funding for the studies included in the review?	• **Yes** if authors report funding of individual studies. • **No** if authors do not report funding.
11: If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	• **Yes** if all the following are present • Meta-analysis justified (e.g., studies comparable, direct comparison). • Explanation of fixed or random effects (must do more than merely report without explanation). • Pooled results reported separately for RCTs and cohort studies. • Assessment of heterogeneity (must address I^2). • **No** if one or more of the above are not present. • If no meta-analysis was done mark as **NM (No meta-analysis)**

Item	Criteria
12: If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	• **Yes** if results are stratified by RoB or if the review only included the lowest RoB studies in the analysis. • **No** if results are not stratified by RoB and review includes a range of RoB outcomes in the analysis. No credit if RoB method from item #9 is not acceptable. • If no meta-analysis was done mark as **NM (No meta-analysis**)
13: Did the review authors account for RoB in individual studies when interpreting or discussing the results of the review?	• **Yes** if there is a discussion of the impact of RoB in the interpretation of results and/or accounting for differences between studies. • **No** if there is no discussion of the impact of RoB in the interpretation of results and/or accounting for differences between studies. No credit if method from #9 is not acceptable.
14: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	• **Yes** if I^2 demonstrates no heterogeneity (<50%) or authors explored reasons for heterogeneity if I^2 is ≥50%. • **No** if I^2 demonstrates heterogeneity (>50%) and authors do not explore reasons for heterogeneity.
15: If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	• **Yes** if there is an attempt to identify publication bias. Must also show awareness of likely impact of publication bias on results. Credit given if they acknowledge publication bias could be a problem but not enough data given or if they have fewer than 10 studies and show no evidence of publication bias. • **No** if there is no attempt to identify or discuss publication bias. • If no meta-analysis was done mark **as NM (No meta-analysis)**
16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	• **Yes** if authors report no competing interests or how they managed potential conflicts of interest. • **No** if there is no discussion or reporting of potential conflicts of interest.

PICO = population, intervention, comparison, outcome; RoB = risk of bias.

Appendix Table C-6. Rating overall Confidence in the Results of the Review (Dettori 2020)

Rating	Criteria
High**:** No or 1 noncritical weakness	The systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.
Moderate**:** More than 1 noncritical weakness*	The systematic review has more than 1 weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.
Low**:** One critical flaw with or without noncritical weaknesses	The review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.

Rating	Criteria
***Critically low*:** More than 1 critical flaw with or without noncritical weaknesses	The review has more than 1 critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

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

Determination of Overall Strength (Quality) of Evidence

Following the assessment of the quality of each individual study included in the report, an *overall* "strength of evidence"/"quality of evidence" for all critical and important *primary* health outcomes and harms based on methods used by GRADE (Grading of Recommendation Assessment, Development and Evaluation) and the Agency for Healthcare Research and Quality (AHRQ) will be reported.[1]

The overall strength of evidence is based on assessment of the following required domains: risk of bias, consistency, directness, and precision. The overall Strength of Evidence (SoE) ranges from high for a body of evidence if new studies are unlikely to change the effect estimates to low if estimates from the currently available body of evidence is very likely to change as new data become available or insufficient if evidence is unavailable or does not permit a conclusion. To evaluate differential efficacy and safety (heterogeneity of effect, interaction), we will focus on RCTs as they have the least potential for bias and confounding thus potentially allowing for causal inference. Further, only RCTs that formally test for interaction between subgroups will be reported. SOE for these studies is based on consideration of the overall study risk of bias (study quality) as well as whether subgroup variables and analyses were specified a priori, the hypothesized impact of a subgroup on the outcome/effect and sample size as evaluation of interaction requires greater sample size are based on recommendations from Oxman and Guyatt[6] and the Instrument to assess the Credibility of Effect Modification (ICEMAN) criteria.[7] The overall strength of evidence reflects our confidence in the effects estimated in the included studies and how likely new studies are to change the estimates. If only poor-quality studies are available for an outcome, SOE will be graded as insufficient.

The strength of evidence for the overall body of evidence for all *critical health outcomes* was assessed by one researcher following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation) as outlined by the Agency for Healthcare Research and Quality (AHRQ). The strength of evidence was based on the highest quality evidence available for a given *primary* outcome. In determining the strength of body of evidence regarding a given *primary* outcome, the following domains were considered:

- **Risk of bias:** the extent to which the included studies have protection against bias.
- **Consistency:** the degree to which the included studies report results are similar in terms of range and variability.
- **Directness:** describes whether the evidence is directly related to patient health outcomes.
- **Precision:** describes the level of certainty surrounding the effect estimates.
- **Publication bias:** is considered when there is concern of selective publishing.

All AHRQ "required" and "additional" domains (risk of bias, consistency, directness, precision, and if possible, publication bias) were assessed. Bodies of evidence consisting of RCTs were initially considered as High strength of evidence (SoE), while those that comprised nonrandomized studies began as Low strength of evidence. The strength of evidence could be downgraded based on the limitations described above. There could also be situations where the *nonrandomized* studies could be upgraded, including the presence of plausible unmeasured confounding and bias that would decrease an observed effect or increase an effect if none was observed, presence of a dose-response relationship, and large magnitude of effect (strength of association) *if no downgrades for domains above*. Publication and reporting bias are difficult to assess. Publication bias is particularly difficult to assess with fewer than 10 RCTs (AHRQ methods guide). When publication bias was unknown in all studies and this domain is often eliminated from the strength of evidence tables for our reports. The final strength of evidence for each **primary** outcome was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows:

High— Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.

Moderate— Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are probably stable but some doubt remains.

Low— Limited confidence that effect size estimates lie close to the true effect for this outcome; important or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or that the estimate is close to the true effect.

Insufficient— We have no evidence, are unable to estimate an effect or have no confidence in the effect estimate for this outcome; OR no available evidence or the body of evidence has unacceptable deficiencies precluding judgment.

Similar methods for determining the overall quality (strength) of evidence related to economic studies have not been reported, thus the overall strength of evidence for outcomes reported in Key Question 4 was not assessed. Appendix Table C-7. Example methodology outline for determining overall strength of evidence (SoE)

Outcome	Strength of Evidence	Conclusions & Comments	Baseline SOE	DOWNGRADE	UPGRADE
Outcome	**HIGH**	Summary of findings	**HIGH** RCTs	**NO** consistent, direct, and precise estimates	**NO**
Outcome	**MODERATE**	Summary of findings	**LOW** Cohort studies	**NO** consistent, direct, and precise estimates; high quality (moderately low ROB)	**YES** Large effect
Outcome	**LOW**	Summary of findings	**HIGH** RCTs	**YES (2)** Inconsistent Indirect	**NO**

Note: All AHRQ "required" and "additional" domains* are assessed. Only those that influence the baseline grade are listed in table.
Baseline strength: HIGH = RCTs. LOW = observational, cohort studies, administrative data studies.
DOWNGRADE: Risk of bias for the individual article evaluations (1 or 2); Inconsistency** of results (1 or 2); Indirectness of evidence (1 or 2); Imprecision of effect estimates (1 or 2); Sub-group analyses not stated *a priori* and no test for interaction (2).
UPGRADE (non-randomized studies): Large magnitude of effect (1 or 2); Dose response gradient (1) done for observational studies ***if no downgrade for domains above***.

*Required domains: risk of bias, consistency, directness, precision. Plausible confounding that would decrease observed effect is accounted for in our baseline risk of bias assessment through individual article evaluation. Additional domains: dose-response, strength of association, publication bias.
**Single study = "consistency unknown", may or may not be downgraded

Appendix Table C-8. Definitions for magnitude of effects, based on mean between-group differences

Outcome	Slight/Small	Moderate	Large/Substantial
QoL	5–10 points on AFEQT	10–20 points on AFEQT	>20 points on AFEQT
	5–10 points on SF-36	10–20 points on SF-36	>20 points on SF-36
	0.1 points on EQ-5D	>0.1 to <0.2 points on EQ-5D	>0.2points on EQ-5D
Symptoms	1.2 to 1.4 RR/HR	1.5 to 1.9 RR/HR	≥2.0 RR/HR
	0.83 to 0.68 RR/HR	0.67 to 0.51 RR/HR	≤0.5 RR/HR

AFEQT = Atrial Fibrillation Effect on QualiTy-of-life questionnaire; EQ-5D = EuroQol 5 dimensions questionnaire; HR = hazard ratio; QoL = quality of life; RR = risk ratio; SF-36 = Short Form 36 questionnaire.

Appendix D. Study Quality: Risk of Bias, QHES, and AMSTAR-2 Evaluation

Appendix Table D-1. Risk of bias ratings for included RCTs

Trial Author, Year	Random-ization adequate? Yes/No/ Unclear	Allocation concealment adequate? Yes/No/ Unclear	Groups similar at baseline? Yes/No/ Unclear	Patient masked? Yes/No/ Unclear	Care provider masked? Yes/No/ Unclear	Outcome assessors masked? Yes/No/ Unclear	Reporting of attrition and crossovers? Yes/No/ Unclear	Overall loss to follow-up acceptable? Yes/No/ Unclear	Differential loss to follow-up acceptable: Yes/No/ Unclear	Intention-to-treat (ITT) analysis? Yes/No/ Unclear	Outcomes prespecified? Yes/No/ Unclear	Risk of Bias Low/Moderate/ High
EARLY-AF Andrade, 2021[1]	Yes	Yes	Yes	No	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	**Moderate**
Cryo-First Kuniss, 2021[2]	Yes	Yes	Yes	No	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	**Moderate**
Ding, 2022[3]	Unclear	Unclear	Yes	No	No	No	Yes	No	Yes	Yes	Yes	**Moderate**
Natale, 2000[4]	Unclear	Unclear	Yes	No	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	**Moderate**
LADIP Da Costa, 2006[5]	Unclear	Unclear	Yes	No	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	**Moderate**
STOP-AF Wazni, 2021[6]	Yes	Unclear	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	**Moderate**
RAAFT-1 Wazni, 2005[7]	Yes	Yes	Yes	No	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	**Moderate**
RAAFT-2 Morillo, 2014[8]	Yes	Unclear	Yes	No	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	**Moderate**
MANTRA-PAF Cosedis Nielsen, 2012[9]	Yes	Yes	Yes	No	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	**Moderate**

Appendix Table D-2. Risk of bias ratings for included NRSIs

Author Year	Did the study attempt to enroll a random sample or consecutive patients meeting inclusion criteria (inception cohort) from same underlying population?	Were the groups comparable at baseline on key prognostic factors?	Did the article report attrition?	Overall loss to follow-up acceptable? (≤20%) Differential loss to follow-up acceptable? (≤10%)	Were the outcomes investigated prespecified and defined?	Did the study clearly describe and use accurate methods for ascertaining outcomes, exposures, and potential confounders?	Were outcome assessors and/or data analysts blinded to treatment?	Did the study perform appropriate statistical analyses on potential confounders or otherwise control for confounding (e.g. restriction, stratification, matching)?	Was the duration of follow-up reasonable for investigated events?	Quality Rating Low/Moderate/High
Chung 2023[10]	Unclear	No	No	No	Yes	Yes	No	Yes	Yes	Moderate
Kim, 2021[11]	Unclear	No	Yes	Yes	Unclear	Yes	No	Yes	Yes	Moderate
Lan, 2009[12]	Yes	Yes	Unclear/Yes	Unclear/Yes	Yes	Yes	Unclear	Yes	Yes	High
Pimental, 2025[13]	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Moderate

Appendix Table D-3. QHES ratings for economic studies

Rating	Possible Points	Criteria for Credit	Aronsson 2015[14] Points	Wazni 2023[15] Points	Andrade 2024[16] Points	Hansen 2024[17] Points	Kuniss 2024[18] Points	Paisey 2024[19] Points
1. Was the study **objective** presented in a clear, specific, and measurable manner?	7	*Authors must fully describe the objective; is it measureable?*	7	7	7	7	7	7
2. Were the **perspective** of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4	*Authors must state perspective, provide rationale AND have done the correct analysis corresponding to the perspective*	0	4	4	4	4	4
3. Were **variable estimates** used in the analysis from the best available source (ie, randomized controlled trial - best, expert opinion - worst)?	8	*No credit if most of estimates are not from the best sources available*	8	0	0	0	0	0
4. If estimates came from a **subgroup analysis**, were the groups prespecified at the beginning of the study?	1	--	1	1	1	1	1	1
5. Was **uncertainty** handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9	*NO credit if they do not give details regarding type of sensitivity analysis, methods (e.g. what assumptions or factors were varied/why), AND the results (what factors are influential, what is the range of ICERs, etc.)*	9	9	9	9	9	9
6. Was **incremental analysis** performed between alternatives for resources and costs?	6	--	6	6	6	6	6	6
7. Was the methodology for **data abstraction** (including the value of health states and other benefits) stated?	5	*No credit if sources of model inputs and process of choosing model inputs not specified*	5	5	5	5	5	5

Rating	Possible Points	Criteria for Credit	Aronsson 2015[14] Points	Wazni 2023[15] Points	Andrade 2024[16] Points	Hansen 2024[17] Points	Kuniss 2024[18] Points	Paisey 2024[19] Points
8. Did the **analytic horizon allow time** for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7	*No credit if time horizon is too short to allow for important outcomes*	7	7	7	7	7	7
9. Was the **measurement of costs** appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8	*No credit if sources of cost data or methods of estimating costs not clearly described*	8	8	8	8	8	8
10. Were the primary **outcome measure(s**) for the economic evaluation clearly stated and did they include the major short-term, long-term and negative outcomes included?	6	*NO credit if major important outcomes are not included or if time horizon did not allow for important outcomes to be measured*	6	6	6	6	6	6
11. Were the health outcomes **measures/scales valid** and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7	*No credit if sources of outcome data or not clearly described or if outcome data is not appropriate for the study population/outcome of interest (i.e. using utility weights from QOL measures that aren't validated or apply to a different population)*	7	7	7	7	7	7
12. Were the **economic model** (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	8	*Must provide explicit detail for methods and should be able to trace/identify specific components, how they were derived, etc.*	8	8	8	8	8	8

Rating	Possible Points	Criteria for Credit	Aronsson 2015[14] Points	Wazni 2023[15] Points	Andrade 2024[16] Points	Hansen 2024[17] Points	Kuniss 2024[18] Points	Paisey 2024[19] Points
13. Were the choice of economic model, main **assumptions, and limitations** of the study stated and justified?	7	*NO credit if insufficient detail of model, assumptions AND limitations are provided (No credit if they do not provide justifications/rationale)*	7	7	7	7	7	7
14. Did the author(s) explicitly discuss direction and magnitude of potential **biases?**	6	*NO credit if no discussion of direction and magnitude of biases*	0	6	6	6	6	6
15. Were the **conclusions/recommendations** of the study justified and based on the study results?	8	*NO credit if conclusions/recommendations are stronger than warranted based on findings*	8	8	8	8	8	8
16. Was there a statement disclosing the **source of funding** for the study?	3	--	3	3	3	3	3	3
--	100	--	**90**	**92**	**92**	**92**	**92**	**92**

AAD = antiarrhythmic drug; AE = adverse events; AF = atrial fibrillation; NR = not reported; QALY = quality-adjusted life year; RFA = radiofrequency ablation; RR = risk ratio

Appendix Table D-4. AMSTAR ratings for included systematic reviews

Study	PICO	Protocol	Design Inclusion	Search	Duplicate selection	Duplicate extraction	Excluded	Study description	RoB
Ullah, 2023[20]	Yes	No	Yes	Yes	Unclear	Unclear	No	Yes	Yes
Liu, 2023[21]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Cardoso, 2022[22]	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Kheir, 2021[23]	No	No	Yes	No	Unclear	Unclear	No	Yes	No
NICE, 2021[24]	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes

RoB = risk of bias

Appendix Table D-5. AMSTAR ratings for included systematic reviews (cont.)

Study	Funding	Meta-analysis	RoB considered in results	RoB in discussion	Discuss heterogeneity	Pub bias	COI	Overall AMSTAR
Ullah, 2023[20]	Yes	Yes	Yes	No	Yes	Yes	Yes	Critically low
Liu, 2023[21]	No	Yes	Yes	No	No	No	Yes	Critically low
Cardoso, 2022[22]	Yes	Yes	Yes	No	Yes	Yes	Yes	Critically low
Kheir, 2021[23]	Yes	Yes	No	No	No	No	Yes	Critically low
NICE, 2021[24]	Yes	Yes	Yes	No	Yes	Yes	Yes	Moderate

RoB = risk of bias; COI = conflict of interest

Appendix E. Additional Demographic and Outcome Data of Included Studies

See separate Excel File named "Appendix E. Data abstraction of included studies" for full data abstraction

Appendix Table E-1. AADs and doses from RCTs of previously untreated paroxysmal AF

Drug	Trial Author, year	Percentage of Pts Starting on Medication	Dosing, Mean (SD)	Treated at or Above Minimum Therapeutic Dose?
Flecainide	EARLY-AF Andrade, 2023[1]	76.5% (114/149)	Median 200mg (IQR 125 to 250)	At minimum
	STOP-AF Wazni, 2021[6]	61.7% (58/94)†	164mg (NR)*	No
	Cryo-FIRST Kuniss, 2021[2]	60.4% (61/101)	145mg (NR)*	No
	Ding, 2022[3]	0%†	-	NA
	RAAFT-1 Wazni, 2005[7]	77.1% (27/35)	200-300mg‡	Above
	RAAFT-2 Morillo, 2014[8]	68.9% (42/61)	175.8mg (50.9)	No
	MANTRA-PAF Cosedis Nielsen, 2012[9]	NR§	200mg (NR)‡	At minimum
Propafenone	EARLY-AF Andrade, 2023[1]	4.7% (7/149)	Median 600mg (IQR 450 to 600)	Above
	STOP-AF Wazni, 2021[6]	7.4% (7/94)†	479mg (NR)*	Above
	Cryo-FIRST Kuniss, 2021[2]	32.7% (33/101)	414mg (NR)*	No
	Ding, 2022[3]	52.5% (52/99)†	430mg (NR)*	No
	RAAFT-1 Wazni, 2005[7]	0%	-	NA
	RAAFT-2 Morillo, 2014[8]	24.6% (15/61)	487.7mg (122.4)	Above
	MANTRA-PAF Cosedis Nielsen, 2012[9]	NR§	600mg (NR)‡	Above
Sotalol	EARLY-AF Andrade, 2023[1]	15.4% (23/149)	Median 160mg (IQR 160 to 240)	At minimum
	STOP-AF Wazni, 2021[6]	7.4% (7/94)†	149mg (NR)*	No
	Cryo-FIRST Kuniss, 2021[2]	5.0% (5/101)	128mg (NR)*	No
	Ding, 2022[3]	31.3% (31/99)†	137mg (NR)*	No
	RAAFT-1 Wazni, 2005[7]	22.9% (8/35)	240-320mg‡	Above
	RAAFT-2 Morillo, 2014[8]	0%	-	NA

Drug	Trial Author, year	Percentage of Pts Starting on Medication	Dosing, Mean (SD)	Treated at or Above Minimum Therapeutic Dose?
	MANTRA-PAF Cosedis Nielsen, 2012[9]	NR§	160mg (NR)‡	At minimum
Dronedarone	EARLY-AF Andrade, 2023[1]	3.4% (5/149)	Median 800mg (IQR 800 to 800)	At minimum
	STOP-AF Wazni, 2021[6]	11.7% (11/94)†	800mg (NR)*	At minimum
	Cryo-FIRST Kuniss, 2021[2]	2.0% (2/101)	800mg (NR)*	At minimum
	Ding, 2022[3]	0%†	-	NA
	RAAFT-1 Wazni, 2005[7]	0%	-	NA
	RAAFT-2 Morillo, 2014[8]	3.3% (2/61)	NR	Unsure
	MANTRA-PAF Cosedis Nielsen, 2012[9]	0%	-	NA
Amiodarone	EARLY-AF Andrade, 2023[1]	0%	Median 200mg (IQR 200mg to 200mg)	At minimum
	STOP-AF Wazni, 2021[6]	2.1% (2/94)†	300mg (NR)*	Above
	Cryo-FIRST Kuniss, 2021[2]	0%	-	NA
	Ding, 2022[3]	8.1% (8/99)†	250mg (NR)*	Above
	RAAFT-1 Wazni, 2005[7]	0%	-	NA
	RAAFT-2 Morillo, 2014[8]	0%	-	NA
	MANTRA-PAF Cosedis Nielsen, 2012[9]	NR§	200mg (NR)‡	At minimum

*Calculated from available dosing information

†First dosing information available at end of blanking period instead of initiation

‡Protocol dosing, actual dosing not reported

§88.5% (131/148) treated with class IC drugs and 10.1% (15/148) treated with class III drugs

Appendix Table E-2. Need for AADs after ablation in RCTs of previously untreated paroxysmal AF.

Trial Publication	Follow-up Period	n CA	N CA	%	Notes
MANTRA-PAD Cosedis Nielsen, 2017[25]	≤5 years	13	125	10.4%	Non-protocol AADs (class I or III) Does not say for recurrence of AAs
EARLY-AF Andrade, 2021[1]	90 days to ≤1 year	26	154	16.9%	Non-protocol AADs after a primary end-point event (i.e., recurrence of atrial tachyarrhythmia); Of these 26, 17 underwent a second ablation provides at a median of 213 days after index ablation
RAAFT-2 Morillo, 2014[8]	≤2 years	6	66	9.1%	Only 6 patents received AAD treatment during follow-up
STOP-AF Wazni, 2021[6]	90 days to ≤1 year	2	104	1.9%	Non-protocol AADs (class I or III AAD after 90 days)
Ding 2022[3]	≤2 years	31	102	30.4%	As the treatment strategy for a recurrent arrhythmia of sufficient clinical severity
RAAFT-1 Wazni 2005[7]	1 year	1	32	3.1%	Required repeat ablation

AAD = antiarrhythmic drug; NA = not applicable.

Note: Kuniss did not report subsequent AAD treatment

Appendix Table E-3. Atrial arrhythmia recurrence and reablation criteria, blanking period events and AAD dosing in RCTs of previously untreated paroxysmal AF.

Trial	Atrial Tachyarrhythmia Recurrence Criteria	Re-treatment Criteria	Are Blanking Period Events Included in Outcomes?	Events Occurring During Blanking Period	AAD Dosing Provided?	AAD dosing listed as a limitation?
EARLY-AF Andrade, 2023[1]	Any AF, AFL, or AT event ≥120 seconds or longer, recorded via 12-lead ECG, ambulatory ECG, ECG rhythm strips, or implantable loop recorder	Recurrence after blanking period of considerable enough severity to warrant therapy change while using therapeutic dose of drug*	No	Repeat ablation: 0.7% (1/153) vs. 0%	Yes, See Appendix Table E-1	No
STOP-AF Wazni, 2021[6]	Any AF, AFl, or AT event ≥30 seconds recorded via ambulatory monitoring or ≥10 seconds on a 12-lead ECG	NR for CA group; Documented AAD side effects, unresolved symptoms, atrial arrhythmia detected outside of trial protocol, ADD PRIMARY ENDPOINT EVENT	No; unclear for subsequent ablation	NR	Yes, See Appendix Table E-1	Yes; Both variability in prescribed AAD and potential undertreatment noted
Cryo-FIRST Kuniss, 2021[2]	Any AF, AFL, or AT event >30 seconds recorded via 7-day Holter ECG or any other ECG recording	Assumed due to recurrence of AF, AFL, or AT	No	Repeat ablation: 3.7% (4/107) vs. NA Crossover to ablation: NA vs. 3.6% (4/111)	Yes, See Appendix Table E-1	Yes; Potential undertreatment noted

Trial	Atrial Tachyarrhythmia Recurrence Criteria	Re-treatment Criteria	Are Blanking Period Events Included in Outcomes?	Events Occurring During Blanking Period	AAD Dosing Provided?	AAD dosing listed as a limitation?
Ding, 2022[3]	Any AF, AFL or AT occurrence, not further defined	Not Allowed	No	Crossover to AAD, no CA received: 2.0% (2/102) vs. NA Crossover to CA: NA vs. 0%	Yes, See Appendix Table E-1	Yes; Potential undertreatment noted
RAAFT-1 Wazni, 2005[7]	Any AF occurrence >15 seconds during Holter or event monitoring	NR; None occurred	No – Included in one Kaplan-Meier curve but recorded separately for other purposes; unclear for subsequent ablations	AF recurrence: (9/33) vs. (20/37) Hospitalization‡: 0 vs. 26 Thromboembolic events: 0% vs. 0%	No†	No
RAAFT-2 Morillo, 2014[8]	Any AF, AFl, or AT event ≥30 seconds documented by ECG or transtelephonic monitor	Allowed if AF recurred after blanking period, not included in primary outcome analysis	No	Repeat ablation: (1/66) vs. NA	Yes, See Appendix Table E-1	No
MANTRA-PAF Cosedis Nielsen, 2012[9]	Any AF or AT periods >1 minute during 7-day Holter recording	Allowed if symptomatic AF recurrence happens after blanking period	No; unclear for subsequent ablations	NR	No†	No

AAD = anti-arrhythmic drug; AF = atrial fibrillation; AFL = atrial flutter; AT = atrial tachycardia; N/A = not applicable; NR = not reported

*Defined as flecainide at a dose of more than 100 mg per day, sotalol at a dose of more than 160 mg per day, propafenone at a dose of more than 300 mg per day, or dronedarone at a dose of 800 mg per day

†Protocol dosing provided but actual dosing not available

‡Recorded as total events, not by number of individuals experiencing event

Appendix Table E-4. Adverse Events Reported for CA vs. AADs in Pimental, 2025[13]

Outcome*	Overall Population n†/N Adj. HR (95% CI)	Paroxysmal AF Population n†/N Adj. HR (95% CI)	Persistent AF Population n†/N Adj. HR (95% CI)
Hospitalization for atrial arrhythmia	(123/2711) vs. (1625/22726), 0.52 (0.40 to 0.68)	(57/1492) vs. (676/9986), 0.52 (0.37 to 0.73)	(51/900) vs. (247/3382), 0.55 (0.37 to 0.81)
Hospitalization for myocardial infarction	(5/2711) vs. (95/22726), 0.48 (95% CI 0.12 to 1.86)	(2/1492) vs. (38/9986), 0.38 (95% CI 0.08 to 1.82)	(2/900) vs. (13/3382), 0.81 (95% CI 0.10 to 6.34)
Hospitalization for ischemic stroke	(12/2711) vs. (200/22726), 0.36 (95% CI 0.13 to 1.02)	(5/1492) vs. (98/9986), 0.53 (95% CI 0.17 to 1.61)	(3/900) vs. (21/3382), 0.12 (95% CI 0.02 to 0.95)
Hospitalization for heart failure	(18/2711) vs. (294/22726), 0.26 (95% CI 0.13 to 0.54)	(3/1492) vs. (262/9986), 0.11 (95% CI 0.02 to 0.49)	(11/900) vs. (103/3382), 0.53 (95% CI 0.23 to 1.20)
Electrical cardioversion due to AF	(66/2711) vs. (804/22726), 0.48 (95% CI 0.34 to 0.68)	(23/1492) vs. (282/9986), 0.48 (95% CI 0.28 to 0.83)	(35/900) vs. (188/3382), 0.60 (95% CI 0.38 to 0.95)
Electrical cardioversion due to AFL	(15/2711) vs. (111/22726), 0.61 (95% CI 0.28 to 1.30)	(7/1492) vs. (48/9986), 1.09 (95% CI 0.38 to 3.14)	(6/900) vs. (15/3382), 1.07 (95% CI 0.36 to 3.15)
Acute coronary syndrome	1.4% (39/2711) vs. NA	1.2% (18/1492) vs. NA	1.0% (9/900) vs. NA
Atrio-esophageal fistula	0% vs. NA	0% vs. NA	0% vs. NA
Bleeding	1.0% (28/2711) vs. NA	0.9% (13/1492) vs. NA	1.1% (10/900) vs. NA
Blood transfusion	0.3% (9/2711) vs. NA	0.3% (5/1492) vs. NA	0.2% (2/900) vs. NA
Cardiac tamponade/perforation	0.6% (15/2711) vs. NA	0.2% (3/1492) vs. NA	0.8% (7/900) vs. NA
Hemorrhagic stroke	0.1% (2/2711) vs. NA	0.1% (2/1492) vs. NA	0% vs. NA
Ischemic stroke	0.9% (25/2711) vs. NA	0.6% (9/1492) vs. NA	1.3% (12/900) vs. NA
Laryngospasm	0.1% (2/2711) vs. NA	0.1% (2/1492) vs. NA	0% vs. NA
Pericarditis	0.7% (19/2711) vs. NA	0.6% (9/1492) vs. NA	0.4% (4/900) vs. NA
Phrenic nerve damage	0.2% (5/2711) vs. NA	0.1% (2/1492) vs. NA	0.3% (3/900) vs. NA
Severe pulmonary stenosis requiring intervention	0% vs. NA	0% vs. NA	0% vs. NA
Thromboembolism	1.2% (32/2711) vs. NA	1.1% (16/1492) vs. NA	1.0% (9/900) vs. NA
Transient ischemic attack	0.5% (13/2711) vs. NA	0.5% (8/1492) vs. NA	0.2% (2/900) vs. NA
Vagal nerve injury	0% vs. NA	0% vs. NA	0% vs. NA
Vascular access complication requiring repair	0.2% (5/2711) vs. NA	0.2% (3/1492) vs. NA	0.11% (1/900) vs. NA
Allergic reaction	NA vs. 1.6% (368/22726)	NA vs. 1.7% (169/9986)	NA vs. 1.3% (45/3382)
Atrial proarrhythmic event	NA vs. 13.8% (3138/22726)	NA vs. 13.2% (1322/9986)	NA vs. 17.8% (602/3382)
Bradycardia	NA vs. 16.0% (3627/22726)	NA vs. 14.6% (1457/9986)	NA vs. 19.9% (672/3382)
Gastrointestinal abnormality excluding moderate/severe diarrhea	NA vs. 1.4% (320/22726)	NA vs. 1.4% (138/9986)	NA vs. 1.4% (46/3382)
Heart failure	NA vs. 9.2% (2089/22726)	NA vs. 8.1% (814/9986)	NA vs. 11.1% (375/3382)

Outcome*	Overall Population n†/N Adj. HR (95% CI)	Paroxysmal AF Population n†/N Adj. HR (95% CI)	Persistent AF Population n†/N Adj. HR (95% CI)
Hypotension	NA vs. 5.1% (1157/22726)	NA vs. 4.3% (430/9986)	NA vs. 5.3% (180/3382)
Liver disease	NA vs. 2.9% (654/22726)	NA vs. 2.8% (280/9986)	NA vs. 2.8% (94/3382)
Major proarrhythmic event (VT/VF)	NA vs. 0.1% (20/22726)	NA vs. 0.1%% (7/9986)	NA vs. 0.1% (3/3382)
Moderate or severe diarrhea	NA vs. 8.3% (1895/22726)	NA vs. 8.9% (885/9986)	NA vs. 8.0% (270/3382)
Optic neuropathy	NA vs. <0.1% (4/22726)	NA vs. <0.1% (1/9986)	NA vs. <0.1% (3/3382)
Pulmonary toxicity	NA vs. 1.9% (437/22726)	NA vs. 1.8% (178/9986)	NA vs. 1.9% (64/3382)
Severe headache	NA vs. 2.0% (443/22726)	NA vs. 2.1% (209/9986)	NA vs. 1.4% (46/3382)
Thyroid dysfunction	NA vs. 7.1% (1617/22726)	NA vs. 6.6% (661/9986)	NA vs. 7.7% (260/3382)
Torsades de Pointes	NA vs. 0%	NA vs. 0%	NA vs. 0%
Any AE	6.0% (162/2711) vs. 47.8% (10861/22726)	5.2% (77/1492) vs. 45.6% (4556/9986)	5.7% (51/900) vs. 52.4% (1774/3382)

Adj = adjusted; AE = adverse event; AF = atrial fibrillation; AFL = atrial flutter; CI = confidence interval; HR = hazard ratio; NA = not applicable; VF = ventricular fibrillation; VT = ventricular tachycardia

*Hospitalization and cardioversion outcomes were assessed over a 1-year post-treatment period (excluding a 3-month blanking period). For safety events associated with treatment modalities, authors assessed complications within 30 days of index CA, and side effects within 1 year of the index AAD treatment.

†Total number of events, not total number of patients experiencing events

Appendix Table E-5. Adverse events reported in NRSIs comparing CA versus AADs, medical therapy, or no rhythm control therapy

Treatment Groups	Serious Adverse Event	NRSI (N=) Follow-up period	Comparator	Incidence, CA vs. Comparator RR or HR (95% CI)
CA vs. AAD/Medical Therapy	Any SAE (CA procedure-related/AAD side effects)*	Lan, 2009 (N=240);[12] 1 year	AAD (amiodarone +/- losartan)	5.8% (7/120) vs. 9.2% (11/120); RR 0.64 (0.26 to 1.59)
	Torsades de pointes	Lan, 2009 (N=240);[12] 1 year	AAD (amiodarone +/- losartan)	0% (0/120) vs. 0% (0/120)
	Ischemic stroke	Kim, 2021 (N=4,887);[26] mean 4.25 years	Medical Therapy†	1.3% (21/1629) vs. 4.7% (152/3258); Adj. HR 0.28 (0.18 to 0.44)‡
	Intracranial hemorrhage	Kim, 2021 (N=4,887);[26] mean 4.25 years	Medical Therapy†	0.2% (4/1629) vs. 0.7% (24/3258); Adj. HR 0.34 (0.12 to 0.97)‡
CA (PVI only) vs. No Rhythm Control	All-cause mortality§	Chung, 2023 (N=NR**);[10] median 2.7 years	No rhythm control (i.e., no CA or AADs)	Adj. HR 0.36 (0.28 to 0.48) Mortality at 5 year follow-up: 1.6% (1.0% to 2.5%)
CA (for atrial flutter only) vs. No Rhythm Control	All-cause mortality§	Chung, 2023 (N=NR**);[10] median 2.7 years	No rhythm control (i.e., no CA or AADs)	Adj. HR 0.51 (0.42 to 0.61) Mortality at 5 year follow-up: 4.5% (3.5% to 5.9%)

AAD = anti-arrhythmic drug; Adj. = adjusted; CA = catheter ablation; NR = not reported; NRSI = non-randomized study of interventions; PVI = pulmonary vein isolation; SAE = serious adverse event

*SAEs included sinus bradycardia, hypotension, significant QT prolongation, hyperthyroidism, hypothyroidism and hepatic deterioration in two drug therapy groups, and pericardial tamponade which required pericardiocentesis, moderate to severe pulmonary vein stenosis and cerebral embolism leading to transient retrograde amnesia in two catheter ablation, respectively.

†Included AADs (18.1%), statins (24.6%), oral anticoagulation (32.4%), and antiplatelet agent (52.5%).

‡Calculated the inverse of the following outcomes from the propensity score matched cohort which used CA as the referent: ischemic stroke, adj HR 3.59, 95% CI 2.27 to 5.66; intracranial hemorrhage, adj HR 2.97, 95% CI 1.03 to 8.57.

§Causes included (from highest to lowest frequency): circulatory diseases, neoplasms, respiratory diseases and digestive diseases.

**Total N=225,173 (28,497 for rhythm control groups and 196,676 for no rhythm controls groups); authors do not provide N's for PVI only or atrial flutter only rhythm control groups.

Appendix F. Additional Information from Economic Studies

Appendix Table F-1. Additional info for economic studies using data from the MANTRA-PAF trial

Methods	Aronsson, 2015[14]
Number of patients	294
Country	Denmark, Finland, Germany, Sweden
Currency	2012 Euros
Perspective	NR
Model	Decision-analytic Markov, Monte Carlo simulations
Time Horizon	Lifetime (until death)
Discount	3%
Model inputs/costs	**Units** RFA procedure: €10,033 Materials: €4,813 **AF AE costs (per cycle)** Ischemic stroke at 1 year: €19,167 Bleeding: €19,225 Stroke >1 year: €7,028 Day in hospital care: €518 Cardioversion: €687 Electrocardiography: €27 Transthoracic echocardiogram: €301 Transesophageal echocardiogram: €409 X-ray: €56 Holter monitoring: €275 Computed tomography: €290 **Resources** Drug costs (per unit): range €0.001 to €0.05 per mg
Utilities	**QALY weights** AAD patients at 24 months: 0.86 RFA patients at 24 months: 0.90 Decrement for ischemic stroke: 0.15 Decrement for hemorrhagic stroke: 0.30

Methods	Aronsson, 2015[14]
	Decrement symptomatic AF: 0.13
Assumptions	• Patients expected to relapse into AF over time, have additional ablations, or be treated with AADs • Crossovers expected • The significant difference in AF and symptomatic AF after 24 months should be taken into account after baseline scenario • Risk of complications obtained from MANTRA-PAF • All patients treated with warfarin at 24 months were expected to be treated with oral anticoagulation for the rest of their lives, regardless of AF-status
Willingness to pay threshold	NR
Sensitivity analyses specifically called out	NR
Scenario analysis	• <50 year old patients and ≥50 year old patients • Crossover not allowed at 24 months • Varied discount rates (0%, 6%) • Time horizon 10 years • No difference in AF between the groups at 2 years or 5 years
QHES	**90**

AAD = antiarrhythmic drug; AE = adverse events; AF = atrial fibrillation; NR = not reported; QALY = quality-adjusted life year; RFA = radiofrequency ablation; RR = risk ratio;

Appendix Table F-2. Additional info for economic studies using data from the EARLY-AF, Cryo-First, and STOP-AF trials

Methods	Wazni, 2023[15]	Andrade 2024[16]	Hansen, 2024[17]	Kuniss, 2024[18]	Paisey, 2024[19]
Number of patients	1000	1000	1000	1000	1000
Country	United States	Canada	Denmark	Germany	UK
Currency	2021 U.S. Dollars	2023 Canadian Dollars	2023 Danish Kroner (Base case in 2023 Euros)	2023 Euros	2021 Pounds Sterling
Perspective	U.S. Medicare payer	Canadian Health Care payer	Danish health care payer	German health care payer	UK NHS and personal social services
Model	Hybrid decision-tree Markov structure	Hybrid decision-tree Markov structure	Hybrid decision-tree Markov structure	Hybrid decision-tree Markov structure	Hybrid decision-tree Markov structure
Time Horizon	Decision tree: 1 year Markov model: 40-years	Decision tree: 1 year Markov model: 40-years	Decision tree: 1 year Markov model: 40-years	Decision tree: 1 year Markov model: 40-years	Decision tree: 1 year Markov model: 40-years
Discount	3%	3%	3%	3%	3.5%
Model inputs/costs	**Units** Cryoballoon procedure: $23,134 Percutaneous and other intracardiac procedures (inpatient): $22,231 Intracardiac catheter ablation procedures (outpatient): $21,464 Evaluation and intracardiac ablation of atrial fibrillation by pulmonary vein isolation: $1,145 3D mapping: $303 Echocardiography: $115 **Intra-operative AE costs** Esophageal injury: $47,923 Cardiac tamponade: $6,720	**Units** Cryoballoon procedure: $11,893 **Intra-operative AE costs** Esophageal injury: $17,586 Cardiac tamponade: $38,708 Pulmonary vein stenosis: $19,268 Vascular complications: $13,709 Persistent phrenic nerve injury: $628 **AF AE costs (per cycle)** AF-related stroke events: range $9,683 to $100,466 Stroke ongoing costs	**Units** Cryoballoon procedure: 33,945 DKK (€4,554) **AF AE costs (per cycle)** AF-related stroke events: 116,429 DKK (€15,615) Stroke ongoing costs: 5,635 DKK (€756) HF: €909 CV-related hospitalizations/visits: range 437 to 14,880 DKK (€59 to €1,996) Pharmaceutical Cardioversion: 9,801 DKK (€1,314) Electrical cardioversion: 9,801 DKK (€1,314)	**Units** Cryoballoon procedure: €8,121 **AF AE costs (per cycle)** AF-related stroke events: €391 to €5,168 Stroke ongoing costs: NR HF: range €166 to €291 CV-related hospitalizations/visits: range €32 to €1,464 Pharmaceutical Cardioversion: €1,206 Electrical cardioversion: €166 **Total pharmaceutical costs (per cycle)** Cryoablation arm: €69 AAD arm: €89	**Units** Cryoballoon procedure: £9,779 **Intra-operative AE costs** Esophageal injury: £26,733 Cardiac tamponade: £2,083 Pulmonary vein stenosis: £2,777 Vascular complications: £1,389 Persistent phrenic nerve injury: £325 **AF AE costs (per cycle)** AF-related stroke events: range £2,196 to £6,812 Stroke ongoing costs: range £293 HF: range £125 to £218

Methods	Wazni, 2023[15]	Andrade 2024[16]	Hansen, 2024[17]	Kuniss, 2024[18]	Paisey, 2024[19]
Model inputs/costs (Continued)	Pulmonary vein stenosis: $2,944 Vascular complications: $7,999 Persistent phrenic nerve injury: $1,742 **AF AE costs (per cycle)** AF-related stroke events: range $4,999 to $63,707 Stroke ongoing costs: $4,999 HF: range $2802 to $3712 CV-related hospitalizations/visits: range $7,155 to $25,661 Pharmaceutical Cardioversion: $263 Electrical cardioversion: $254 **Total pharmaceutical costs (per cycle)** Cryoablation arm: $108 AAD arm: $143 **Resources** Drug costs (per cycle): range $14.36 to $686 Other costs: NR	HF: range $235 to $412 HF: $1,049 CV-related hospitalizations/visits: range $162 to $2,872 Pharmaceutical Cardioversion: $2,447 Electrical cardioversion: $2,447 **Total pharmaceutical costs (per cycle)** Cryoablation arm: $33.58 AAD arm: $58.06 **Resources*** Cryoballoon: $5,495 Flexcath sheath: $1,250 Achieve catheter: $1,250 Achieve cable: $250 Amplatz wire: $100 Introducer: $175 Needle: $400 CS Catheter: $300 Cable: $75 Cryoablation umbilical cord: $225 Cryoablation electrical cable: $375 EP physiologist: $600 Catheterization: $27.81/hour Anti-coagulation at enrollment (per cycle): range $10.04 to $804 AADs (per cycle): range $25.36 to $423.77	**Total pharmaceutical costs (per cycle)** Cryoablation arm: 475 DKK (€64) AAD arm: 666 DKK (€89)	**Resources** Drug costs (per cycle): range €5.70 to €480 Other costs: NR	CV-related hospitalizations/visits: range £191 to £1362 Pharmaceutical Cardioversion: £1,538 Electrical cardioversion: £1,538 **Total pharmaceutical costs (per cycle)** Cryoablation arm: £38.37 AAD arm: £48.69 **Resources** Cryoballoon: £4,118 Flexcath sheath: £768 Achieve catheter: £768 Introducer: £130 Needle: £106 CS Catheter: £307 Cable: £30 Anti-coagulation at enrollment (per cycle): range £2.44 to £177 AADs (per cycle): range £5.74 to £205

Methods	Wazni, 2023[15]	Andrade 2024[16]	Hansen, 2024[17]	Kuniss, 2024[18]	Paisey, 2024[19]
Utilities	**Health state decrements** LT-persistent: 0.08 Permanent: 0.11 AE decrements Stroke: range 0.00 to 0.65 HF: range 0.00 to 0.30	**Health state decrements** LT-persistent: 0.08 Permanent: 0.11 AE decrements Stroke: range 0.00 to 0.65 HF: range 0.00 to 0.30	**Health state decrements** LT-persistent: 0.08 Permanent: 0.11 AE decrements Stroke: range 0.00 to 0.65 HF: range 0.00 to 0.30	**Health state decrements** LT-persistent: 0.08 Permanent: 0.11 AE decrements Stroke: range 0.00 to 0.60 HF: range 0.00 to 0.33	**Health state decrements** LT-persistent: 0.08 Permanent: 0.11 AE decrements Stroke: range 0.00 to 0.60 HF: range 0.00 to 0.33
Assumptions	Assumptions based on clinical opinions, but not described	Not described well	Not described well	• Utility decrement applied to the ST-episode and LT-persistent states were equivalent • RR parameters for AF recurrence and resolution, stroke, HF, and re-ablation success assumptions based on clinical opinions, but not described well.	• Utility decrement applied to the ST-episode and LT-persistent states were equivalent • RR parameters for AF recurrence and resolution, stroke, HF, and re-ablation success assumptions based on clinical opinions, but not described well.
Willingness to pay threshold	$50,000, $100,000, $150,000	NR	€23,200	€35,000	£20,000, £30,000
Sensitivity analyses specifically called out	Probabilistic sensitivity analysis across 5000 model iterations EQ-5D-3L multiplied by EHRA utility decrements Outcome data collected during 12-week blanking period removed	Probabilistic sensitivity analysis across 5000 model iterations EQ-5D-3L multiplied by EHRA utility decrements Outcome data collected during 12-week blanking period removed	Probabilistic sensitivity analysis across 5000 model iterations EQ-5D-3L multiplied by EHRA utility decrements Outcome data collected during 12-week blanking period removed	Probabilistic sensitivity analysis across 5000 model iterations EQ-5D-3L multiplied by EHRA utility decrements Outcome data collected during 12-week blanking period removed	Probabilistic sensitivity analysis across 5000 model iterations EQ-5D-3L replaced by AFEQT and multiplied by EHRA utility decrements Outcome data collected during 12-week blanking period removed

Methods	Wazni, 2023[15]	Andrade 2024[16]	Hansen, 2024[17]	Kuniss, 2024[18]	Paisey, 2024[19]

Scenario analysis	• Pharmaceutical agent costs
	• Cardiovascular-related healthcare costs
	• AF recurrence and resolution risk (±10%)
	• Ablation success rate (-30%)
	• Stroke incidence rate (-30%)
	• Utility decrements
	• RR of stroke
	• RR of heart failure in the permanent state (+10%)
	• Scenario specifics
	  ○ Number of drugs received varied
	  ○ Percentage of patients that moved between phases varied
	• Proportion of total drug costs paid by Medicare varied by drug and brand
		• 12-week blanking period
		• Alternative discount rates (0%, 1.5%, 5%)
		• Alternative cryoablation procedures (±20% costs)
		• Stroke event and follow-up (±20% costs)
		• Follow-up costs of heart failure (UK to Canadian)
		• Alternative EQ-5D-3L utility
		• RR of AF symptom recurrence (+10%)
		• RR of AF symptom resolution (+10%)
		• Probability of successful re-ablation (-30%)
		• Incidence rate of stroke (-30%)
		• Specific stroke RR (+10%)
			• Alternative discount rates (recommended by Danish Ministry of Health)
			• Applying 12-month blanking period
			• Alternative utility decrements based on EHRA class
			• Cryoablation procedure costs (±20%)
			• Stroke event and ongoing costs (±20%)
			• Replace ongoing follow-up costs of heart failure associated with NYHA class, estimated by Danish study
			• RR of symptom occurrence (+10%)
			• RR of AF symptom resolution (+10%)
			• Probability of successful re-ablation procedure (-30%)
			• Incidence rate of stroke (-30%)
			• Health-state specific stroke RR values (+10%)
			• Alternative time horizon (10 years)
				• AF recurrence (details NR)
				• AF resolution (details NR)
				• Ablation success rate (details NR)
				• Stroke incidence rate (details NR)
				• Health state-specific RR of stroke (details NR)
				• RR of heart failure in the permanent state (details NR)
				• 12-week blanking period removed
				• Alternative sources for cost inputs (details NR)
					• AF recurrence (+10%)
					• AF resolution (+10%)
					• Ablation success rate (-30%)
					• Stroke incidence rate (-30%)
					• EQ-5D replaced by AFEQT with additional utility decrement for EHRA class
					• Health state-specific RR of stroke (details NR)
					• RR of heart failure in the permanent state (+10%)
					• 12-week blanking period removed
					• Alternative sources for cost inputs (details NR)
					• 2022/2023 cost used for ablation procedure cost

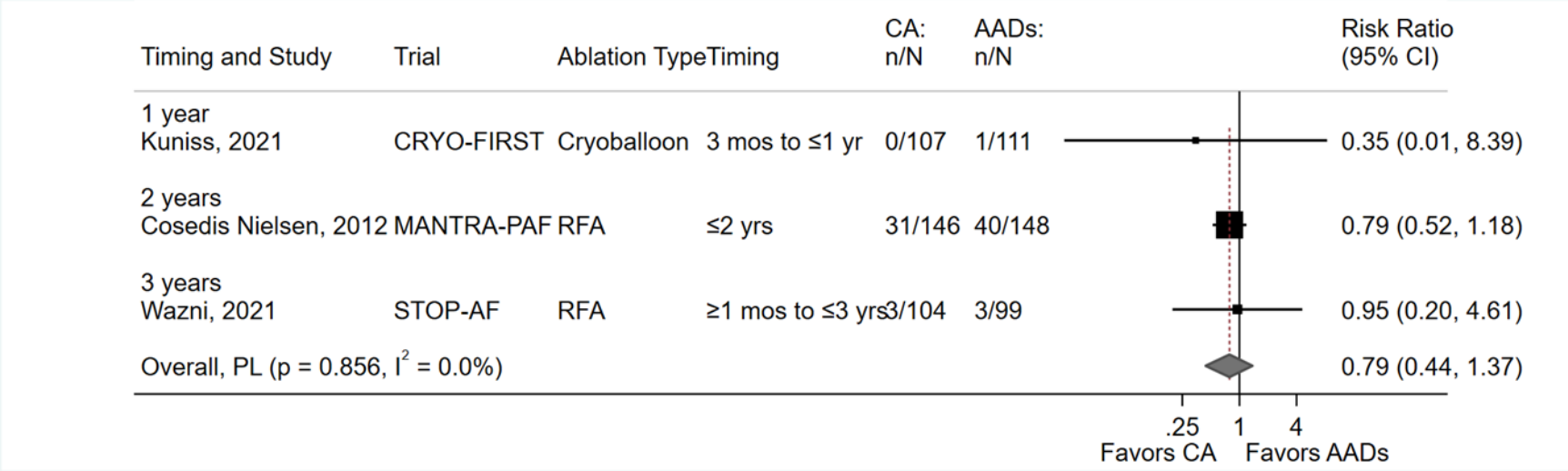
QHES	**92**	**92**	**92**	**92**	**92**

AAD = antiarrhythmic drug; AE = adverse events; AF = atrial fibrillation; AFEQT = AF Quality of Life Survey; EHRA = European Heart Rhythm Association; HF = heart failure; NR = not reported; NYHA = New York Heart Association; RR = risk ratio.

* All provided by Medtronic.

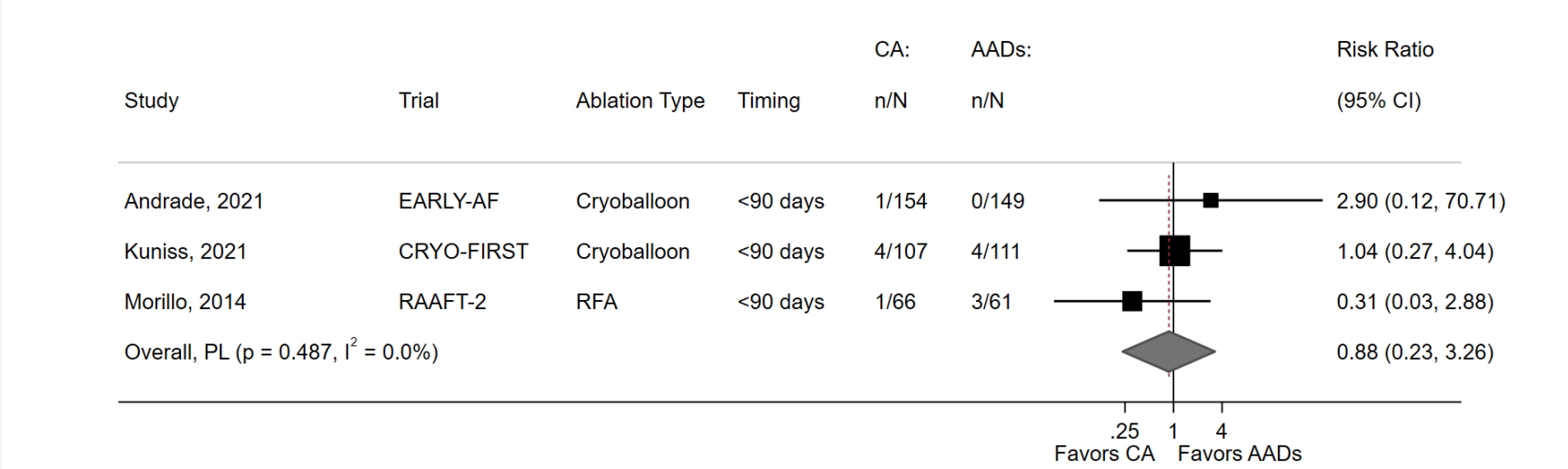
Appendix G. Additional Forest Plots

Appendix Figure G-1. Occurrence of atrial flutter in trials comparing CA to AADs for treatment of AF



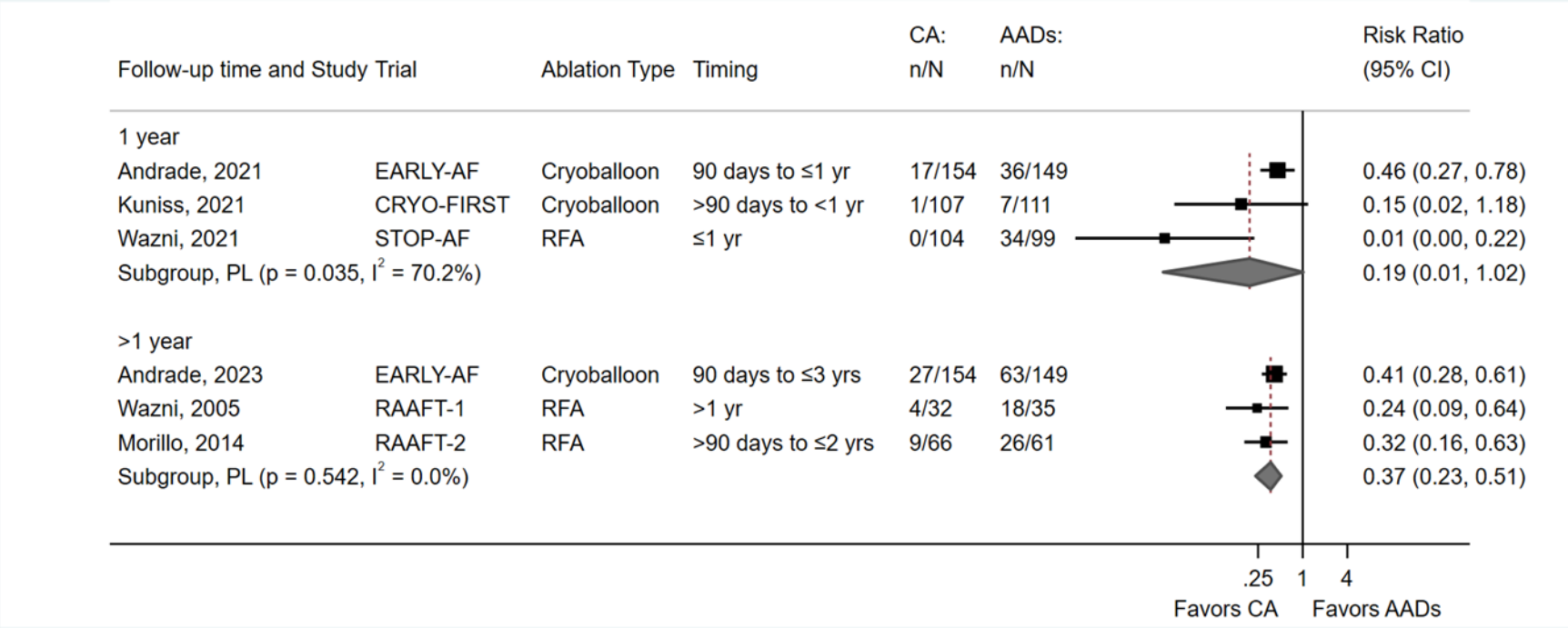
AAD = antiarrhythmic drug; CA = catheter ablation; CI = confidence interval; RFA = radiofrequency ablation

Appendix Figure G-2. Subsequent ablation during the blanking period in trials comparing CA to AADs for treatment of AF



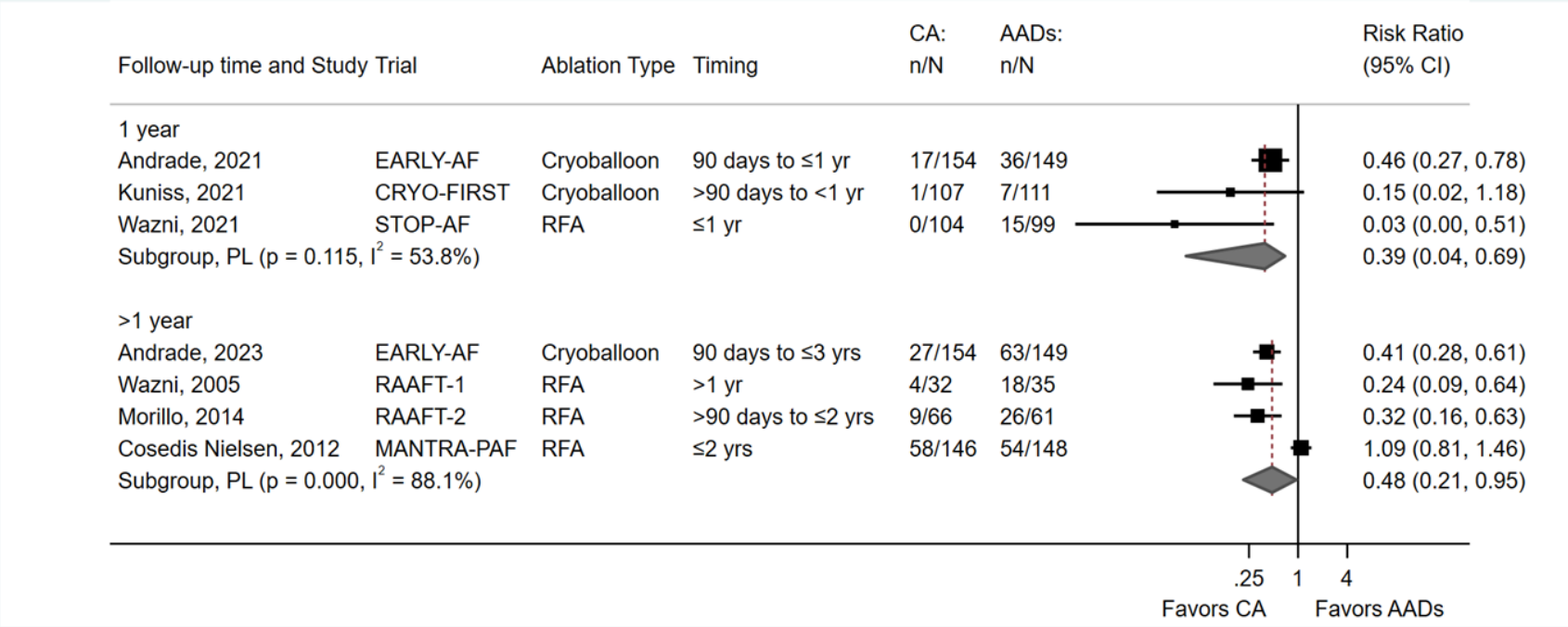
AAD = antiarrhythmic drug; CA = catheter ablation; CI = confidence interval; RFA = radiofrequency ablation

Appendix Figure G-3. Subsequent ablation post blanking period in trials comparing CA to AADs for treatment of AF – Sensitivity analysis; no Cosedis-Nielsen, 2012 (MANTRA-PAF)



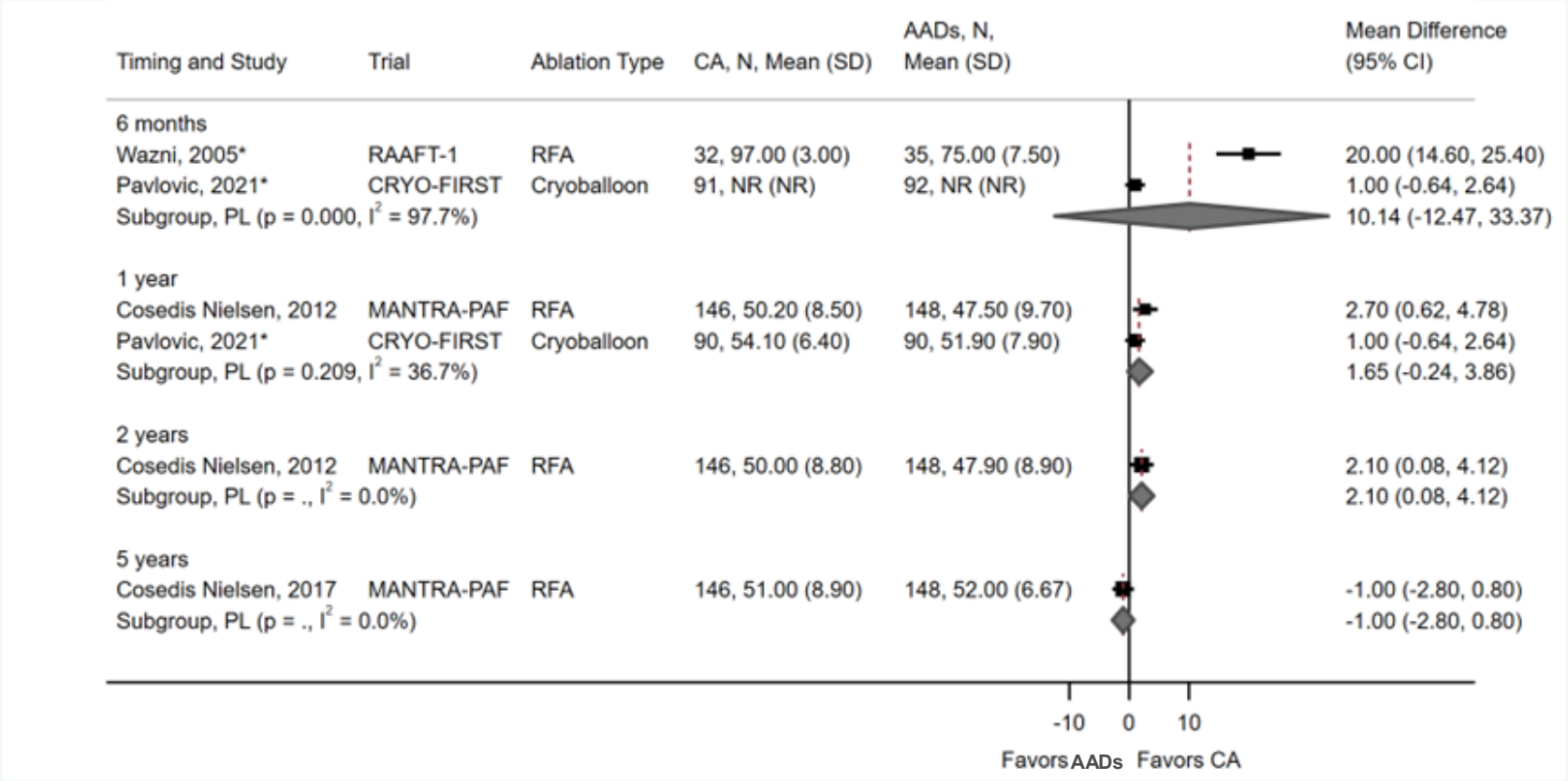
AAD = antiarrhythmic drug; CA = catheter ablation; CI = confidence interval; RFA = radiofrequency ablation

Appendix Figure G-4. Subsequent ablation post blanking period in trials comparing CA to AADs for treatment of AF – Sensitivity analysis; alternative results for Wazni 2021



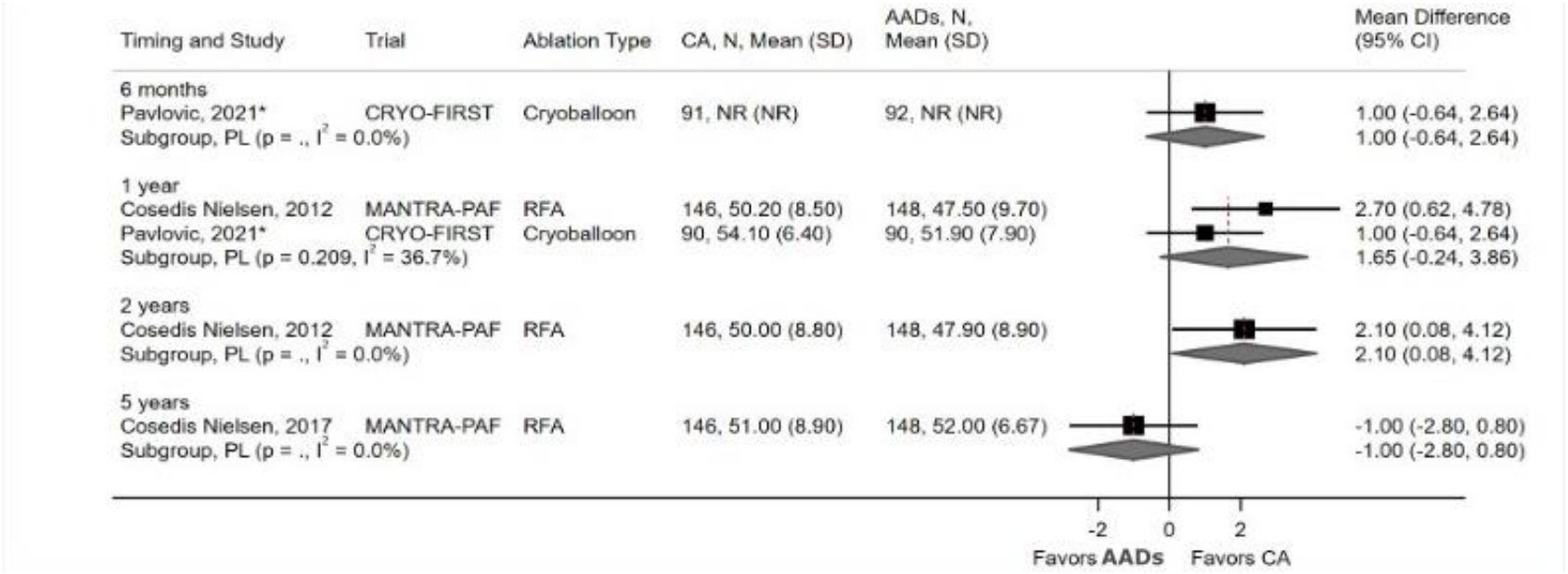
AAD = antiarrhythmic drug; CA = catheter ablation; CI = confidence interval; RFA = radiofrequency ablation

Appendix Figure G-5. SF-36 PCS and physical function scores (scale 0-100) in trials comparing CA to AADs for treatment of AF



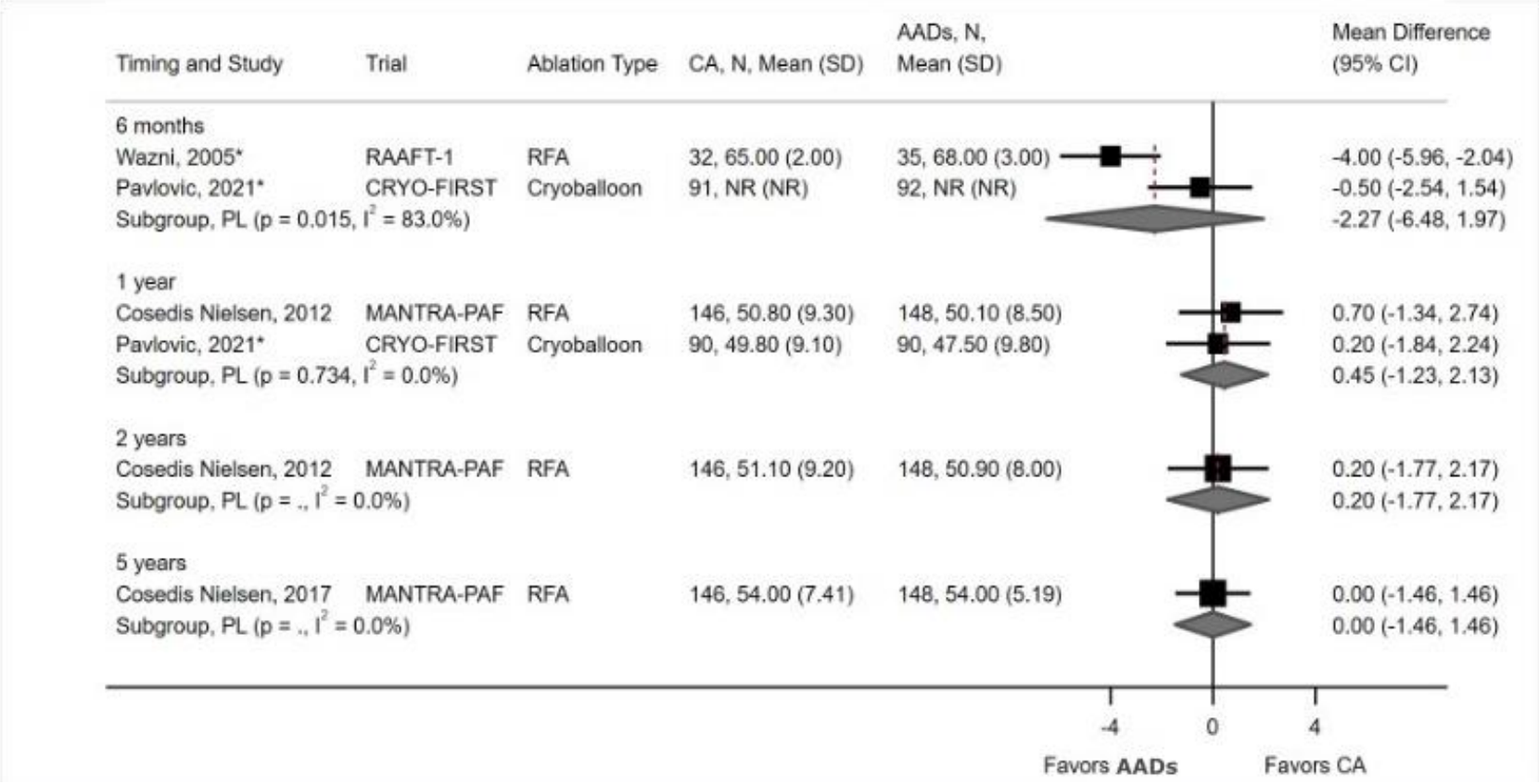
AAD = antiarrhythmic drug; CA = catheter ablation; CI = confidence interval; RFA = radiofrequency ablation; SD = standard deviation

Appendix Figure G-6. SF-36 PCS and physical function scores (scale 0-100) in trials comparing CA to AADs for treatment of AF – Sensitivity analysis; Excluding Wazni, 2005 (used SF-36 physical functioning while other studies used SF-36 PCS)



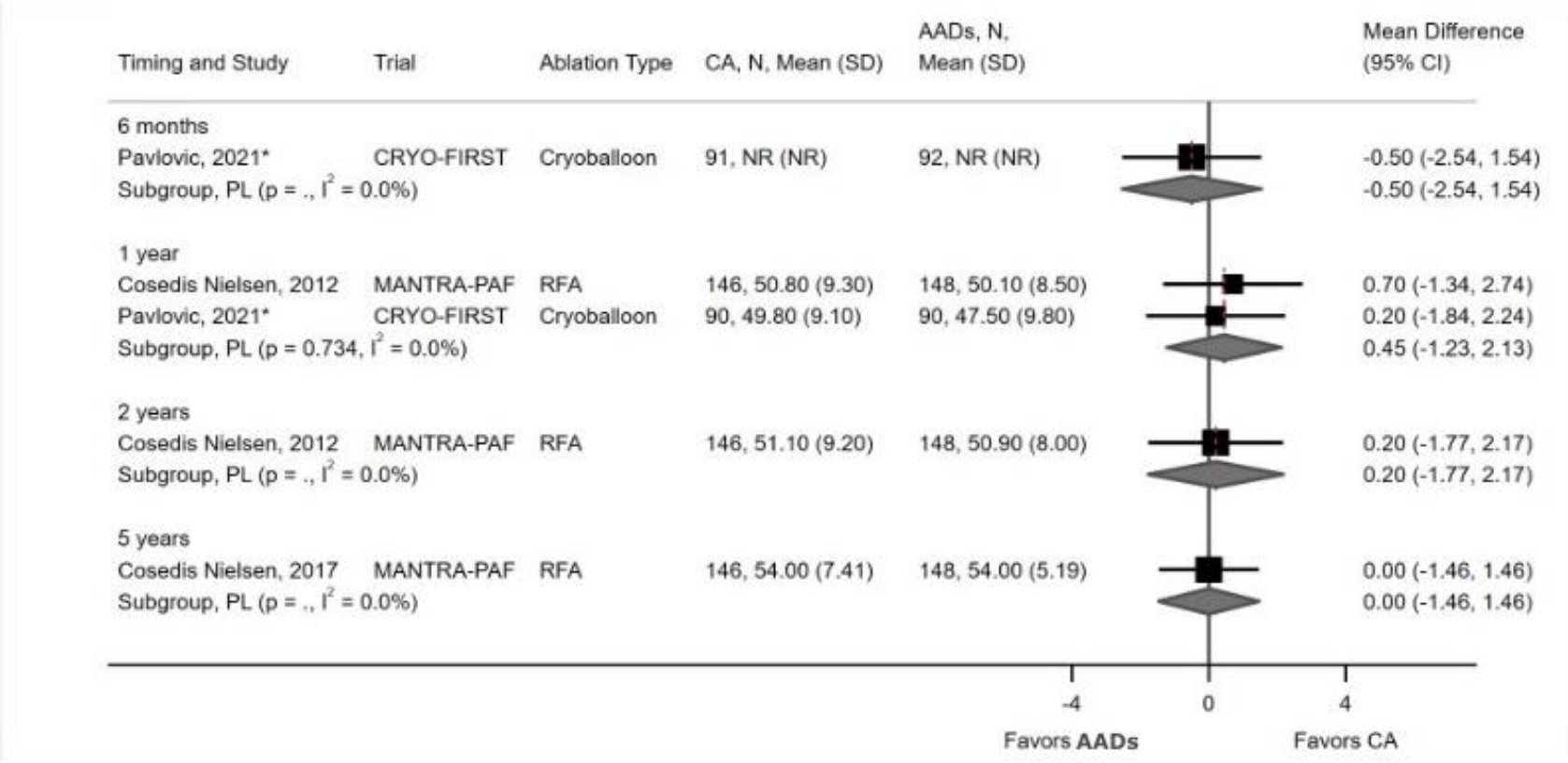
AAD = antiarrhythmic drug; CA = catheter ablation; CI = confidence interval; RFA = radiofrequency ablation; SD = standard deviation

Appendix Figure G-7. SF-36 MCS and mental health scores (scale 0-100) in trials comparing CA to AADs for treatment of AF



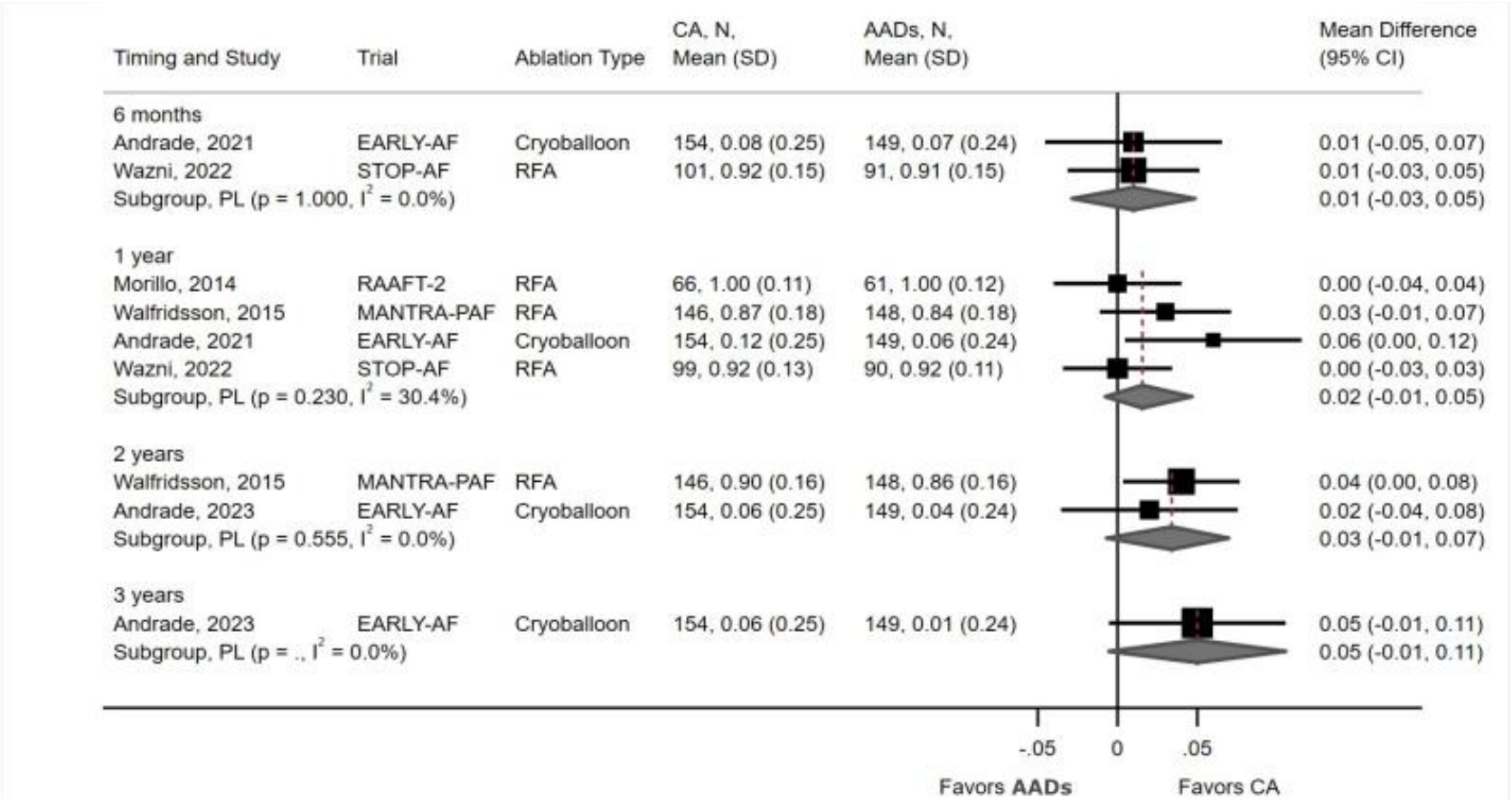
AAD = antiarrhythmic drug; CA = catheter ablation; CI = confidence interval; RFA = radiofrequency ablation; SD = standard deviation

Appendix Figure G-8. SF-36 MCS and mental health scores (scale 0-100) in trials comparing CA to AADs for treatment of AF – Sensitivity analysis; Excluding Wazni, 2005 (used SF-36 mental health while other studies used SF-36 MCS)



AAD = antiarrhythmic drug; CA = catheter ablation; CI = confidence interval; RFA = radiofrequency ablation; SD = standard deviation

Appendix Figure G-9. EQ-5D scores (scale 0-1) in trials comparing CA to AADs for treatment of AF



AAD = antiarrhythmic drug; CA = catheter ablation; CI = confidence interval; RFA = radiofrequency ablation; SD = standard deviation

Appendix H. Differential Efficacy Analysis

Appendix Table H-1. Differential Efficacy Subgroup Analysis

Author, Year Outcome Follow-up	Subgroup	CA, % (n/N)	AADs, % (n/N)	HR or RR (95% CI)	P-value for Interaction
Ding 2022[3] Progression to Persistent Atrial Tachyarrhythmia 3 years	≥65 years	7.7% (2/26)	27.8% (10/36)	HR 0.21 (0.05 to 0.98)	0.222
	<65 years	0% (0/76)	10.6% (7/66)	NC	0.222
	Female	2.4% (1/41)	28.6% (12/42)	HR 0.08 (0.01 to 0.59)	0.702
	Male	1.6% (1/61)	8.3% (5/60)	HR 0.18 (0.02 to 1.55)	0.702
	AF duration >18 months	1.5% (1/65)	14.5% (9/62)	HR 0.10 (0.01 to 0.82)	0.971
	AF duration ≤18 months	2.7% (1/37)	20.0% (8/40)	HR 0.11 (0.01 to 0.91)	0.971
	LA diameter ≥40 mm	3.1% (1/32)	26.2% (11/42)	HR 0.11 (0.01 to 0.82)	0.865
	LA diameter <40 mm	1.4% (1/70)	10.0% (6/60)	HR 0.14 (0.02 to 1.12)	0.865
	History of heart failure (Y)	14.3% (1/7)	40.0% (4/10)	HR 0.26 (0.03 to 2.37)	0.417
	History of heart failure (N)	1.1% (1/95)	12.3% (13/92)	HR 0.07 (0.01 to 0.54)	0.417
	History of coronary artery disease (Y)	4.0% (1/25)	18.5% (5/27)	HR 0.18 (0.02 to 1.52)	0.598
	History of coronary artery disease (N)	1.3% (1/77)	9.6% (12/75)	HR 0.08 (0.01 to 0.60)	0.598
	History of hypertension (Y)	1.9% (1/54)	23.4% (11/47)	HR 0.07 (0.01 to 0.51)	0.473
	History of hypertension (N)	2.1% (1/48)	10.9% (6/55)	HR 0.20 (0.02 to 1.62)	0.473
	Previous diabetes (Y)	0% (0/16)	6.7% (1/15)	NC	0.554
	Previous diabetes (N)	2.3% (2/86)	18.4% (16/87)	HR 0.12 (0.03 to 0.51)	0.554
	Previous stroke or TIA (Y)	0% (0/8)	0% (0/10)	NC	0.670
	Previous stroke or TIA (N)	2.1% (2/94)	9.5% (17/92)	HR 0.10 (0.02 to 0.45)	0.670
	Previous sleep apnea (Y)	0% (0/8)	0% (0/8)	NC	0.677
	Previous sleep apnea (N)	2.1% (2/94)	17.0% (16/94)	HR 0.12 (0.03 to 0.50)	0.677
Wazni 2021 (STOP-AF)[6] Treatment Failure* 1 year	Age 18–53	17.2% (5/29)	33.3% (8/24)	RR 0.52 (0.19 to 1.38)†	NR
	Age 54–62	20.8% (5/24)	59.1% (13/22)	RR 0.35 (0.15 to 0.83)†	NR
	Age 63–69	25.9% (7/27)	48.0% (12/25)	RR 0.54 (0.25 to 1.15)†	NR
	Age ≥70	37.5% (9/24)	64.3% (18/28)	RR 0.58 (0.32 to 1.05)†	NR
	Male	31.7% (13/41)	57.1% (24/42)	RR 0.55 (0.33 to 0.93)†	NR

Author, Year Outcome Follow-up	Subgroup	CA, % (n/N)	AADs, % (n/N)	HR or RR (95% CI)	P-value for Interaction
	Female	20.6% (13/63)	47.4% (27/57)	RR 0.44 (0.25 to 0.76)†	NR
	White	23.4% (22/94)	51.6% (47/91)	RR 0.45 (0.3 to 0.69)†	NR
	Other	50.0% (3/6)	42.9% (3/7)	RR 1.17 (0.36 to 3.76)†	NR
	Not Stated (Race)	25.0% (1/4)	100.0% (1/1)	RR 0.25 (0.05 to 1.36)†	NR
	Hispanic	50.0% (1/2)	66.7% (2/3)	RR 0.75 (0.15 to 3.72)†	NR
	Non-Hispanic	22.7% (22/97)	52.7% (48/91)	RR 0.43 (0.28 to 0.65)†	NR
	Not Reported (Ethnicity)	60.0% (3/5)	20.0% (1/5)	RR 3.0 (0.45 to 19.93)†	NR

AAD = antiarrhythmic drug; CA = catheter ablation; HR = hazard ratio; NC = not calculable; NR = not reported; RR = risk ratio

*defined as experiencing any of the following events: initial failure of the procedure; any subsequent atrial fibrillation surgery or ablation in the left atrium; or atrial arrhythmia recurrence, cardioversion, or use of class I or III antiarrhythmic drugs (ablation group only) outside the 90-day blanking period. For the subgroup analyses, the authors reported the inverse of the primary outcome which is freedom from these events.

†RRs calculated from data provided by studies

Appendix Table H-2. Differential Efficacy Analysis for Alhede 2018 (MANTRA-PAF)

Author, Year Outcome Follow-up	Subgroup	CA, HR (95% CI)	AADs, HR (95% CI)	P-value for Interaction	Conclusion
Alhede 2018[27] (MANTRA-PAF) AF Recurrence 2 years	AF Recurrence: Higher age (≥57 years vs. <57 years)	HR 1.9 (1.1 to 3.2)	HR 0.9 (0.6 to 1.6)	0.02	Higher age was associated with a significantly higher AF recurrence after catheter ablation but not in patients treated with antiarrhythmic medication
	AF recurrence: High SVEC burden at 3 months and age ≥57 years	HR 3.1 (1.4 to 7.9)	HR 8.5 (3.3 to 21.7)	0.04	High SVEC burden was associated with higher risk of AF recurrence after catheter ablation in patients 57–70 years (HR 3.1 [1.4–7.9], p = 0.005), but not in younger patients: (HR 2.0 [0.9–4.3], p = 0.09). This difference was not found in patients treated with antiarrhythmic medication (b57 years: HR 5.2 [2.7–10.0], p b 0.0001 vs 57–70 years: HR 8,5 [3.3–21.7], p b 0.0001, p =0.04 for interaction).
	AF recurrence: High SVEC burden at 3 months and age <57 years	HR 1.9 (0.9 to 4.3)	HR 5.2 (2.7 to 10.0)		

AF = atrial fibrillation; CA = catheter ablation; CI = confidence interval; HR = hazard ratio; SVEC = supraventricular ectopic complex

Appendix Table H-2. Differential Efficacy Analysis for Alhede 2018 (MANTRA-PAF) (cont.)

Author, Year Outcome Follow-up	Treatment group	Higher age (≥57 years vs. <57 years)	High SVEC burden at 3 months and age ≥57 years	AF recurrence: High SVEC burden at 3 months and age <57 years
Alhede 2018[27] (MANTRA-PAF) AF Recurrence 2 years	CA, HR (95% CI)	HR 1.9 (1.1 to 3.2)	HR 3.1 (1.4 to 7.9)	HR 1.9 (0.9 to 4.3)
	AADs, HR (95% CI)	HR 0.9 (0.6 to 1.6)	HR 8.5 (3.3 to 21.7)	HR 5.2 (2.7 to 10.0)
	P-value for Interaction	0.02	0.004	-
	Conclusion	Higher age was associated with a significantly higher AF recurrence after catheter ablation but not in patients treated with antiarrhythmic medication	High SVEC burden was associated with higher risk of AF recurrence after catheter ablation in patients 57–70 years (HR 3.1 [1.4–7.9], p = 0.005), but not in younger patients: (HR 2.0 [0.9–4.3], p = 0.09). This difference was not found in patients treated with antiarrhythmic medication (b57 years: HR 5.2 [2.7–10.0], p b 0.0001 vs 57–70 years: HR 8,5 [3.3–21.7], p b 0.0001, p =0.04 for interaction).	-

AAD = antiarrhythmic drug; AF = atrial fibrillation; CA = catheter ablation; CI = confidence interval; HR = hazard ratio; SVEC = supraventricular ectopic complex

Appendix Table H-3. CA vs. AADs: Subgroup Analyses of recurrence of any atrial tachyarrhythmia* after 2 years of Follow-up (Andrade 2021)[1]

Subgroup	Event No./Total No.	HR (95% CI), CA vs. AADs
High volume center†	53.2% (123/231)	0.42 (0.29, 0.60)
Low volume center	61.1% (44/72)	0.77 (0.42, 1.40)
Left Atrial Enlargement (Yes)	60.7% (68/112)	0.39 (0.24, 0.64)
Left Atrial Enlargement (No)‡	34.8% (16/46)	0.54 (0.20, 1.44)
Atrial Fibrillation Duration ≥1 year	56.4% (114/202)	0.48 (0.33, 0.70)
Atrial Fibrillation Duration <1 year	52.5% (53/101)	0.49 (0.28, 0.84)

CI = confidence interval; MD = mean difference.

*Primary endpoint was first recurrence of any atrial tachyarrhythmia (atrial fibrillation, atrial flutter, or atrial tachycardia) lasting 30 seconds or longer between 91 and 365 days after the initiation of an antiarrhythmic drug or the catheter ablation procedure)

†Procedure volume above or below the median

‡Either enlarged with a left atrial diameter of ≥41 mm, a left atrial volume ≥59 ml, or a left atrial volume index ≥29 ml per square meter or not enlarged

Appendix I. FDA Approved Devices

Appendix Table I-1. FDA Approved Radiofrequency Ablation and Cryoablation Devices for Catheter Ablation

Procedure/Device	Brief description	FDA Approval (Date)	Indications	Contraindications
HexaGen RF	Radiofrequency ablation (RF)	P240013 (10/24/2024)	Cardiac electrophysiological mapping (stimulation and electrogram recording); treatment of drug-refractory, recurrent, symptomatic persistent AF (<1 year episode duration); RFA of CTI-dependent AFL	Active systemic infection; Previous cardiac surgery in past 8 weeks; intracardiac thrombus or myxoma; coronary vessels smaller than the expandable ablation electrode; patients with prosthetic valves; via transaortic retrograde approach in patients with aortic valve replacement; via transeptic approach in patients with an interatrial baffle or patch
Ampere/TactiFlex/TactiSys Quartz Abbott	Radiofrequency ablation	P220013 (5/18/2023)	Cardiac electrophysiological mapping (stimulation and electrogram recording); treatment of drug-refractory, recurrent, symptomatic paroxysmal AF and concomitant AFL	NR
EPT-1000 XP RF System Boston Scientific	Radiofrequency ablation	P020025 (8/25/2003)	Treatment of sustained or recurrent type I AFL in patients 18 or older	Active systemic infection; via transseptal approach in patients with left atrial thrombus or myxoma; via retrograde approach in patients with aortic valve replacement
IBI-1500T9 RF System Irvine Biomedical	Radiofrequency ablation	P060019 (3/16/2007)	CA procedures (mapping, stimulation, ablation) for treatment of typical AFL; CA of cardiac arrhythmias (i.e., SVTs and AFL)	Active systemic infection; intracardiac thrombus; ventriculotomy or atriotomy in last 4 weeks

Procedure/Device	Brief description	FDA Approval (Date)	Indications	Contraindications
IBI 1500T9-CP V1.6 RF System Abbott	Radiofrequency ablation	P110016 (1/25/2012)	CA procedures (mapping, stimulation, ablation) for treatment of typical AFL	Active systemic infection; intracardiac thrombus; ventriculotomy or atriotomy in last 4 weeks
Therapy Dual 8 Ablation System Irvine Biomedical	Radiofrequency ablation	P040042 (11/18/2005)	CA procedures (mapping, stimulation, ablation) for treatment of typical AFL	Active systemic infection; intracardiac thrombus; ventriculotomy or atriotomy in last 4 weeks
QDOT MICRO System Biosense Webster	Radiofrequency ablation	P210027 (11/23/2022)	Cardiac electrophysiological mapping (stimulation and recording); Treatment of type I AFL in patients 18 or older; Treatment of drug-refractory, recurrent, symptomatic paroxysmal AF	Ventriculotomy or atriotomy in last 12 weeks; myxoma or intracardiac thrombus; patients with prosthetic valves; in coronary arterial vasculature; active systemic infection; via transseptal approach in patients with interatrial baffle or patch; via retrograde transaortic approach in patients with aortic valve replacement; with a long sheath or short introducer < 8.5F
DiamondTemp System Medtronic	Radiofrequency ablation	P200028 (1/28/2021)	Cardiac electrophysiological mapping (stimulation and recording); treatment of drug refractory, recurrent, symptomatic paroxysmal AF	Active systemic infection; patients with prosthetic valves; intracardiac thrombus or myxoma; via transseptal approach in patients with interatrial baffle; patients unable to receive heparin or acceptable alternative; pregnant women, children <18 years; hemodynamically unstable patients
Stockert 70 System Biosense Webster	Radiofrequency ablation	P990071 (5/32/2000)	CA procedures	Active systemic infection; via transseptal approach in patients with left atrial thrombus, myoma, or interatrial baffle/patch; via retrograde transaortic approach in patients with aortic valve replacement

Procedure/Device	Brief description	FDA Approval (Date)	Indications	Contraindications
Blazer/INTELLANAV/OpalHDx Open-Irrigated Ablation Catheter Boston Scientific	Radiofrequency ablation	P150005 (2/24/2016)	Cardiac electrophysiological mapping; delivering diagnostic pacing stimuli; RFA of sustained or recurrent type I AFL in patients 18 or older	Active systemic infection; patients with mechanical prosthetic heart valve in catheter's intended path; patients unable to receive heparin or acceptable alternative anticoagulant; patients with vena cava embolic protection filter devices or known femoral thrombus (when femoral entry is required); hemodynamically unstable patients; myxoma or intracardiac thrombus; ventriculotomy or atriotomy in last 8 weeks
NAVISTAR/CELSIUS DS Catheter Biosense Webster	Radiofrequency Ablation	P010068 (9/27/2002)	Cardiac electrophysiological mapping (stimulating and recording); RFA of type I AFL in patients 18 or older	Active systemic infection; via transseptal approach in patients with left atrial thrombus or myxoma; via retrograde approach in patients with aortic valve replacement
Navistar/Celsius Thermocool Biosense Webster	Radiofrequency Ablation	P030031 (11/5/2004)	Cardiac electrophysiological mapping (stimulating and recording); I AFL in patients 18 or older	Active systemic infection; intracardiac mural thrombus; ventriculotomy or atriotomy in last 4 weeks
Tacticath Quartz/Tactisys Quartz St Jude Medical	Radiofrequency Ablation	P130026 (10/24/2014)	Cardiac electrophysiological mapping; treatment of drug-refractory, recurrent, symptomatic paroxysmal AF	Ventriculotomy or atriotomy in last 4 weeks; patients with prosthetic valves; active systemic infection; in coronary vasculature; myxoma or intracardiac thrombus; via transseptal approach in patients with interatrial baffle or patch; via retrograde transaortic approach in patients with aortic valve replacement

Procedure/Device	Brief description	FDA Approval (Date)	Indications	Contraindications
Arctic Front/Arctic Front Advance Medtronic	Cryoablation	P100010 (12/17/2010)	Treatment of drug-refractory, recurrent, symptomatic paroxysmal AF	Use in ventricle; active systemic infection; in situations where manipulation of catheter within heart would be unsafe (e.g., intracardiac thrombus); patients with cryoglobulinemia; patients with one or more pulmonary vein stents
POLARx/SMARTFREEZE Boston Scientific	Cryoablation	P220032 (8/8/2023)	Treatment of drug-refractory, recurrent, symptomatic paroxysmal AF; Console is intended for cryoablation and electrical mapping of pulmonary veins for PVI	Active systemic infection; myxoma or intracardiac thrombus; patients with synthetic heart valve; in ventricle of heart where device may become entrapped in a valve or chordae structures; recent ventriculotomy or atriotomy; patients with pulmonary vein stents; patients with cryoglobulinemia; where insertion into or manipulation in atrium is unsafe; in patients with intra-atrial septal patch or other surgical intervention in or adjacent to the intra-atrial septum; in patients with interatrial baffle or patch; in patients with hypercoagulopathy or inability to tolerate anticoagulant therapy during an electrophysiology procedure; in patients with contraindication to invasive electrophysiological mapping procedure where insertion or manipulation of catheter in cardiac chambers is deemed unsafe; patients with previously implanted percutaneous left atrial appendage occlusion device

Procedure/Device	Brief description	FDA Approval (Date)	Indications	Contraindications
CRYOCOR Ablation System Boston Scientific	Cryoablation	P050024 (8/1/2007)	Ablation of isthmus-dependent right atrial AFL in patients 18 or older	Active systemic infection; intracardiac mural thrombus; ventriculotomy or atriotomy in last 4 weeks; patients with cryoglobulinemia

AF = atrial fibrillation; AFL = atrial flutter; CTI = cavotricuspid isthmus; NR = not reported; PVI = pulmonary vein isolation; RFA = radiofrequency ablation; SVTs = supraventricular tachycardias

Appendix Table I-2. FDA Approved Pulsed Field Ablation and Laser Ablation Devices for Catheter Ablation

Procedure/Device	Brief description	FDA Approval (Date)	Indications	Contraindications
PulseSelect System Medtronic	Pulsed field ablation	P230017 (12/13/2023)	Cardiac electrophysiological mapping; treatment of drug-refractory, recurrent, symptomatic paroxysmal AF or persistent AFL (episode duration <1 year)	Active systemic infection; known sensitivity to heparin; blood clotting abnormalities; permanently implanted metallic objects in left atrium
Affera Sphere-9/Hexagen PF Medtronic	Pulsed field ablation/Pulsed field ablation (PF)	P240013 (10/24/2024)	Cardiac electrophysiological mapping; treatment of drug-refractory, recurrent, symptomatic persistent AFL(episode duration <1 year); treatment of CTI-dependent AFL	Active systemic infection; cardiac surgery in last 8 weeks; intracardiac thrombus or myxoma; in coronary vessels with diameter smaller than expandable ablation electrode; patients with prosthetic valves; via transaortic retrograde approach in patients with aortic valve replacement; via transseptal approach in patients with interatrial baffle or patch/
Globe System Kardium	Pulsed field ablation	P240044 (8/27/2025)	Anatomical and electrophysiological mapping and stimulation of cardiac tissue; delivery of ablation energy for treatment of drug-refractory, recurrent, symptomatic paroxysmal AF	Pediatric patients; patients with material around the atrium that could become dislodged during the procedure (e.g., intracardiac thrombus, myxoma, tumor); active systemic infection; intolerance to anticoagulation medications

Procedure/Device	Brief description	FDA Approval (Date)	Indications	Contraindications
FARAPULSE System Boston Scientific	Pulsed field ablation	P230030 (1/30/2024)	PVI in treatment of paroxysmal AF	Active systemic infection; patients with mechanical prosthetic heart valve catheter must pass through; patients with conditions where insertion into or manipulation in the cardiac chambers is unsafe (e.g., intracardiac thrombus, myxoma, recent atriotomy, etc.); bleeding disorder with inability to receive heparin or acceptable alternative anticoagulant therapy; patients with vena cava embolic protection filter devices or known femoral thrombus (where femoral entry required); contraindication to invasive electrophysiological procedure where insertion or manipulation of catheter in cardiac chambers is deemed unsafe (e.g., recent ventriculotomy, atriotomy, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, percutaneous coronary intervention, coronary stent procedure, unstable angina); patients with congenital heart disease where underlying abnormality increases risk of ablation procedure (e.g., severe rotational anomalies of heart or great vessels); via transseptal approach in patients with interatrial baffle or patch

Procedure/Device	Brief description	FDA Approval (Date)	Indications	Contraindications
VARIPULSE/TRIPULSE System Johnson & Johnson	Pulsed field ablation	P240006 (11/6/2024)	Cardiac electrophysiological mapping (stimulating and recording); treatment of drug-refractory, recurrent, symptomatic paroxysmal AF in patients 22 years or older	Atriotomy in last 8 weeks; myxoma or intracardiac thrombus; patients with prosthetic valves; use in coronary arterial vasculature; active systemic infection; via transseptal approach in patients with interatrial baffle or patch; via retrograde transaortic approach; use in ventricles; recent history of myocardial infarction; pregnant women; use in arterial or jugular access sites
Heartlight System Cardiofocus	Laser ablation	P150026 (4/1/2016)	Treatment of drug-refractory, recurrent, symptomatic paroxysmal AF	Ventriculotomy or atriotomy in last 4 weeks; patients with prosthetic valves; active systemic infection; unstable angina; patients with interatrial baffle or patch; use in ventricles; patients with conditions where the manipulation of catheter in heart would be unsafe (e.g., intracardiac thrombus and myxoma); patients with pulmonary vein stents

AF = atrial fibrillation; AFL = atrial flutter; CTI = cavotricuspid isthmus; PVI = pulmonary vein isolation

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Appendix K. Clinical Peer Review

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